

COMPOUNDS FOR THE DEGRADATION OF EGFR KINASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to International Application No. PCT/CN2023/097387, filed May 31, 2023, and to International Application No. PCT/CN2023/125498, filed October 19, 2023, and to International Application No. PCT/CN2024/090756, filed April 30, 2024, the disclosures of each of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] Disclosed herein are novel bifunctional compounds formed by conjugating EGFR inhibitor moieties with E3 ligase Ligand moieties, which function to recruit targeted proteins to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof.

BACKGROUND OF THE INVENTION

[0003] Proteolysis targeting chimera (PROTAC) consists of two covalently linked protein-binding molecules: one capable of engaging an E3 ubiquitin ligase, and another that binds to the protein of interest (POI) a target meant for degradation (Sakamoto KM et al., *Proc. Natl. Acad. Sci.* 2001, 98: 8554–9.; Sakamoto K. M. et al., *Methods Enzymol.* 2005; 399:833-847). Rather than inhibiting the target protein's enzymatic activity, recruitment of the E3 ligase to the specific unwanted proteins results in ubiquitination and subsequent degradation of the target protein by the proteasome. The whole process of ubiquitination and proteasomal degradation is known as the ubiquitin–proteasome pathway (UPP) (Ardley H. et al., *Essays Biochem.* 2005, 41, 15–30; Komander D. et al., *Biochem.* 2012, 81, 203–229; Grice G. L. et al., *Cell Rep.* 2015, 12, 545–553; Swatek K. N. et al., *Cell Res.* 2016, 26, 399–422). Proteasomes are protein complexes which degrade unneeded, misfolded or abnormal proteins into small peptides to maintain health and productivity of the cells. Ubiquitin ligases, also called an E3 ubiquitin ligase, directly catalyze the transfer of ubiquitin from the E2 to the target protein for degradation. Although the human genome encodes over 600 putative E3 ligases, only a limited number of E3 ubiquitin ligases have been widely applied by small molecule PROTAC technology: cereblon (CRBN), Von Hippel–Lindau (VHL), mouse double minute 2 homologue (MDM2) and cellular inhibitor of apoptosis protein (cIAP) (Philipp O. et al., *Chem. Biol.* 2017, 12, 2570-2578), recombinant Human Ring Finger Protein 114 (RNF114) (Spradlin, J. N. et al. *Nat. Chem. Biol.* 2019, 15, 747-755) and DDB1 And CUL4 Associated Factor 16 (DCAF16) (Zhang, X. et al. *Nat. Chem. Biol.* 2019, 15, 737-746). For example, cereblon (CRBN) forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cullin-4A (CUL4A) to ubiquitinate a number of other proteins followed by the degradation via proteasomes. (Yi-An Chen, et al., *Scientific Reports* 2015, 5, 1–13). Immunomodulatory drugs (IMiDs), including thalidomide, lenalidomide, and pomalidomide, function as monovalent promoters of PPIs by binding to the cereblon (CRBN) subunit of the CRL4A^{CRBN} E3 ligase complex and recruiting neosubstrate proteins. (Matyskiela, M. E. et al., *Nat Chem Biol* 2018, 14, 981–987). As a consequence, the ability of thalidomide, and its derivatives, to recruit CRBN has been widely applied in proteolysis-targeting chimeras (PROTACs) related studies (Christopher T. et al. *ACS Chem. Biol.* 2019, 14,

342–347; Honorine L. et al, *ACS Cent. Sci.* 2016, 2, 927–934). PROTACs have great potential to eliminate protein targets that are “undruggable” by traditional inhibitors or are non-enzymatic proteins. (Chu TT. et al., *Cell Chem Biol.* 2016; 23:453-461. Qin C. et al., *J Med Chem* 2018; 61: 6685-6704. Winter GE. et al., *Science* 2015;348:1376-1381.) PROTACs as useful modulators promoting the selective degradation of a wide range of target proteins have been reported in antitumor studies. (Lu J. et al., *Chem Biol.* 2015;22(6):755-763; Ottis P. et al., *Chem Biol.* 2017; 12(4):892-898.; Crews C. M. et al., *J Med Chem.* 2018; 61(2):403-404; Neklesa T.K. et al., *Pharmacol Ther.* 2017, 174:138-144.; Cermakova K. et al., *Molecules*, 2018,23(8).; An S. et al., *EBioMedicine*, 2018.; Lebraud H. et al., *Essays Biochem.* 2017;61(5): 517-527.; Sun Y.H. et al., *Cell Res.* 2018;28:779–81; Toure M. et al., *Angew Chem Int Ed Engl.* 2016;55(6):1966-1973; Yonghui Sun et al., *Leukemia*, volume 33, pages 2105–2110(2019); Shaodong Liu et al., *Medicinal Chemistry Research*, volume 29, pages 802–808(2020); and has been disclosed or discussed in patent publications, e.g., US20160045607, US20170008904, US20180050021, US20180072711, WO2002020740, WO2014108452, WO2016146985, WO2016149668, WO2016197032, WO2016197114, WO2017011590, WO2017030814, WO2017079267, WO2017182418, WO2017197036, WO2017197046, WO2017197051, WO2017197056, WO2017201449, WO2018071606, WO2021178920, WO2021127283, WO2021127190, WO202111871 and WO202111913.

[0004] Epidermal growth factor receptor (EGFR) that belongs to the ErbB family is a transmembrane receptor tyrosine kinase (RTK), which plays a fundamentally key role in cell proliferation, differentiation, and motility (Y. Yarden, et al., *Nat. Rev. Mol. Cell Biol.* 2001; 2:127-137.). Homo- or heterodimerization of EGFR and other ErbB family members activates cytoplasmic tyrosine kinase domains to initiate intracellular signaling. Overexpression or activating mutations of EGFR are associated the development of many types of cancers, such as pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, and non-small cell lung cancer (Yewale C., et al. *Biomaterials.* 2013, 34 (34): 8690-8707). The activating mutations in the EGFR tyrosine kinase domain (L858R mutation and exon-19 deletion) have been identified as oncogenic drivers for NSCLC (Konduri, K., et al. *Cancer Discovery* 2016, 6 (6), 601-611). The first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib have approved for NSCLC patients with EGFR activation mutations (M. Maemondo, *N. Engl. J. Med.* 362 (2010) 2380-2388). Although most patients with EGFR mutant NSCLC respond to these therapies, patients typically develop resistance after an average of one year on treatment. There are several mechanisms of acquired resistance to gefitinib and erlotinib, including a secondary threonine 790 to methionine 790 mutation (T790M), is also called “gatekeeper” T790M mutation (Xu Y., et al. *Cancer Biol Ther.* 2010, 9 (8): 572-582). Therefore, the second-generation EGFR-TKIs afatinib and the third-generation EGFR-TKIs osimertinib (AZD9291) were developed as irreversible EGFR inhibitors that bind to Cys797 for the treatment of patients with T790M mutation. In particular, osimertinib that largely spares WT EGFR has achieved greater clinical response rate in NSCLC patients with EGFR T790M. However, several recent studies have reported a tertiary Cys797 to Ser797 (C797S) point mutation with osimertinib clinical therapy (Thress KS, et al. *Nat. Med.* 2015, 21 (6): 560-562). Thus, there is a need for drugs which can overcome EGFR (C797S) resistance obstacle in non-small cell lung cancer (NSCLC). EGFR-Targeting PROTACs serve as a potential strategy to overcome drug resistance mediated by these mutants, which has been disclosed or discussed in patent publications, e.g.

WO2018119441, WO2019149922, WO2019183523, WO2019121562, US20190106417, WO202157882, WO2021123087, WO2021133809, WO2021168074, WO2021208918 and WO2021216440.

[0005] A number of EGFR-targeting PROTACs which were designed to degrade EGFR mutant proteins have been published (Zhang X., et al. *Eur. J. Med. Chem.* 2020, 192, 112199.; Zhang H, et al. *Eur. J. Med. Chem.* 2020, 189, 112061.; Lu X, *Med. Res. Rev.* 2018, 38(5):1550-1581. He K., et al. *Bioorg. Med. Chem. Lett.* 2020, 15, 127167). Most of these published molecules are based on first, second, and third generation of EGFR inhibitors (WO2021023233, WO2019121562 and WO2018119441) or allosteric EGFR inhibitors (WO2021127561). However, there were no data which showed those EGFR-Targeting PROTACs degrading all the main EGFR mutations, such as Del19, L858R, Del19/T790M, L858R/T790M, Del19/T790M/C797S, L858R/T790M/C797S.

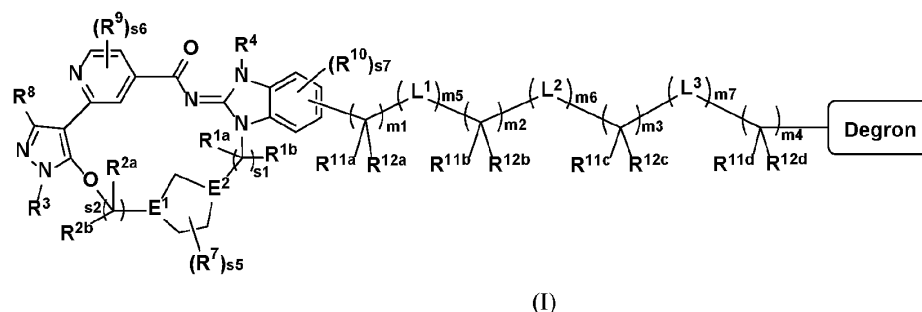
[0006] The present application provides novel bifunctional compounds and compositions for the treatment of serious diseases affected by EGFR modulation, especially for the treatment of cancer, preferably selected from pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, and non-small cell lung cancer.

SUMMARY OF THE INVENTION

[0007] One objective of the present disclosure is to provide compounds and derivatives formed by conjugating EGFR inhibitor moieties with E3 ligase Ligand moieties, which function to recruit targeted proteins to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof.

[0008] The compounds described herein, or salts thereof, are useful in the treatment of a disease that can be affected by EGFR modulation. The present disclosure provides the use of the compounds described herein or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of a disease that can be affected by EGFR modulation. The present disclosure further provides a compound described herein or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease that can be affected by EGFR modulation. The present application further provides a method of treating a proliferative disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the compounds described herein or a pharmaceutically acceptable salt thereof.

[0009] Aspect 1. A compound of Formula (I):



(I)

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof,

wherein:

E¹ is N or CR⁵;

E² is N or CR⁶;

R^{1a}, R^{1b}, R^{2a} and R^{2b} are each independently absent, hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl or -CN; wherein each said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl and -CN;

R³ and R⁴ are each independently hydrogen, -C₁₋₆alkyl, or -C₃₋₈cycloalkyl; wherein each said -C₁₋₆alkyl or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, hydroxy, halogen, and -C₁₋₆alkoxy;

R⁵ and R⁶ are each independently absent, hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl or -CN; wherein each said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl and -CN; or

R⁵ and R⁶ with the carbon atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁₋₈alkyl;

R⁷ is each independently hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl or -CN; wherein each said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl and -CN; or

two R⁷ with the carbon atom(s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁₋₈alkyl;

R⁸ and R⁹ are each independently selected from hydrogen, halogen, -C₁₋₆alkyl and C₃₋₈cycloalkyl; wherein each of -C₁₋₆alkyl or C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, hydroxy, and -C₁₋₆alkoxy;

R¹⁰ is each independently selected from hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, 5- to 12-membered heteroaryl, -NR^{10a}R^{10b}, -OR^{10a}, -SR^{10a}, -C(O)R^{10a}, -CO₂R^{10a}, -C(O)NR^{10a}R^{10b}, -NR^{10a}COR^{10b}, -NR^{10a}CO₂R^{10b}, -NR^{10a}SO₂R^{10b}, and -CN; wherein each of -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one R^{10c};

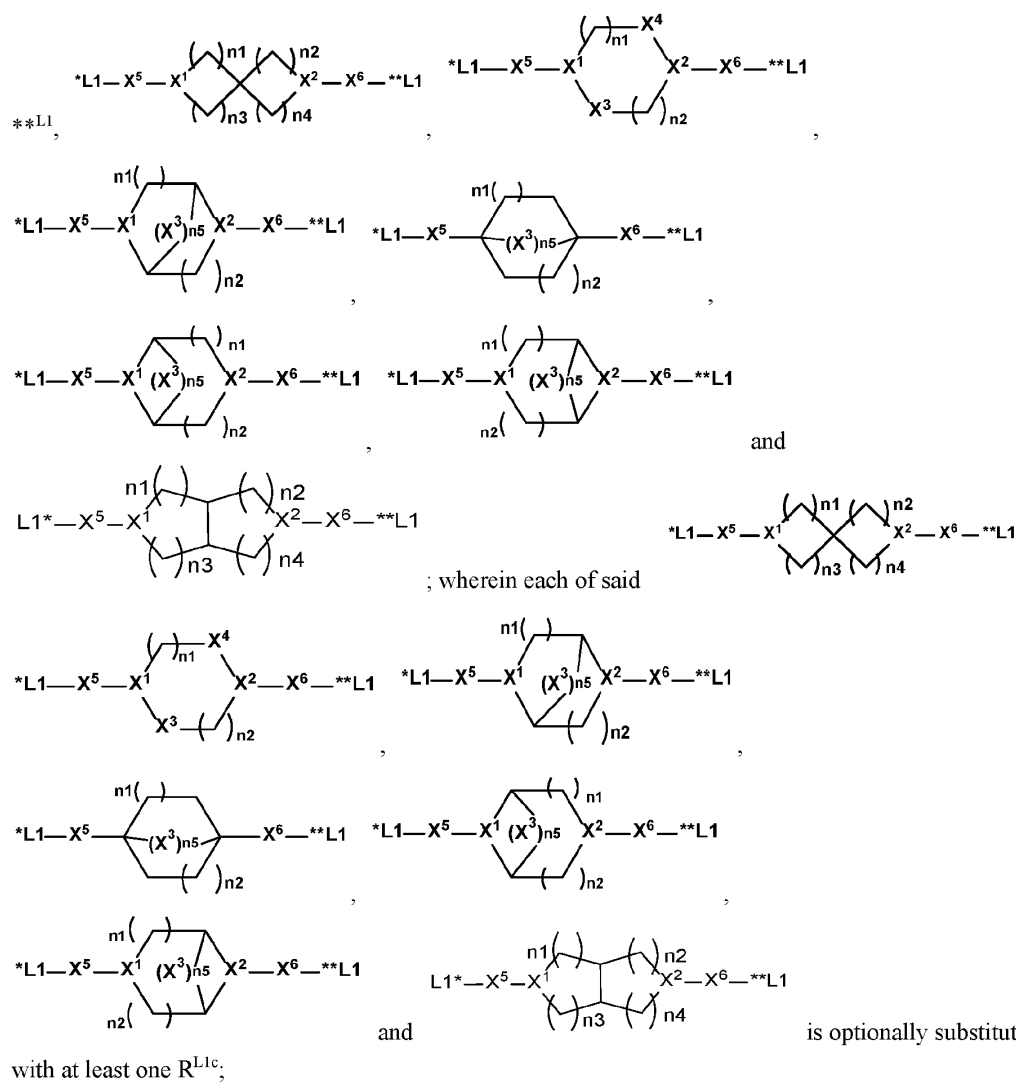
R^{10a} and R^{10b} are each independently selected from hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, and 5- to 12-membered heteroaryl; wherein each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{10d};

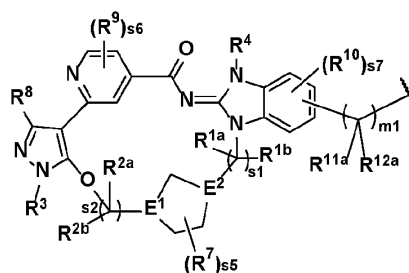
R^{10c} and R^{10d} are each independently selected from halogen, hydrogen, -C₁₋₈alkyl, -C₁₋₈alkoxy, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, 5- to 12-membered heteroaryl, oxo (=O), -NR^{10e}R^{10f}, -OR^{10e}, -SR^{10e}, -SO₂R^{10e}, -SO₂NR^{10e}R^{10f}, -C(O)R^{10e}, -CO₂R^{10e}, -C(O)NR^{10e}R^{10f}, -NR^{10e}COR^{10f}, -NR^{10e}CO₂R^{10f}, -NR^{10e}SO₂R^{10f}, and -CN;

R^{10e} and R^{10f} are each independently selected from hydrogen, -C₁-C₈alkyl, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl;

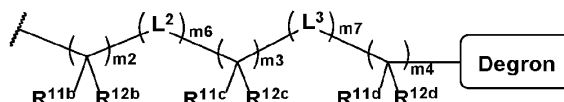
R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c} and R^{12d} are each independently absent, oxo, hydrogen, halogen, -C₁-alkyl, -C₂-alkenyl, -C₂-alkynyl, -C₁-alkoxy, or -C₃₋₈cycloalkyl; wherein each of said -C₁-alkyl, -C₂-alkenyl, -C₂-alkynyl, -C₁-alkoxy or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, -C₁-alkyl, -C₂-alkenyl, -C₂-alkynyl, -C₁-alkoxy, and -CN;

L¹ is selected from -O-, -NR^a-, -C(O)-, *^{L1}-C(O)NR^a-**^{L1}, *^{L1}-C(O)O-*^{L1}, *^{L1}-NR^aC(O)-**^{L1}, *^{L1}-OC(O)-



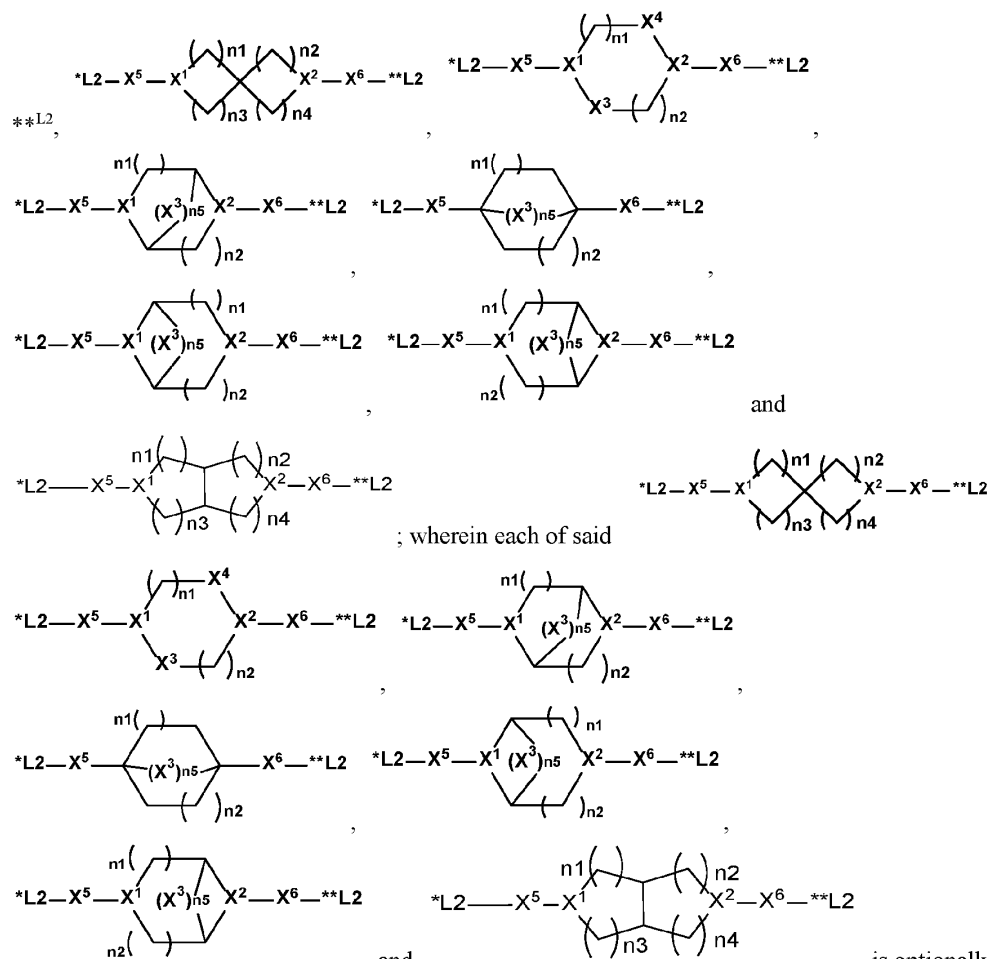


wherein *L1 refers to the position attached to the $(R^7)_{s5}$ moiety, and



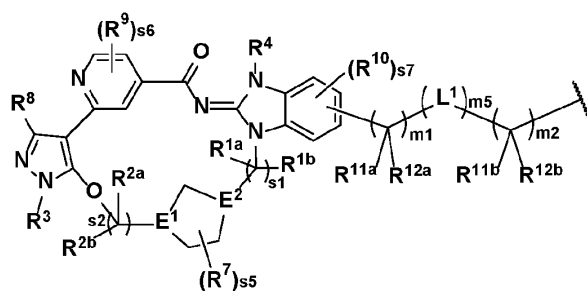
****L1** refers to the position attached to the R^{11b} R^{12b} R^{11c} R^{12c} R^{11d} R^{12d} moiety;

L² is selected from -O-, -NR^a-, -C(O)-, *L²-C(O)NR^a-*L², *L²-C(O)O-*L², *L²-NR^aC(O)-*L², *L²-OC(O)-

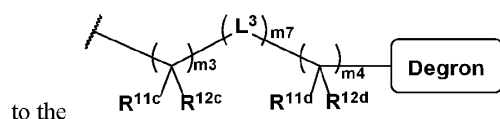
substituted with at least one R^{L2c};

is optionally

wherein *L2 refers to the position attached to the



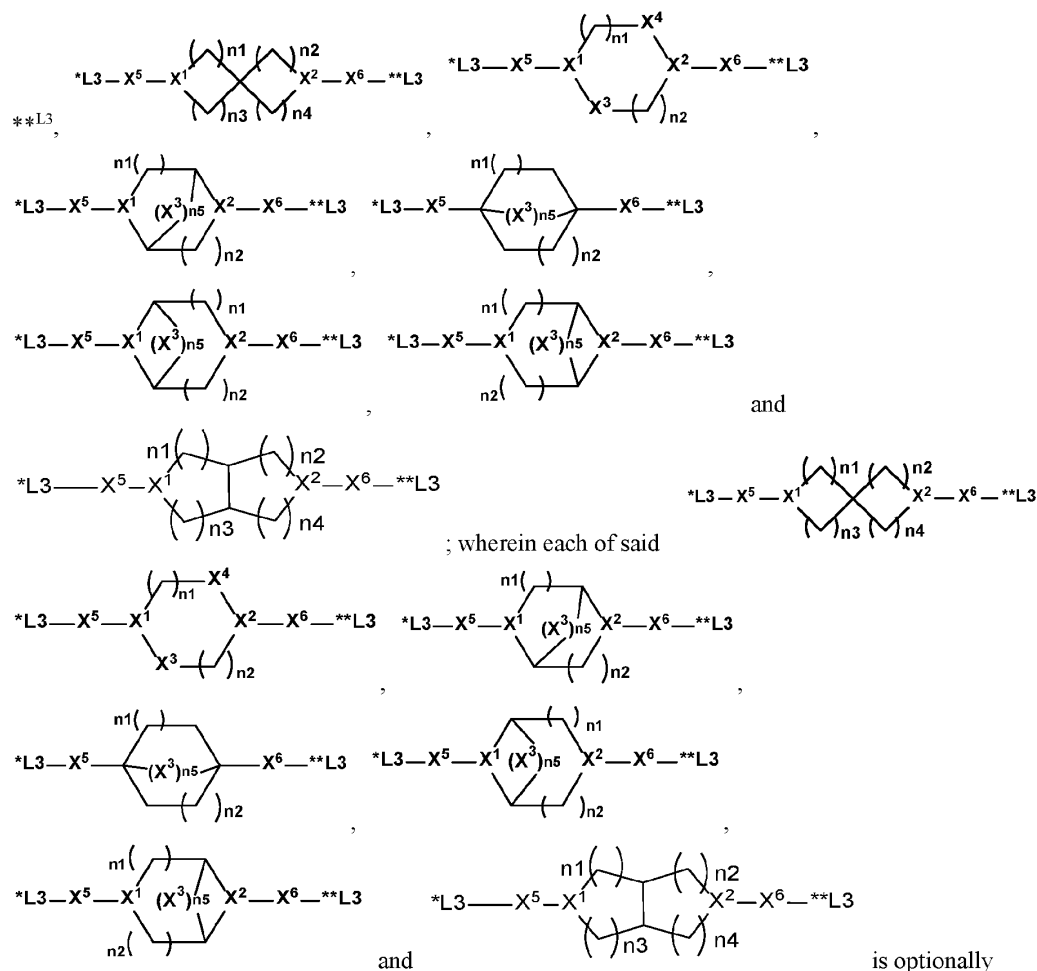
moiety, and **L2 refers to the position attached



to the

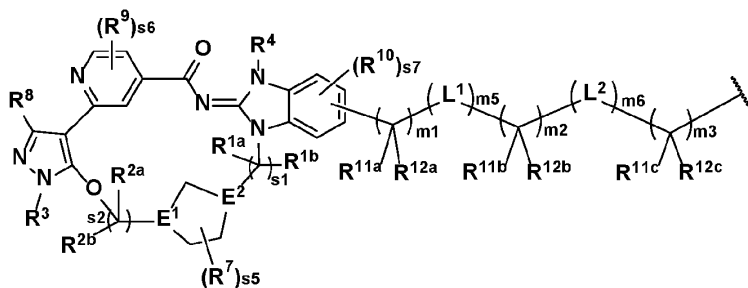
moiety;

L^3 is selected from $-O-$, $-NR^a-$, $-C(O)-$, $^{*L3}-C(O)NR^a-^{**L3}$, $^{*L3}-C(O)O-^{**L3}$, $^{*L3}-NR^aC(O)-^{**L3}$, $^{*L3}-OC(O)-$

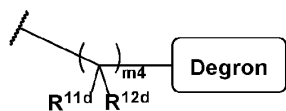


substituted with at least one R^{L3c} ,

wherein $^{*L^3}$ refers to the position attached to the



moiety, and $^{**L^3}$ refers to the



position attached to the

moiety;

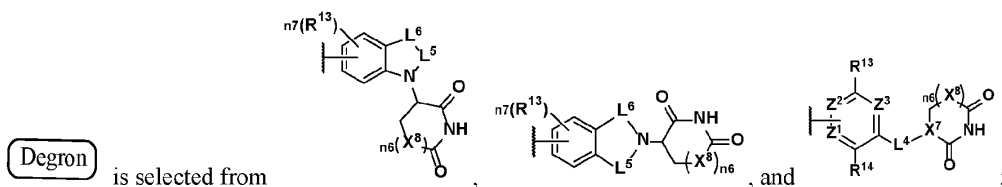
each of said R^{L1c} , R^{L2c} and R^{L3c} are independently absent, oxo (=O), halogen, hydroxy, -CN, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl; wherein each of said -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ,

R^{Lca} is independently absent, oxo (=O), halogen, hydroxy, -CN, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl or 5- to 12-membered heteroaryl; or

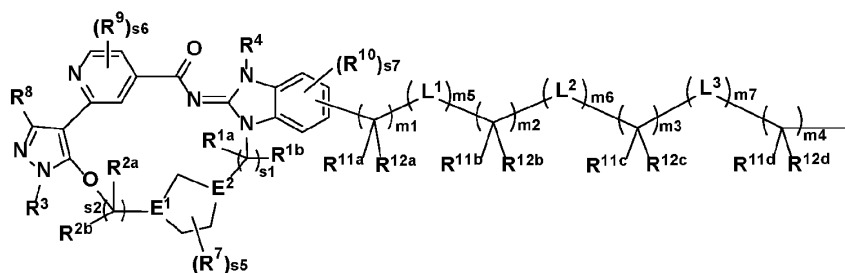
two R^{L1c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;

two R^{L2c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;

two R^{L3c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;

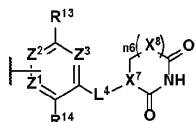


Z^1 , Z^2 and Z^3 are each independently N or CR^z, provided that Z^1 , Z^2 and Z^3 are not N at the same time; R^z, at each occurrence, is independently absent, hydrogen, halogen, -C₁-C₈alkyl, -NR^{za}R^{zb}, -OR^{za}, -SR^{za}, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, or CN; wherein each of -C₁-C₈alkyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{zc};



wherein the

moiety



is linked to the

moiety via any one of Z^1 or Z^2 which is CR^z and R^z is absent;

R^{Za} and R^{Zb} are each independently absent, hydrogen, -C₁-C₈alkyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl; wherein each of said -C₁-C₈alkyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{Zd};

R^{Zc} and R^{Zd} are each independently halogen, hydroxy, -C₁-C₈alkyl, -C₁-C₈alkoxy, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl;

R¹³ and R¹⁴ are each independently absent, hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, -C_{6-C12}aryl, 5- to 12-membered heteroaryl, -CN, -SO₂R^{13a}, -SO₂NR^{13a}R^{13b}, -COR^{13a}, -CO₂R^{13a}, -CONR^{13a}R^{13b}, -NR^{13a}R^{13b}, -NR^{13a}COR^{13b}, -NR^{13a}CO₂R^{13b}, or -NR^{13a}SO₂R^{13b}, wherein each of -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, -C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, -C_{6-C12}aryl or 5- to 12-membered heteroaryl is optionally substituted with halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-C12}aryl, 5- to 12-membered heteroaryl, oxo, -CN, -OR^{13c}, -SO₂R^{13c}, -SO₂NR^{13c}R^{13d}, -COR^{13c}, -CO₂R^{13c}, -CONR^{13c}R^{13d}, -NR^{13c}R^{13d}, -NR^{13c}COR^{13d}, -NR^{13c}CO₂R^{13d}, or -NR^{13c}SO₂R^{13d}.

at each occurrence, R^{13a}, R^{13b}, R^{13c} and R^{13d} are each independently absent, hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl;

L^4, L^5 and L^6 are each independently absent, a single bond, -O-, -NR^a-, -(CR^aR^b)_{n8}-, -O(CR^aR^b)_{n8}-, -

$$\text{NR}^a(\text{CR}^a\text{R}^b)_{n8}\text{- or -C(O)-};$$

at each occurrence, X^1 , X^2 and X^7 are each independently -CR^a, or N;

at each occurrence, X³, X⁴ and X⁸ are each independently -NR^a-, -O-, -S- or -CR^aR^b-;

at each occurrence, X⁵ and X⁶ are each independently absent, a single bond, -C(O)-, -NR^a- or -O-;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, halogen, CN, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, -C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, -C₆-C₁₂aryl and 5- to 12-membered heteroaryl; wherein each of said -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, -C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, -C₆-C₁₂aryl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from halogen, hydroxy, halogen, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, -C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, -C₆-C₁₂aryl and 5- to 12-membered heteroaryl; or

R^a and R^b together with the carbon atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, -C₁-C₈alkyl, -C₂-C₈alkenyl, -C₂-C₈alkynyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl and 5- to 12-membered heteroaryl;

m_1, m_2, m_3 and m_4 are each independently 0, 1 or 2; provided that $m_1+m_2+m_3+m_4 \leq 4$;

m5, m6 and m7 are each independently 0, 1 or 2; provided that $m5+m6+m7 \geq 1$;

n_1, n_2, n_3, n_4 and n_5 are each independently 0, 1, 2 or 3;

n6 is each independently 0, 1, 2, 3 or 4;

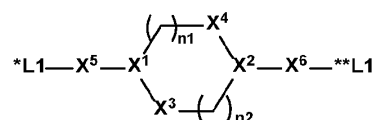
n7 and n8 are each independently 0, 1, 2 or 3;

s1 and s2 are each independently 0, 1, 2 or 3;

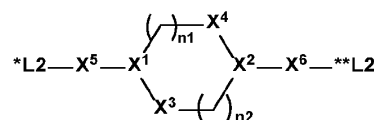
s_5, s_6 and s_7 are each independently 0, 1, 2 or 3;

provided that:

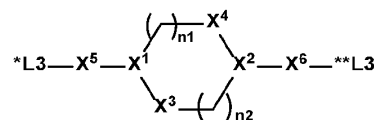
for any one of L¹, L² or L³, when X¹ is N, X⁵ is single bond, absent, or -C(O)-; and/or when X² is N, X⁶ is single bond, absent, or -C(O)-;



when L¹ is , when X¹ is N, then X⁵ is a single bond, absent, or -C(O)-, X³ is -CR^aR^b-; when X² is N, X⁶ is single bond, absent, or -C(O)-, X⁴ is -CR^aR^b-;

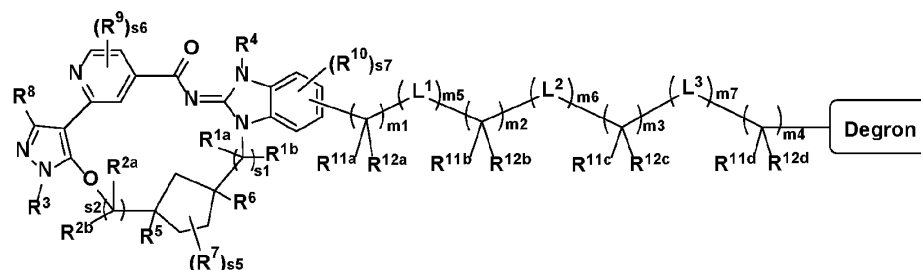


when L² is , when X¹ is N, then X⁵ is a single bond, absent, or -C(O)-, X³ is -CR^aR^b-; when X² is N, then X⁶ is a single bond, absent, or -C(O)-, X⁴ is -CR^aR^b-;



when L^3 is $\text{X}^3-\text{C}(\text{O})\text{N}_2$, when X^1 is N, X^5 is a single bond, absent, or $-\text{C}(\text{O})-$, and/or X^3 is $-\text{CR}^a\text{R}^b-$; when X^2 is N, X^6 is a single bond, absent, or $-\text{C}(\text{O})-$, and/or X^4 is $-\text{CR}^a\text{R}^b-$.

[0010] Aspect 2. The compound of aspect 1, wherein the compound is selected from compounds of formula (IIa).

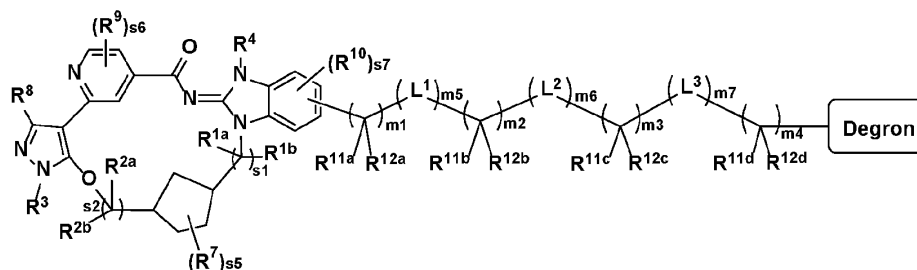


(IIa);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug

thereof wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

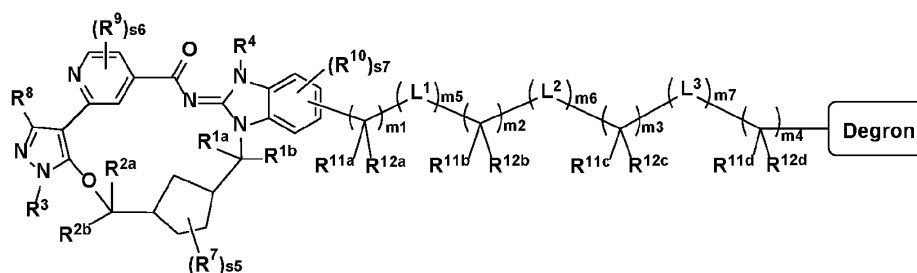
[0011] In one embodiment, the compound is selected from compounds of formula (IIb):



(IIb);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

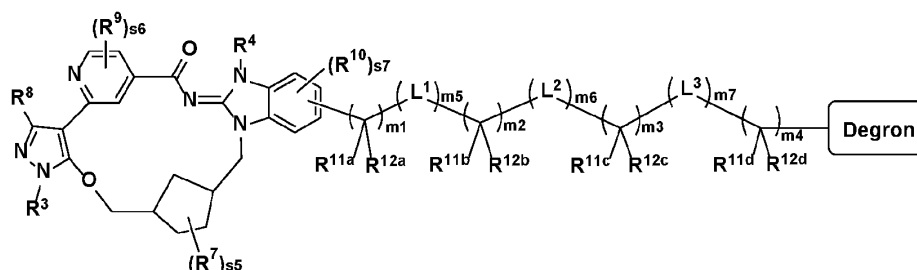
[0012] In one embodiment, the compound is selected from compounds of formula (IIc):



(IIc);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

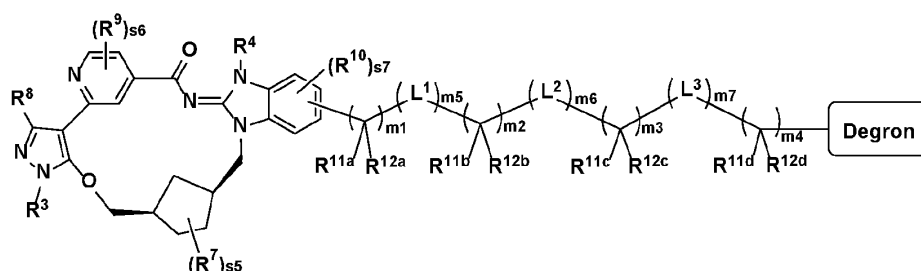
[0013] In one embodiment, the compound is selected from compounds of formula (IId):



(IId);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

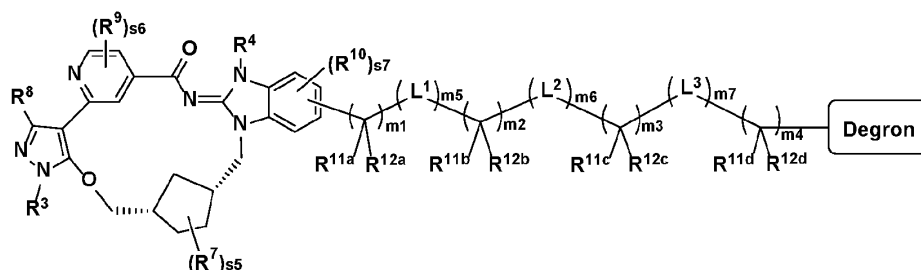
[0014] In one embodiment, the compound is selected from compounds of formula (IIe):



(IIe),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

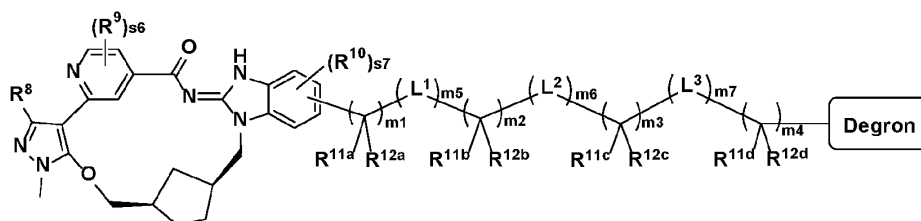
[0015] In one embodiment, the compound is selected from compounds of formula (IIf):



(IIf);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

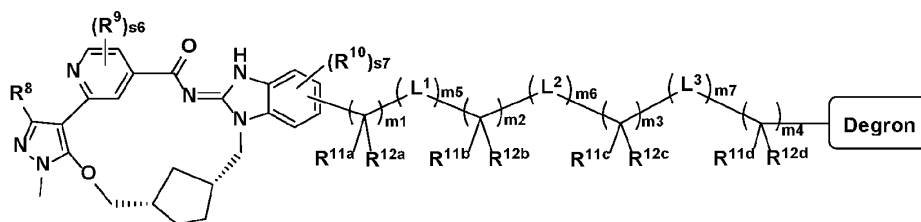
[0016] In one embodiment, the compound is selected from compounds of formula (IIg):



(IIg),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

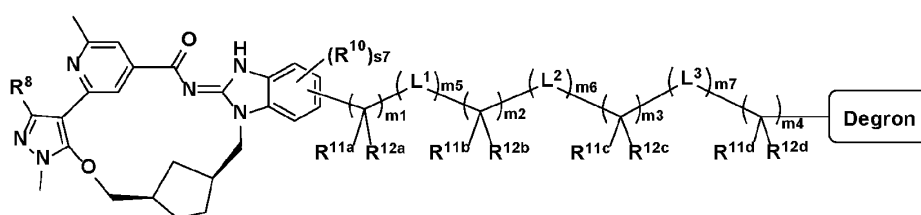
[0017] In one embodiment, the compound is selected from compounds of formula (IIh):



(IIIh),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

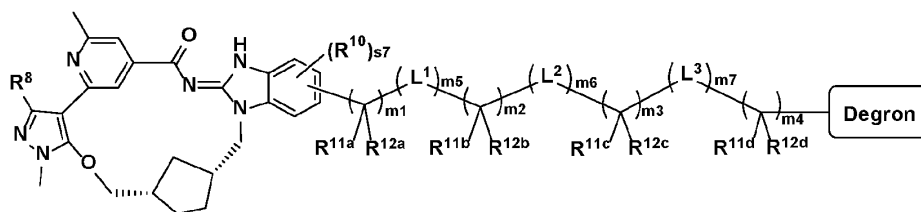
[0018] In one embodiment, the compound is selected from compounds of formula (IIIi):



(IIIi),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

[0019] In one embodiment, the compound is selected from compounds of formula (IIj):

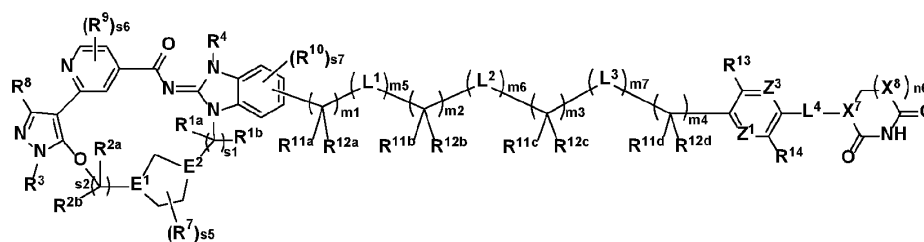


(IIj);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof,

wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

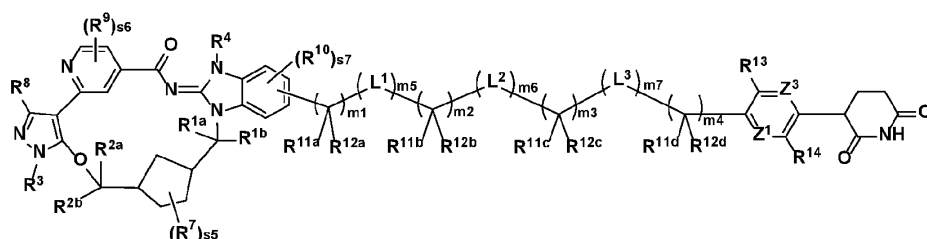
[0020] **Aspect 3.** The compound of aspect 1, wherein the compound is selected from compounds of formula (IIIa):



(IIIa),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c}, R^{12d}, L¹, L², L³, s1, s2, s5, s6, s7, m1, m2, m3, m4, m5, m6, m7 and Degron are as defined in aspect 1.

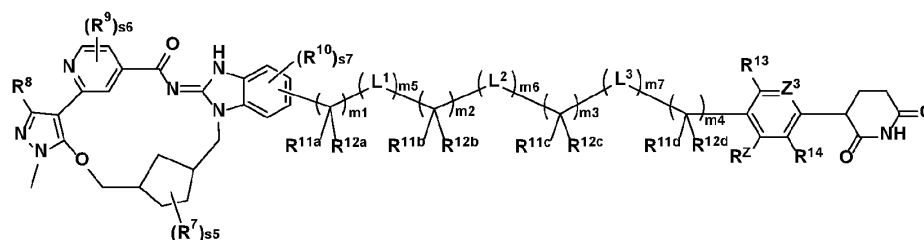
[0021] In one embodiment, the compound is selected from compounds of formula (IIIb):



(IIIb);

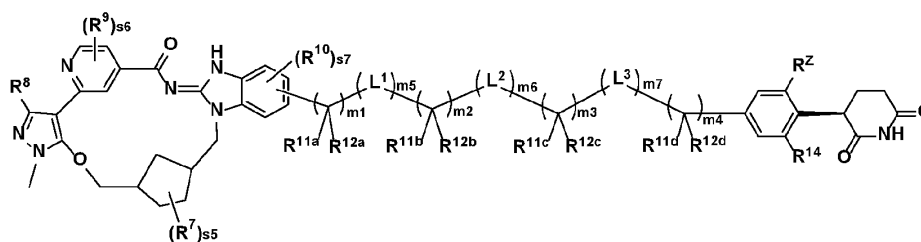
or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c}, R^{12d}, L¹, L², L³, s1, s2, s5, s6, s7, m1, m2, m3, m4, m5, m6, m7 and Degron are as defined in aspect 1.

[0022] In one embodiment, the compound is selected from compounds of formula (IIIc):

(IIIc)₂

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c}, R^{12d}, L¹, L², L³, s1, s2, s5, s6, s7, m1, m2, m3, m4, m5, m6, m7 and Degron are as defined in aspect 1.

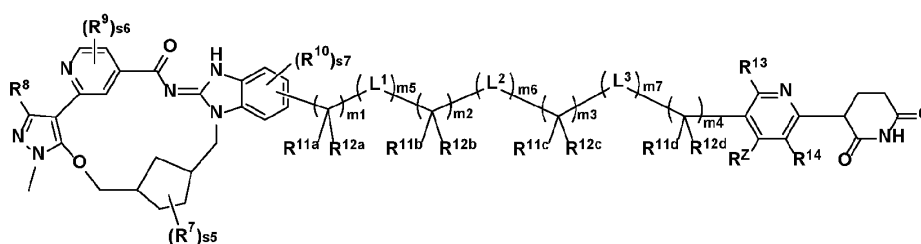
[0023] In one embodiment, the compound is selected from compounds of formula (III_d):



(IIIId),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

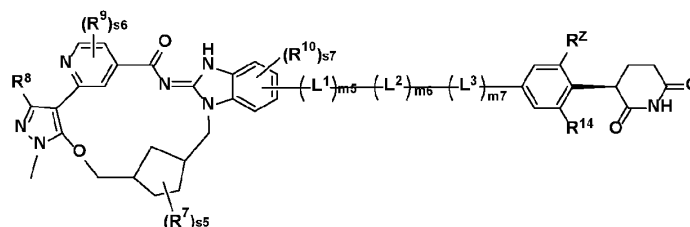
[0024] In one embodiment, the compound is selected from compounds of formula (IIIe):



(IIIe);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

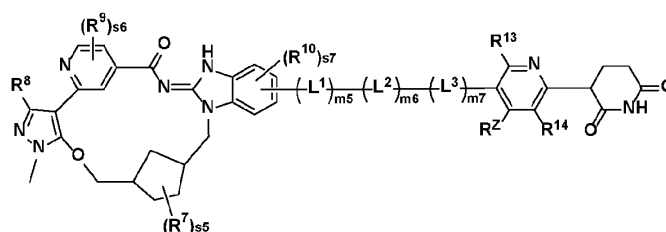
[0025] In one embodiment, the compound is selected from compounds of formula (IIIIf):



(IIIIf);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

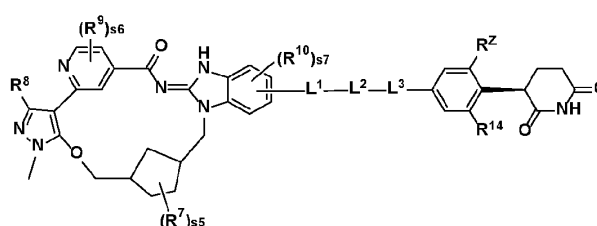
[0026] In one embodiment, the compound is selected from compounds of formula (IIIg):



(IIIg);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

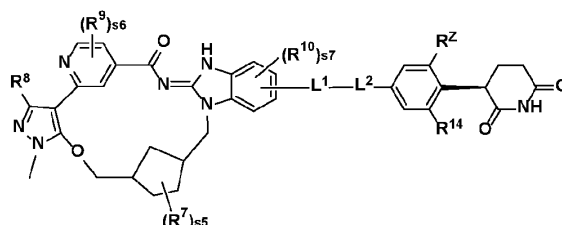
[0027] In one embodiment, the compound is selected from compounds of formula (IIIh):



(IIIh);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

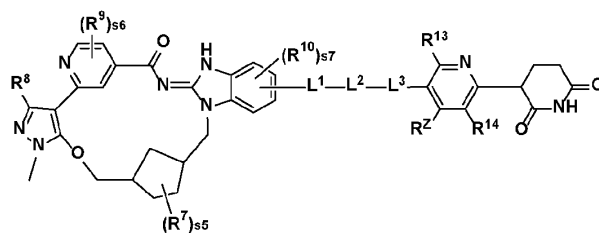
[0028] In one embodiment, the compound is selected from compounds of formula (IIIi):



(IIIi);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

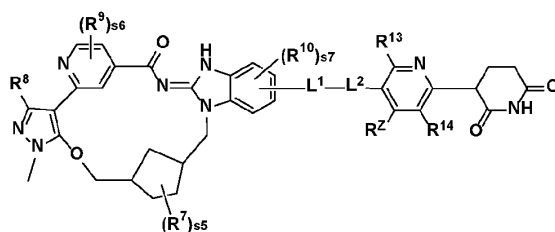
[0029] In one embodiment, the compound is selected from compounds of formula (IIIj):



(IIIj);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

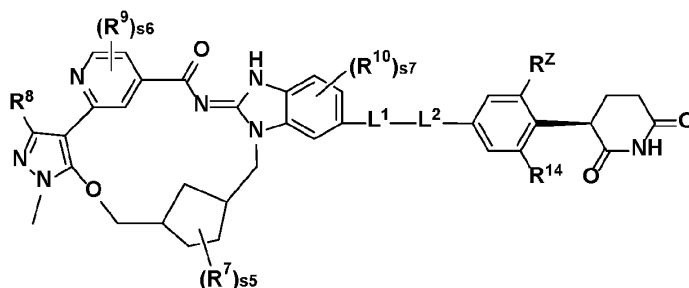
[0030] In one embodiment, the compound is selected from the compounds of formula (IIIk):



(IIIk);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof, wherein, R^{1a} , R^{1b} , R^{2a} , R^{2b} , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , L^1 , L^2 , L^3 , $s1$, $s2$, $s5$, $s6$, $s7$, $m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $m7$ and Degron are as defined in aspect 1.

[0031] In one embodiment, the compound is selected from the compounds of formula (IIIIm):



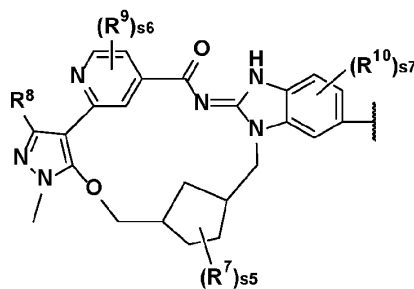
(IIIIm);

wherein

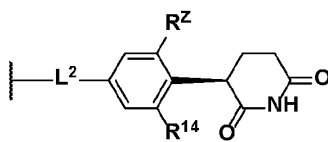
R^7 is each independently absence, hydrogen, halogen or $-C_{1-3}$ alkyl;

R^8 and R^9 are each independently selected from hydrogen, halogen, and $-C_1-C_3$ alkyl;

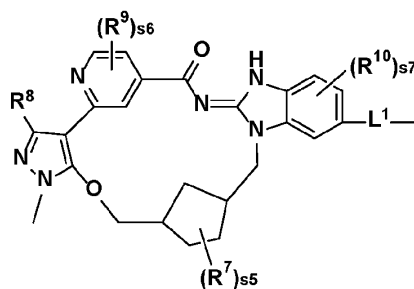
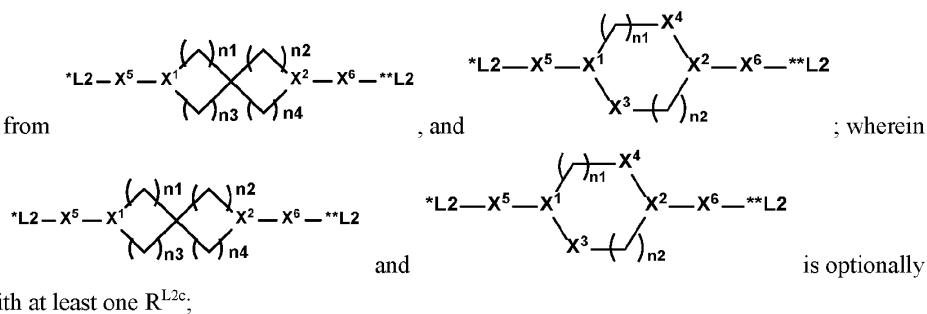
R^{10} is each independently selected from hydrogen, halogen, or $-C_1-C_3$ alkyl;



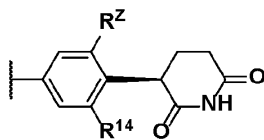
wherein ^{*L1} refers to the position attached to the (R⁷)_{s5} moiety, and



**L1 refers to the position attached to the moiety;



wherein ^{*L2} refers to the position attached to the $(R^7)_{s5}$ moiety, and



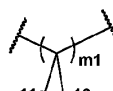
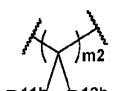
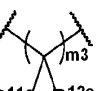
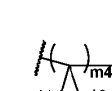
*L2 refers to the position attached to the moiety;

each of said R^{L1c} and R^{L2c} are independently absent, oxo (=O), halogen, hydroxy, -C₁-C₃alkyl or -C₁-C₃alkoxy; each of said -C₁-C₃alkyl and -C₁-C₃alkoxy is optionally substituted with at least one R^{Lca} , R^{Lca} is each independently absent, halogen, hydroxy, or -C₁-C₃alkoxy; or two R^{L1c} together with the atoms to which they are attached, form a 3- to 5-membered ring, said ring comprising 0-1 heteroatoms independently selected from nitrogen and oxygen; two R^{L2c} together with the atoms to which they are attached, form a 3- to 5-membered ring, said ring comprising 0-1 heteroatoms independently selected from nitrogen and oxygen; R^z , at each occurrence, is independently absent, hydrogen, halogen, -C₁-C₃alkyl or -C₁-C₃alkoxy; R^{14} , at each occurrence, is independently absent, hydrogen, halogen, -C₁-C₃alkyl or -C₁-C₃alkoxy; at each occurrence, X^1 and X^2 are each independently -CH or N; at each occurrence, X^3 and X^4 are each independently -NH- and -CH₂-; at each occurrence, X^5 and X^6 are each independently absent, a single bond, -C(O)- or -NR^a-; at each occurrence, R^a is independently selected from hydrogen, -C₁-C₃alkyl; n_1 , n_2 , n_3 and n_4 are each independently 0, 1, or 2; s_5 , s_6 and s_7 are each independently 0, 1, or 2.

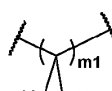
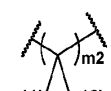
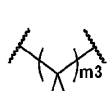
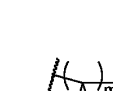
[0032] **Aspect 4.** The compound of any one of the preceding aspects, wherein $m_1+m_2+m_3+m_4 \leq 3$.

[0033] **Aspect 5.** The compound of any one of the preceding aspects, wherein $m_1+m_2+m_3+m_4 = 0, 1, 2$, or 3. **In one embodiment**, $m_1+m_2+m_3+m_4 = 0, 1$ or 2. **In one embodiment**, $m_1+m_2+m_3+m_4 = 0$. **In one embodiment**, $m_1+m_2+m_3+m_4 = 1$. **In one embodiment**, $m_1+m_2+m_3+m_4 = 2$.

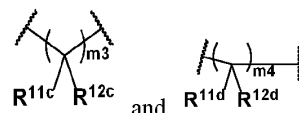
[0034] **Aspect 6.** The compound of any one of the preceding aspects, wherein the total number of -CH₂-

groups in the    and  moieties combined is no more than 4,

[0035] **In one embodiment**, the total number of -CH₂- groups in the

   and  moieties combined is no more than 3,

[0036] In one embodiment, the total number of $-\text{CH}_2-$ groups in the



moieties combined is no more than 2.

[0037] **Aspect 7.** The compound of any one of the preceding aspects, wherein R^3 and R^4 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; said methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, hydroxyl, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy.

In one embodiment, R^3 is $-\text{C}_{1-3}$ alkyl, wherein said $-\text{C}_{1-3}$ alkyl or $-\text{C}_{3-8}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, hydroxyl, halogen, $-\text{C}_{1-6}$ alkoxy. In one embodiment, R^3 is $-\text{C}_{1-3}$ alkyl. In one embodiment, R^4 is hydrogen. In one embodiment, R^3 and R^4 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl. In one embodiment, R^3 and R^4 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. In one embodiment, R^3 is independently methyl, and R^4 is hydrogen.

[0038] **Aspect 8.** The compound of any one of the preceding aspects, wherein $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-\text{C}_2$ -alkenyl, $-\text{C}_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or $-\text{CN}$; wherein each said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-\text{C}_2$ -alkenyl, $-\text{C}_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or $-\text{CN}$.

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently absent, hydrogen, halogen, or $-\text{C}_{1-6}$ alkyl;

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen, halogen, or $-\text{C}_{1-3}$ alkyl;

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen, or $-\text{C}_{1-3}$ alkyl;

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CN}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3$.

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-\text{CF}_3$ or $-\text{CHF}_2$, or $-\text{CH}_2\text{OCH}_3$.

In one embodiment, $\text{R}^{1\text{a}}$, $\text{R}^{1\text{b}}$, $\text{R}^{2\text{a}}$ and $\text{R}^{2\text{b}}$ are each independently hydrogen.

[0039] **Aspect 9.** The compound of any one of the preceding aspects, wherein R^5 and R^6 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CN$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$.

In one embodiment, R^5 and R^6 are each independently hydrogen, halogen, $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$, $-C_{3-6}cycloalkyl$ or $-CN$; each said $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$, or $-C_{3-6}cycloalkyl$ is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-8}alkoxy$, $-C_{3-8}cycloalkyl$ or $-CN$.

In one embodiment, R^5 and R^6 are each independently hydrogen, halogen, $-C_{1-3}alkyl$, $-C_{1-3}alkoxy$, or $-C_{3-6}cycloalkyl$.

In one embodiment, R^5 and R^6 are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-CF_3$, $-CHF_2$, or $-CH_2OCH_3$.

[0040] **Aspect 10.** The compound of any one of the preceding aspects, wherein R^5 and R^6 with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl.

In one embodiment, R^5 and R^6 with the carbon atoms to which they are attached, form a 3-, 4-, 5- or 6-membered ring, said ring is optionally substituted with at least one substituent selected from F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl.

[0041] **Aspect 11.** The compound of any one of the preceding aspects, wherein R^7 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CN$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$;

In one embodiment, R^7 is each independently absent, hydrogen, halogen, $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$, $-C_{3-6}cycloalkyl$ or $-CN$; wherein each said $-C_{1-6}alkyl$, $-C_{1-6}alkoxy$ or $-C_{3-6}cycloalkyl$ is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-6}alkoxy$, $-C_{3-6}cycloalkyl$ and $-CN$.

In one embodiment, R^7 is each independently absent, hydrogen, halogen, $-C_{1-3}alkyl$, or $-C_{1-3}alkoxy$.

In one embodiment, R^7 are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-CF_3$ or $-CHF_2$, $-CH_2OCH_3$.

In one embodiment, R^7 are each independently hydrogen.

[0042] **Aspect 12.** The compound of any one of the preceding aspects, wherein two R^7 with the carbon atom(s) to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl.

In one embodiment, two R^7 with the carbon atom(s) to which they are attached, form a 3-, 4-, 5- or 6-membered ring, wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl.

[0043] Aspect 13. The compound of any one of the preceding aspects, wherein R^8 and R^9 are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl; wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, hydroxy, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

In one embodiment, R^8 and R^9 are each independently selected from hydrogen, halogen, and $-C_1-C_6$ alkyl; wherein said $-C_1-C_6$ alkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, hydroxy, and $-C_1-C_6$ alkoxy.

In one embodiment, R^8 and R^9 are each independently selected from hydrogen, halogen, and $-C_1-C_3$ alkyl; wherein said $-C_1-C_3$ alkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, and hydroxy.

In one embodiment, R^8 and R^9 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CH_2OH$, or $-CH_2CH_2OH$.

In one embodiment, R^8 is independently hydrogen, methyl, $-CF_3$, $-CHF_2$, or $-CH_2OH$, and R^9 is F, methyl or $-CH_2OH$.

[0044] Aspect 14. The compound of any one of the preceding aspects, wherein R^{10} is each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, $-NR^{10a}R^{10b}$, $-OR^{10a}$, $-SR^{10a}$, $-C(O)R^{10a}$, $-CO_2R^{10a}$, $-C(O)NR^{10a}R^{10b}$, $-NR^{10a}COR^{10b}$, $-NR^{10a}CO_2R^{10b}$, $-NR^{10a}SO_2R^{10b}$ and -CN; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl and phenyl is optionally substituted with at least one R^{10c} ;

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl and phenyl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl or phenyl is optionally substituted with at least one substituent R^{10d} ;

R^{10c} and R^{10d} are each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, oxo (=O), $-NR^{10e}R^{10f}$, $-OR^{10e}$, $-SR^{10e}$, $-SO_2R^{10e}$, $-SO_2NR^{10e}R^{10f}$, $-C(O)R^{10e}$, $-CO_2R^{10e}$, $-C(O)NR^{10e}R^{10f}$, $-NR^{10e}COR^{10f}$, $-NR^{10e}CO_2R^{10f}$, $-NR^{10e}SO_2R^{10f}$ and -CN;

R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl;

In one embodiment, R^{10} is each independently selected from hydrogen, halogen, $-C_1-C_6alkyl$, $-C_3-C_6cycloalkyl$, $-NR^{10a}R^{10b}$, $-OR^{10a}$, $-C(O)R^{10a}$, $-CO_2R^{10a}$, $-C(O)NR^{10a}R^{10b}$, and $-CN$; wherein each of $-C_1-C_6alkyl$ or $-C_3-C_6cycloalkyl$, is optionally substituted with at least one R^{10c} ;

R^{10a} and R^{10b} are each independently selected from hydrogen, $-C_1-C_6alkyl$, $-C_3-C_6cycloalkyl$, 3- to 8-membered heterocyclyl, $C_6-C_{12}aryl$, and 5- to 12-membered heteroaryl, wherein each of said $-C_1-C_6alkyl$, $-C_3-C_6cycloalkyl$, 3- to 8-membered heterocyclyl, $C_6-C_{12}aryl$, or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{10d} ;

R^{10c} and R^{10d} are each independently selected from halogen, hydrogen, $-C_1-C_6alkyl$, $-C_1-C_6alkoxy$, $-C_3-C_6cycloalkyl$, oxo ($=O$), $-NR^{10e}R^{10f}$, $-OR^{10e}$, $-CO_2R^{10e}$, $-C(O)NR^{10e}R^{10f}$, $-NR^{10e}COR^{10f}$, and $-CN$;

R^{10e} and R^{10f} are each independently selected from hydrogen, $-C_1-C_3alkyl$, $-C_3-C_6cycloalkyl$, 3- to 8-membered heterocyclyl, $C_6-C_{12}aryl$, and 5- to 12-membered heteroaryl.

In one embodiment, R^{10} is each independently selected from hydrogen, halogen, $-C_1-C_3alkyl$, $-C_3-C_6cycloalkyl$, $-NR^{10a}R^{10b}$, $-OR^{10a}$, $-C(O)R^{10a}$, $-CO_2R^{10a}$, $-C(O)NR^{10a}R^{10b}$, and $-CN$; wherein each of $-C_1-C_6alkyl$ or $-C_3-C_6cycloalkyl$, is optionally substituted with at least one halogen, hydrogen, oxo ($=O$), $-NR^{10e}R^{10f}$ or $-OR^{10e}$;

R^{10a} and R^{10b} are each independently selected from hydrogen, $-C_1-C_3alkyl$ and $-C_3-C_6cycloalkyl$, wherein each of said $-C_1-C_3alkyl$ or $-C_3-C_6cycloalkyl$ is optionally substituted with at least one substituent halogen, hydrogen, oxo ($=O$), $-NR^{10e}R^{10f}$ or $-OR^{10e}$;

R^{10e} and R^{10f} are each independently selected from hydrogen or $-C_1-C_3alkyl$.

In one embodiment, R^{10} is each independently selected from hydrogen, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, $-NR^{10a}R^{10b}$, $-OR^{10a}$, $-SR^{10a}$, $-C(O)R^{10a}$, $-CO_2R^{10a}$, $-C(O)NR^{10a}R^{10b}$, $-NR^{10a}COR^{10b}$, $-NR^{10a}CO_2R^{10b}$, $-NR^{10a}SO_2R^{10b}$ and $-CN$; each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl or phenyl is optionally substituted with at least one R^{10c} ;

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl and phenyl;

R^{10c} is each independently selected from hydrogen, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, oxo ($=O$), $-NR^{10e}R^{10f}$, $-OR^{10e}$ and $-CN$;

R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl.

In one embodiment, R^{10} is each independently selected from hydrogen, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3- to 8-membered

heterocyclyl, $-\text{NR}^{10a}\text{R}^{10b}$, $-\text{OR}^{10a}$, $-\text{CO}_2\text{R}^{10a}$, and $-\text{C}(\text{O})\text{NR}^{10a}\text{R}^{10b}$; each of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{10c} ;

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-membered heterocyclyl, 4-membered heterocyclyl, 5-membered heterocyclyl and 6-membered heterocyclyl;

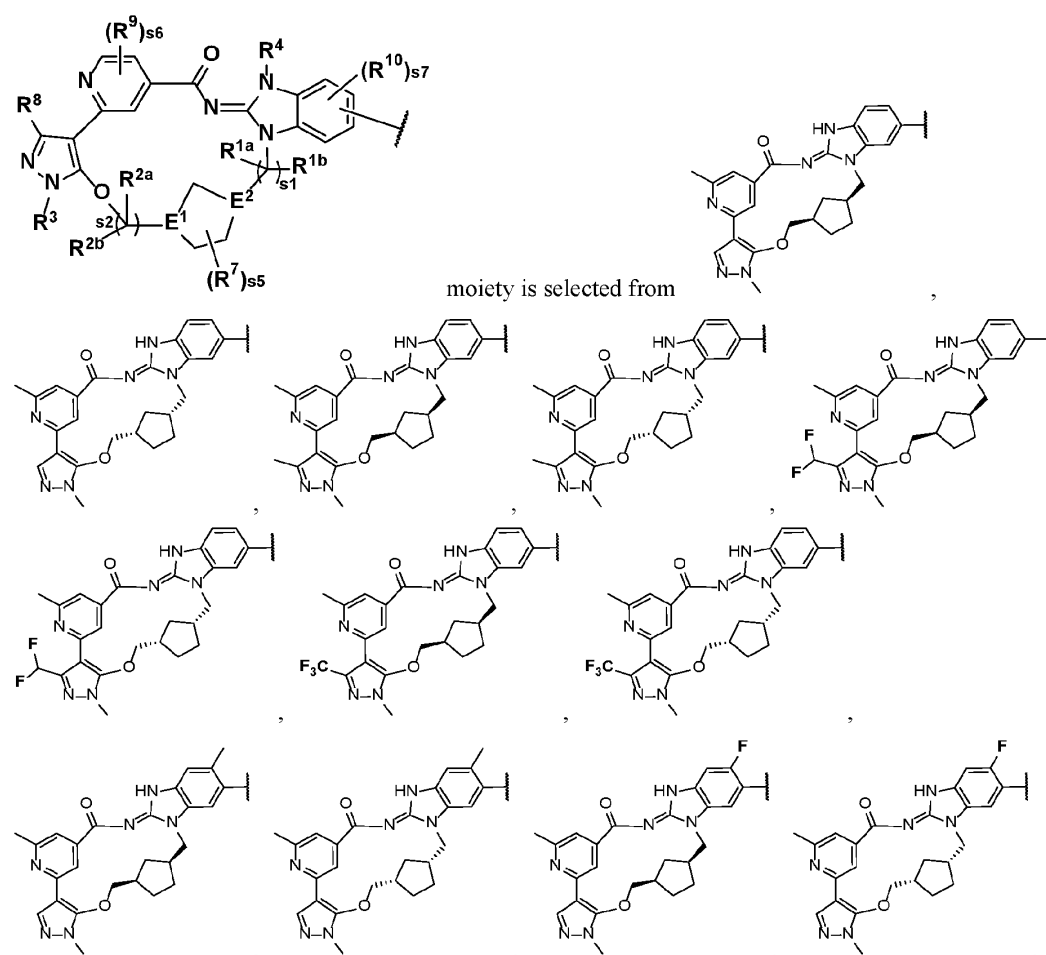
R^{10c} is each independently selected from hydrogen, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, oxo ($=\text{O}$), $-\text{NR}^{10e}\text{R}^{10f}$, $-\text{OR}^{10e}$ and $-\text{CN}$;

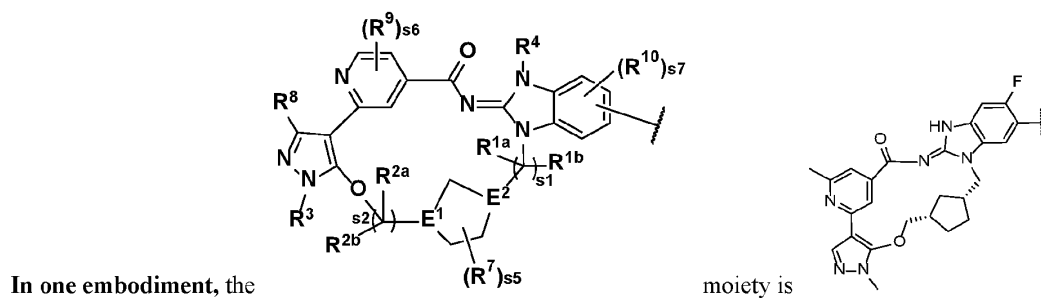
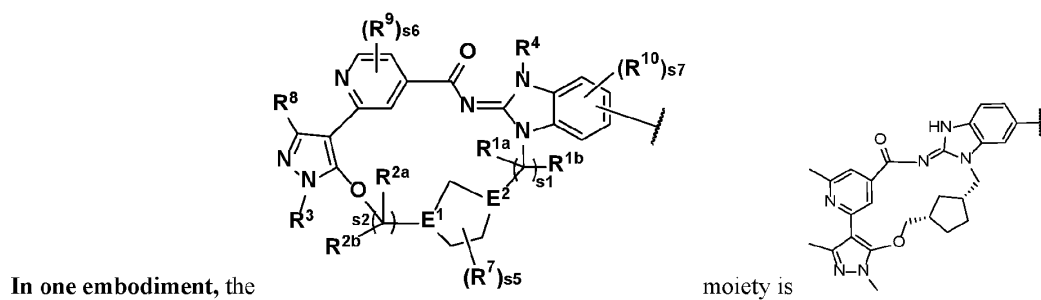
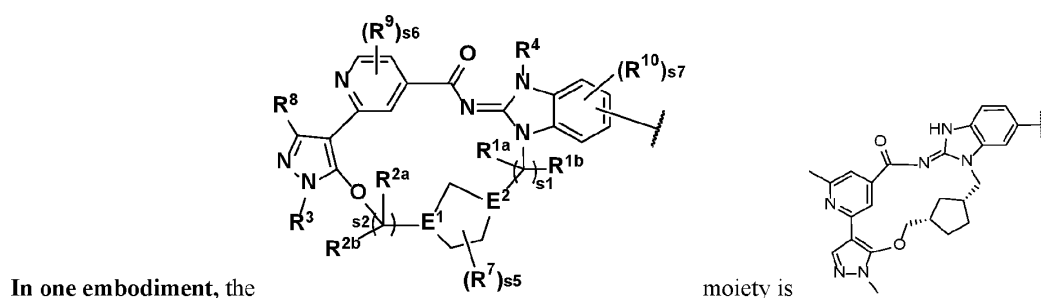
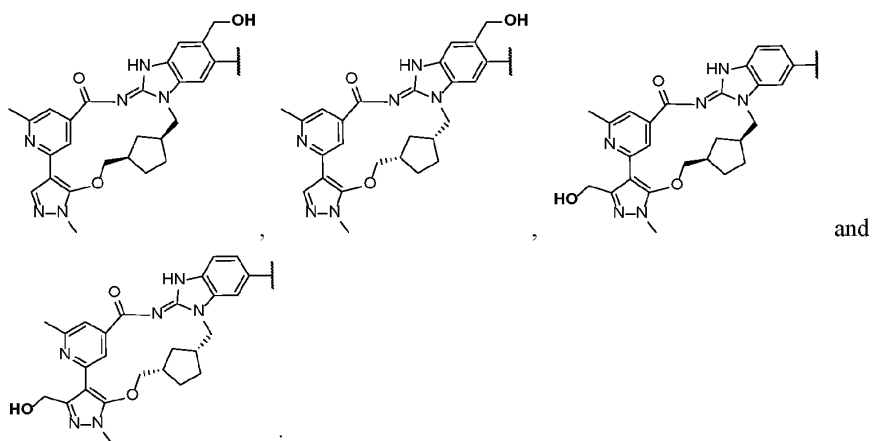
R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, and cyclopentyl.

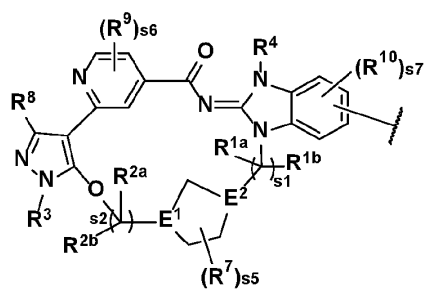
In one embodiment, R^{10} is each independently selected from H, F, Cl, Br, methyl, ethyl, propyl (n-propyl or iso-propyl), butyl(n-butyl, sec-butyl, iso-butyl or tert-butyl), cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, , , , $-\text{COOH}$, $-\text{CONH}_2$, $-\text{CH}_2\text{OCH}_3$, and $-\text{CH}_2\text{OH}$.

[0045] Aspect 15. The compound of any one of the preceding aspects, wherein the

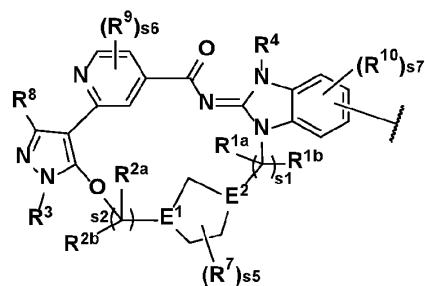
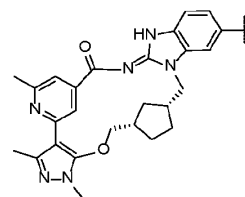






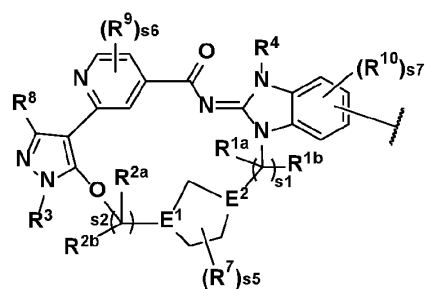
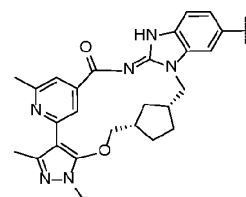
In one embodiment, the

moiety is



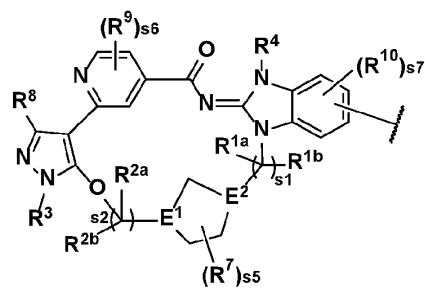
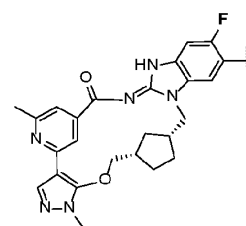
In another embodiment, the

moiety is



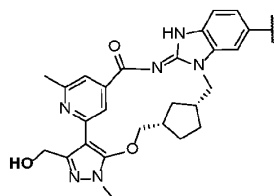
In another embodiment, the

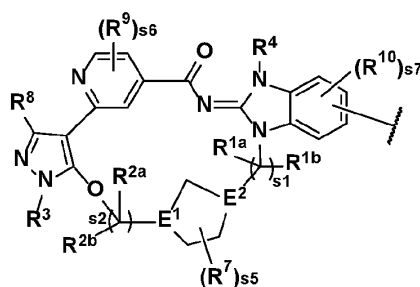
moiety is



In another embodiment, the

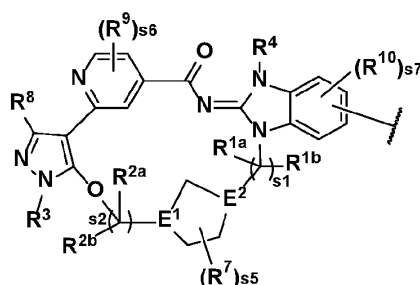
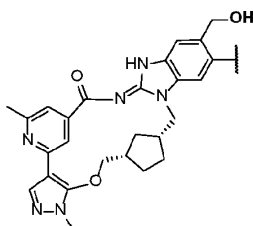
moiety is





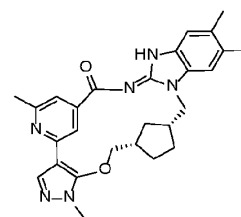
In another embodiment, the

moiety is



In another embodiment, the

moiety is



[0046] Aspect 16. The compound of any one of the preceding aspects, wherein R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy or $-CN$.

In one embodiment, R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently absent, oxo, hydrogen, halogen, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy or $-C_{3-6}$ cycloalkyl; wherein each of said $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy or $-C_{3-6}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-6}$ alkoxy and $-CN$.

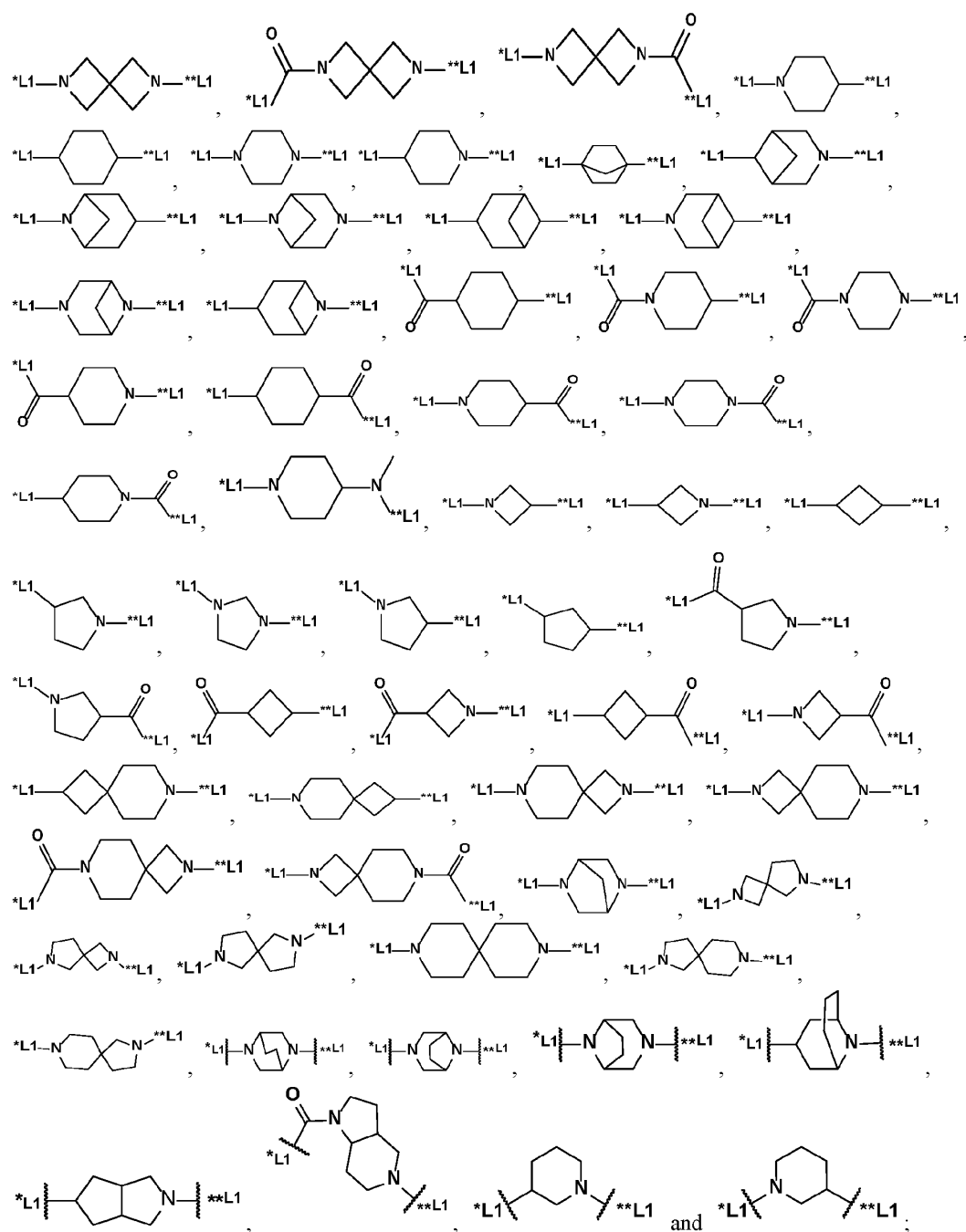
In one embodiment, R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently absent, oxo, hydrogen, halogen, $-C_{1-3}$ alkyl or $-C_{1-3}$ alkoxy.

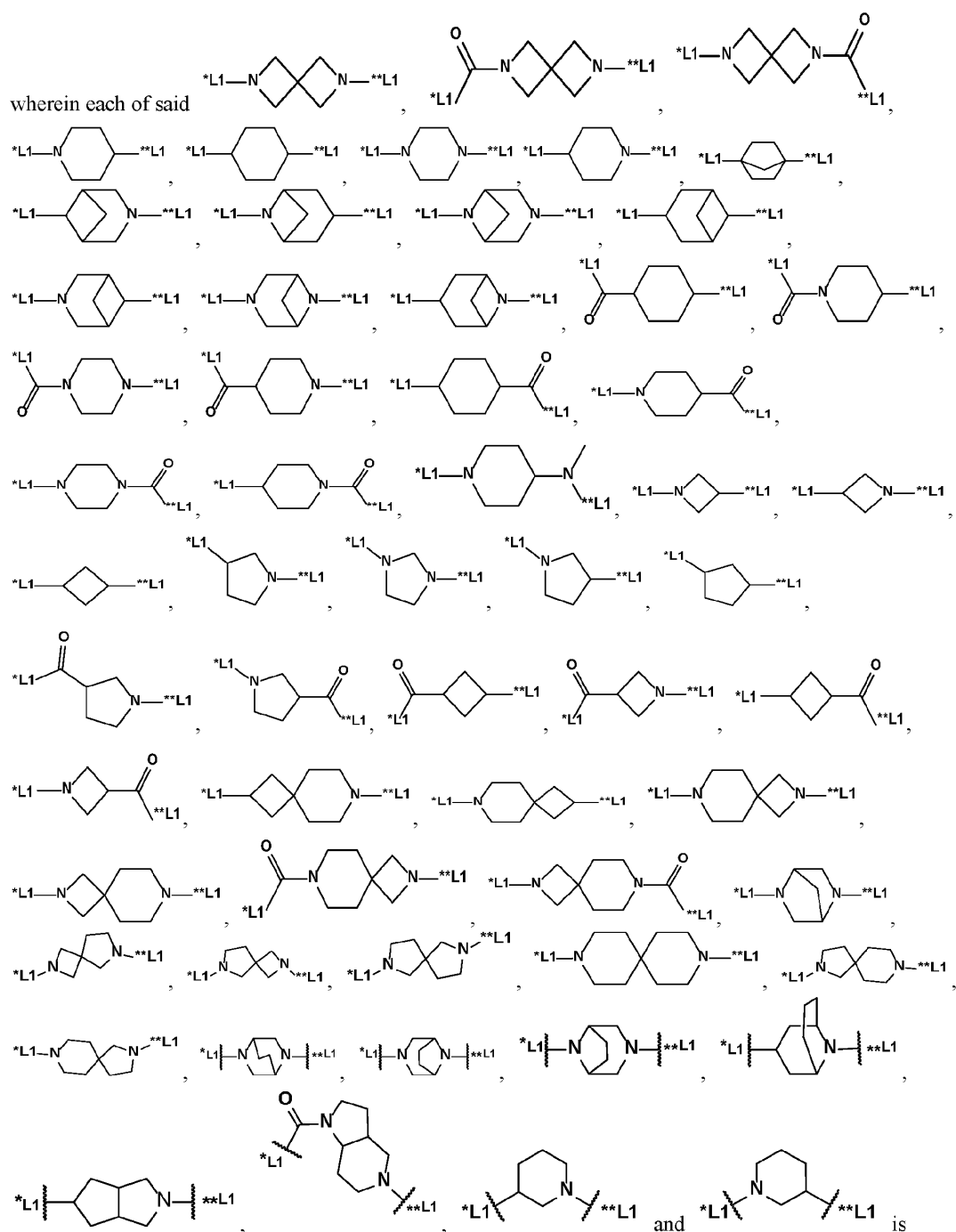
In one embodiment, R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or

cyclooctyl; preferably, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c} and R^{12d} are each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl or propyl.

In one embodiment, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c} and R^{12d} are each independently hydrogen or methyl.

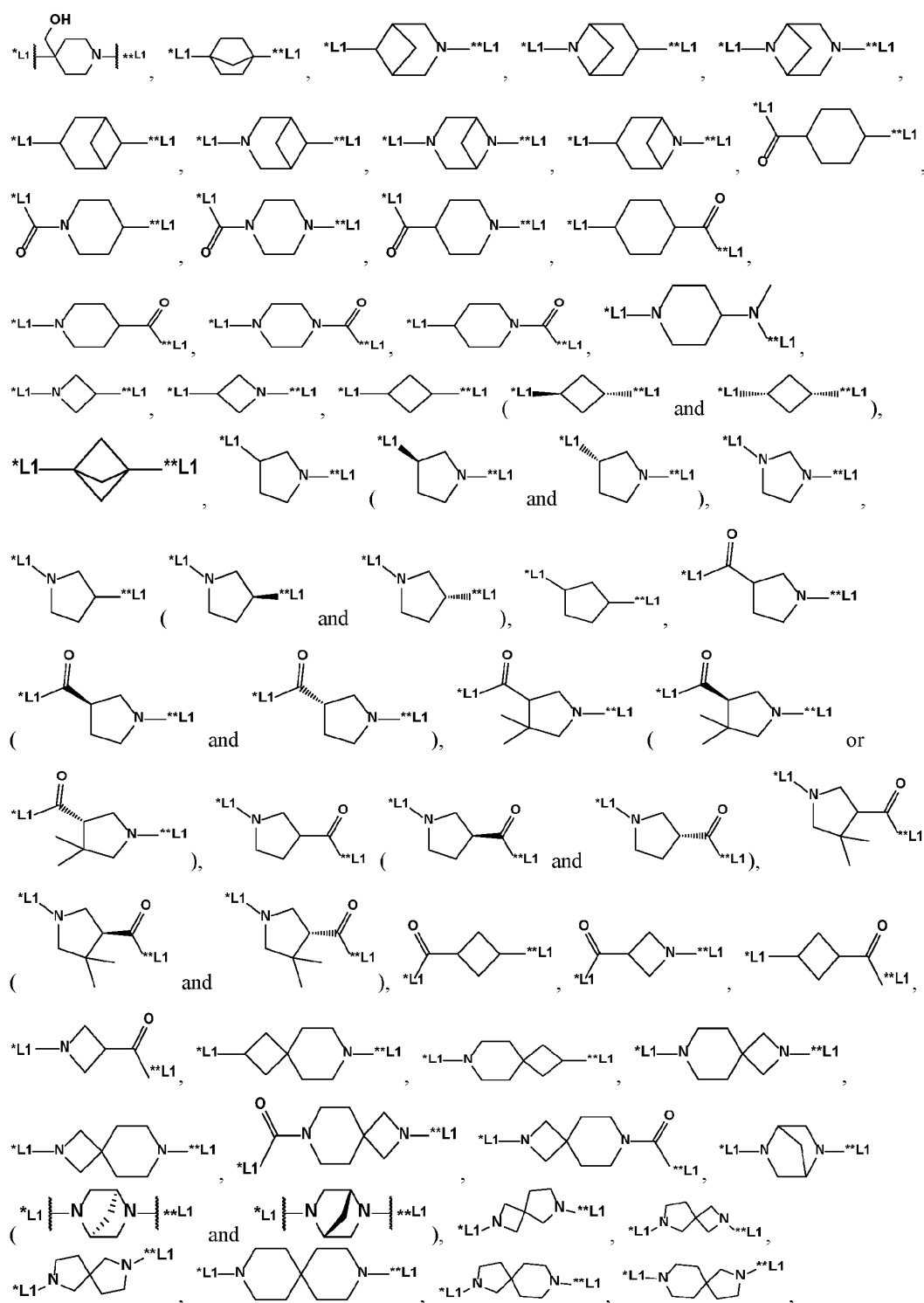
[0047] Aspect 17. The compound of any one of the preceding aspects, wherein L¹ is selected from -O-, -C(O)-, -N(R^a)-, ^{*L1}-C(O)N(R^a)-^{**L1}, ^{*L1}-C(O)O-^{**L1}, ^{*L1}-N(R^a)C(O)-^{**L1}, ^{*L1}-OC(O)-^{**L1},

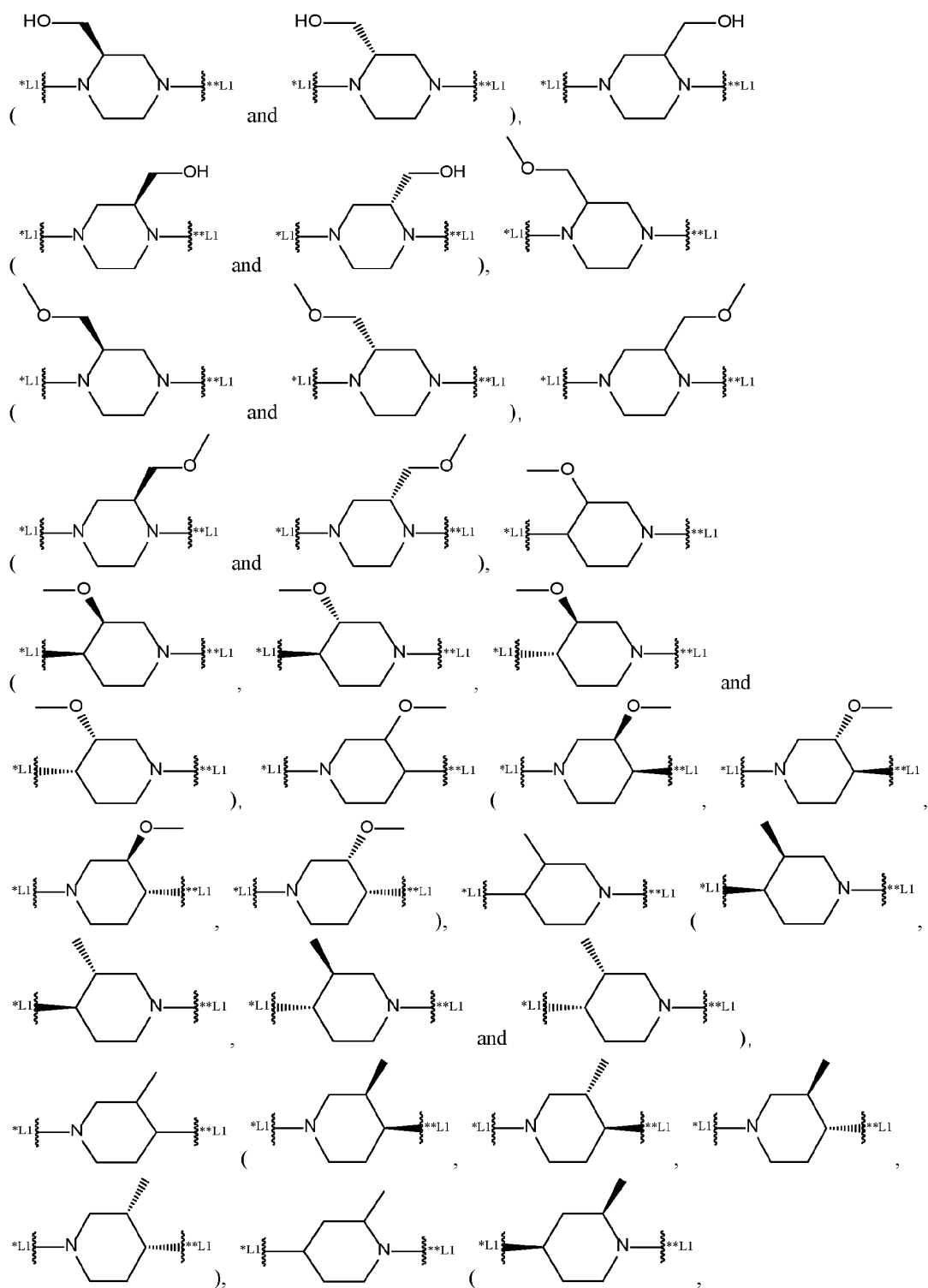


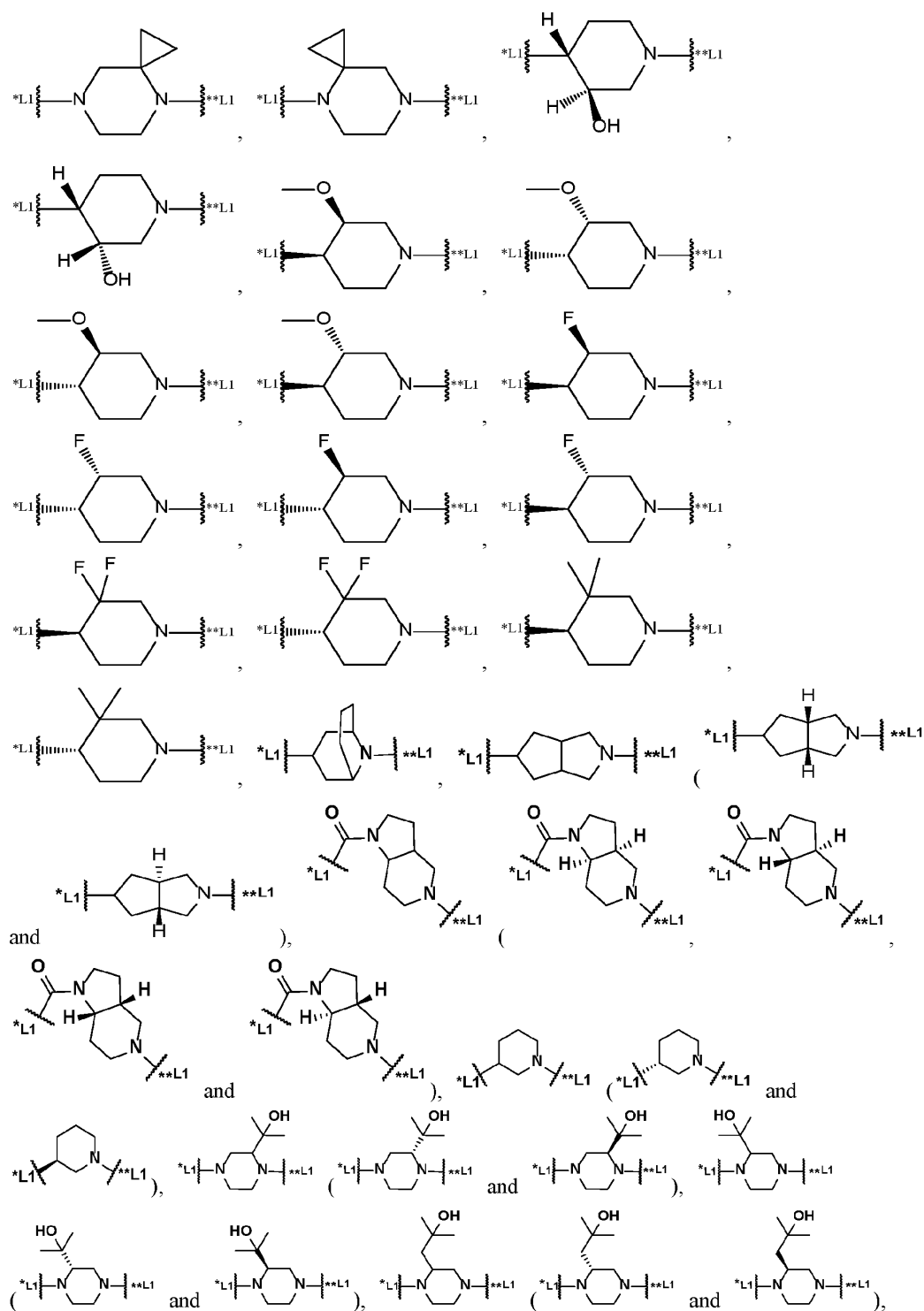


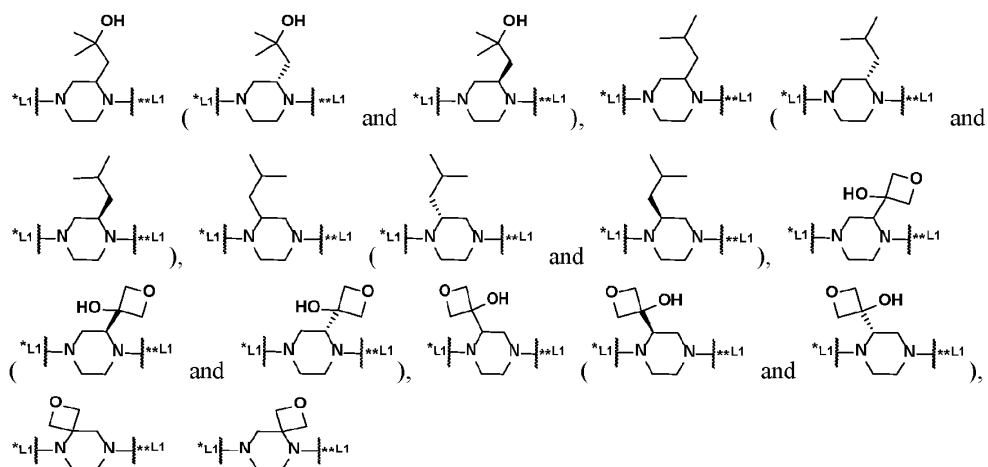
optionally substituted with at least one R^{L1c} ,

wherein each of said R^{L1c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; each of said methyl, ethyl, propyl, butyl,

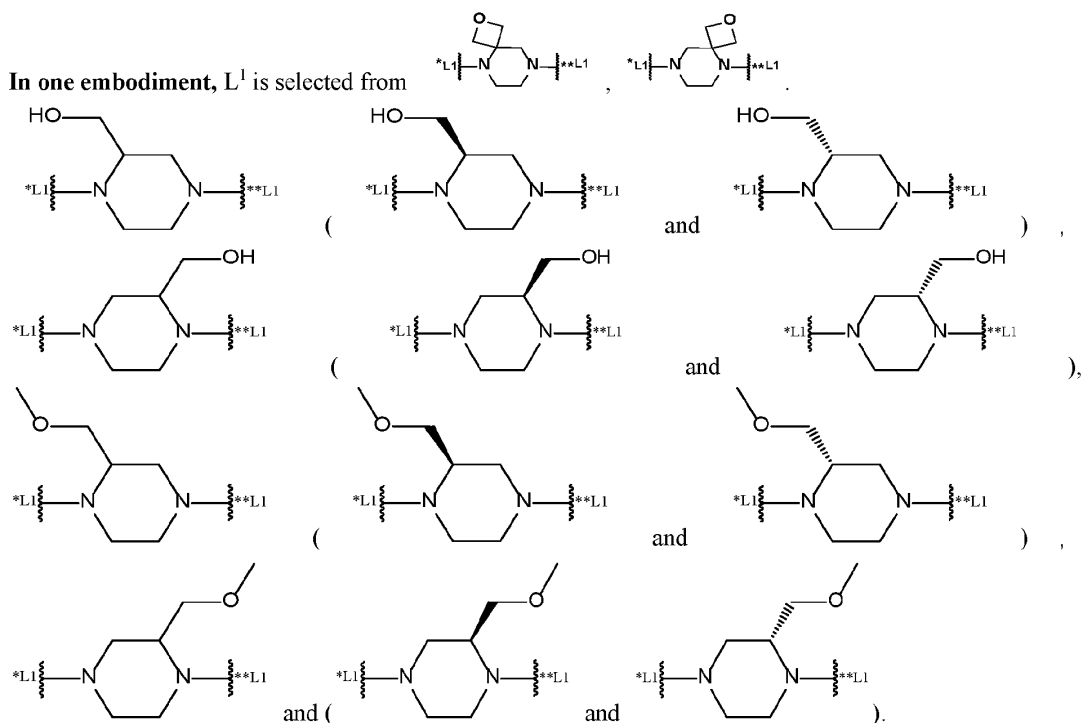




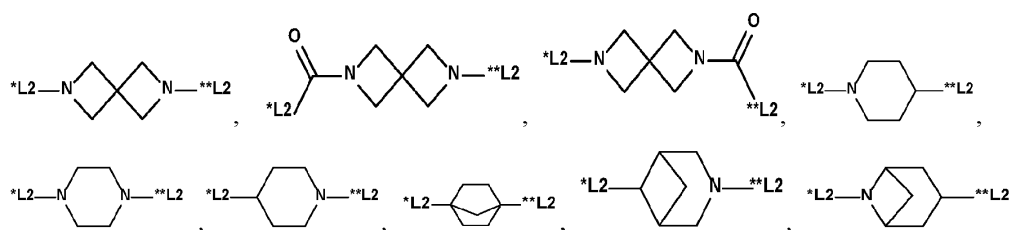


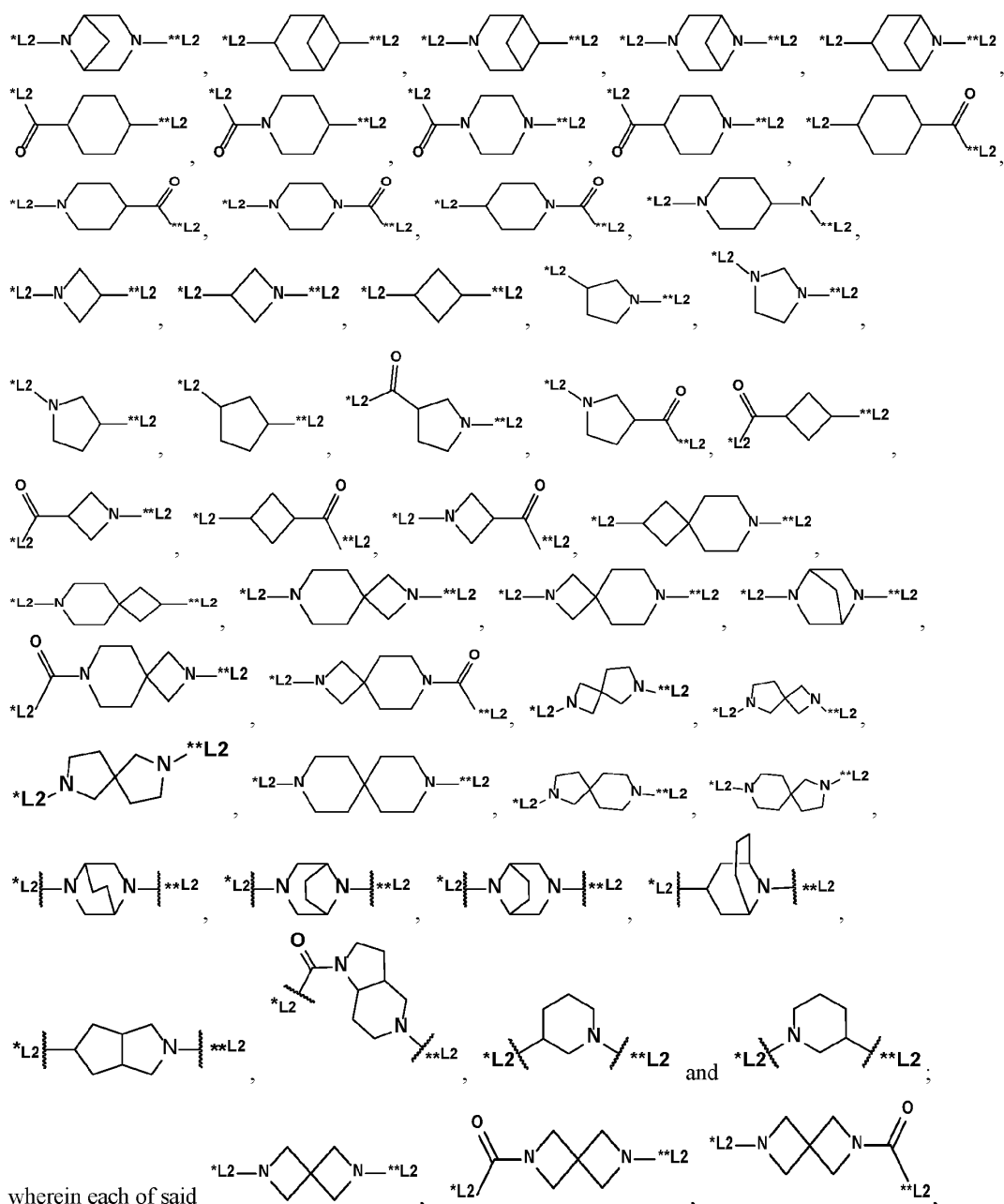


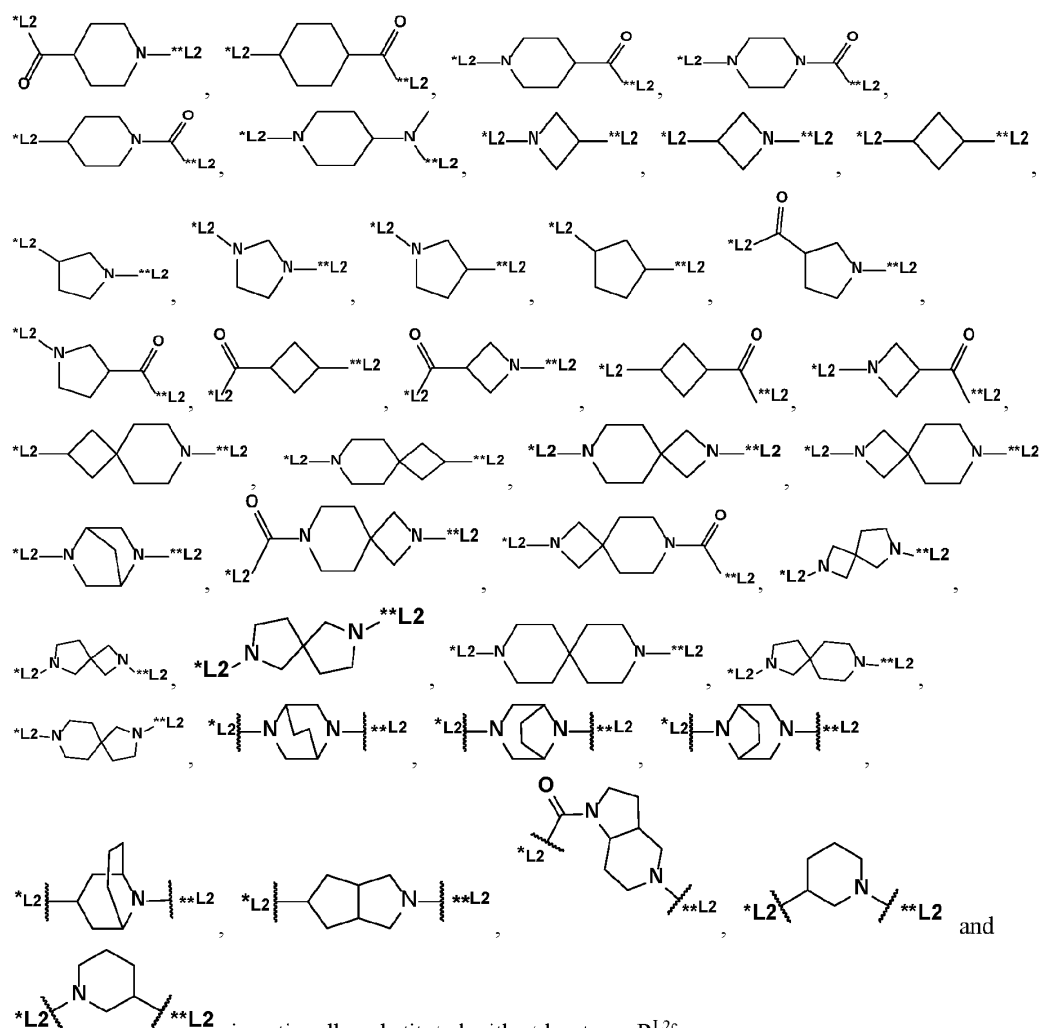
In one embodiment, L^1 is selected from



[0049] Aspect 19. The compound of any one of the preceding aspects, wherein L^2 is selected from -O-, -C(O)-, -N(R^a)-, $^{*}L^2$ -C(O)N(R^a)- $^{**}L^2$, $^{*}L^2$ -C(O)O- $^{**}L^2$, $^{*}L^2$ -N(R^a)C(O)- $^{**}L^2$, $^{*}L^2$ -OC(O)- $^{**}L^2$,







$*L_2$ is optionally substituted with at least one R^{L2c} .

each of said R^{L2c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ,

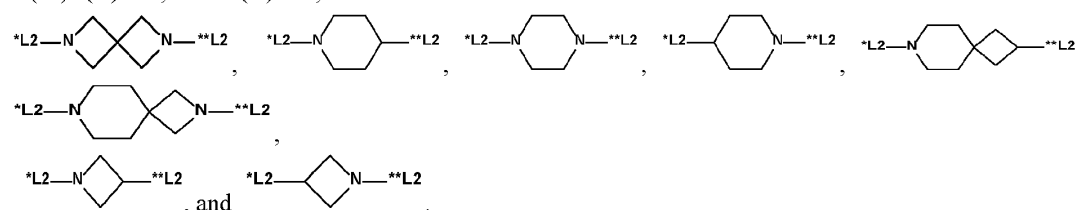
R^{Lca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; or

two R^{L2c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur;

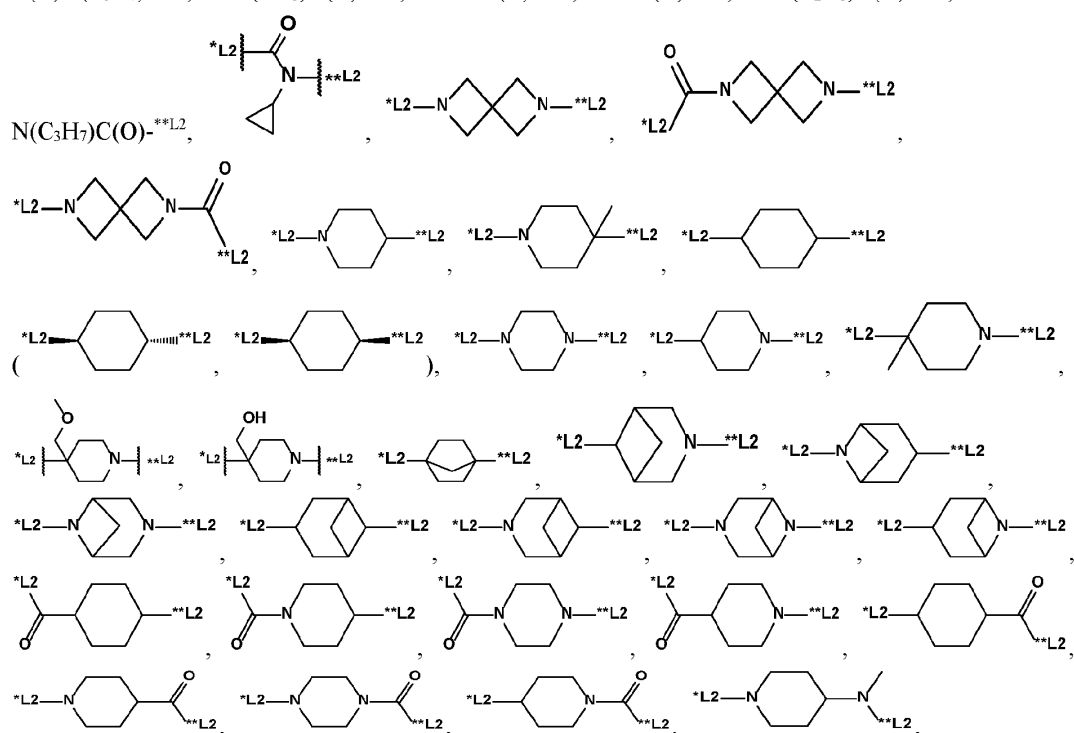
said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl;

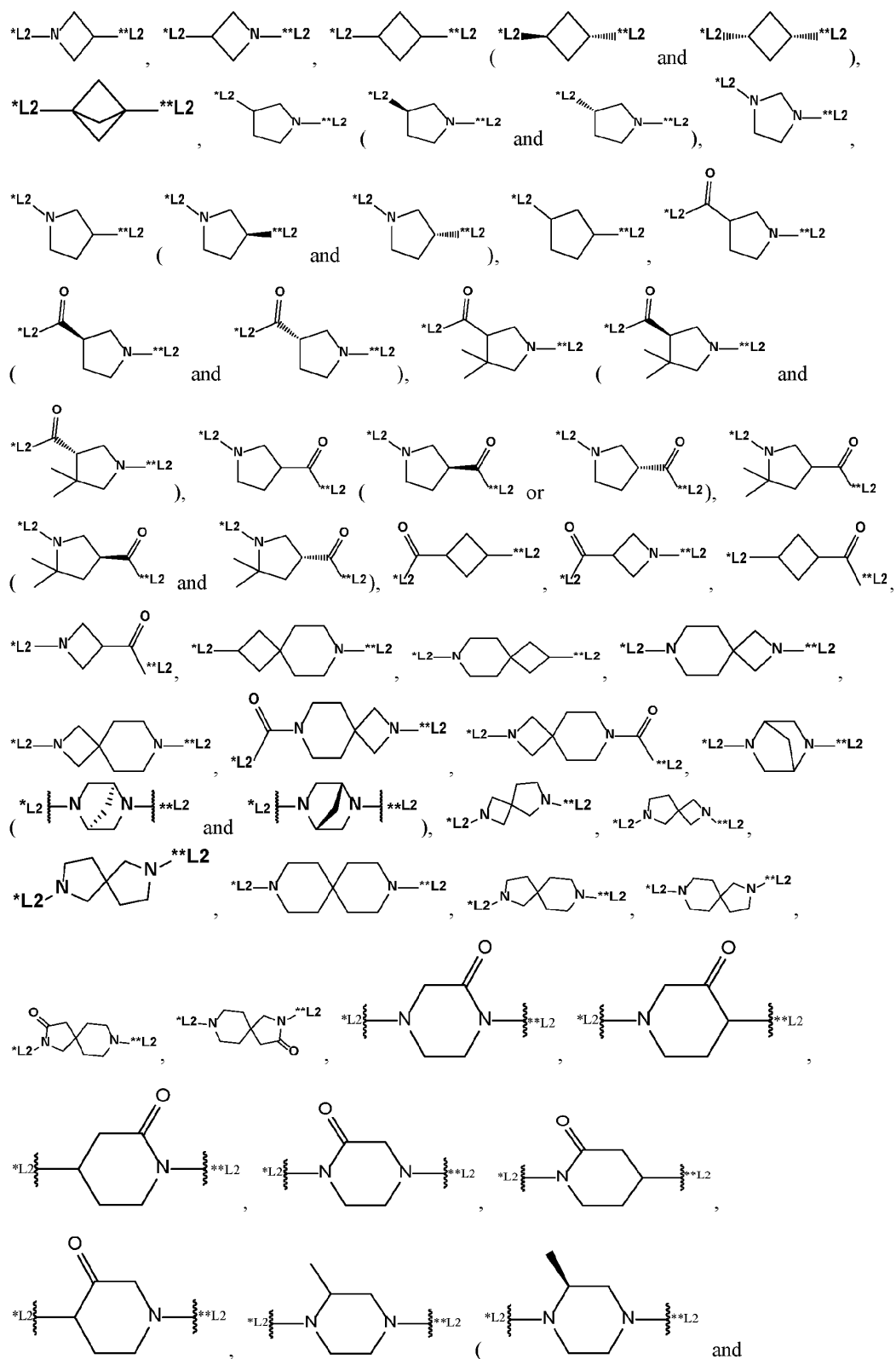
R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent hydroxy, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

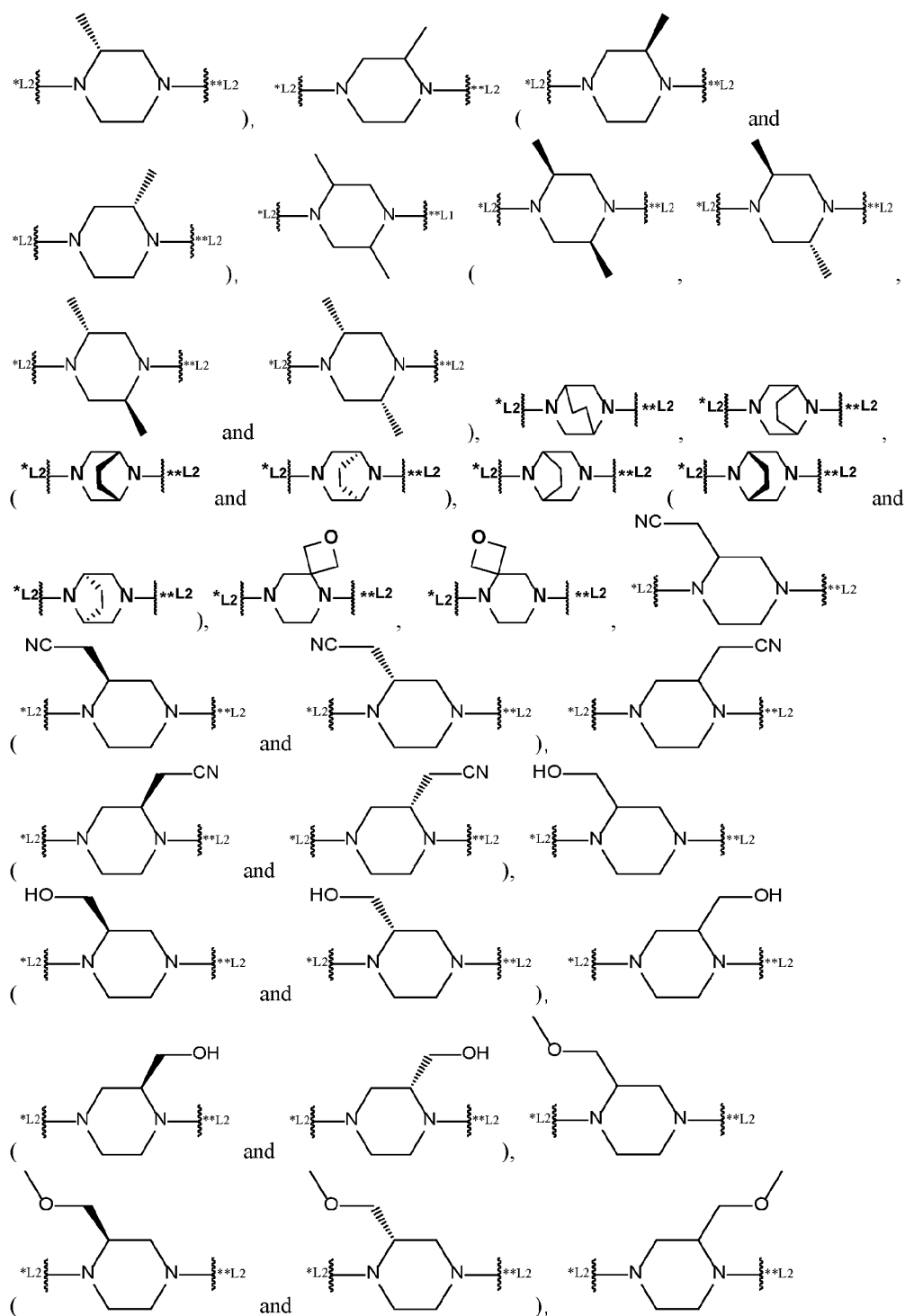
In one embodiment, L^2 is selected from $-O-$, $-C(O)-$, $-N(R^a)-$, $^{*}L^2-C(O)N(R^a)-^{**}L^2$, $^{*}L^2-C(O)O-^{**}L^2$, $^{*}L^2-N(R^a)C(O)-^{**}L^2$, $^{*}L^2-OC(O)-^{**}L^2$,

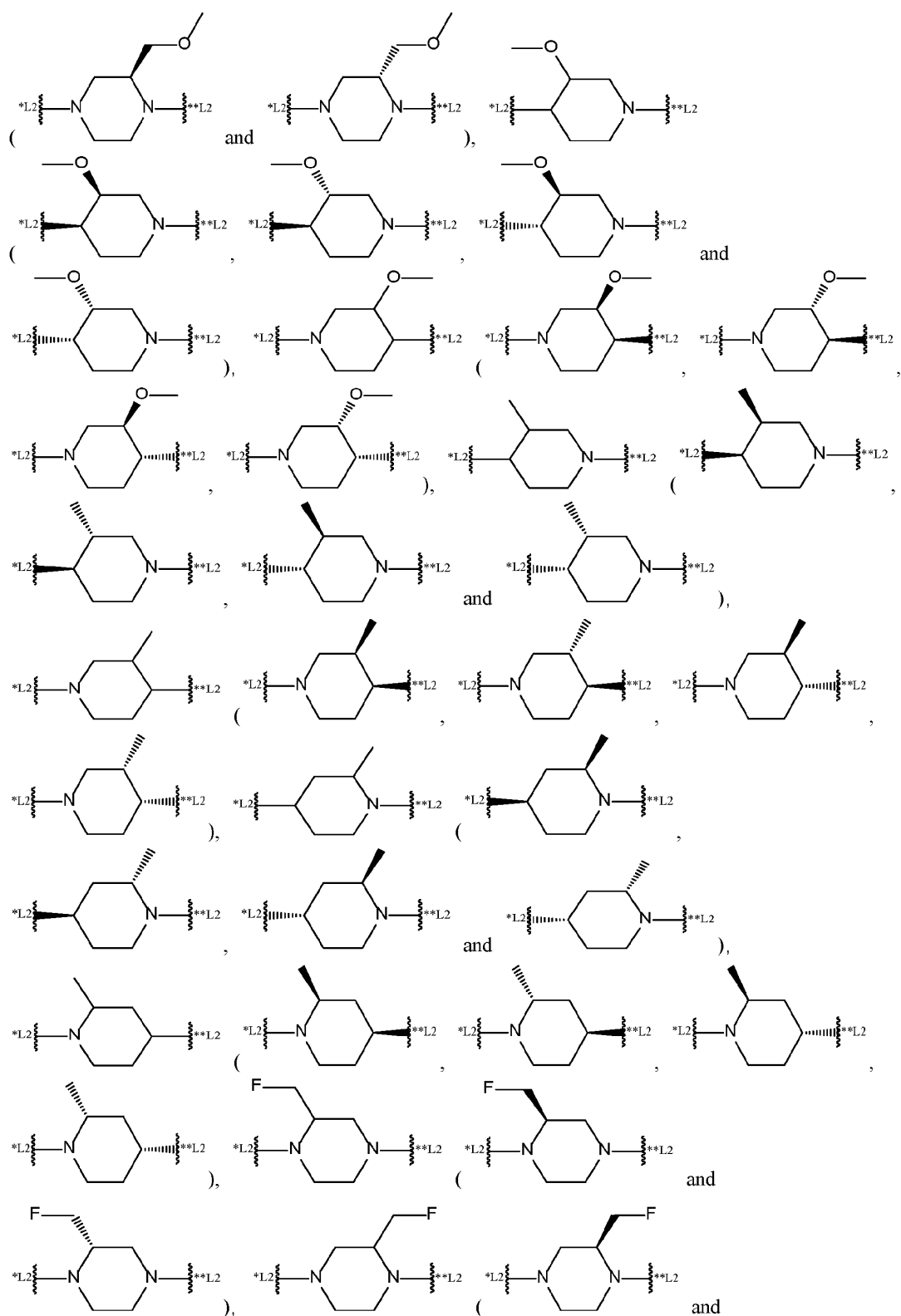


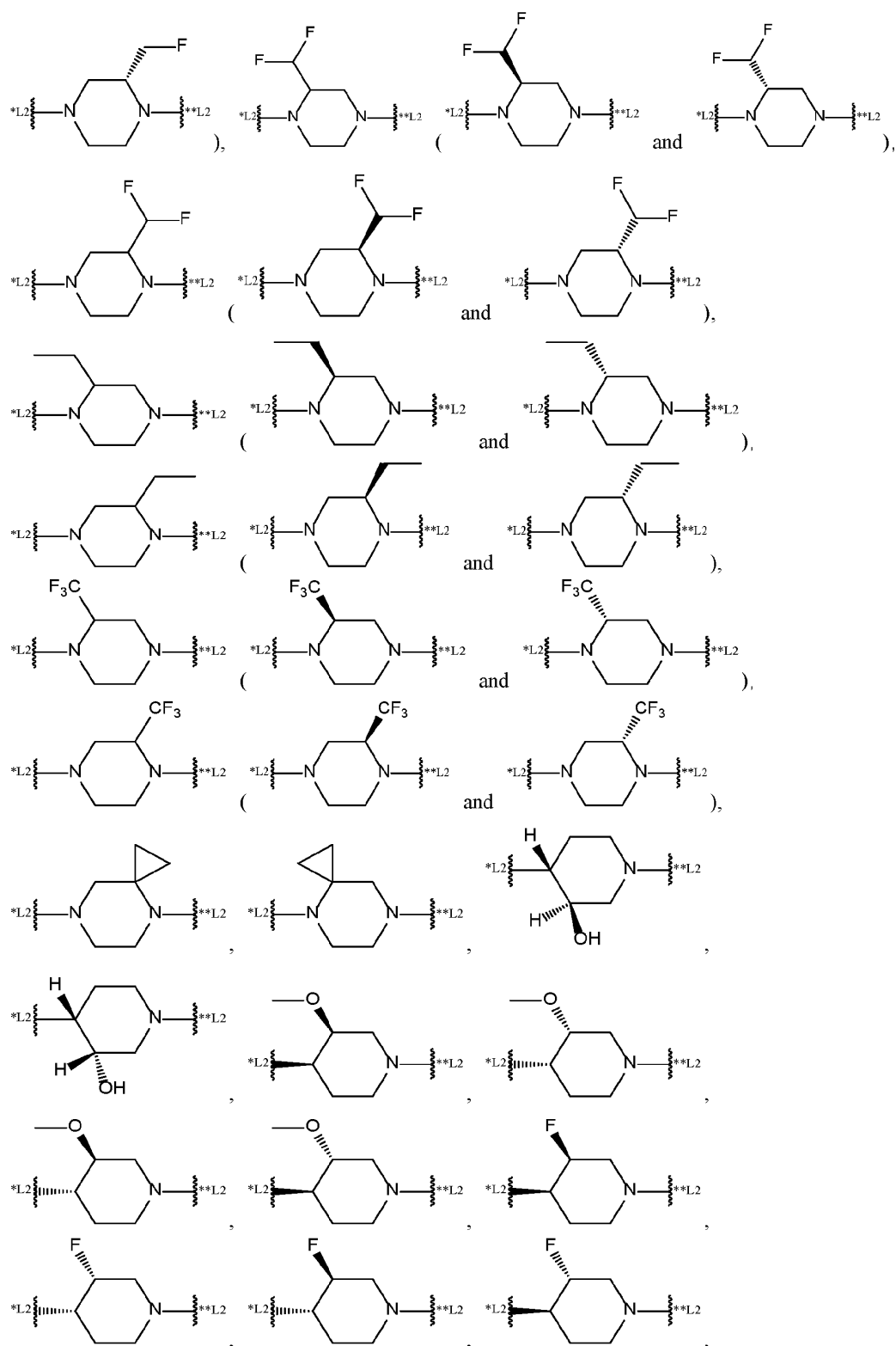
[0050] Aspect 20. The compound of any one of the preceding aspects, wherein L^2 is selected from $-O-$, $-N(CH_3)-$, $-C(O)-$, $-NH-$, $^{*}L^2-C(O)N(CH_3)-^{**}L^2$, $^{*}L^2-C(O)NH-^{**}L^2$, $^{*}L^2-C(O)O-^{**}L^2$, $^{*}L^2-C(O)N(C_2H_5)-^{**}L^2$, $^{*}L^2-C(O)N(C_3H_7)-^{**}L^2$, $^{*}L^2-N(CH_3)C(O)-^{**}L^2$, $^{*}L^2-NHC(O)-^{**}L^2$, $^{*}L^2-OC(O)-^{**}L^2$, $^{*}L^2-N(C_2H_5)C(O)-^{**}L^2$, $^{*}L^2-$

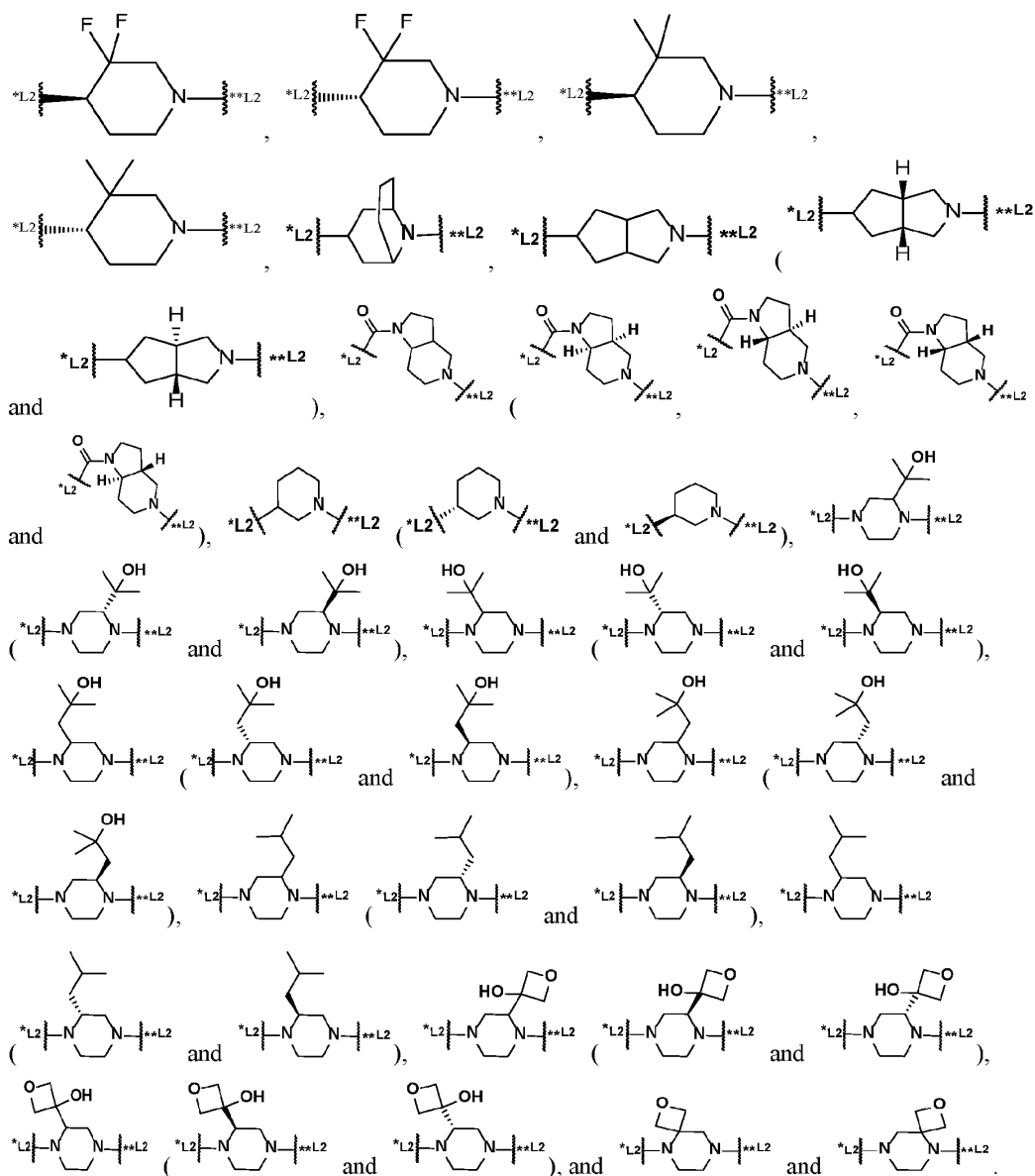




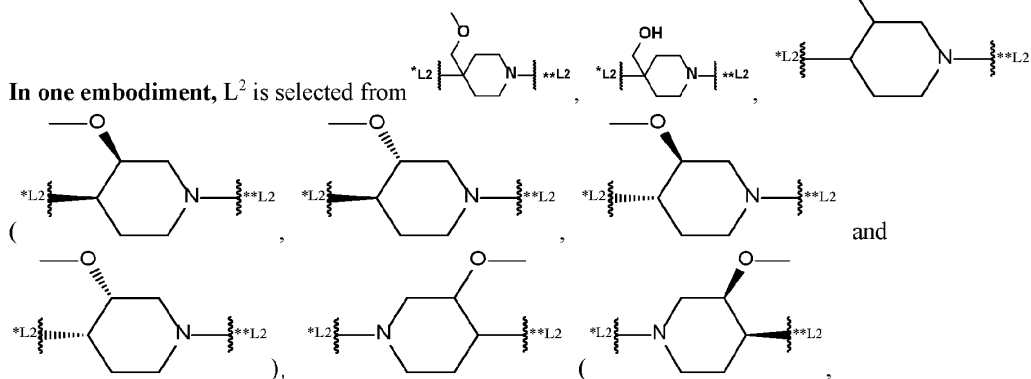


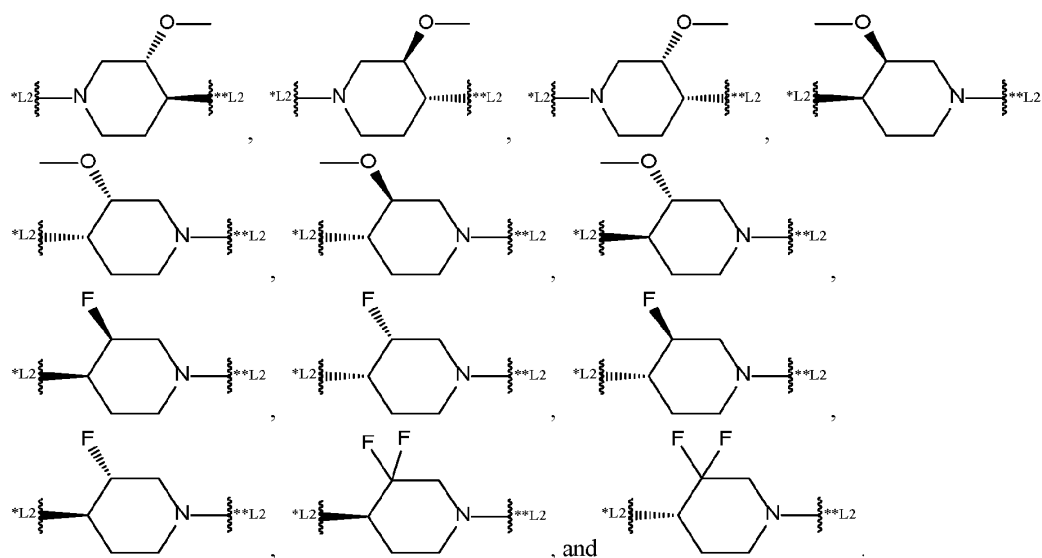




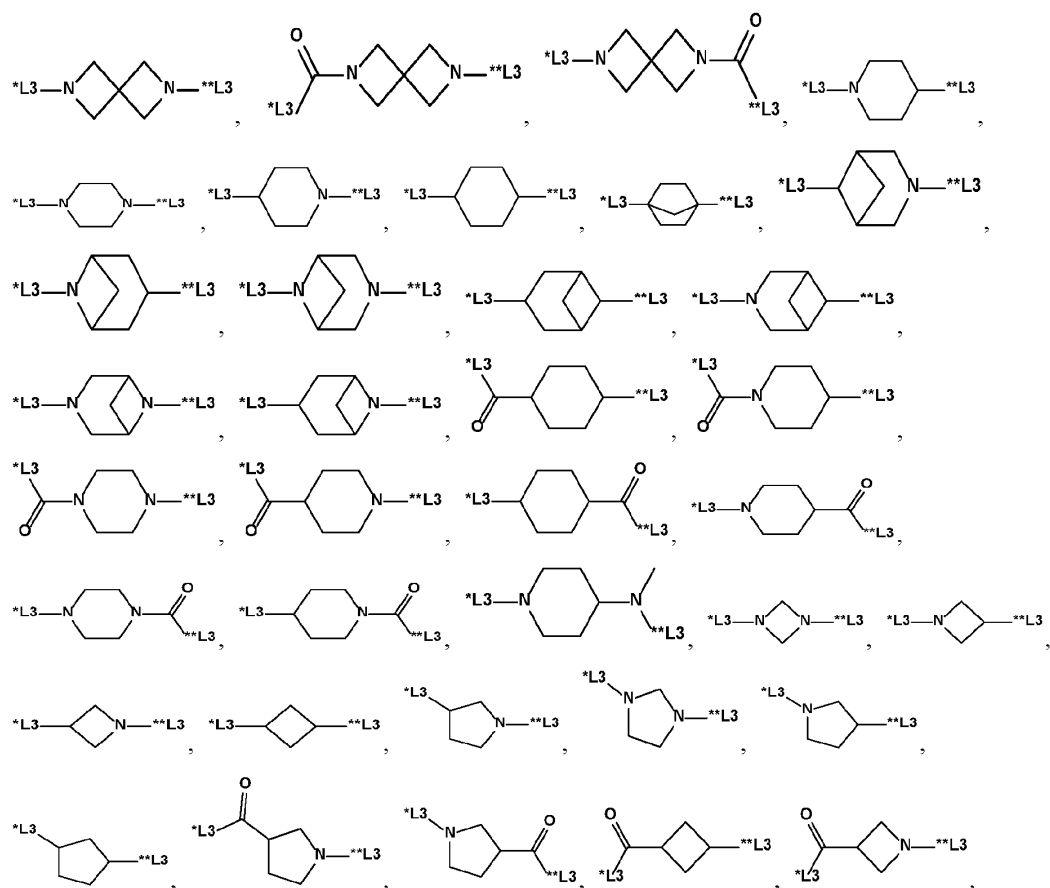


In one embodiment, L^2 is selected from

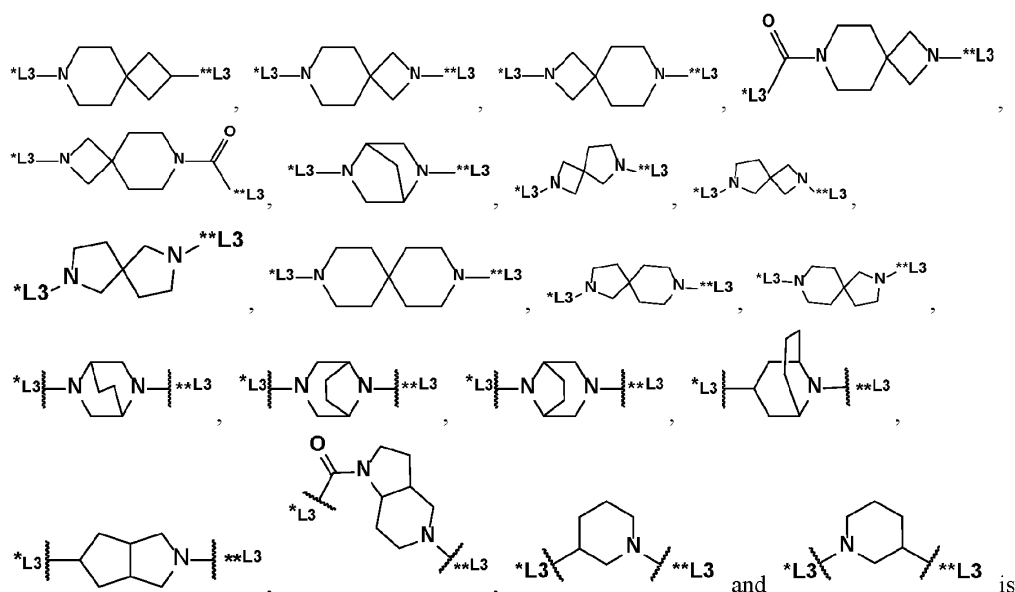




[0051] Aspect 21. The compound of any one of the preceding aspects, wherein L^3 is selected from -O-, -N(R^a)-, -C(O)-, $^{*}L^3$ -C(O)N(R^a)- $^{**}L^3$, $^{*}L^3$ -C(O)O- $^{**}L^3$, $^{*}L^3$ -N(R^a)C(O)- $^{**}L^3$, $^{*}L^3$ -OC(O)- $^{**}L^3$,



[illegible]



optionally substituted with at least one R^{L3c} ;

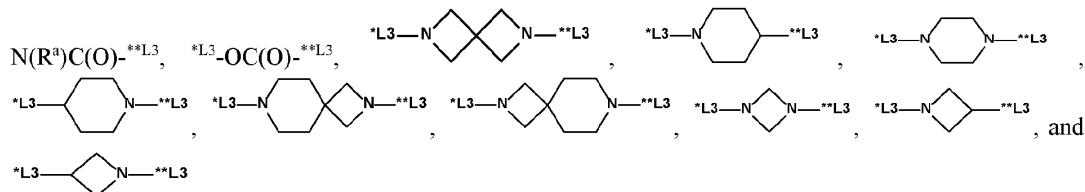
each of said R^{L3c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ,

R^{Lca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; or

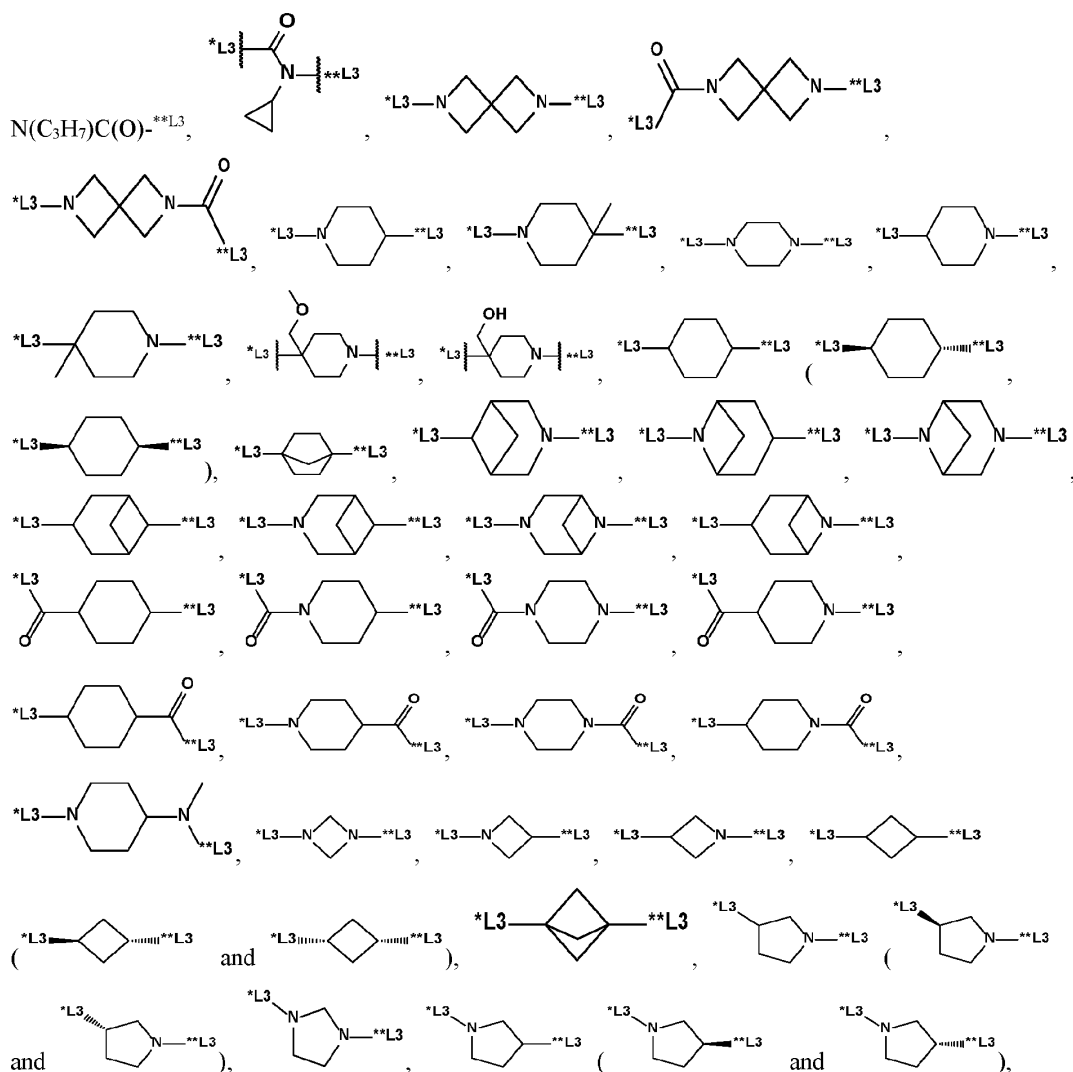
two R^{L3c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl;

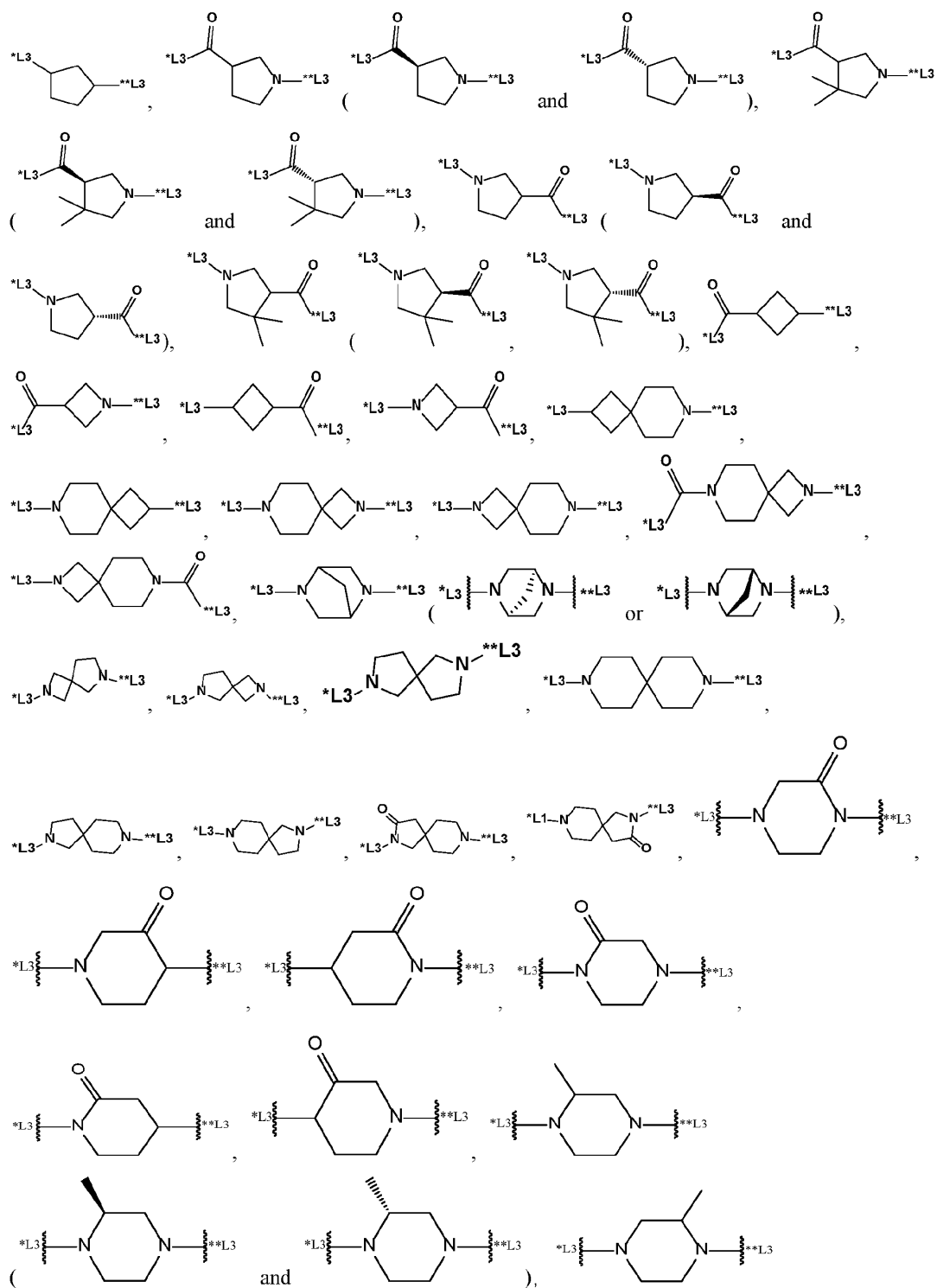
R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent selected from hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl.

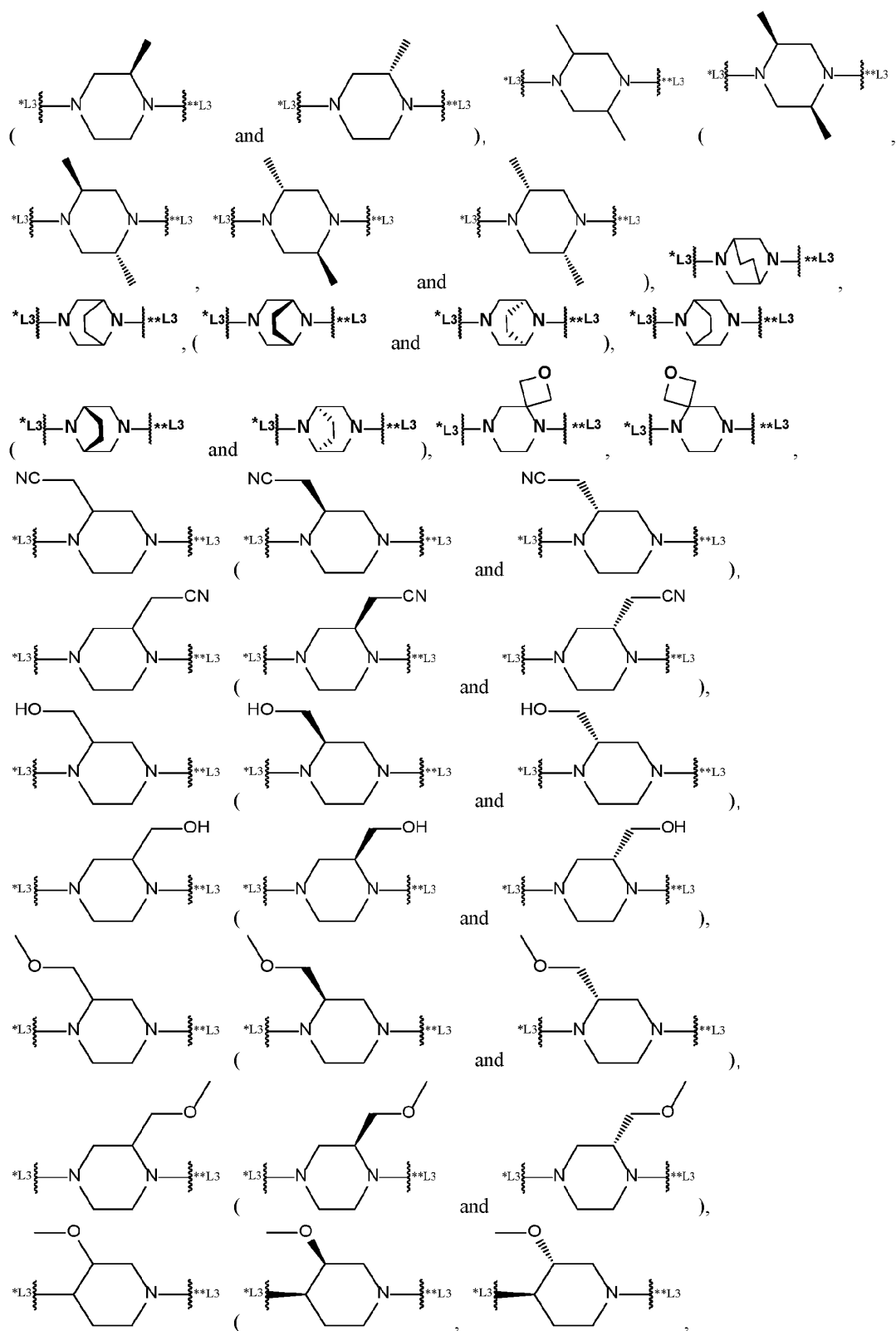
In one embodiment, L³ is selected from -O-, -C(O)-, -N(R^a)-, ^{*L3}-C(O)N(R^a)-^{**L3}, ^{*L3}-C(O)O-^{**L3}, ^{*L3}-

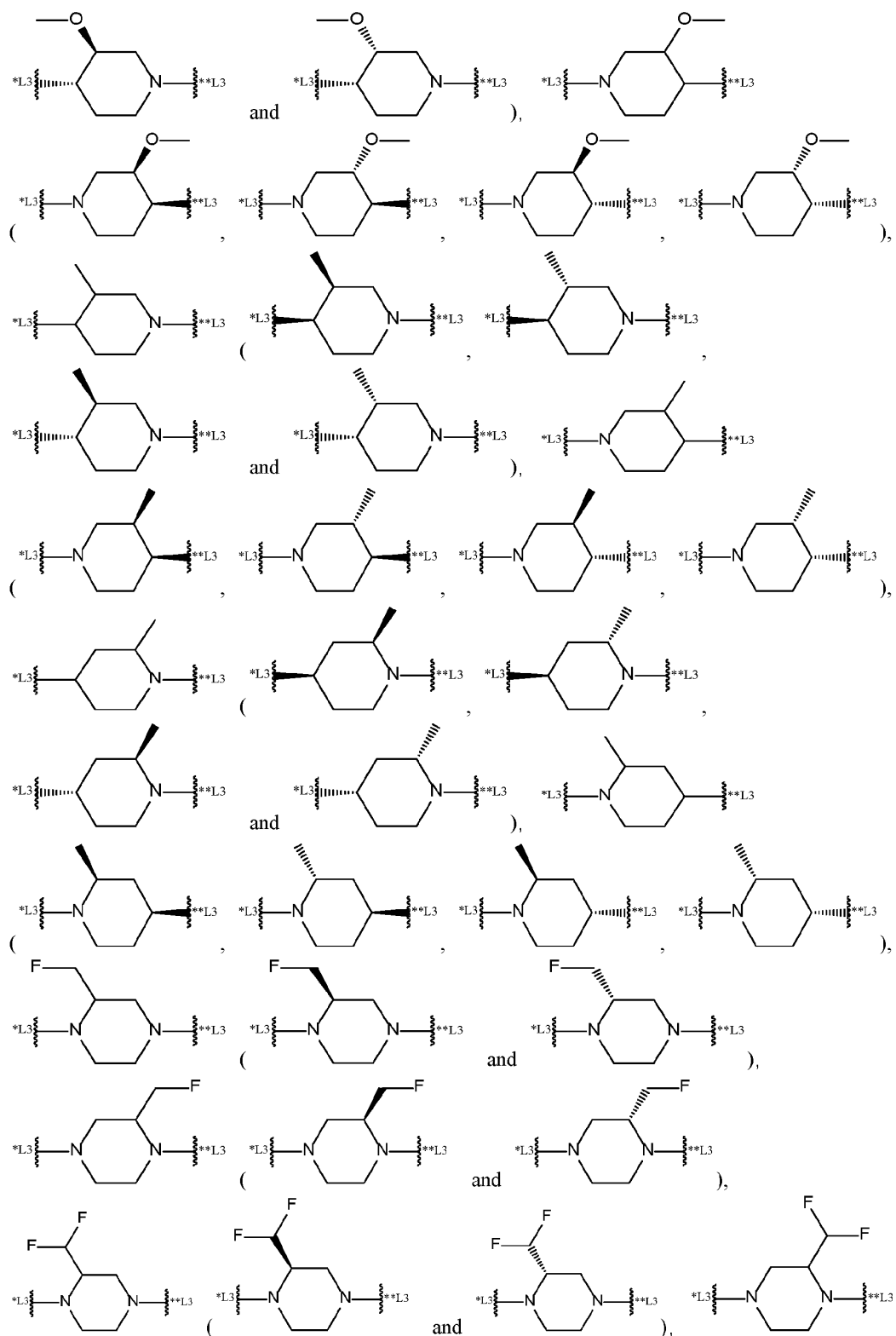


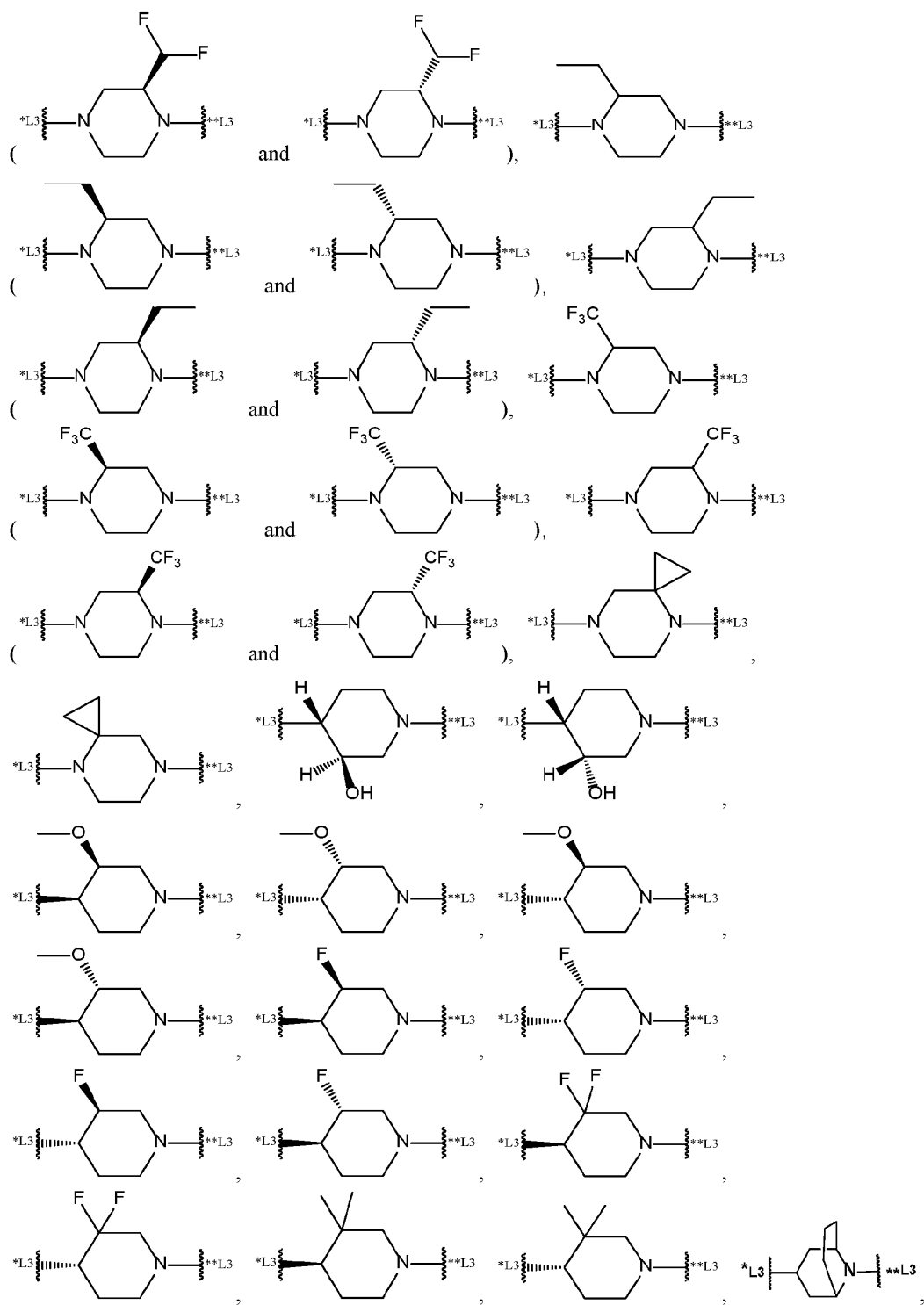
[0052] Aspect 22. The compound of any one of the preceding aspects, wherein L³ is selected from -O-, -N(CH₃)-, -C(O)-, -NH-, *L³-C(O)N(CH₃)-*L³, *L³-C(O)NH-*L³, *L³-C(O)O-*L³, *L³-C(O)N(C₂H₅)-*L³, *L³-C(O)N(C₃H₇)-*L³, *L³-N(CH₃)C(O)-*L³, *L³-NHC(O)-*L³, *L³-OC(O)-*L³, *L³-N(C₂H₅)C(O)-*L³, *L³-

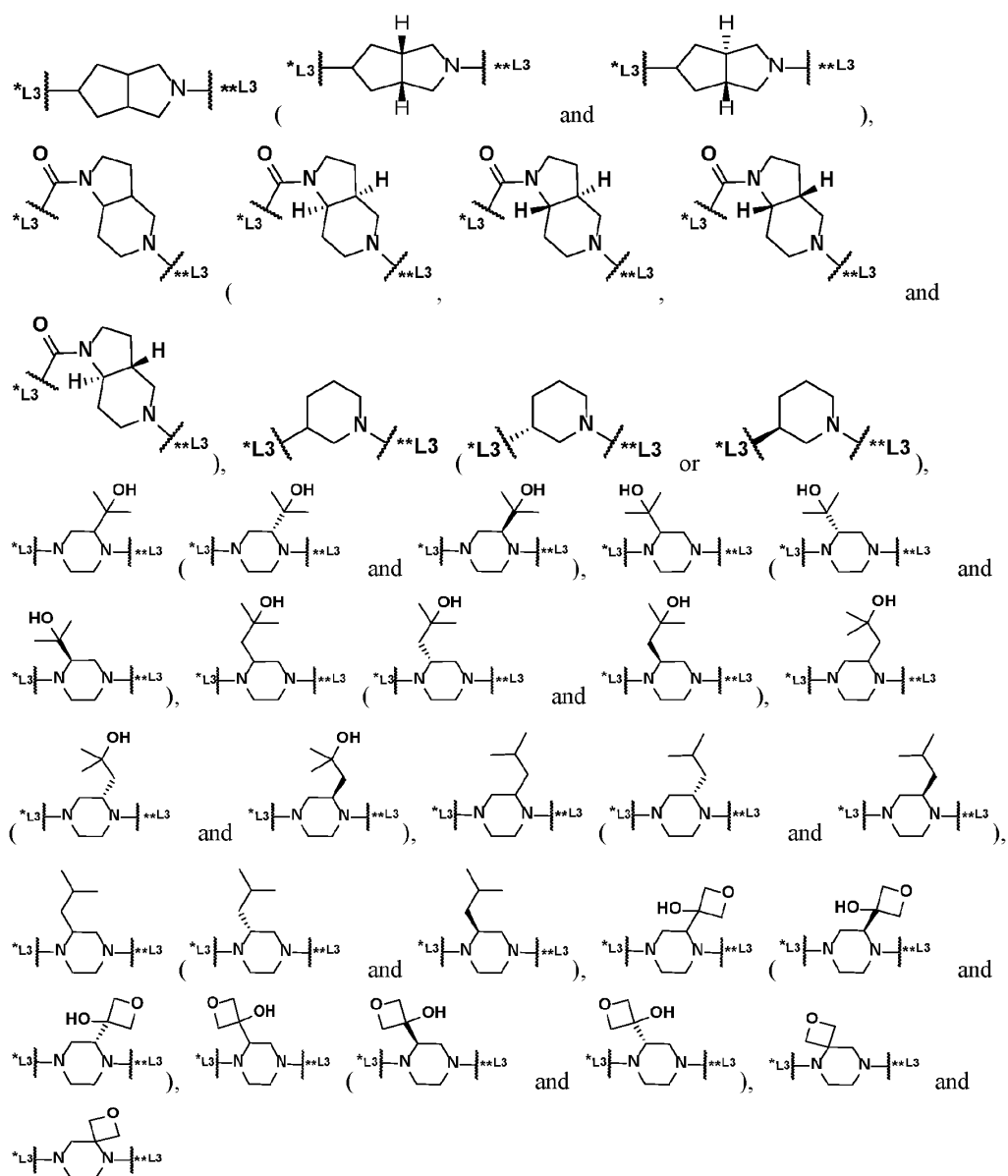




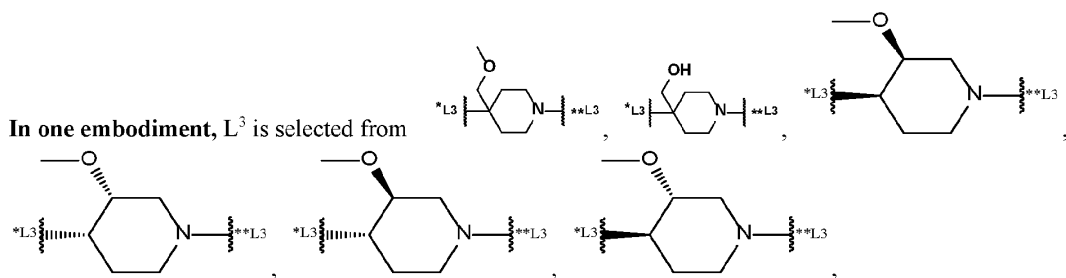


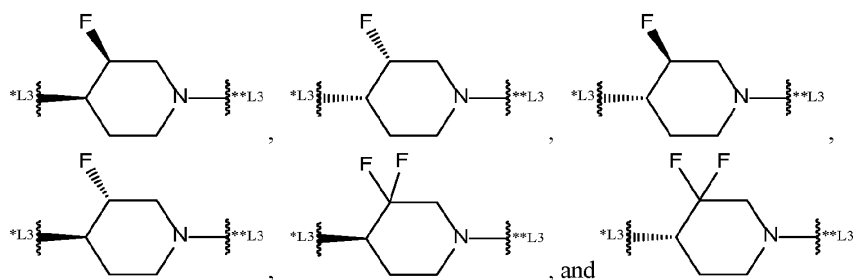




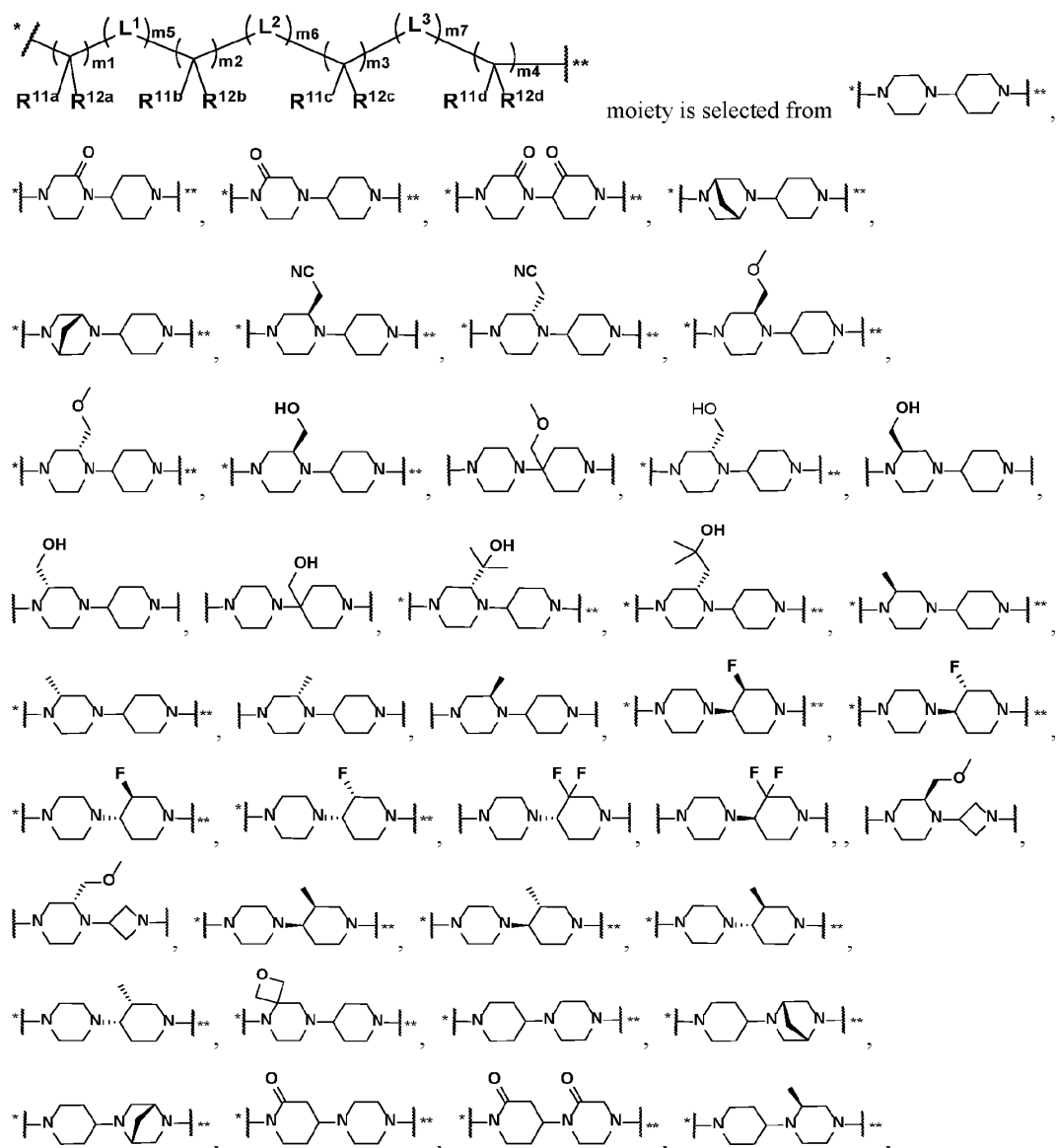


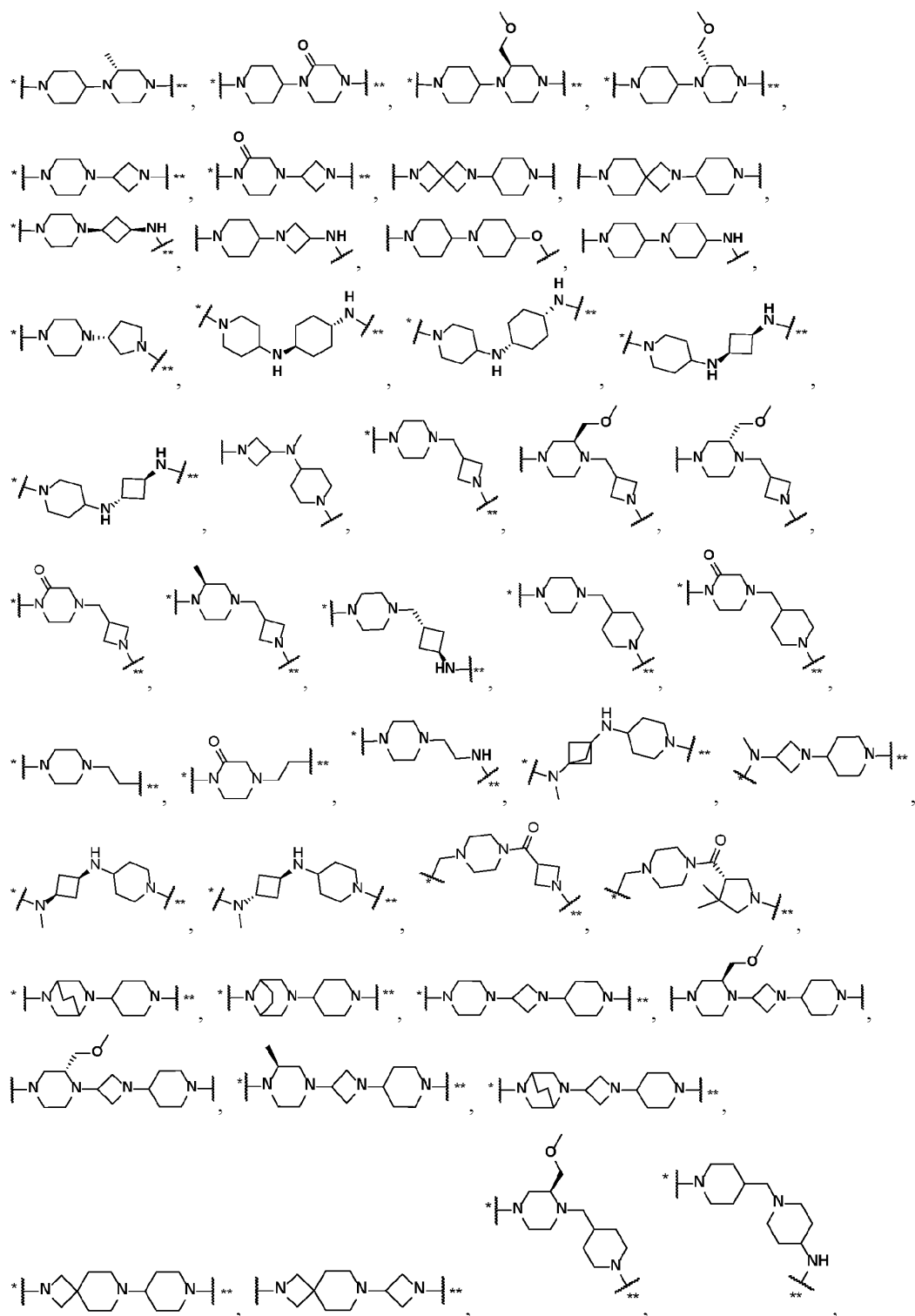
In one embodiment, L^3 is selected from

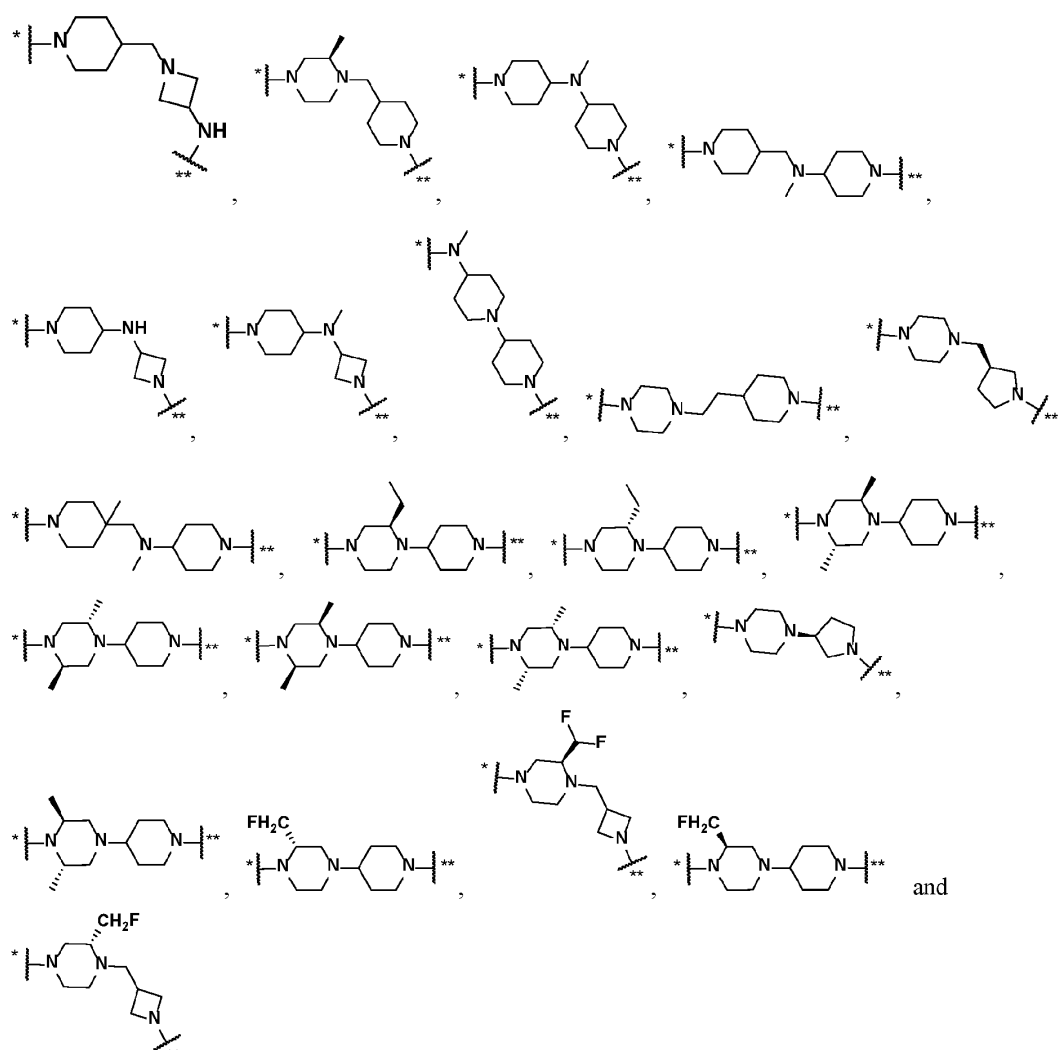




[0053] Aspect 23. The compound of any one of the preceding aspects, wherein







[0054] **Aspect 24.** The compound of any one of the preceding aspects, wherein L^4 is independently selected from a single bond, $-O-$, $-NR^a-$, $-(CR^aR^b)_{n8}-$, $-O(CR^aR^b)_{n8}-$, $-NR^a(CR^aR^b)_{n8}-$ and $-C(O)-$; wherein at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl, each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from hydroxy, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl,

cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl;

In one embodiment, L^4 is independently selected from a single bond.

In one embodiment, L^4 is independently selected from -O-.

In one embodiment, L^4 is independently selected from $-NR^a$ -, wherein R^a is independently selected from hydrogen, methyl, ethyl or propyl.

In one embodiment, L^4 is independently selected from -NH-.

In one embodiment, L^4 is independently selected from $-NCH_3$ -.

In one embodiment, L^4 is independently selected from $-(CR^aR^b)_{n8}$ -, wherein R^a and R^b are each independently selected from hydrogen, methyl, ethyl or propyl; $n8$ is 1 or 2.

In one embodiment, L^4 is independently selected from $-CH_2$ -.

[0055] Aspect 25. The compound of any one of the preceding aspects, wherein X^7 is independently selected from $-CR^a$, and N;

R^a is independently selected from hydrogen, hydroxy, -F, -Cl, -Br, -I, -CN, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

In one embodiment, X^7 is independently selected from -CH, $-C(CH_3)$, or N;

In one embodiment, X^7 is independently selected from -CH.

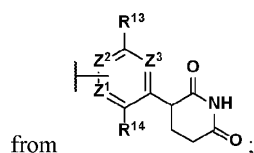
[0056] Aspect 26. The compound of any one of the preceding aspects, wherein X^8 is independently selected from $-NR^a$ -, -O-, -S- and $-CR^aR^b$;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, -F, -Cl, -Br, -I, -CN, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

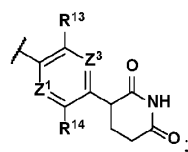
In one embodiment, X^8 is independently selected from -NH- and -CH₂-;

In one embodiment, X^8 is independently selected from -CH₂-.

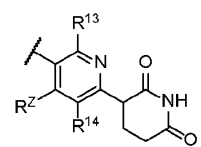
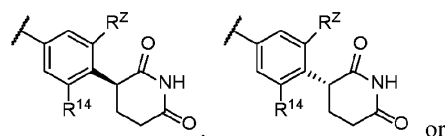
[0057] Aspect 27. The compound of any one of the preceding aspects, wherein Degron is selected



In one embodiment, Degron is selected from



In one embodiment, Degron is selected from



[0058] Aspect 28. The compound of any one of the preceding aspects, wherein at most one of Z^1 , Z^2 and Z^3 is N;

In one embodiment, Z^1 , Z^2 and Z^3 are each independently CR²;

In one embodiment, Z^1 is N, Z^2 and Z^3 are each independently CR².

[0059] Aspect 29. The compound of any one of the preceding aspects, wherein R^Z, at each occurrence, is independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -NR^{Za}R^{Zb}, -OR^{Za}, -SR^{Za}, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl and CN; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{Zc};

R^{Za} and R^{Zb} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl, wherein each of said hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{Zd};

R^{Zc} and R^{Zd} are each independently -F, -Cl, -Br, -I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl.

In one embodiment, R^z is selected from H, $-CH_3$, $-C_2H_5$, F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OC_2H_5$, $-C_3H_7$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_3$, $-SCF_3$, $-CF_3$ or $-CH(OH)CH_3$.

In one embodiment, R^z is H. **In one embodiment**, R^z is $-CH_3$. **In one embodiment**, R^z is F.

[0060] Aspect 30. The compound of any one of the preceding aspects, wherein R^{13} and R^{14} are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, 3- to 8-membered heterocyclyl, $-C_6-C_{12}aryl$, 5- to 12-membered heteroaryl, $-CN$, $-SO_2R^{13a}$, $-SO_2NR^{13a}R^{13b}$, $-COR^{13a}$, $-CO_2R^{13a}$, $-CONR^{13a}R^{13b}$, $-NR^{13a}R^{13b}$, $-NR^{13a}COR^{13b}$, $-NR^{13a}CO_2R^{13b}$, and $-NR^{13a}SO_2R^{13b}$; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, 3- to 8-membered heterocyclyl, $-C_6-C_{12}aryl$, 5- to 12-membered heteroaryl is optionally substituted with F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, 3- to 8-membered heterocyclyl, $-C_6-C_{12}aryl$, 5- to 12-membered heteroaryl, oxo, $-CN$, $-OR^{13c}$, $-SO_2R^{13c}$, $-SO_2NR^{13c}R^{13d}$, $-COR^{13c}$, $-CO_2R^{13c}$, $-CONR^{13c}R^{13d}$, $-NR^{13c}R^{13d}$, $-NR^{13c}COR^{13d}$, $-NR^{13c}CO_2R^{13d}$, or $-NR^{13c}SO_2R^{13d}$,

R^{13a} , R^{13b} , R^{13c} and R^{13d} are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, 3- to 8-membered heterocyclyl, $-C_6-C_{12}aryl$, or 5- to 12-membered heteroaryl;

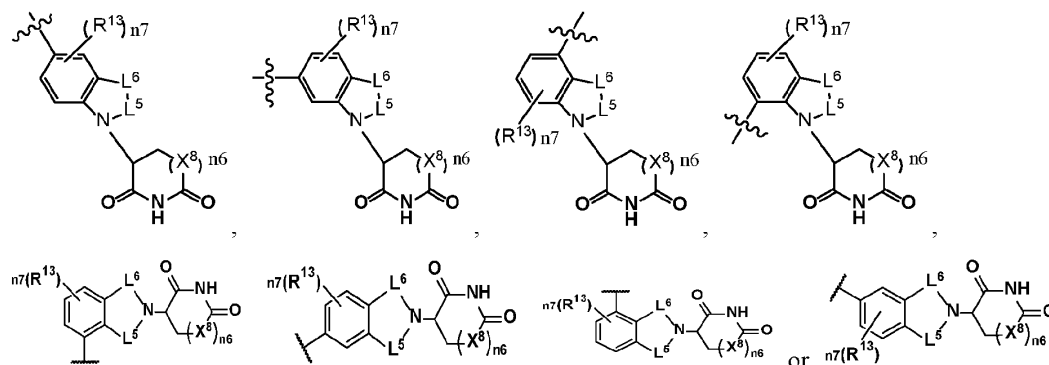
In one embodiment, R^{13} and R^{14} are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CN$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_3$, $-SCF_3$, or phenyl.

In one embodiment, R^{13} and R^{14} are each independently selected from hydrogen, F, methyl.

In one embodiment, R^{13} is independently selected from hydrogen, F, methyl.

In one embodiment, R^{14} is independently selected from hydrogen, F, methyl.

[0061] **Aspect 31.** The compound of any one of the preceding aspects, wherein Degron is



[0062] **Aspect 32.** The compound of any one of the preceding aspects, wherein L^5 and L^6 are each independently selected from a single bond, $-O-$, $-NR^a-$, $-(CR^aR^b)_{n8}-$, $-O(CR^aR^b)_{n8}-$, $-NR^a(CR^aR^b)_{n8}-$ and $-C(O)-$;

X^8 is $-CR^aR^b-$;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent hydroxy, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

In one embodiment, L^5 and L^6 are each independently a single bond, $-O-$, $-NR^a-$, $-(CR^aR^b)_{n8}-$, or $-C(O)-$; wherein R^a and R^b are each independently selected from hydrogen and $-C_{1-3}Alkyl$; $n8$ is 1.

In one embodiment, L^5 and L^6 are each independently a single bond, , $-O-$, $-NH-$, $-NMe-$, $-N(CH_2CH_3)-$, $-CH_2-$, $-CHF-$, $-CF_2-$, $-C(CH_3)_2-$ or $-CO-$;

X^8 is CH_2 ; and

$n6$ is 0 or 1.

[0063] **Aspect 33.** The compound of any one of the preceding aspects, wherein R^{13} is independently selected from hydrogen, F , Cl , Br , I , methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_2$ - 8 alkenyl, $-C_2$ - 8 alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, 5- to 12-membered heteroaryl, $-CN$, $-SO_2R^{13a}$, $-SO_2NR^{13a}R^{13b}$, $-COR^{13a}$, $-CO_2R^{13a}$, $-CONR^{13a}R^{13b}$, $-NR^{13a}R^{13b}$, $-NR^{13a}COR^{13b}$, $-NR^{13a}CO_2R^{13b}$, and $-NR^{13a}SO_2R^{13b}$, wherein each of methyl, ethyl, propyl, butyl, pentyl,

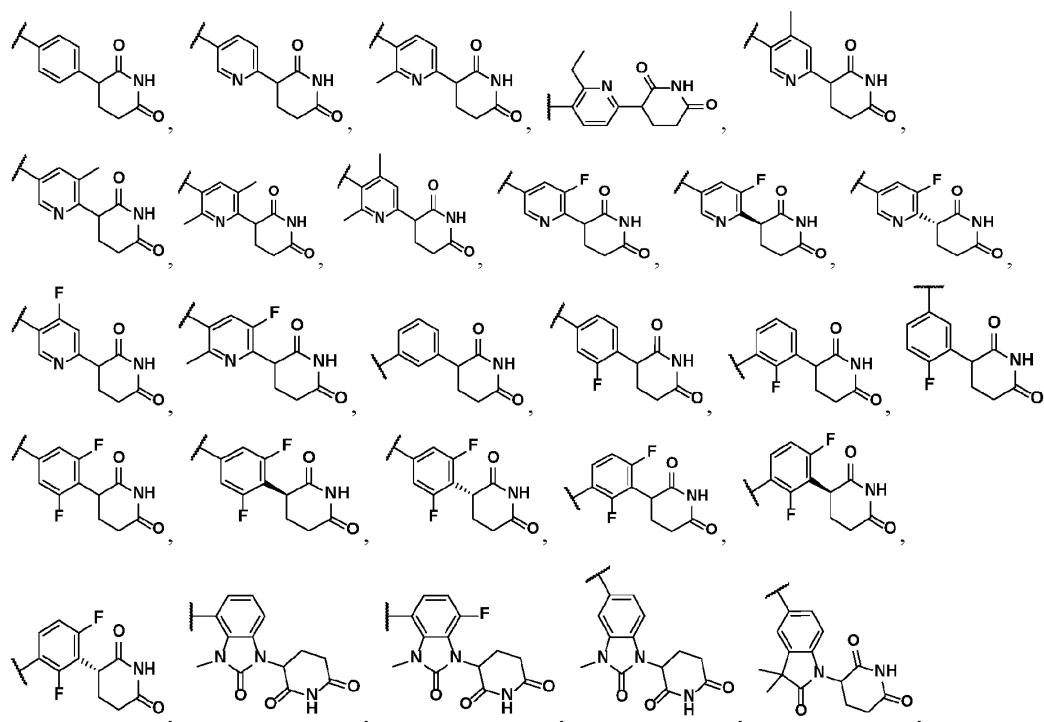
hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, 5- to 12-membered heteroaryl is optionally substituted with F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, 5- to 12-membered heteroaryl, oxo, $-CN$, $-OR^{13c}$, $-SO_2R^{13c}$, $-SO_2NR^{13c}R^{13d}$, $-COR^{13c}$, $-CO_2R^{13c}$, $-CONR^{13c}R^{13d}$, $-NR^{13c}R^{13d}$, $-NR^{13c}COR^{13d}$, $-NR^{13c}CO_2R^{13d}$, or $-NR^{13c}SO_2R^{13d}$,

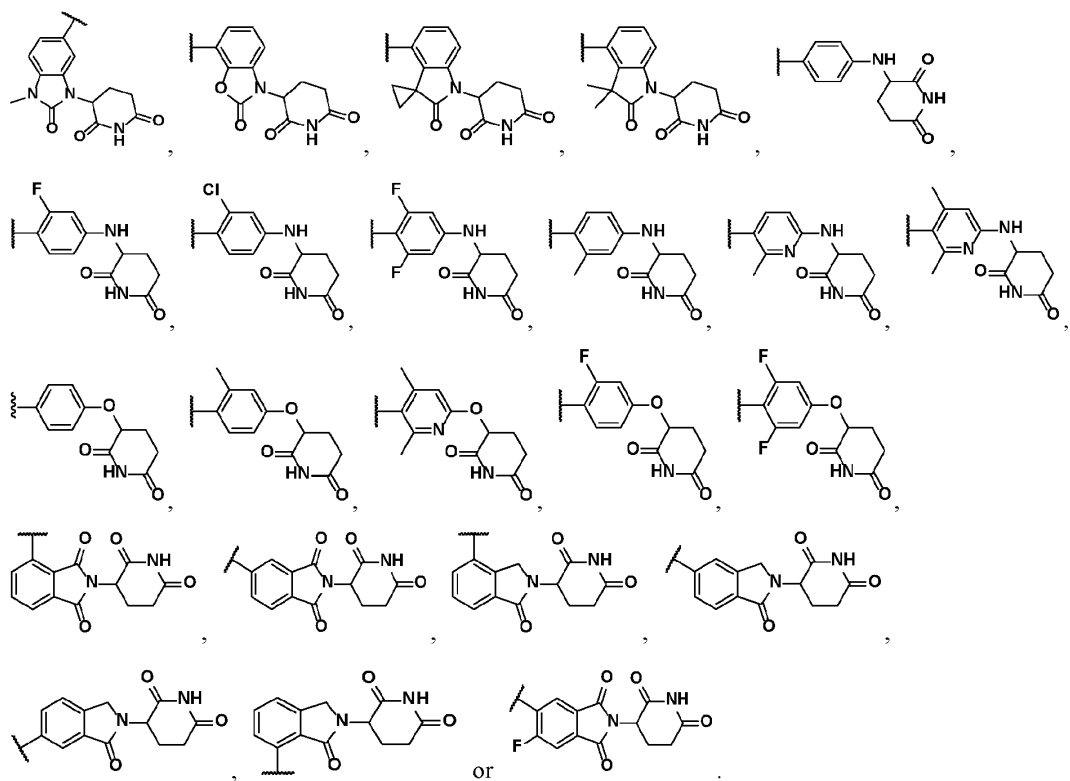
at each occurrence, R^{13a} , R^{13b} , R^{13c} and R^{13d} are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, or 5- to 12-membered heteroaryl;

In one embodiment, R^{13} is independently selected from hydrogen, F, Cl, Br, I, CN, $-C_1-C_8$ alkyl, and $-C_1-C_8$ alkoxy; preferably R^{13} is independently selected from hydrogen, F, Cl, Br, I, CN, $-Me$, $-Et$, $-C_3H_7$, $-C_4H_9$, $-OMe$, $-OEt$, $-OC_3H_7$ and $-OC_4H_9$;

n_7 is 0, 1 or 2.

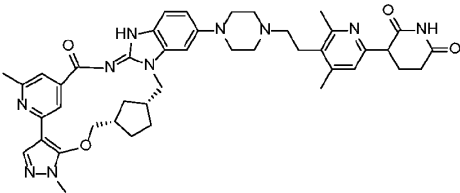
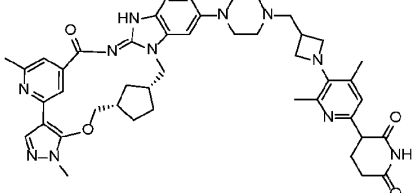
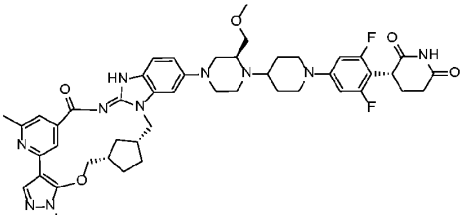
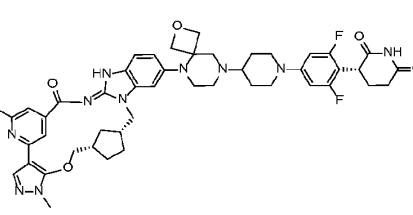
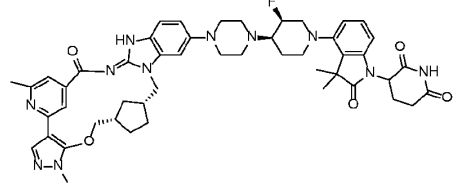
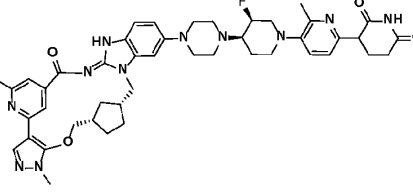
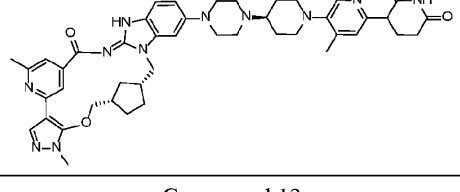
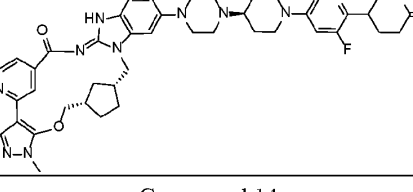
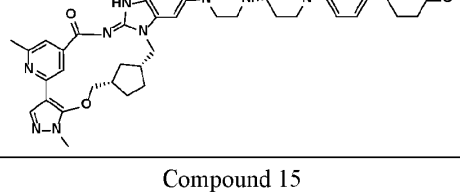
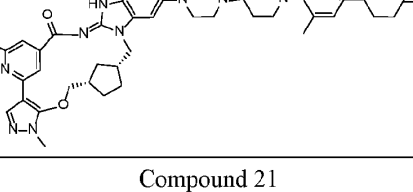
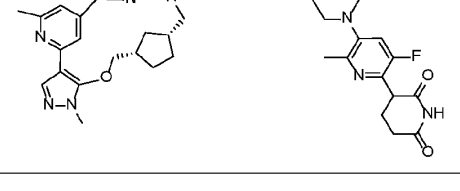
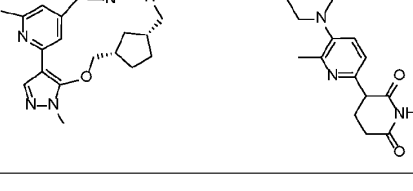
[0064] **Aspect 34.** The compound of any one of the preceding aspects, wherein Degron is

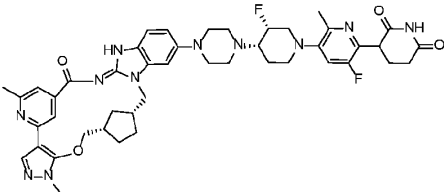
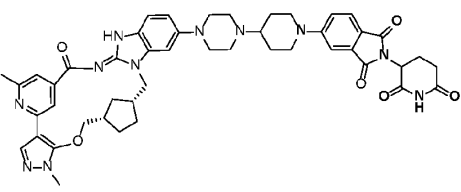
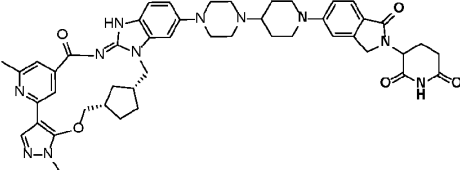
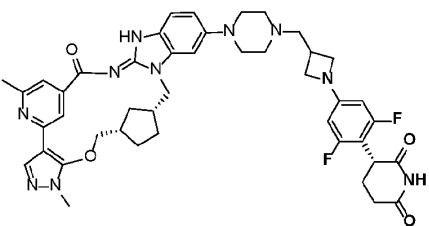
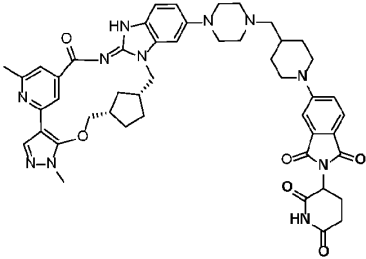
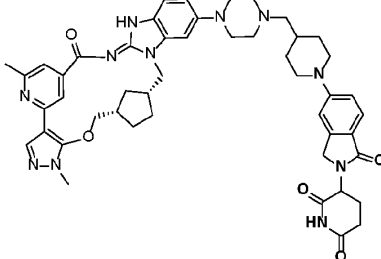
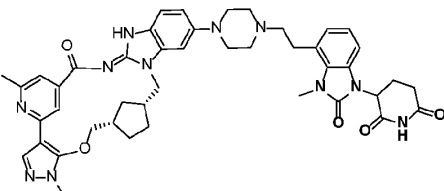
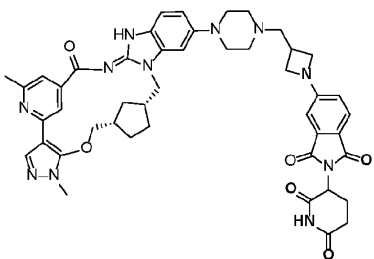
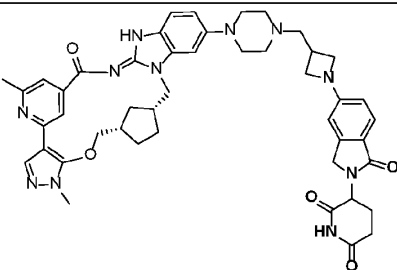
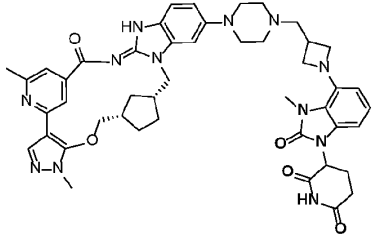


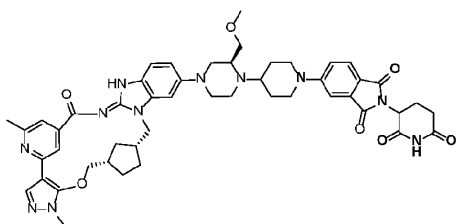


[0065] Aspect 35. The compound of any one of the preceding aspects is selected from

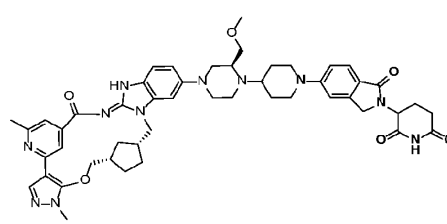
Compound 1	Compound 2
Compound 3	Compound 4
Compound 5	Compound 6

	
Compound 7	Compound 8
	
Compound 9	Compound 10
	
Compound 11	Compound 12
	
Compound 13	Compound 14
	
Compound 15	Compound 21
	

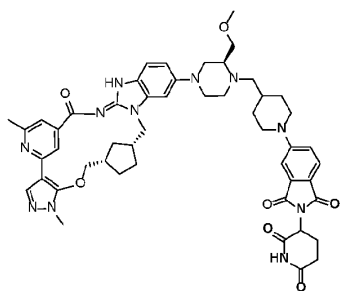
Compound 22	Compound 23
	
Compound 27	Compound 28
	
Compound 29	Compound 30
	
Compound 31	Compound 32
	
Compound 33	Compound 34
	
Compound 35	Compound 36



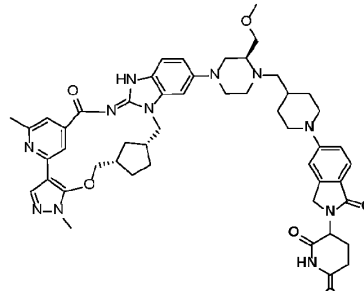
Compound 37



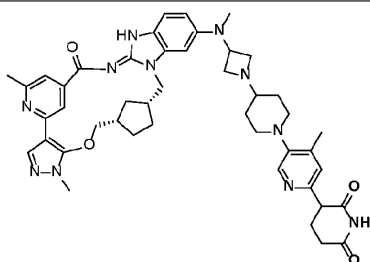
Compound 38



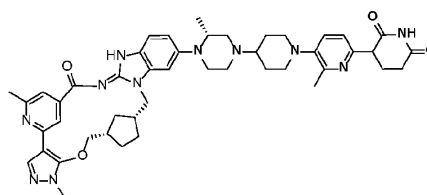
Compound 39



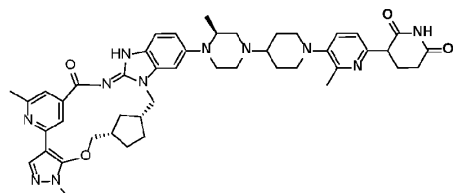
Compound 40



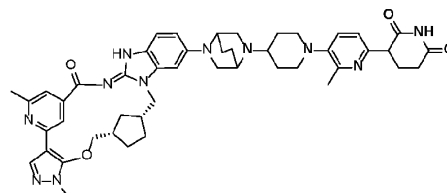
Compound 41



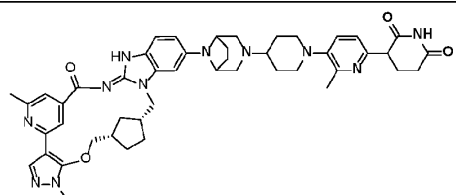
Compound 42



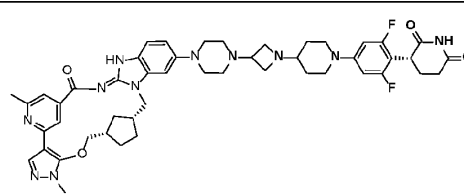
Compound 43



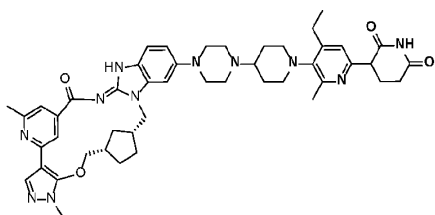
Compound 44



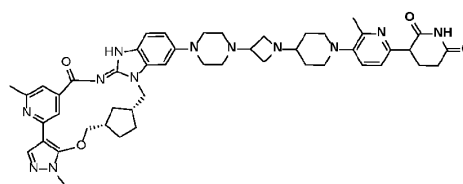
Compound 45



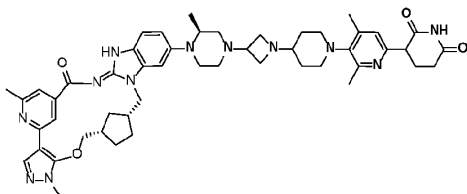
Compound 46



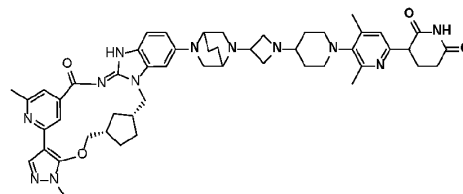
Compound 47



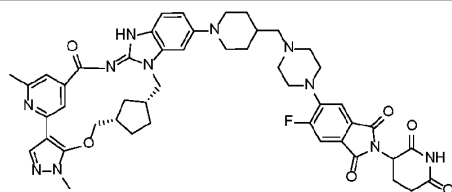
Compound 49



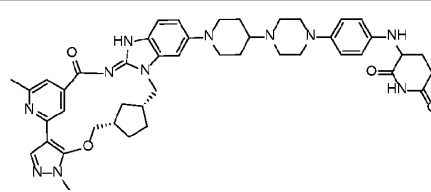
Compound 50



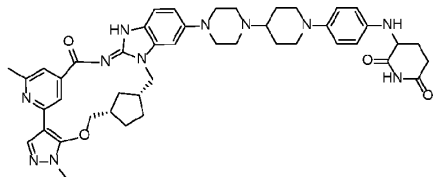
Compound 51



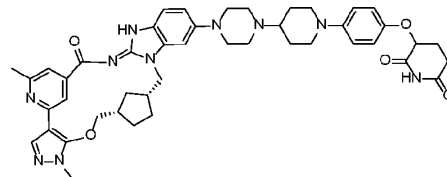
Compound 54



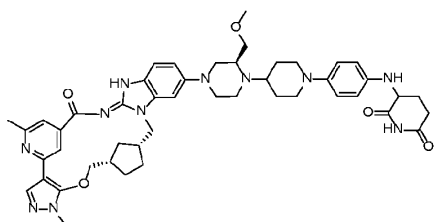
Compound 55



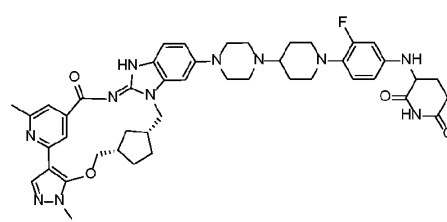
Compound 56



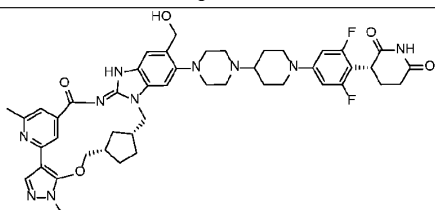
Compound 57



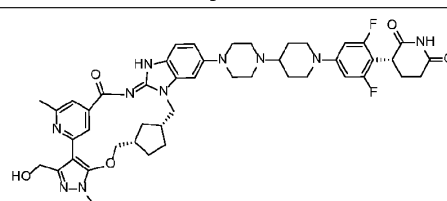
Compound 58



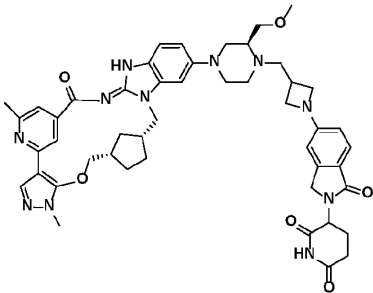
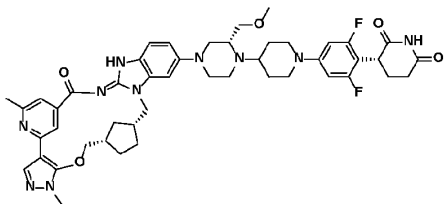
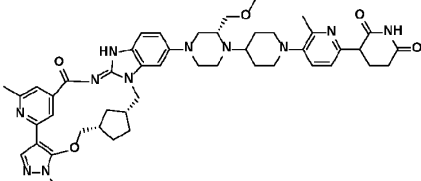
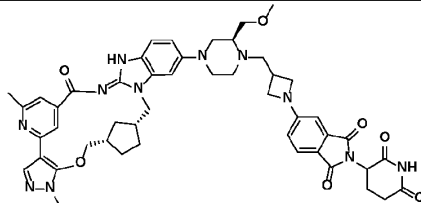
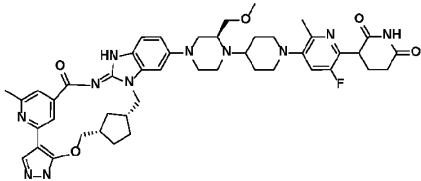
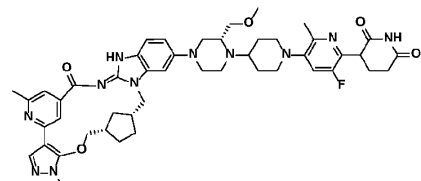
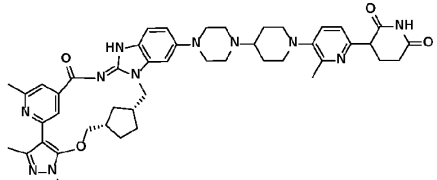
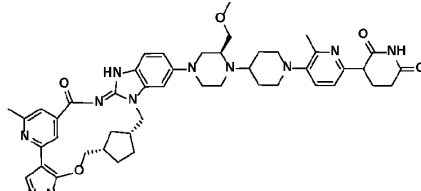
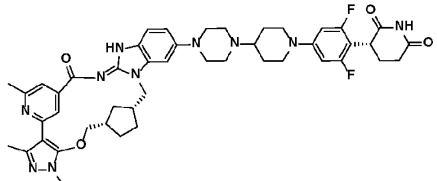
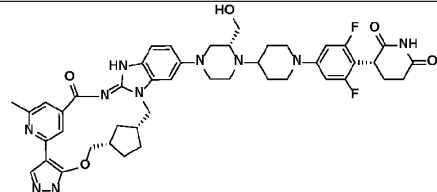
Compound 59

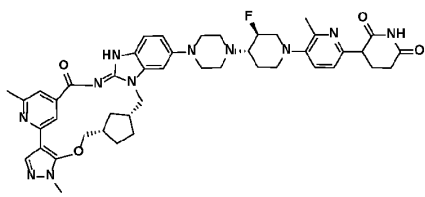
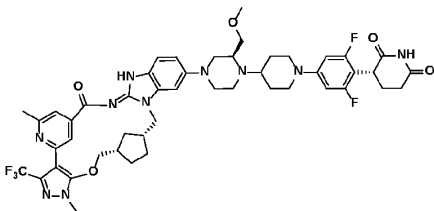
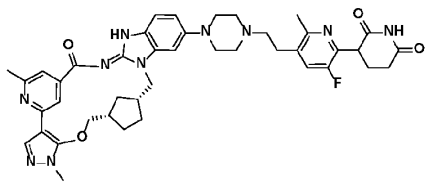
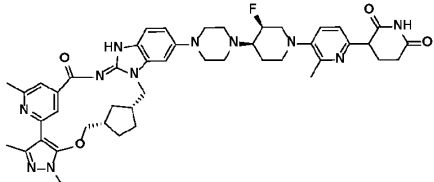
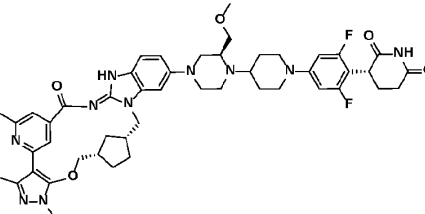
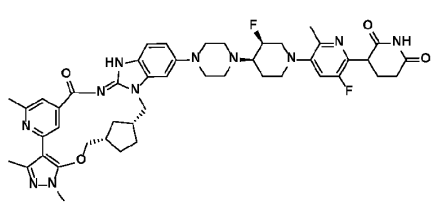
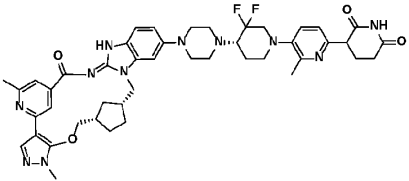
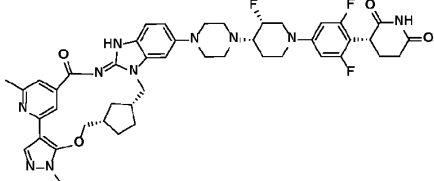
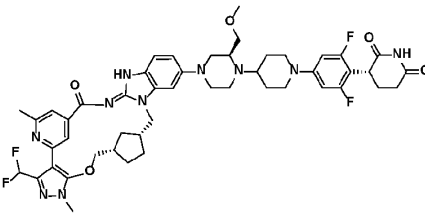
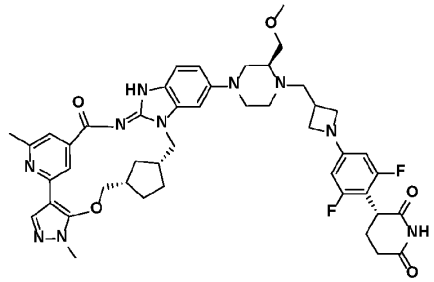


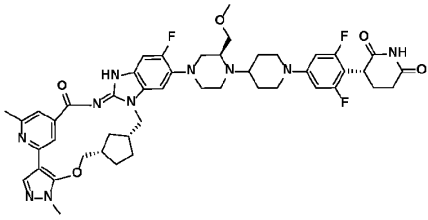
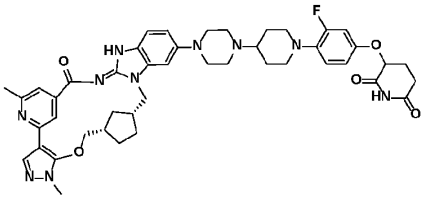
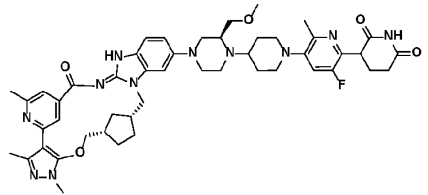
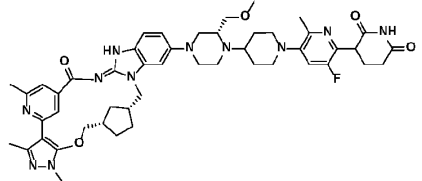
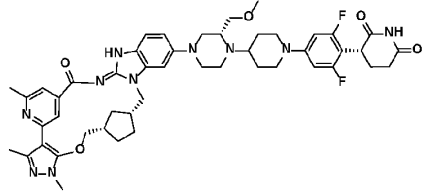
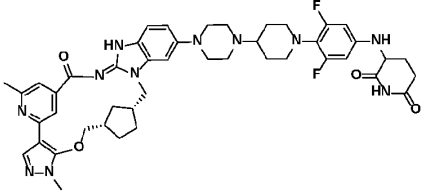
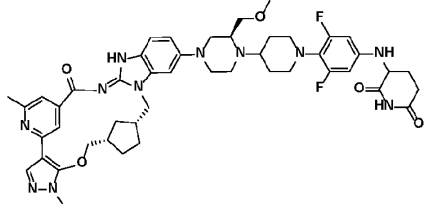
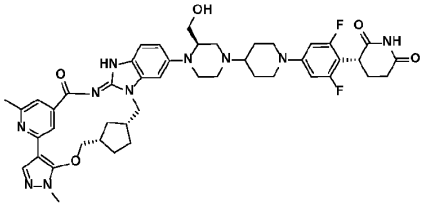
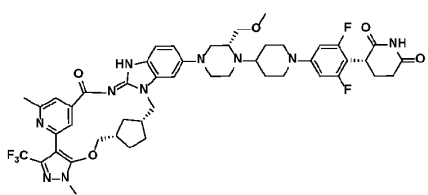
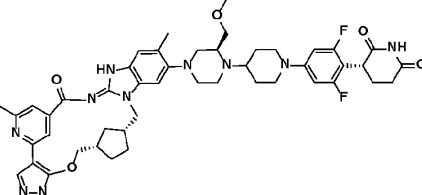
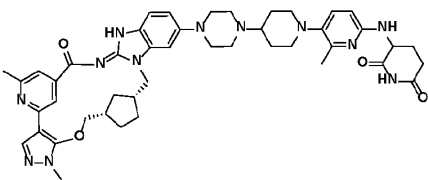
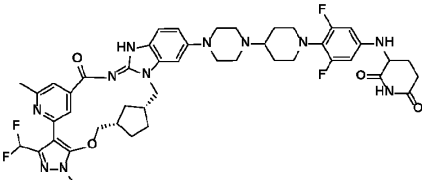
Compound 60



Compound 61

	
Compound 63	Compound 64
	
Compound 65	Compound 69
	
Compound 70	Compound 71
	
Compound 72	Compound 73
	
Compound 74	Compound 75

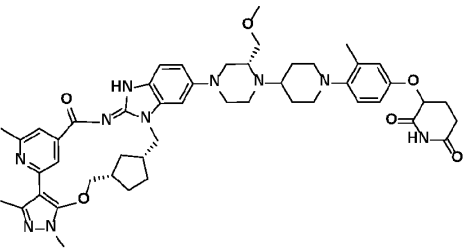
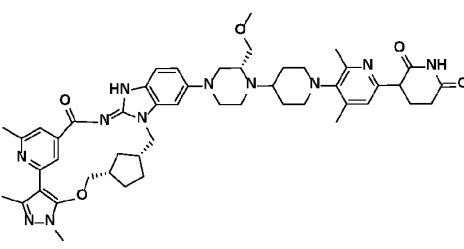
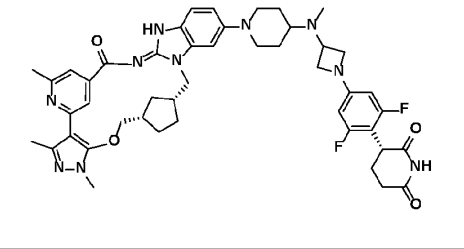
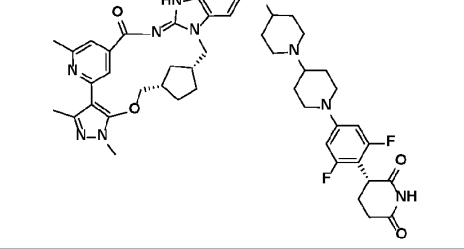
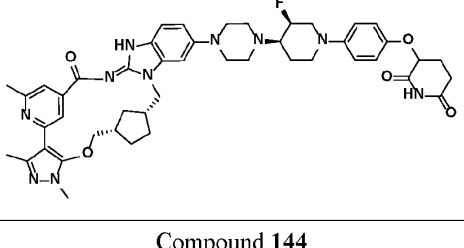
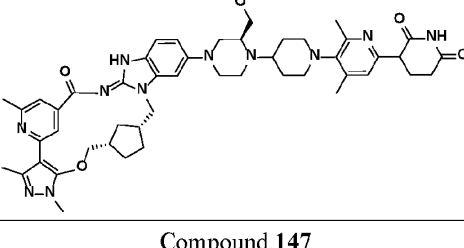
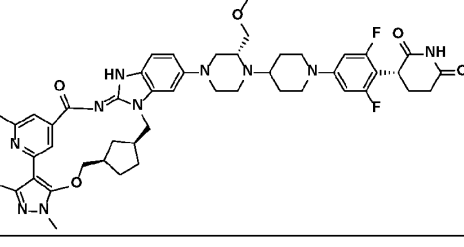
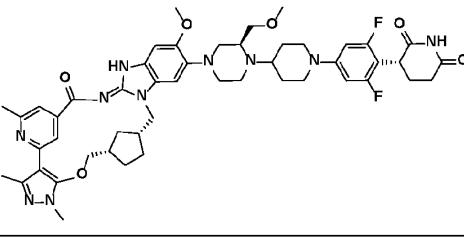
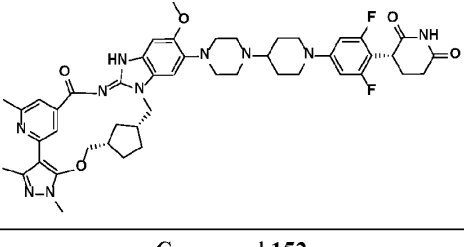
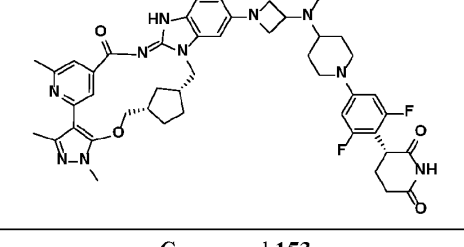
	
Compound 76	Compound 77
	
Compound 78	Compound 79
	
Compound 80	Compound 82
	
Compound 83	Compound 84
	
Compound 85	Compound 86

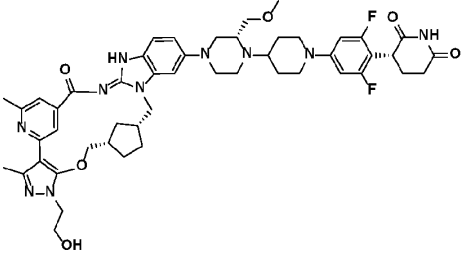
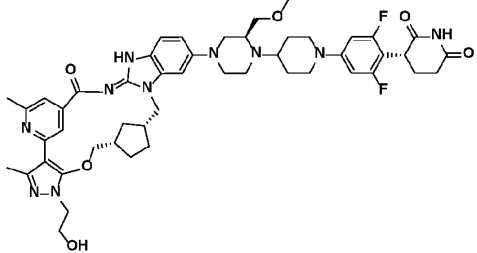
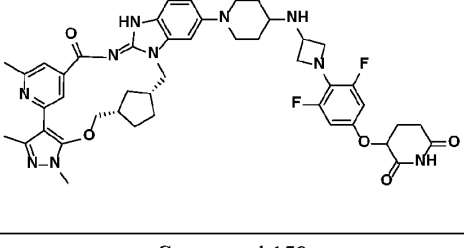
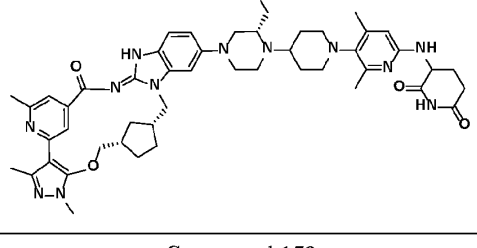
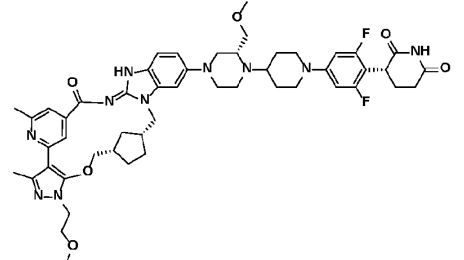
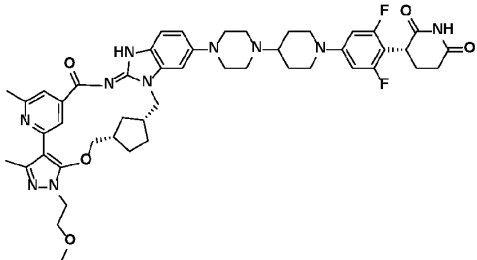
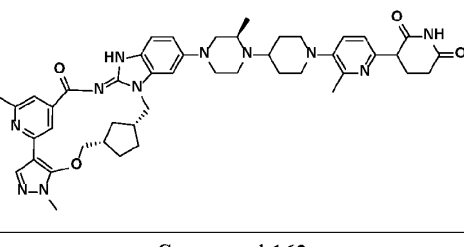
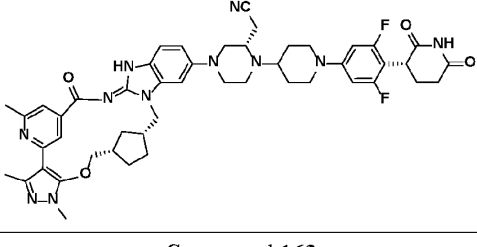
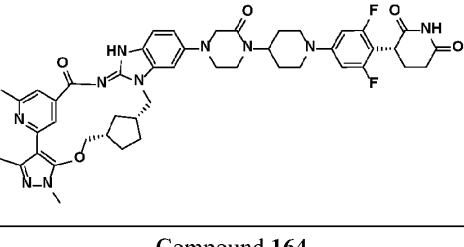
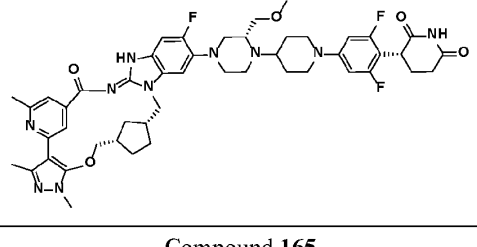
	
Compound 87	Compound 88
	
Compound 89	Compound 90
	
Compound 91	Compound 92
	
Compound 93	Compound 94
	
Compound 95	Compound 96
	

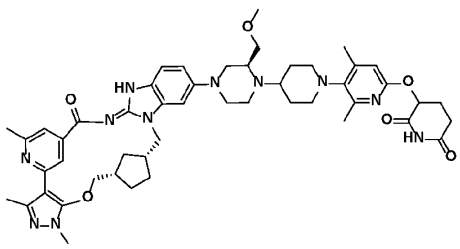
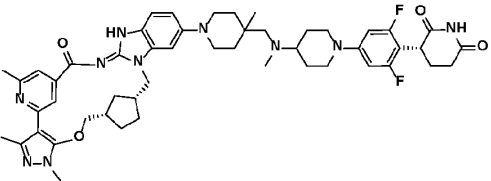
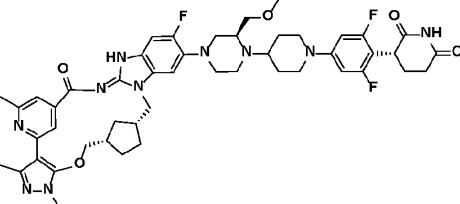
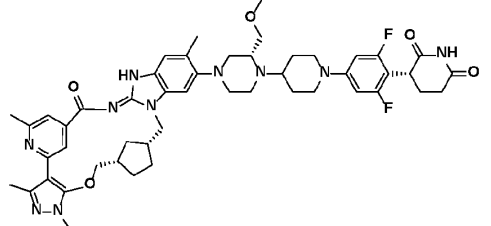
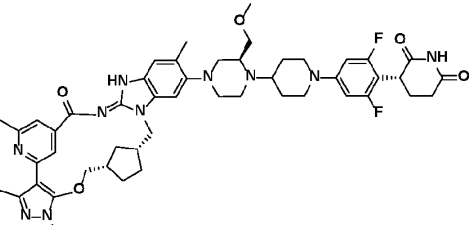
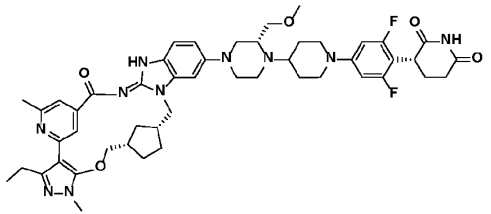
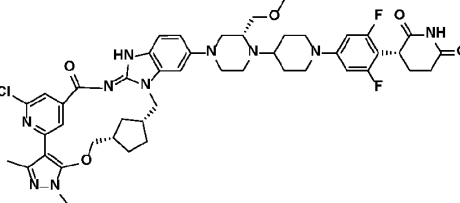
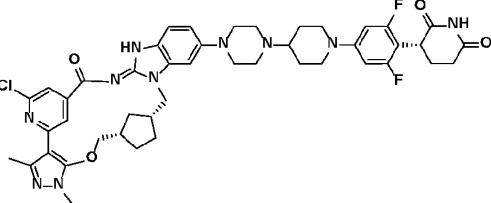
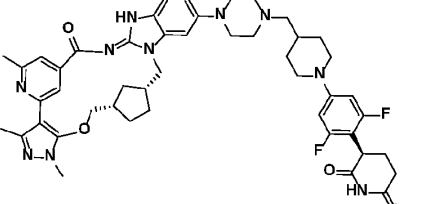
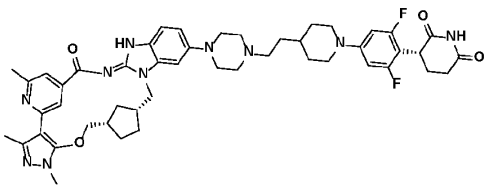
Compound 98	Compound 99
Compound 100	Compound 101
Compound 102	Compound 103
Compound 104	Compound 105
Compound 106	Compound 108
Compound 111	Compound 112
Compound 113	Compound 114

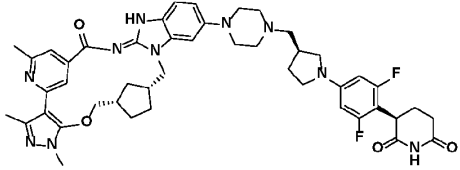
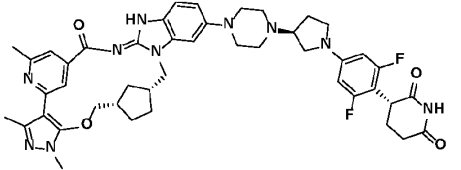
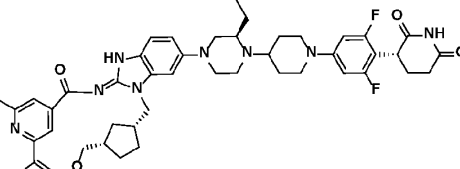
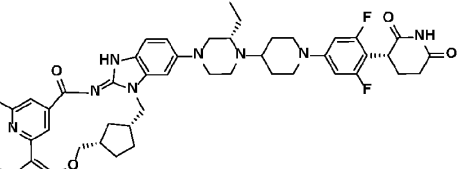
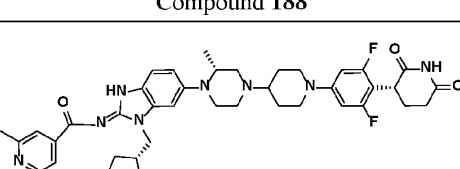
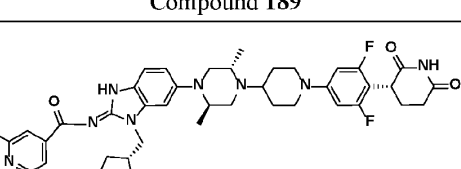
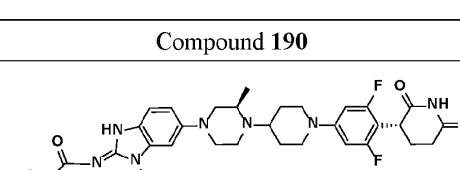
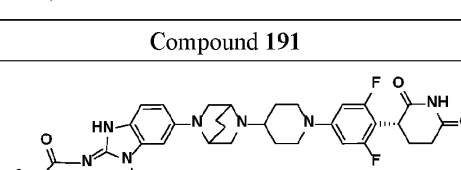
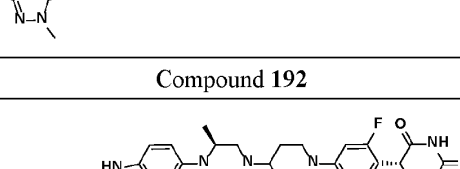
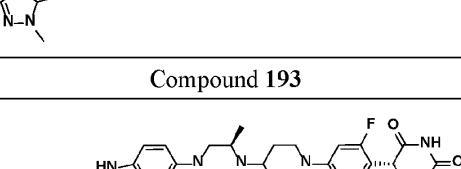
Compound 115	Compound 116
Compound 117	Compound 118
Compound 119	Compound 120
Compound 121	Compound 122
Compound 123	Compound 124

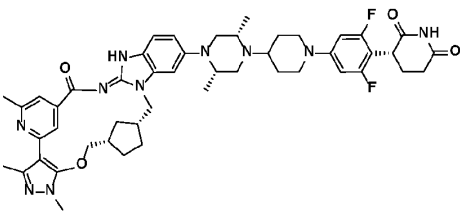
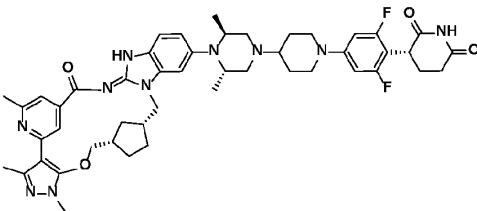
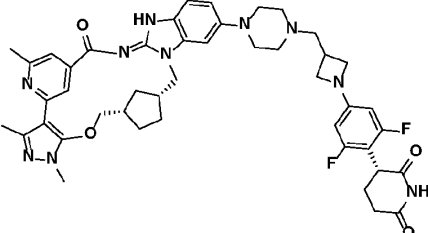
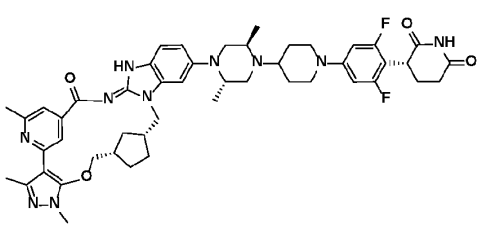
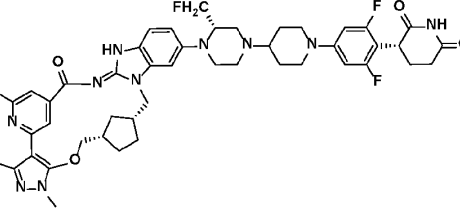
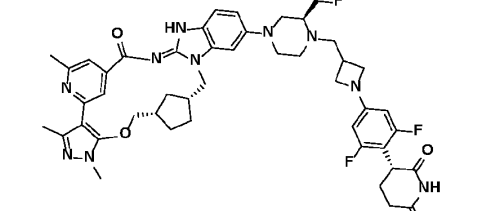
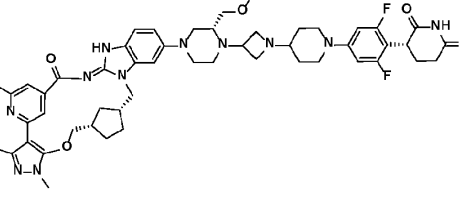
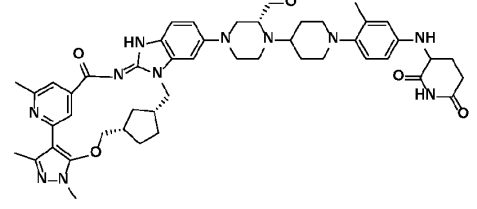
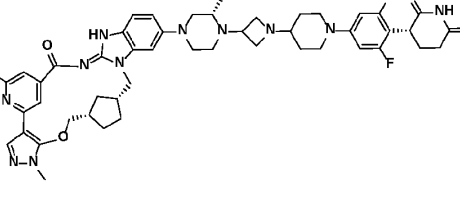
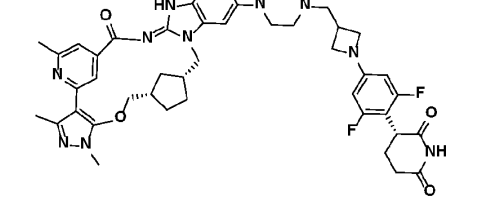
Compound 125	Compound 126
Compound 127	Compound 129
Compound 131	Compound 132
Compound 133	Compound 134
Compound 135	Compound 136
Compound 137	Compound 138

	
Compound 140	Compound 141
	
Compound 142	Compound 143
	
Compound 144	Compound 147
	
Compound 150	Compound 151
	
Compound 152	Compound 153

	
Compound 156	Compound 157
	
Compound 158	Compound 159
	
Compound 160	Compound 161
	
Compound 162	Compound 163
	
Compound 164	Compound 165

	
Compound 167	Compound 168
	
Compound 169	Compound 172
	
Compound 173	Compound 175
	
Compound 176	Compound 179
	
Compound 182	Compound 183

	
Compound 184	Compound 186
	
Compound 188	Compound 189
	
Compound 190	Compound 191
	
Compound 192	Compound 193
	
Compound 195	Compound 196

	
Compound 197	Compound 198
	
Compound 199	Compound 200
	
Compound 202	Compound 205
	
Compound 206	Compound 207
	
Compound 208	Compound 210

Compound 211	Compound 213
214	

[0066] **Aspect 36.** A pharmaceutical composition comprising a compound of any one of Aspects 1-35 or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug, together with pharmaceutically acceptable excipients.

In one embodiment, A pharmaceutical composition comprising a compound of any one of Aspects 1-35 or a pharmaceutically acceptable salt, stereoisomer, or tautomer, together with pharmaceutically acceptable excipients.

In one embodiment, A pharmaceutical composition comprising a compound of any one of Aspects 1-35 together with pharmaceutically acceptable excipients. **In one embodiment,** A pharmaceutical composition comprising a compound of any one of Aspects 1-35 or a pharmaceutically acceptable salt together with pharmaceutically acceptable excipients. **In one embodiment,** A pharmaceutical composition comprising a compound of any one of Aspects 1-35 or a pharmaceutically acceptable stereoisomer together with pharmaceutically acceptable excipients. **In one embodiment,** A pharmaceutical composition comprising a compound of any one of Aspects 1-35 or a pharmaceutically acceptable tautomer together with pharmaceutically acceptable excipients.

[0067] **Aspect 37.** A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35 or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof.

In one embodiment, A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35 or a pharmaceutically acceptable salt, stereoisomer, or a tautomer thereof.

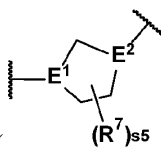
In one embodiment, A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35. **In one embodiment,** A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35 or a pharmaceutically acceptable salt thereof. **In one embodiment,** A method of treating a disease that can be

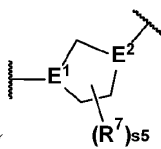
affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35 or a pharmaceutically acceptable stereoisomer thereof. **In one embodiment**, A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Aspects 1-35 or a pharmaceutically acceptable tautomer thereof.

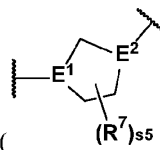
[0068] **Aspect 38.** The method of Aspect 37, wherein the disease is selected from cancer, preferred pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, or non-small cell lung cancer.

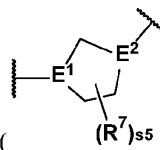
[0069] **Aspect 39.** Use of a compound of any one of Aspects 1-35 or a pharmaceutically acceptable salt, stereoisomer, tautomer or prodrug thereof in the preparation of a medicament for treating a disease that can be affected by EGFR modulation.

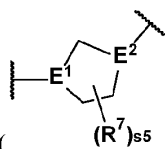
[0070] **Aspect 40.** The use of Aspect 39, wherein the disease is cancer, preferred pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, or non-small cell lung cancer.

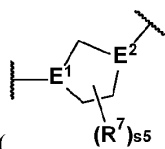


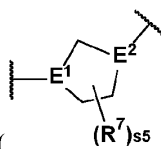
[0071] The 5-membered ring moiety (), preferably ) makes the molecules of this application have much lower toxicity than the 3- or 4- membered ring molecules. The toxicity can be tested

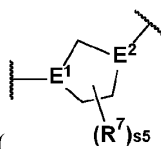


by the common methods of the field. The 5-membered ring moiety (), preferably ) makes the molecules of this application have much better activity on L858R mutation and L858R/C797S double mutation of EGFR than the 3- or 4- membered ring molecules. At the same time, the 5-membered



ring moiety (), preferably ) makes the molecules of this application have comparable or better activity on Del19 single mutation, Del19/C797S double mutation, Del19/T790M/C797S triple mutation and L858R/T790M/C797S triple mutation of EGFR with the 3- or 4- membered ring molecules. The degradation activity can be tested by the methods recorded in this



application. The 5-membered ring moiety (), preferably ) makes the molecules of this application have better rat PK than the 3- or 4- membered ring molecules.

DETAILED DESCRIPTION OF THE INVENTION

[0072] The following terms have the indicated meanings throughout the specification:

[0073] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0074] The following terms have the indicated meanings throughout the specification:

[0075] As used herein, including the appended claims, the singular forms of words such as "a", "an", and "the", include their corresponding plural references unless the context clearly indicates otherwise.

[0076] The term "or" is used to mean, and is used interchangeably with, the term "and/or" unless the context clearly dictates otherwise.

[0077] The term "alkyl" includes a hydrocarbon group selected from linear and branched, saturated hydrocarbon groups comprising from 1 to 18, such as from 1 to 12, further such as from 1 to 10, more further such as from 1 to 8, or from 1 to 6, or from 1 to 4, carbon atoms. Examples of alkyl groups comprising from 1 to 6 carbon atoms (i.e., C₁₋₆ alkyl) include, but not limited to, methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1,1-dimethylethyl or t-butyl ("t-Bu"), 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl groups.

[0078] The term "propyl" includes 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr").

[0079] The term "butyl" includes 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1,1-dimethylethyl or t-butyl ("t-Bu").

[0080] The term "pentyl" includes 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl.

[0081] The term "hexyl" includes 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl.

[0082] The term "alkylene" refers to a divalent alkyl group by removing two hydrogen from alkane. Alkylene includes but not limited to methylene, ethylene, propylene, and so on.

[0083] The term "halogen" includes fluoro (F), chloro (Cl), bromo (Br) and iodo (I).

[0084] The term "alkenyl" includes a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and from 2 to 18, such as from 2 to 8, further such as from 2 to 6, carbon atoms. Examples of the alkenyl group, e.g., C₂₋₆ alkenyl, include, but not limited to ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-dienyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups.

[0085] The term "alkenylene" refers to a divalent alkenyl group by removing two hydrogen from alkene. Alkenylene includes but not limited to, vinylidene, butenylene, and so on.

[0086] The term "alkynyl" includes a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one C≡C triple bond and from 2 to 18, such as 2 to 8, further such as from 2 to 6, carbon atoms. Examples of the alkynyl group, e.g., C₂₋₆ alkynyl, include, but not limited to ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butylnyl, 2-butylnyl, and 3-butylnyl groups.

[0087] The term "alkynylene" refers to a divalent alkynyl group by removing two hydrogen from alkyne. Alkynylene includes but not limited to ethynylene and so on.

[0088] The term "cycloalkyl" includes a hydrocarbon group selected from saturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups including fused, bridged or spiro cycloalkyl.

[0089] For example, the cycloalkyl group may comprise from 3 to 12, such as from 3 to 10, further such as 3 to 8, further such as 3 to 6, 3 to 5, or 3 to 4 carbon atoms. Even further for example, the cycloalkyl group may be selected from monocyclic group comprising from 3 to 12, such as from 3 to 10, further such as 3 to 8, 3 to 6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. In particular, examples of the saturated monocyclic cycloalkyl group, e.g., C₃₋₈cycloalkyl, include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In a preferred embodiment, the cycloalkyl is a monocyclic ring comprising 3 to 6 carbon atoms (abbreviated as C₃₋₆ cycloalkyl), including but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of the bicyclic cycloalkyl groups include those having from 7 to 12 ring atoms arranged as a fused bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. Further Examples of the bicyclic cycloalkyl groups include those arranged as a bicyclic ring selected from [5,6] and [6,6] ring systems.

[0090] The term "spiro cycloalkyl" includes a cyclic structure which contains carbon atoms and is formed by at least two rings sharing one atom.

[0091] The term "fused cycloalkyl" includes a bicyclic cycloalkyl group as defined herein which is saturated and is formed by two or more rings sharing two adjacent atoms. Examples of fused cycloalkyl, fused cycloalkenyl, or fused cycloalkynyl include but are not limited to bicyclo[1.1.0]butyl, bicyclo[2.1.0]pentyl, bicyclo[3.1.0]hexyl, bicyclo[4.1.0]heptyl, bicyclo[3.3.0]octyl, bicyclo[4.2.0]octyl, decalin, as well as benzo 3 to 8 membered cycloalkyl, benzo C₄₋₆ cycloalkenyl, 2,3-dihydro-1H-indenyl, 1H-indenyl, 1, 2, 3,4-tetralyl, 1,4-dihydronaphthyl, etc. Preferred embodiments are 8 to 9 membered fused rings, which refer to cyclic structures containing 8 to 9 ring atoms within the above examples.

[0092] The term "bridged cycloalkyl" includes a cyclic structure which contains carbon atoms and is formed by two rings sharing two atoms which are not adjacent to each other. The term "7 to 10 membered bridged cycloalkyl" includes a cyclic structure which contains 7 to 12 carbon atoms and is formed by two rings sharing two atoms which are not adjacent to each other.

[0093] The term "aryl" used alone or in combination with other terms includes a group selected from: 5- and 6-membered carbocyclic aromatic rings, e.g., phenyl; bicyclic ring systems such as 7 to 12 membered bicyclic ring systems, wherein at least one ring is carbocyclic and aromatic, e.g., naphthyl and indanyl; and tricyclic ring systems such as 10 to 15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, e.g., fluorenyl.

[0094] The terms "aromatic hydrocarbon ring" and "aryl" are used interchangeably throughout the disclosure herein. In some embodiments, a monocyclic or bicyclic aromatic hydrocarbon ring has 5 to 10 ring-forming carbon atoms (i.e., C₅₋₁₀ aryl). Examples of a monocyclic or bicyclic aromatic hydrocarbon ring include, but not limited to, phenyl, naphth-1-yl, naphth-2-yl, anthracenyl, phenanthrenyl, and the like. In some embodiments, the aromatic hydrocarbon ring is a naphthalene ring (naphth-1-yl or naphth-2-yl) or phenyl ring. In some embodiments, the aromatic hydrocarbon ring is a phenyl ring.

[0095] Specifically, the term "bicyclic fused aryl" includes a bicyclic aryl ring as defined herein. The typical bicyclic fused aryl is naphthalene.

[0096] The term "heteroaryl" includes a group selected from:

5-, 6- or 7-membered aromatic, monocyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, in some embodiments, from 1 to 2, heteroatoms, selected from nitrogen (N), sulfur (S) and oxygen (O), with the remaining ring atoms being carbon;

7- to 12-membered bicyclic rings comprising at least one heteroatom, for example, from 1 to 4, or, in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and

11- to 14-membered tricyclic rings comprising at least one heteroatom, for example, from 1 to 4, or in some embodiments, from 1 to 3, or, in other embodiments, 1 or 2, heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

[0097] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. When the heteroaryl group contains more than one heteroatom ring member, the heteroatoms may be the same or different. The nitrogen atoms in the ring(s) of the heteroaryl group can be oxidized to form N-oxides.

[0098] Specifically, the term "bicyclic fused heteroaryl" includes a 7- to 12-membered, preferably 7- to 10-membered, more preferably 9- or 10-membered fused bicyclic heteroaryl ring as defined herein. Typically, a bicyclic fused heteroaryl is 5-membered/5-membered, 5-membered/6-membered, 6-membered/6-membered, or 6-membered/7-membered bicyclic. The group can be attached to the remainder of the molecule through either ring.

[0099] "Heterocyclyl", "heterocycle" or "heterocyclic" are interchangeable and include a non-aromatic heterocyclyl group comprising one or more heteroatoms selected from nitrogen, oxygen or optionally

oxidized sulfur as ring members, with the remaining ring members being carbon, including monocyclic, fused, bridged, and spiro ring, i.e., containing monocyclic heterocyclyl, bridged heterocyclyl, spiro heterocyclyl, and fused heterocyclic groups.

[00100] The term "H" or "hydrogen" disclosed herein includes Hydrogen and the non-radioisotope deuterium.

[00101] The term "at least one substituent" disclosed herein includes, for example, from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents, provided that the theory of valence is met. For example, "at least one substituent F" disclosed herein includes from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents F.

[0100] The term "divalent" refers to a linking group capable of forming covalent bonds with two other moieties. For example, "a divalent cycloalkyl group" refers to a cycloalkyl group obtained by removing two hydrogen from the corresponding cycloalkane to form a linking group. the term "divalent aryl group", "divalent heterocyclyl group" or "divalent heteroaryl group" should be understood in a similar manner.

[0101] Compounds disclosed herein may contain an asymmetric center and may thus exist as enantiomers. "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. Where the compounds disclosed herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds disclosed herein and/or pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[0102] When compounds disclosed herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

[0103] When compounds disclosed herein contain a di-substituted cyclic ring system, substituents found on such ring system may adopt *cis* and *trans* formations. *Cis* formation means that both substituents are found on the upper side of the 2 substituent placements on the carbon, while *trans* would mean that they were on opposing sides. For example, the di-substituted cyclic ring system may be cyclohexyl or cyclobutyl ring.

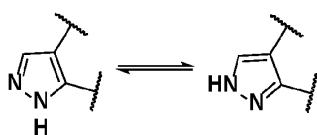
[0104] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash

chromatography. One skilled in the art could select and apply the techniques most likely to achieve the desired separation.

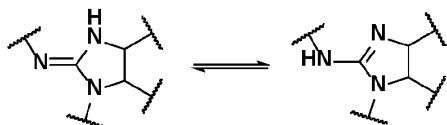
[0105] "Diastereomers" refer to stereoisomers of a compound with two or more chiral centers but which are not mirror images of one another. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0106] A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. *Stereochemistry of Organic Compounds*. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." *J. Chromatogr.*, 113(3) (1975): pp. 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: Wainer, Irving W., Ed. *Drug Stereochemistry: Analytical Methods and Pharmacology*. New York: Marcel Dekker, Inc., 1993.

[0107] Some of the compounds disclosed herein may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl $-\text{CH}_2\text{C}(\text{O})-$ groups (keto forms) may undergo tautomerism to form hydroxyl $-\text{CH}=\text{C}(\text{OH})-$ groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable. For another example, compounds including pyrazolyl may undergo tautomerism to form a different ring like below:



For another example, compounds including guanidinyll in the ring may undergo tautomerism to form a different ring like below:



[0108] "Prodrug" refers to a derivative of an active agent that requires a transformation within the body to release the active agent. In some embodiments, the transformation is an enzymatic transformation. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the active agent.

[0109] "Deuterated analog" refers to a derivative of an active agent that an arbitrary ^1H atom is substituted with deuterium. In some embodiments, the deuterated site is on the Warhead moiety. In some embodiments, the deuterated site is on the Linker moiety. In some embodiments, the deuterated site is on the Degron moiety.

[0110] "Pharmaceutically acceptable salts" refer to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A pharmaceutically acceptable salt may be prepared in situ during the final isolation and purification of the compounds disclosed herein, or separately by reacting the free base function with a suitable organic acid or by reacting the acidic group with a suitable base. The term also includes salts of the stereoisomers (such as enantiomers and/or diastereomers), tautomers and prodrugs of the compound of the invention.

[0111] In addition, if a compound disclosed herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

[0112] The terms "administration", "administering", "treating" and "treatment" herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, mean contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. The term "administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term "subject" herein includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, and rabbit) and most preferably a human.

[0113] The term "treated", "treating" or "treatment" as used herein also generally refers to the acquisition of the desired pharmacological and/or physiological effect. The effect may be prophylactic according to the prevention of the disease or its symptoms in whole or in part; and/or may be therapeutic according to the partial or complete stabilization or cure of the disease and/or the side effect due to the disease. As used herein, "treated", "treating" or "treatment" encompasses any treatment for the disease of a patient, including: (a) prevention of the disease or condition in the patient that may be predisposed to the disease or condition but has not yet been diagnosed; (b) inhibition of the symptoms of the disease, i.e., preventing its development; or (c) remission of the symptoms of the disease, i.e., causing regression of the disease or symptoms in whole or in part.

[0114] The term "effective amount" or "therapeutically effective amount" refers to an amount of the active ingredient, such as compound that, when administered to a subject for treating a disease, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment for the disease, disorder, or symptom. The term "therapeutically effective amount" can vary with the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age of the subject to be treated, and/or the weight of the subject to be treated. An appropriate amount in any given instance can be apparent to those skilled in the art or can be determined by routine experiments. In some embodiments, "therapeutically effective amount" is an amount of at least one compound and/or at least one stereoisomer, tautomer or prodrug thereof, and/or at least one pharmaceutically acceptable salt thereof disclosed herein effective to "treat" as defined herein, a disease or disorder in a subject. In the case of combination therapy, the term "therapeutically effective amount" refers to the total amount of the combination objects for the effective treatment of a disease, a disorder or a condition.

[0115] The term "disease" refers to any disease, discomfort, illness, symptoms or indications, and can be interchangeable with the term "disorder" or "condition".

[0116] Throughout this specification and the claims which follow, unless the context requires otherwise, the term "comprise", and variations such as "comprises" and "comprising" are intended to specify the presence of the features thereafter, but do not exclude the presence or addition of one or more other features. When used herein the term "comprising" can be substituted with the term "containing", "including" or sometimes "having".

[0117] Throughout this specification and the claims which follow, the term " C_{n-m} " or " C_n-C_m " indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-8} , C_{1-6} , C_1-C_8 , C_1-C_6 and the like.

[0118] Unless otherwise specified, the percentages, proportions, ratios or parts used in the present application are by weight or volume. It can be determined easily by those skilled in the art.

[0119] Hereinafter, the present application will demonstrate the beneficial effects of the present application by way of examples. Those skilled in the art will recognize that these examples are illustrative and not restrictive. These examples do not limit the scope of the present application in any way. The experimental methods described in the following examples, unless otherwise specified, are conventional methods; the reagents and materials, unless otherwise specified, are commercially available.

[0120] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

EXAMPLES

[0121] The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.), but some experimental errors and deviations should be accounted for. Unless indicated otherwise, temperature is in degrees Centigrade. Reagents were purchased from commercial

suppliers such as Sigma-Aldrich, Alfa Aesar, or TCI, and were used without further purification unless indicated otherwise. Unless indicated otherwise, the reactions set forth below were performed under a positive pressure of nitrogen or argon or with a drying tube in anhydrous solvents; the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe; and glassware was oven dried and/or heat dried.

[0122] ¹H NMR spectra were recorded on an Agilent instrument operating at 400 MHz. ¹HNMR spectra were obtained using CDCl₃, CD₂Cl₂, CD₃OD, D₂O, d₆-DMSO, d₆-acetone or (CD₃)₂CO as solvent and tetramethylsilane (0.00 ppm) or residual solvent (CDCl₃: 7.25 ppm; CD₃OD: 3.31 ppm; D₂O: 4.79 ppm; d₆-DMSO: 2.50 ppm; d₆-acetone: 2.05; (CD₃)₂CO: 2.05) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintuplet), sx (sextuplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0123] LCMS-1: LC-MS spectrometer (Agilent 1260 Infinity) Detector: MWD (190-400 nm), Mass detector: 6120 SQ Mobile phase: A: water with 0.1% Formic acid, B: acetonitrile with 0.1% Formic acid Column: Poroshell 120 EC-C18, 4.6x50 mm, 2.7µm Gradient method: Flow: 1.8 mL/min Time (min) A (%) B (%)

Time (min)	A(%)	B(%)
0.00	95	5
1.5	5	95
2.0	5	95
2.1	95	5
3.0	95	5

[0124] LCMS -2: LC-MS spectrometer (Agilent 1260 Infinity II) Detector: MWD (190-400 nm), Mass detector: G6125C SQ Mobile phase: A: water with 0.1% Formic acid, B: acetonitrile with 0.1% Formic acid Column: Poroshell 120 EC-C18, 4.6x50 mm, 2.7µm Gradient method: Flow: 1.8 mL/min Time (min) A (%) B (%)

Time (min)	A(%)	B(%)
0.00	95	5
1.5	5	95
2.0	5	95
2.1	95	5
3.0	95	5

[0125] LCMS-3: LC-MS spectrometer (Agilent 1290 Infinity II) Detector: MWD (190-400 nm), Mass detector: G6125C SQ Mobile phase: A: water with 0.1% Formic acid, B: acetonitrile with 0.1% Formic acid

Column: Poroshell 120 EC-C18, 4.6x50 mm, 2.7pm Gradient method: Flow: 1.2 mL/min Time (min) A (%)
B (%)

Time (min)	A(%)	B(%)
0.00	90	10
1.5	5	95
2.0	5	95
2.1	90	10
3.0	90	10

[0126] Preparative HPLC was conducted on a column (150 x 21.2 mm ID, 5 pm, Gemini NXC 18) at a flow rate of 20 ml/min, injection volume 2 ml, at room temperature and UV Detection at 214 nm and 254 nm.

[0127] In the following examples, the abbreviations below may be useful:

(BPin) ₂	4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane
Ac ₂ O	acetic anhydride
AcCl	Acetyl chloride
ACN or MeCN	Acetonitrile
AcOH or HOAc	Acetic acid
AcONa or NaOAc	Sodium acetate
BINAP	(±)-2,2'-Bis(diphenylphosphino)-1,1'-BINAPhthyl
Bn	benzyl
BnBr	Benzyl Bromide
Boc	t-Butyloxy carbonyl
Cbz	Benzyloxycarbonyl
DCM	Dichloromethane
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DIBAL-H	Diisobutylaluminium hydride
DIEA or DIPEA	N, N-diisopropylethylamine
DMAP	4-N, N-dimethylaminopyridine
DMP	Dess-Martin periodinane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
Dppf	1, 1''-bis(diphenylphosphino)ferrocene
EA or EtOAc	Ethyl acetate
EtOH	ethanol
FA	Formic acid

h, hr or hrs	Hour
HATU	2-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Hex	Hexane
HPLC	High Performance Liquid Chromatography
IBX	2-Iodoxybenzoic acid
IPA	2-propanol
i-PrOH	Isopropyl alcohol
KHMDS	Potassium bis(trimethylsilyl)amide
LiHMDS	Lithium bis(trimethylsilyl)amide
KOAc or AcOK	Potassium Acetate
MeCN or ACN	Acetonitrile
MeOH	Methanol
Min	Minutes
ms or MS	Mass spectrum
MsCl	Methanesulfonyl chloride
MsOH	Methanesulfonic acid
MTBE	Methyl tert-butyl ether
o/n	overnight
Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium
PE	Petroleum ether
PhMe	Toluene
PMB	4-Methoxybenzyl
PPA	Polyphosphoric acid
R.T. or r.t.	Room temperature
Rt	Retention time
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SEMCI	2-(Trimethylsilyl)ethoxymethyl chloride
STAB	Sodium Triacetoxymethylborohydride; Sodium triacetoborohydride
Sat.	saturated
SFC	Supercritical Fluid Chromatography
TBAF	Tetra-butyl ammonium fluoride
TBDPS	tert-Butyldiphenylsilyl
TBS	tert-Butyldimethylsilyl
TBSCl	tert-Butyldimethylsilyl chloride
Ti(OiPr) ₄	Titanium tetraisopropanolate

t-Bu	tert-butyl
t-BuOH	tert-Butanol
t-BuONa	Sodium tert-butoxide
t-BuOK	Potassium tert-butoxide
TEA	Triethylamine
Tf ₂ O	Triflic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSOK	Potassium trimethylsilanolate
Ts	para-Toluenesulfonyl
TsCl	4-Toluenesulfonyl chloride
TsOH	p-toluenesulfonic acid
TsOH,Py	Pyridinium toluene-4-sulphonate
Xphos or X-phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Johnphos	(2-Biphenyl)di-tert-butylphosphine
TCFH	N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate
CDI	1,1'-Carbonyldiimidazole
aq.	Aqueous
DCE	Dichloroethane
DEA	N,N-Diethylaniline
DIAD	Diisopropyl azodicarboxylate
DMA	N,N-Dimethylacetamide
DMC	Dimethyl carbonate
LCMS	Liquid Chromatography Mass Spectrometry
LDA	Lithium diisopropylamide
NCS	N-Chlorosuccinimide
NMR	Nuclear Magnetic Resonance
dtbpf	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
Pd(dtbpf)Cl ₂	[1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene]dichloropalladium(II)
Pd-PEPPSI-IPentCl	[1,3-bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-imidazol-2-ylidene]-dichloro-(3-chloropyridin-1-ium-1-yl)palladium
PPh ₃	triphenylphosphine
PPh ₃ O	Triphenylphosphine oxide
Prep-HPLC	Preparative-scale High-Performance Liquid Chromatography
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl

RuPhos Pd G3	Methanesulfonato(2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II)
T ₃ P	Propylphosphonic anhydride
9-BBN	9-borabicyclo[3.3.1]nonane
CAN	Ammonium cerium(IV) nitrate
DEA	Diethylamine
Del19	exon 19 deletion
DIAD	Diisopropyl azodicarboxylate
DMA	N,N-Dimethylacetamide
FBS	Fetal bovine serum
HTRF	Homogeneous Time Resolved Fluorescence
LDA	Lithium diisopropylamide
Ms	Mesylate
MtBE	tert-Butyl methyl ether
NCS	N-Chlorosuccinimide
NMP	1-Methyl-2-Pyrrolidone
NMR	Nuclear Magnetic Resonance
Pd(PPh ₃) ₂ Cl ₂	Bis(triphenylphosphine)palladium(II) dichloride
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
Pd-PEPPSI-IPentCl	[1,3-bis[2,6-bis(1-propylbutyl)phenyl]-4,5-dichloro-imidazol-2-ylidene]-dichloro-(3-chloropyridin-1-ium-1-yl)palladium
Pd-Ruphos-G3 or Pd-G3 RuPhos or RuPhos Pd G3	(2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate
PE	Petroleum ether
PPh ₃	Triphenylphosphine
Prep-SFC	preparative supercritical fluid chromatography
PS	Penicillin-Streptomycin Solution
RT	room temperature
Ruphos	{2-[2,6-bis(propan-2-yloxy)phenyl]phenyl}dicyclohexylphosphane
t-BuONO	tert-Butyl nitrite

General Synthesis for the intermediates

[0128] Compounds disclosed herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

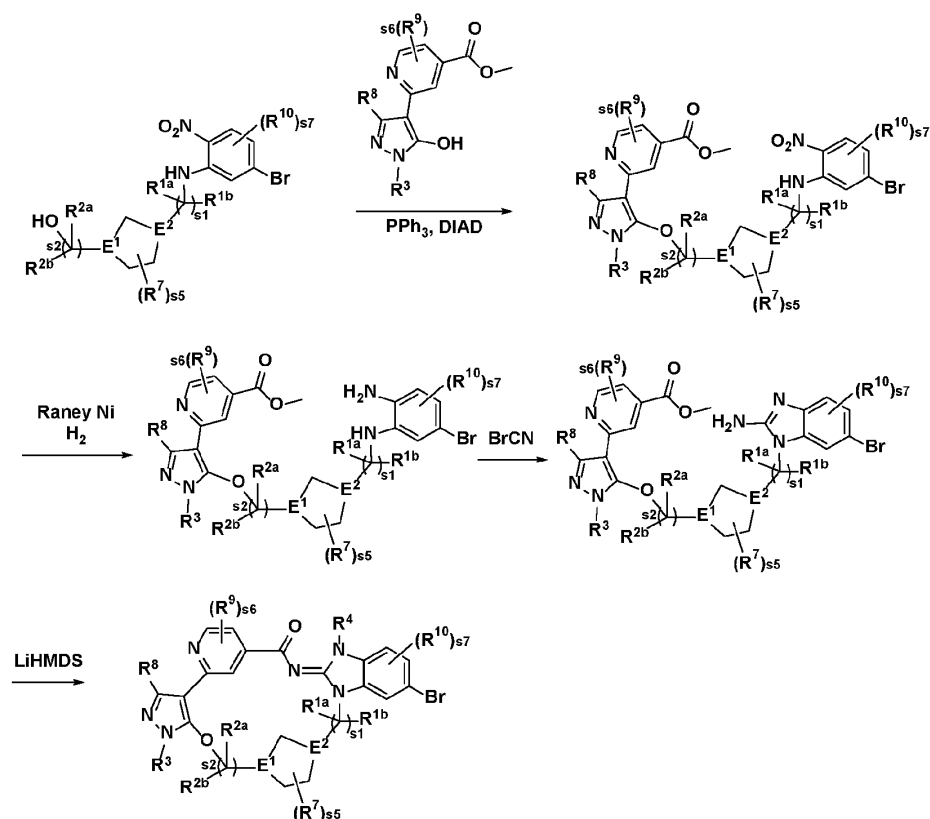
[0129] The reaction for preparing compounds disclosed herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials, the intermediates, or products at the temperatures at which the

reactions are carried out, e.g., temperatures which can range from the solvent's boiling temperature. A given reaction can be carried out in one solvent or mixture of solvents.

[0130] The selection of appropriate protecting group, can be readily determined by one skilled in the art. In the synthesis schemes, some protection/deprotection steps are not shown and can be incorporated before, after or in between any steps. The protecting group shown in the synthesis schemes may or may not be used based on reaction conditions. The sequences of reactions may vary and provide similar results.

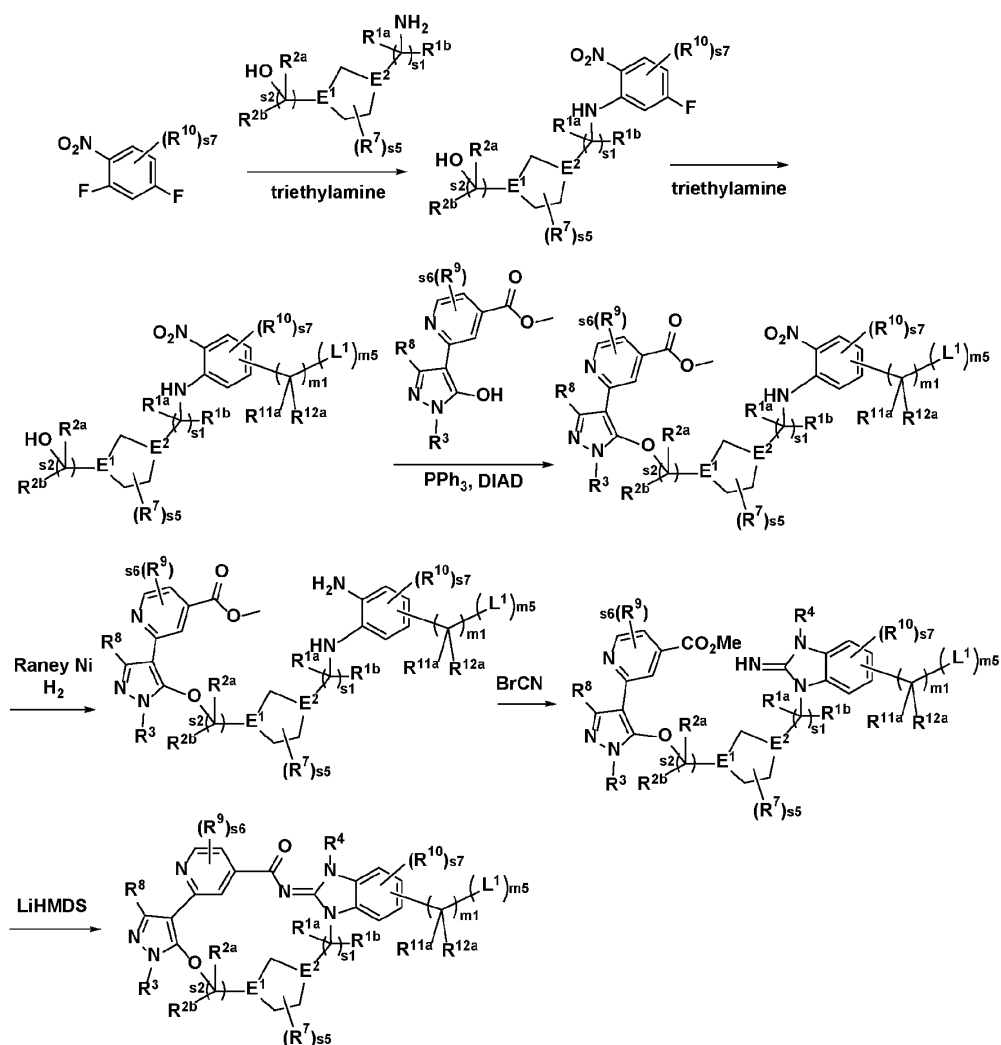
[0131] Reactions can be monitored according to any suitable method known in the art, such as NMR, UV, HPLC, LC-MS and TLC. Compounds can be purified by a variety of methods, including prep-HPLC and silica gel chromatography. Unless specified, prep-HPLC uses a buffered acetonitrile/water systems and silica gel chromatography (including column chromatography and prep-TLC) uses PE/EtOAc, EtOAc/MeOH or DCM/MeOH systems as mobile phases. NMR spectra are recorded using a Bruker or Varian instrument with preset pulse sequences.

Scheme I: General route 1



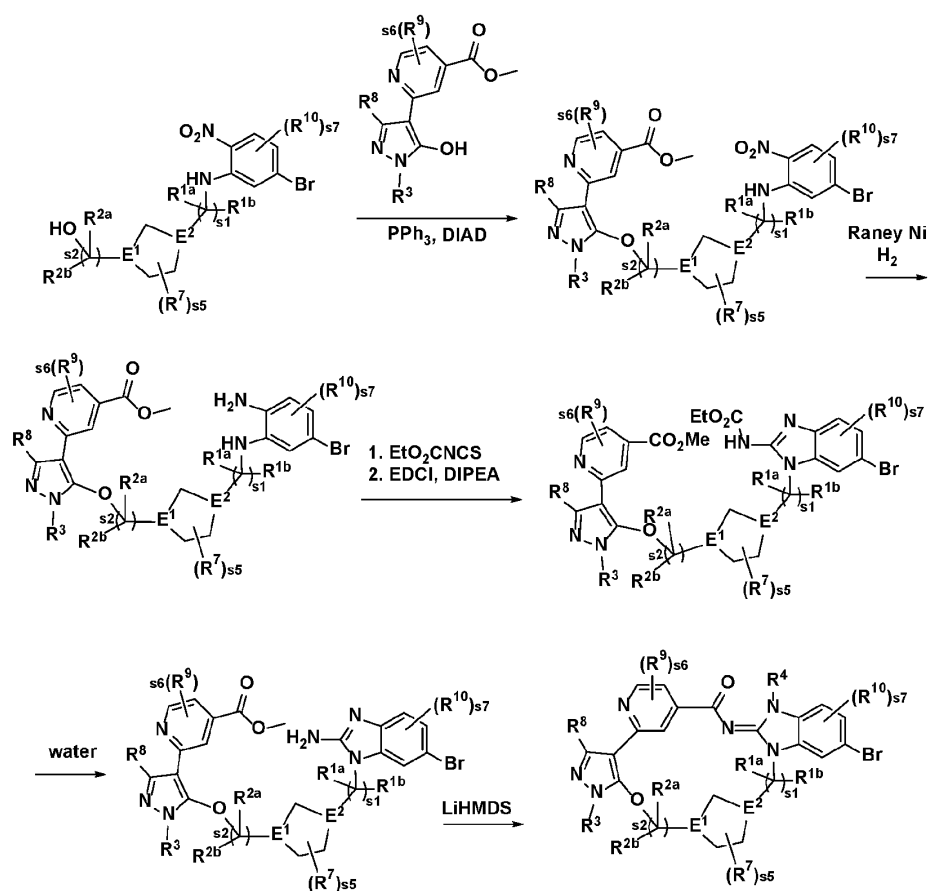
Intermediates can be synthesized through General route 1, such as Intermediate 1, 57 or 75.

Scheme II: General route 2



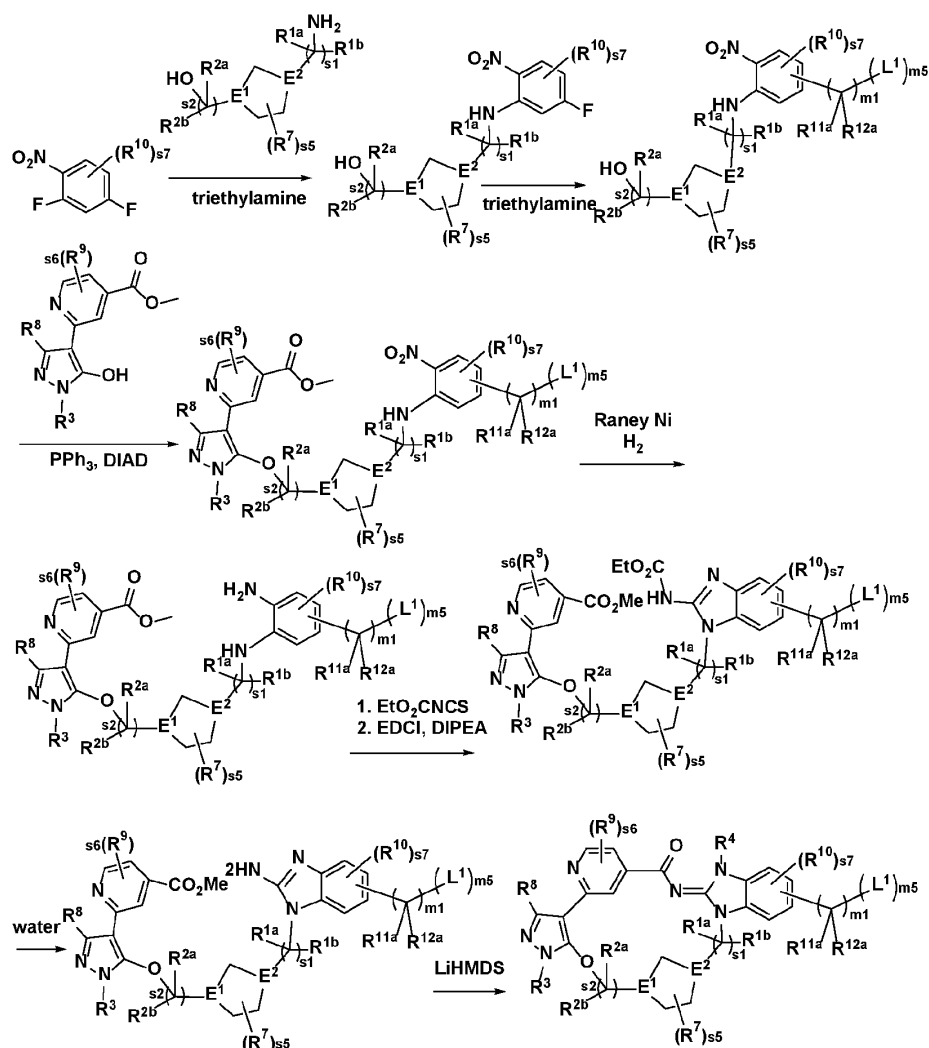
Intermediates can be synthesized through General route 2, such as Intermediate 135.

Scheme III: General route 3



Intermediates can be synthesized through General route 3, such as Intermediate 134.

Scheme IV: General route 4

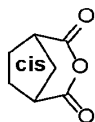


Intermediates can be synthesized through General route IV, such as Intermediate 137.

Intermediate synthesis

[0132] Intermediate 1: (7¹R,7³S,E)-5⁶-bromo-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

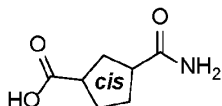
[0133] Step1: 3-oxabicyclo[3.2.1]octane-2,4-dione



A 2 L round bottom flask equipped with a magnetic stirrer were charged with *cis*-cyclopentane-1,3-dicarboxylic acid (100 g, 633 mmol) and Ac₂O (600 ml). The mixture was stirred for 12 hours at 140 °C. The mixture was concentrated under reduced pressure. The residue was triturated with PE to afford the crude

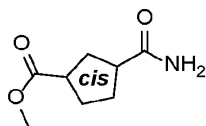
product (70 g, 496.4 mmol, 78.5%). ^1H NMR (400 MHz, DMSO) δ 3.18 (q, $J = 3.9$ Hz, 2H), 2.35 (d, $J = 12.4$ Hz, 1H), 2.17 – 2.01 (m, 2H), 1.90 (t, $J = 7.5$ Hz, 2H), 1.69 (dt, $J = 12.4, 4.2$ Hz, 1H).

[0134] Step 2: *cis*-3-carbamoylcyclopentane-1-carboxylic acid



A 2 L round bottom flask equipped with a magnetic stirrer were charged with (1R,5S)-3-oxabicyclo[3.2.1]octane-2,4-dione (70 g, 496.4 mmol), THF (700 ml) and $\text{NH}_3\text{-MeOH}$ 7M (4 eq) at 0 °C. The mixture was stirred for 12 hours at RT. The residue was quenched by MeOH (500 ml) at 0 °C. The mixture was concentrated under reduced pressure to afford crude product (56 g, 354.4 mmol, 74.4%). $[\text{M}+\text{H}]^+ = 158$.

[0135] Step 3: methyl *cis*-3-carbamoylcyclopentane-1-carboxylate



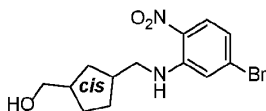
A 1 L round bottom flask equipped with a magnetic stirrer, were charged with *cis*-3-carbamoylcyclopentane-1-carboxylic acid (56 g, 354.4 mmol) and MeOH (600 mL). The temperature was lowered to 0 °C, and H_2SO_4 (34.7 g, 354 mmol) was added dropwise into the mixture while maintaining temperature at 0 °C. The resulting mixture was stirred at RT for 12 hrs. The mixture was concentrated under reduced pressure to afford crude product (49 g, 284.8 mmol, 80.3%). $[\text{M}+\text{H}]^+ = 172$.

[0136] Step 4: ((*cis*)-3-(aminomethyl)cyclopentyl)methanol



A 1 L round bottom flask equipped with a magnetic stirrer, were charged with methyl *cis*-3-carbamoylcyclopentane-1-carboxylate (49 g, 284.8 mmol) and THF (500 mL). The temperature was lowered to 0 °C, and $\text{BH}_3\text{-THF}$ (1140 ml, 1140 mmol) was added dropwise into the mixture while maintaining temperature at 0 °C. The resulting mixture was stirred at RT for 24 hrs. The residue was quenched by MeOH (500 ml) at 0 °C. The mixture was concentrated under reduced pressure to afford crude product (35 g, 269.2 mmol, 79.5%). $[\text{M}+\text{H}]^+ = 130$.

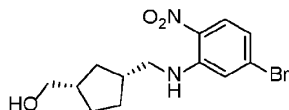
[0137] Step 5: (((*cis*)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methanol



A 1 L round bottom flask equipped with a magnetic stirrer, were charged with (((*cis*)-3-(aminomethyl)cyclopentyl)methanol (35 g, 269.2 mmol), 4-bromo-2-fluoro-1-nitrobenzene (64.8 g, 295.9 mmol), DIEA (104.2 g, 807.8 mmol), and DMSO (500 mL). The mixture was stirred at 80 °C under N_2 for 4 hrs. After cooled to room temperature, the mixture was poured into EA (500 mL), and washed with brine (200 mL), water (3' 200 mL), brine (200 mL) in turn, then dried over anhydrous Na_2SO_4 , concentrated in vacuum.

The residue was purified by column chromatography (EA/PE, 24%) to afford the title product (20 g, 60.8 mmol, 22.6%). $[M+H]^+ = 329$.

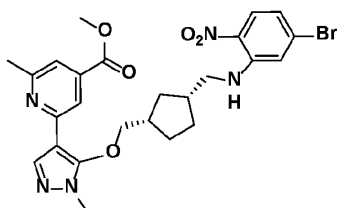
[0138] Step 6: ((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methanol



The crude product (20 g) was purified by Prep-SFC with the following conditions ((Lux 3u Cellulose-3 4.6*50 mm, 3 μ m), Temperature: 35 $^{\circ}$ C, Flow (mL/min): 4, solvent A: CO₂, solvent B: IPA (0.5% 2 mM NH₃-MeOH), gradient (B%): 10% to 50% in 2.0 min, hold 1.0 min at 50%, retention time 0.971 min) to afford ((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methanol (5.6 g, 28.1%, ee=96.08%). $[M+H]^+ = 329$. The crude product could also be purified by chiral HPLC with the following conditions: column (chiralpak IC-3 4.6 x 50 mm, 3 mm), mobile phase (Hex (0.1% DEA): EtOH = 80:20), flow 1.0 mL/min, temp 25 $^{\circ}$ C, retention time 2.836 min.

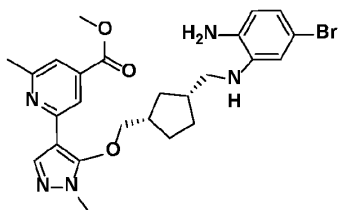
¹H NMR (300 MHz, DMSO-d₆) δ 8.14 (t, $J = 5.6$ Hz, 1H), 7.98 (d, $J = 9.1$ Hz, 1H), 7.27 (d, $J = 2.1$ Hz, 1H), 6.83 (dd, $J = 9.1, 2.0$ Hz, 1H), 4.45 (t, $J = 5.3$ Hz, 1H), 4.34 (s, 1H), 3.43 (s, 1H), 2.23 (dt, $J = 15.3, 7.5$ Hz, 1H), 2.11 – 1.83 (m, 2H), 1.81 – 1.54 (m, 1H), 1.45 – 1.20 (m, 2H), 1.06 (t, $J = 7.0$ Hz, 2H), 1.00 – 0.71 (m, 1H).

[0139] Step 7: methyl 2-(5-(((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methoxy))-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate



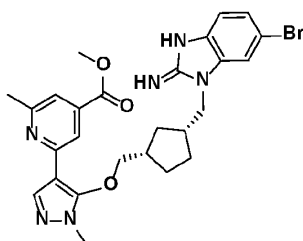
To a stirred solution of ((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methanol (5.1 g, 15.5 mmol), methyl 2-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (4.2 g, 17.0 mmol), and PPh₃ (4.9 g, 18.6 mmol) in THF (100 mL) was added DIAD (3.8 g, 18.6 mmol). Then the mixture was stirred for 2 h at room temperature. Then the mixture was concentrated and purified by silica gel column chromatography, eluted with EtOAc/PE (0-80%) to afford the product mixed with PPh₃O (9.3 g); $[M+H]^+ = 558.3$.

[0140] Step 8: methyl 2-(5-(((1S,3R)-3-(((2-amino-5-bromophenyl)amino)methyl)cyclopentyl)methoxy))-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate



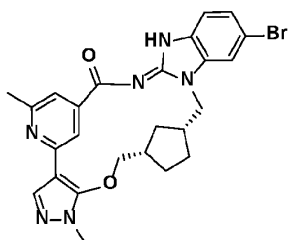
To a stirred solution of methyl 2-(5-(((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (9.3 g, 16.7 mmol) in THF (100 mL) was added Raney nickel (4.5 g). The resulting mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 2 hr. Then the mixture was filtered and the filtrate was concentrated. The resulting mixture (8.4 g) was used for next step without purification. $[M+H]^+ = 528.3$.

[0141] Step 9: methyl 2-(5-(((1S,3R)-3-(((6-bromo-2-imino-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate



A solution of methyl 2-(5-(((1S,3R)-3-(((2-amino-5-bromophenyl)imino)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (8.4 g, 15.9 mmol) and BrCN (2.5 g, 23.8 mmol) in MeOH (50 mL) was stirred for 4 h at room temperature. Then the mixture was concentrated and diluted with DCM (200 mL), and then washed with sat. aq. NaHCO_3 (3 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-15%) to afford the product (7.1 g, 80.7%); $[M+H]^+ = 553.4$.

[0142] Step 10: (7¹R,7³S,E)-5⁶-bromo-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

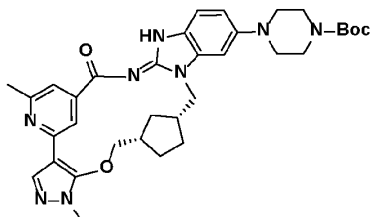


To a stirred solution of methyl 2-(5-(((1S,3R)-3-(((6-bromo-2-imino-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (3.2 g, 5.8 mmol) in 80 mL THF was added LiHMDS (1N in THF, 14.5 mL) at room temperature for 15 min. The resulting mixture was stirred at room temperature for 1 hr. Then the mixture was diluted with EA (100 mL), washed with sat. aq. NH_4Cl (2 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and

concentrated under reduced pressure. The residue was suspended in 100 mL EA and stirred at room temperature for 1 h. Then the mixture was filtered to afford the product (2.6 g, 86.2%); $[M+H]^+ = 521.2$.

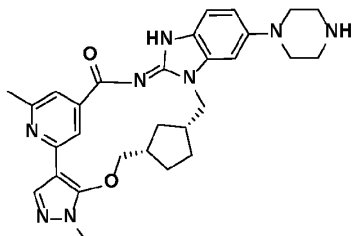
[0143] Intermediate 2: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

[0144] Step 1: tert-butyl 4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate



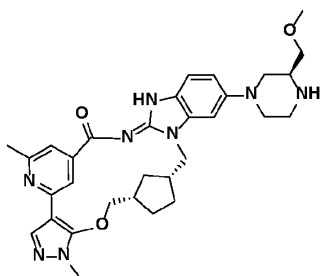
The solution of intermediate 1 (1.0 g, 1.92 mmol), tert-butyl piperazine-1-carboxylate (535 mg, 2.88 mmol), Pd₂(dba)₃ (360 mg, 0.4 mmol), Ruphos (360 mg, 0.8 mmol) and NaO^tBu (550 mg, 5.75 mmol) in DMA (30 mL) was stirred at 100 °C for 2 hrs. The reaction was concentrated in vacuo, the residue was purified by silica gel column (DCM:CH₃OH=15:1) to afford tert-butyl 4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate (1.0 g, 83.2%). $[M+H]^+ = 627$.

[0145] Step 2: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



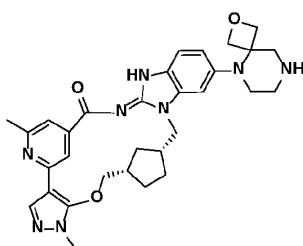
To a mixture of tert-butyl 4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate (1.0 g, 1.6 mmol) in DCM (20 mL) was added TFA (7 mL). The reaction mixture was stirred at r.t for 2 hrs, and the resulting mixture was concentrated in vacuum. The residue was treated with sat. aq. NaHCO₃ to pH=7-8, then extracted with DCM:MeOH(10:1) (100 mL x 3). The combined organic phase was washed with brine (80 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to afford (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one (700 mg, 83.3%). $[M+H]^+ = 527$.

[0146] Intermediate 3: (7¹R,7³S,E)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



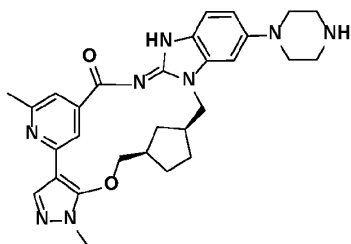
The title compound was prepared in a manner similar to that in Intermediate 2. $[M+H]^+ = 571.5$

[0147] Intermediate 4: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazolo-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in Intermediate 2. $[M+H]^+ = 569.5$

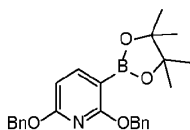
[0148] Intermediate 5: (7¹S,7³R,E)-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazolo-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+ = 527.5$

[0149] Intermediate 6: 2,6-bis(benzyloxy)-3-(4-bromo-2,6-difluorophenyl)pyridine

Step 1: 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

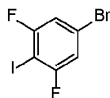


4 reactions were carried out in parallel.

To a solution of 2,6-dibenzyloxy-3-bromo-pyridine (2.00 kg, 5.40 mol, 1.00 eq) in dioxane (12.0 L) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (760 g, 5.94 mol, 862 mL, 1.10 eq) and TEA (1.09 kg, 10.8 mol, 1.50 L, 2.00 eq), degassed and purged with N₂, then Pd(PPh₃)₂Cl₂ (189 g, 270 mmol, 0.05 eq) was added to the mixture. The mixture was stirred at 90 °C for 16 hrs. The reaction mixture was filtered and concentrated. 4 reactions were combined. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl

acetate = 1/0 to 0/1). 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.80 kg, 13.9 mol, 64.3% yield) was obtained. $[M+H]^+ = 418.3$

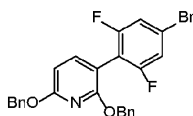
[0150] Step 2: 5-bromo-1,3-difluoro-2-iodobenzene



5 reactions were carried out in parallel.

To a solution of 1-bromo-3,5-difluoro-benzene (1.00 kg, 5.18 mol, 595 mL) in THF (4.00 L) was added LDA (2 M, 2.59 L) at -70 °C. The mixture was stirred at -70 °C for 1 hr. Then to the mixture was added solution of I₂ (1.33 kg, 5.23 mol, 1.05 L) in THF (1.00 L) at -70 °C. The mixture was stirred at -70 °C for 1 hr. The reaction mixture was poured into H₂O (5.00 L), extracted with EtOAc (3.00 L x 2), 5 reactions were combined, the combined organic layers were washed by brine (5.00 L), dried over Na₂SO₄, filtered and concentrated in vacuum at 40 °C to give a residue. The crude product was triturated with petroleum ether (6.00 L). Compound 5-bromo-1,3-difluoro-2-iodobenzene (4.50 kg, 14.1 mol, 54.4% yield) was obtained. $[M+H]^+ = 318.8$.

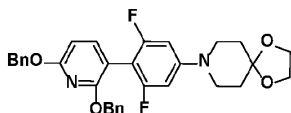
[0151] Step 3: 2,6-bis(benzyloxy)-3-(4-bromo-2,6-difluorophenyl)pyridine



To a solution of 5-bromo-1,3-difluoro-2-iodobenzene (4.50 kg, 14.1 mol) and 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.89 kg, 14.1 mol) in dioxane (22.5 L) and H₂O (4.50 L) was added Pd(PPh₃)₄ (1.63 kg, 1.41 mol), K₃PO₄ (8.99 kg, 42.3 mol). The mixture was stirred at 90 °C for 12 hrs. The mixture was filtered and filtrate was extracted with EtOAc (5.00 L), the combined organic was washed with brine (5.00 L), dried over Na₂SO₄, concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether : Ethyl acetate = 1 : 0 to 1 : 1). Compound 2,6-bis(benzyloxy)-3-(4-bromo-2,6-difluorophenyl)pyridine (3.00 kg, 6.01 mol, 42.5% yield, 96.5% purity) was obtained. ¹H NMR (400 MHz, CHLOROFORM-d) 7.47 - 7.40 (m, 1H), 7.39 - 7.34 (m, 2H), 7.34 - 7.29 (m, 2H), 7.29 - 7.25 (m, 4H), 7.25 - 7.17 (m, 2H), 7.12 - 7.05 (m, 2H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.32 (s, 2H), 5.28 (s, 2H); $[M+H]^+ = 482.1$.

[0152] Intermediate 7: (R)-3-(2,6-difluoro-4-(4-oxopiperidin-1-yl)phenyl)piperidine-2,6-dione

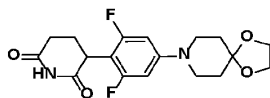
[0153] Step 1: 8-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)-1,4-dioxo-8-azaspiro[4.5]decane



To the solution of intermediate 6 (30 g, 62.24 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (10.68 g, 74.69 mmol) and Cs₂CO₃ (40.58 g, 124.48 mmol) in 500 mL dioxane, Pd₂(dba)₃ (2.85 g, 3.11 mmol) and Xantphos (3.6 g, 6.22 mmol) was added at N₂ atmosphere. The mixture was stirred at 80°C for 16 hours under N₂ protected. The mixture was diluted with EtOAc and filtered. The filtrate was concentrated in vacuum and purified by

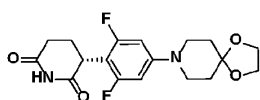
silica column chromatography (EA:PE=0-80%) to afford the crude product. The crude was recrystallized with MeOH and filtered. The filter cake was dried to afford the title compound (26.8 g, 79% yield); $[M+H]^+ = 544.9$.

[0154] Step 2: 3-(2,6-difluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione



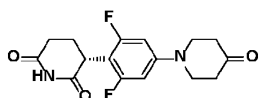
To the solution of 8-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)-1,4-dioxo-8-azaspiro[4.5]decane (26.8 g, 49.26 mmol) in 400 mL DMF and 80 mL iPrOH, Pd/C (27 g, 10 wt. %, wet) was added. The mixture was stirred at 45°C for 16 hours at H₂ atmosphere (4 bar). The mixture was filtered and the filter cake was washed with DMF. The combined liquid was concentrated in vacuum to afford the title compound (15 g, 83.2% yield); $[M+H]^+ = 367.1$.

[0155] Step 3: (R)-3-(2,6-difluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione



The title compound was purified by chiral HPLC (CHIRALPAK IF (2*25cm, 5μm), MtBE(0.1%DEA):(MeOH:DCM=1:1)=50:50, 100 bar, 20 ml/min) and the title compound corresponded to peak A @ 0.990 min/254 nm (4.47 g, 37% yield from 12 g racemate); $[M+H]^+ = 367.1$.

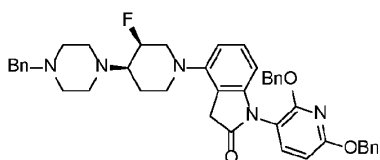
[0156] Step 4: (R)-3-(2,6-difluoro-4-(4-oxopiperidin-1-yl)phenyl)piperidine-2,6-dione



(R)-3-(2,6-difluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)piperidine-2,6-dione (1 g, 2.73 mmol) was placed in 100 mL round bottom flask with a magnetic stir bar. Then, 10 mL 8N HCl aqueous was added. The mixture was stirred at room temperature for 30 minutes. The mixture was added dropwise to sat. aq. NaHCO₃ solution and finally pH=6-7. The liquid was extracted with DCM and separated. The organic phase was concentrated in vacuum and purified with silica gel column chromatography (MeOH:DCM=0-5%) to afford the title compound (850 mg, 96.7% yield); $[M+H]^+ = 323.1$.

[0157] Intermediate 9: 3-(4-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

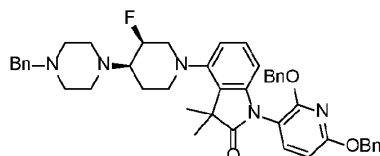
[0158] Step 1: 4-((3S,4R)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-1-(2,6-bis(benzyloxy)pyridin-3-yl)indolin-2-one



The solution of 1-(2,6-bis(benzyloxy)pyridin-3-yl)-4-bromoindolin-2-one (1 g, 2 mmol, see step 2 in intermediate 10 synthesis), 1-benzyl-4-((3S,4R)-3-fluoropiperidin-4-yl)piperazine (831 mg, 3 mmol, prepared in a manner similar to that in intermediate 20), ^tBuONa (576 mg, 6 mmol), Pd-PEPPSI-IPentCl

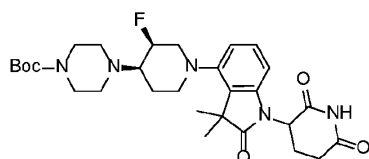
(195 mg, 0.2 mmol) in DMA (15 mL) was degassed under reduced pressure and purged with N₂ for five times, and stirred under N₂ at 90 °C for 1 hour. After cooled to rt, the mixture was diluted with DCM (100 mL), then filtered through a pad of celite. The filtrate was washed with brine (150 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by silica column chromatography (EA/PE, 40%) to afford product (810 mg, 60%). [M+H]⁺ = 698.3.

[0159] Step 2: 4-((3S,4R)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-1-(2,6-bis(benzyloxy)pyridin-3-yl)-3,3-dimethylindolin-2-one



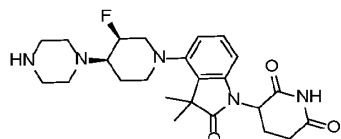
4-((3S,4R)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-1-(2,6-bis(benzyloxy)pyridin-3-yl)indolin-2-one (697 mg, 1 mmol) in DMF (10 mL) and stirred under N₂ at 0 °C. NaH (100 mg, 2.5 mmol, 60% in oil) added at this temperature. After 30 min CH₃I (355 mg, 2.5 mmol) was added and stirred under N₂ at room temperature for 1 hour. To this reaction solution was quenched with 20 mL water, it was extracted with DCM. The organic layer was washed with brine, saturated aqueous sodium thiosulfate and water, dried over anhydrous sodium sulfate. It was filtered and the resulting residue was concentrated, it was purified by using column chromatography (EA/PE, 40%) to afford product (500 mg, 69%). [M+H]⁺ = 726.5.

[0160] Step 3: tert-butyl 4-((3S,4R)-1-(1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-4-yl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate



Under N₂, to a solution of 4-((3S,4R)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-1-(2,6-bis(benzyloxy)pyridin-3-yl)-3,3-dimethylindolin-2-one (726 mg, 1 mmol) in DMF/PrOH (5 mL/5 mL) was added 10% Pd/C (100 mg) and (Boc)₂O at room temperature. And then the mixture was exchanged with H₂ two times and stirred under H₂ atmosphere at 50 °C for 15 hours. The mixture was filtered through a pad of Celite and washed with MeOH (50 mL). The filtrate was concentrated under vacuum to obtain the product (500 mg, 90%); [M+H]⁺ = 558.5.

[0161] Step 4: 3-(4-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione

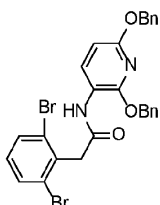


To a solution of tert-butyl 4-((3S,4R)-1-(1-(2,6-dioxopiperidin-3-yl)-3,3-dimethyl-2-oxoindolin-4-yl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate (279 mg, 0.5 mmol) in DCM (3 mL) was added TFA (1 mL).

The reaction was stirred at room temperature for 2 hours and then concentrated in vacuo. The residue was dissolved in DCM (20 mL), washed with sat. NaHCO₃ solution (3 x 20 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the product (180 mg, 78.6%); [M+H]⁺ = 458.5.

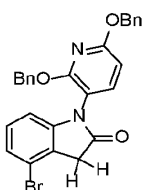
[0162] Intermediate 10: 3-(3,3-dimethyl-2-oxo-4-(4-oxopiperidin-1-yl)indolin-1-yl)piperidine-2,6-dione

[0163] Step 1: N-(2,6-bis(benzyloxy)pyridin-3-yl)-2-(2,6-dibromophenyl)acetamide



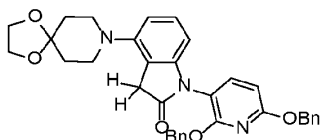
To a solution of 2-(2,6-dibromophenyl)acetic acid (10 g, 34.2 mmol), 2,6-bis(benzyloxy)pyridin-3-amine (11.5 g, 37.6 mmol), DIEA (13.3 g, 102.6 mmol) in DMF (200 ml), were added HATU (19.5 g, 51.3 mmol) at 0 °C. The mixture was stirred at RT overnight. The mixture was diluted with EA (500 mL) and then get solid filter. The mixture was concentrated under reduced pressure to afford crude product (15 g, 75.7%). [M+H]⁺ = 581.

[0164] Step 2: 1-(2,6-bis(benzyloxy)pyridin-3-yl)-4-bromoindolin-2-one



A 500 mL round bottom flask equipped with a magnetic stirrer, were charged with N-(2,6-bis(benzyloxy)pyridin-3-yl)-2-(2,6-dibromophenyl)acetamide (15 g, 25.9 mmol), ((2-bromoethoxy)methyl)benzene (15.4 g, 71.5 mmol), K₂CO₃ (17.8 g, 129.5mmol), CuCl (2.56 g, 25.9 mmol), pentane-2,4-dione (5.17 g, 51.8 mmol) and NMP (200 mL). The mixture was degassed under vacuum and purged with N₂ for three times. The resulting mixture was stirred for 3 hours at 85 °C under N₂. After cooled to rt, the mixture was diluted with ethyl acetate (300 mL), then filtered through a pad of celite. The filtrate was washed with brine (300 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by silica column chromatography (EA/PE, 15%) to afford product (8.00 g, 61.8%). [M+H]⁺ = 501.

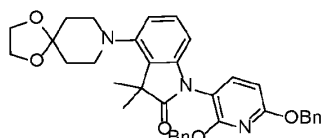
[0165] Step 3: 1-(2,6-bis(benzyloxy)pyridin-3-yl)-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)indolin-2-one



The solution of 1-(2,6-bis(benzyloxy)pyridin-3-yl)-4-bromoindolin-2-one (8 g, 15.9 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (3.43 g, 23.9 mmol), Cs₂CO₃ (15.62 g, 47.7 mmol), Pd-PEPPSI-IPentCl (0.67 g, 0.80

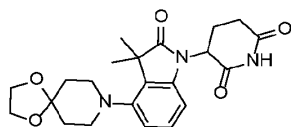
mmol) in dioxane (120 mL) was degassed under reduced pressure and purged with N₂ for five times, and stirred under N₂ at 100 °C overnight. After cooled to rt, the mixture was diluted with ethyl acetate (100 mL), then filtered through a pad of celite. The filtrate was washed with brine (150 mL), dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The residue was purified by silica column chromatography (EA/PE, 40%) to afford product (2 g, 22.2%). [M+H]⁺ = 564.

[0166] Step 4: 1-(2,6-bis(benzyloxy)pyridin-3-yl)-3,3-dimethyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)indolin-2-one



The solution of 1-(2,6-bis(benzyloxy)pyridin-3-yl)-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)indolin-2-one (2 g, 3.55 mmol) and NaH (0.71 g, 17.75 mmol) in DMF (20 mL) was stirred at 0 °C for 30 min. Then CH₃I (2.5 g, 17.75 mmol) was added dropwise into the mixture while maintaining temperature at 0 °C. The resulting mixture was stirred at RT for 4 hrs. The mixture was poured into EA (20 mL), and washed with brine (20 mL), water (3 × 20 mL), brine (20 mL) in turn, then dried over anhydrous Na₂SO₄, concentrated in vacuum. The residue was purified by silica column chromatography (EA/PE, 15%) to afford product (1.5 g, 71.4%). [M+H]⁺ = 592.

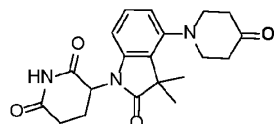
[0167] Step 5: 3-(3,3-dimethyl-2-oxo-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)indolin-1-yl)piperidine-2,6-dione



A 100 mL round bottom flask equipped with a magnetic stirrer were charged with 1-(2,6-bis(benzyloxy)pyridin-3-yl)-3,3-dimethyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)indolin-2-one (1.5 g, 2.53 mmol), DCM/ETOH (10 mL/20 mL), and Pd/C (10 wt%, 1.5 g). The resulting mixture was degassed under reduced pressure and purged with H₂ for five times, then stirred at RT for overnight. The mixture was diluted with DCM/MEOH (50 mL/50 mL), then sonicated in an ultrasonic washer for 5 minutes, followed by filtration through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by silica column chromatography (PE/EA=1:1) to afford product (560.1 mg, 53.6%). [M+H]⁺ = 414.

¹H NMR (300 MHz, DMSO) δ 11.05 (s, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.21 (s, 1H), 3.93 (s, 4H), 3.32 (s, 2H), 2.87 (t, *J* = 5.5 Hz, 5H), 1.94 (s, 1H), 1.86 – 1.71 (m, 4H), 1.40 (s, 6H).

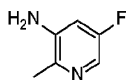
[0168] Step 6: 3-(3,3-dimethyl-2-oxo-4-(4-oxopiperidin-1-yl)indolin-1-yl)piperidine-2,6-dione



The compound was prepared in a procedure similar to that in intermediate 7 step 4.

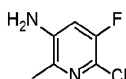
[0169] **Intermediate 11:** 2',6'-bis(benzyloxy)-3-fluoro-5-iodo-6-methyl-2,3'-bipyridine

[0170] Step 1: 5-fluoro-2-methylpyridin-3-amine



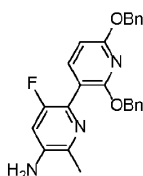
To a solution of 2-bromo-5-fluoropyridin-3-amine (20 g, 105.26 mmol) in dioxane/H₂O (200/40 mL) were added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (15.91 g, 126.32 mmol), Pd(dppf)Cl₂ (8.59 g, 10.53 mmol), and K₂CO₃ (43.57 g, 315.79 mmol). The resulting solution was stirred overnight at 120°C under N₂ atmosphere. After cooled to room temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0~10%) to afford 5-fluoro-2-methylpyridin-3-amine (12 g, 90.1%). [M+H]⁺ = 127.1

[0171] Step 2: 6-chloro-5-fluoro-2-methylpyridin-3-amine



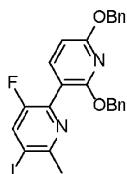
To a stirred mixture of 5-fluoro-2-methylpyridin-3-amine (6 g, 47.62 mmol) in DMF (120 mL) were added NCS (8.43 g, 47.62 mmol) at 0°C. The mixture was stirred overnight at 60°C. After cooled to room temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EA/PE (0~50%) to afford 6-chloro-5-fluoro-2-methylpyridin-3-amine (3 g, 39.5%). [M+H]⁺ = 161.0.

[0172] Step 3: 2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-amine



To a solution of 6-chloro-5-fluoro-2-methylpyridin-3-amine (3 g, 18.63 mmol) in dioxane/H₂O (30/5 mL) were added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (9.32 g, 22.36 mmol), Pd(dppf)Cl₂ (1.52 g, 1.86 mmol), and K₂CO₃ (7.71 g, 55.89 mmol). The resulting solution was stirred overnight at 100 °C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product was purified by silica column chromatography (EA/PE = 0-50%) to afford 2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-amine (5 g, 64.3 %). [M+H]⁺ = 416.2

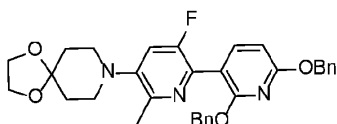
[0173] Step 4: 2',6'-bis(benzyloxy)-3-fluoro-5-iodo-6-methyl-2,3'-bipyridine



To a solution of 2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-amine (3 g, 7.23 mmol) in ACN (30 mL) were added KI (6 g, 36.14 mmol), CuI (1.65 g, 8.67 mmol), and t-BuONO (3.72 g, 36.14 mmol). The resulting solution was stirred overnight at 80 °C under N₂ atmosphere. After cooling to rt, the mixture was diluted with H₂O and extracted with EtOAc. The combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product purified by silica column chromatography (EA/PE = 0-15%) to afford 2',6'-bis(benzyloxy)-3-fluoro-5-iodo-6-methyl-2,3'-bipyridine (2.5 g, 65.79 %). [M+H]⁺ = 527.1

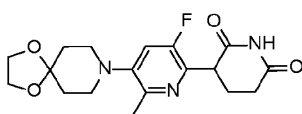
[0174] **Intermediate 12:** 3-(3-fluoro-6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione

[0175] Step 1: 8-(2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane



A mixture of intermediate 11 (5.2 g, 9.89 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (2.11 g, 14.83 mmol), Ruphos (0.94 g, 0.20 mmol), Pd₂(dba)₃ (0.9 g, 0.99 mmol), and Cs₂CO₃ (9.7 g, 29.66 mmol) in 1,4-dioxane (50 mL) was stirred for 8 h at 100 °C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc, the combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product was purified by silica column chromatography (EA/PE = 0-30%) to afford 8-(2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (4.5 g, 85.0 %). [M+H]⁺ = 542.0

[0176] Step 2: 3-(3-fluoro-6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione

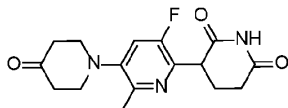


To a stirred solution of 8-(2',6'-bis(benzyloxy)-3-fluoro-6-methyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (4.5 g, 8.31 mmol) in THF (100 mL) was added Pd/C (10 wt%, 4.5 g). The resulting mixture was degassed under reduced pressure and purged with H₂ for five times, then stirred overnight at rt. The resulting mixture was filtered, and the filter cake was washed with THF. The filtrate was concentrated under reduced pressure. And the residue was purified by column chromatography (EA/PE, 30-50%) to afford 3-(3-fluoro-6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione (3.53 g, 9.8 mmol, 83.0%).

¹H NMR (300 MHz, DMSO) δ 10.86 (s, 1H), 7.35 (d, *J* = 12 Hz, 1H), 4.13 (m, 1H), 3.32 (s, 1H), 2.94 (t, *J* =

6 Hz, 4H), 2.71 (m, 1H), 2.62 – 2.50 (m, 1H), 2.37 (d, $J = 3$ Hz, 3H), 2.26 – 2.15 (m, 1H), 2.03 (m, 1H), 1.78 (t, $J = 6$ Hz, 4H), 1.36 (s, 1H), 1.22 (d, $J = 12$ Hz, 1H), 0.99 – 0.80 (m, 1H).

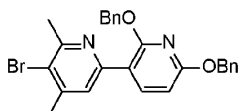
[0177] Step 3: 3-(3-fluoro-6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The compound was prepared in a procedure similar to that in intermediate 7 step 4.

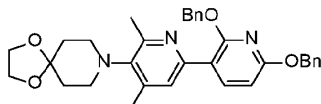
[0178] **Intermediate 13:** 3-(4,6-dimethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione

[0179] Step 1: 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine



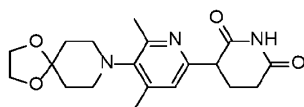
To a solution of 3-bromo-6-chloro-2,4-dimethylpyridine (9 g, 40.91 mmol) in dioxane/H₂O (100/20 mL) were added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (17.1 g, 40.91 mmol), Pd(PPh₃)₄ (4.64 g, 4.10 mmol), and K₂CO₃ (16.94 g, 122.73 mmol). The resulting solution was stirred for 5 h at 100°C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc, the combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product purified by silica column chromatography (EA/PE = 0-50%) to afford 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine (12 g, 62.2 %). [M+H]⁺ = 475.1

[0180] Step 2: 8-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane



To a stirred mixture of 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine (2.3 g, 4.84 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (1.0 g, 7.26 mmol), and Cs₂CO₃ (4.7 g, 14.52 mmol) in DMF (20 mL) was added Pd-PEPPSI-IPentCl (406.7 mg, 0.48 mmol). The resulting mixture was stirred for 5 h at 100 °C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc, the combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product purified by silica column chromatography (EA/PE = 0-30%) to afford 8-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (1.5 g, 57.7 %). [M+H]⁺ = 538.3

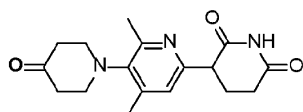
[0181] Step 3: 3-(4,6-dimethyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione



To a stirred solution of 8-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-

azaspiro[4.5]decane (3.4 g, 8.31 mmol) in THF (50 mL) was added Pd/C (10 wt%, 3.5 g). The resulting mixture was degassed under reduced pressure and purged with H₂ for five times, then stirred overnight at rt. The resulting mixture was filtered, the filter cake was washed with THF. The filtrate was concentrated under reduced pressure. And the residue was purified by column chromatography (EA/PE = 30-50%) to afford 3-(4,6-dimethyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione (2.09 g, 83.0%). [M+H]⁺ = 360.2. ¹H NMR (300 MHz, DMSO) δ 10.77 (s, 1H), 6.96 (s, 1H), 3.92 (s, 4H), 3.83 (m, 1H), 3.03 (t, *J* = 6 Hz, 4H), 2.62 – 2.51 (m, 2H), 2.39 (s, 3H), 2.26 (s, 3H), 2.18 (m, 1H), 2.12 – 2.00 (m, 1H), 1.72 (t, *J* = 6 Hz, 4H).

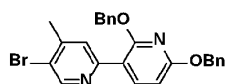
[0182] Step 4: 3-(4,6-dimethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The compound was prepared in a procedure similar to that in intermediate 7 step 4.

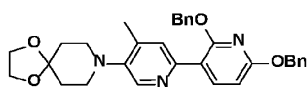
[0183] **Intermediate 14:** 3-(4-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione

[0184] Step 1: 2',6'-bis(benzyloxy)-5-bromo-4-methyl-2,3'-bipyridine



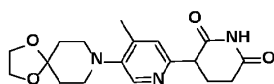
To the solution of 5-bromo-2-iodo-4-methylpyridine (4.8 g, 16.1 mmol), 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.7 g, 16.1 mmol) and K₂CO₃ (4.5 g, 32.2 mmol) in 100 mL 1,4-dioxane and 20 mL H₂O was added Pd(dppf)Cl₂ (1.2 g, 1.61 mmol). The mixture was stirred at 90 °C for 16 hours. The mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica column chromatography (PE:EA=100:1-5:1) to afford the product (6.7 g, 90.5%). [M+H]⁺ = 461.5.

[0185] Step 2: 8-(2',6'-bis(benzyloxy)-4-methyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane



To the solution of 2',6'-bis(benzyloxy)-5-bromo-4-methyl-2,3'-bipyridine (6.7 g, 14.5 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (5.2 g, 36.3 mmol) and Cs₂CO₃ (9.4 g, 29.0 mmol) in 80 mL DMA, were added Pd₂(dba)₃ (2.6 g, 2.9 mmol) and RuPhos (2.7 g, 5.8 mmol). The mixture was stirred at 100 °C for 16 hours under nitrogen atmosphere. The mixture was filtered through a celite pad and washed with DCM. The filtrate was concentrated under reduced pressure to give the crude residue, which was purified by silica column chromatography (PE:EA=50:1-2:1) to afford the product (5.3 g, 69.7%). [M+H]⁺ = 524.5.

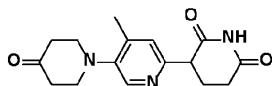
[0186] Step 3: 3-(4-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione



To the solution of 8-(2',6'-bis(benzyloxy)-4-methyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (5.3 g, 10.1 mmol) in 75 mL DMF and 75 mL iPrOH, Pd/C (2.0 g, 10 wt. %, wet) was added. The mixture was

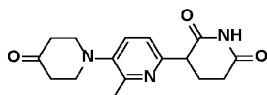
stirred at 50 °C for 20 hours under hydrogen atmosphere (balloon). The mixture was cooled to room temperature and filtered by celite directly. The filtrate was concentrated in vacuum to afford the desired product (2.7 g, 77.1%). $[M+H]^+ = 346.6$.

[0187] Step 4: 3-(4-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



3-(4-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione (2.7 g, 7.8 mmol) was placed in 250 mL round bottom flask with a magnetic stir bar. Then 45 mL 8N HCl aqueous was added. The mixture was stirred at room temperature for 2 hours. The mixture was added dropwise to sat. aq. NaHCO_3 and the pH was adjusted to 6-7. The liquid was extracted with DCM (40 mL x 3) and separated. The combined organic phase was concentrated in vacuum and purified with combiflash (DCM: MeOH= 25:1) to afford the title compound (2.2 g, 93.6% yield). $[M+H]^+ = 302.5$.

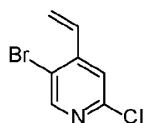
[0188] **Intermediate 15:** 3-(6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a procedure similar to that in intermediate 14.

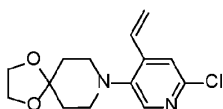
[0189] **Intermediate 16:** 3-(4-ethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione

[0190] Step 1: 5-bromo-2-chloro-4-vinylpyridine



To a stirred mixture of 5-bromo-2-chloro-4-iodopyridine (16 g, 50.3 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (7.75 g, 50.3 mmol), and Na_2CO_3 (16.00 g, 150.9 mmol) in 1,4-Dioxacyclohexane (200 mL) and H_2O (40 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (3.65 g, 5.03 mmol). The resulting mixture was degassed under reduced pressure and purged with N_2 for three times. Then it was stirred at 100 °C for 5 hours. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography (EA/PE = 20-30%) to afford 5-bromo-2-chloro-4-vinylpyridine (6.8 g, 62.0%). $[M+H]^+ = 218$.

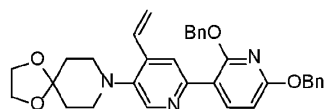
[0191] Step 2: 8-(6-chloro-4-vinylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane



To a stirred mixture of 5-bromo-2-chloro-4-vinylpyridine (6.8 g, 31.2 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (4.46 g, 31.2 mmol), and Cs_2CO_3 (20.3 g, 62.4 mmol) in 1,4-dioxacyclohexane (140 mL) was added Pd-PEPPSI-IPentCl (1.3 g, 1.56 mmol). The resulting mixture was degassed under reduced pressure and purged with N_2 for three times. Then it was stirred overnight at 100 °C. The reaction mixture was filtered through a

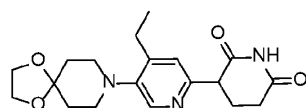
celite pad, and the filtrate was concentrated. The residue was purified by column chromatography (EA/PE = 26-28%) to afford 8-(6-chloro-4-vinylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane (4.2 g, 47.9%). $[M+H]^+ = 281$.

[0192] Step 3: 8-(2',6'-bis(benzyloxy)-4-vinyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane



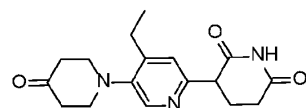
To a stirred mixture of 8-(6-chloro-4-vinylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane (4.2 g, 14.95 mmol), 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (6.23 g, 14.95 mmol), and K_2CO_3 (6.19 g, 44.85 mmol) in 1,4-Dioxacyclohexane (50 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (1.09 g, 1.5 mmol). The resulting mixture was degassed under reduced pressure and purged with N_2 for three times. Then it was stirred at 100 °C for 5 hours. The reaction mixture was diluted with water and extracted with EA. The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by column chromatography (EA/PE = 20-30%) to afford 8-(2',6'-bis(benzyloxy)-4-vinyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (6.3 g, 78.9%). $[M+H]^+ = 536$

[0193] Step 4: 3-(4-ethyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione



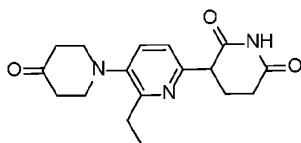
To a stirred solution of 8-(2',6'-bis(benzyloxy)-4-vinyl-[2,3'-bipyridin]-5-yl)-1,4-dioxo-8-azaspiro[4.5]decane (6.3 g, 11.8 mmol) in THF (150 mL) was added Pd/C (10 wt%, 6.3 g). The resulting mixture was degassed under reduced pressure and purged with H_2 for five times, then stirred overnight at 50 °C. The reaction mixture was diluted with THF/DCM(1:1), then filtered through a Celite pad. The filtrate was concentrated under vacuum. And the residue was purified by column chromatography (EA/PE, 30-50%) to afford 3-(4-ethyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)piperidine-2,6-dione. (3.53 g, 9.8 mmol, 83.05%). $[M+H]^+ = 360$. 1H NMR (300 MHz, DMSO) δ 10.80 (s, 1H), 8.19 (s, 1H), 7.20 (s, 1H), 3.99 – 3.90 (m, 1H), 3.32 (s, 1H), 2.96 (t, $J = 3$ Hz, 4H), 2.72 – 2.50 (m, 3H), 2.26 – 2.04 (m, 1H), 1.76 (t, $J = 6$ Hz, 4H), 1.20 (t, $J = 9$ Hz, 3H), 1.07 (s, 2H).

[0194] Step 5: 3-(4-ethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The compound was prepared in a procedure similar to that in intermediate 14 step 4.

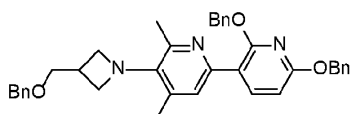
[0195] Intermediate 17: 3-(6-ethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The compound was prepared in a procedure similar to that in intermediate 16.

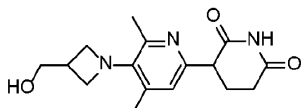
[0196] Intermediate 18: (1-(6-(2,6-dioxopiperidin-3-yl)-2,4-dimethylpyridin-3-yl)azetidin-3-yl)methyl methanesulfonate

[0197] Step 1: 2',6'-bis(benzyloxy)-5-(3-((benzyloxy)methyl)azetidin-1-yl)-4,6-dimethyl-2,3'-bipyridine



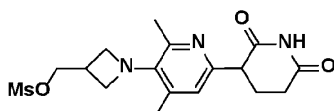
The solution of 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine (5 g, 10.5 mmol), 3-((benzyloxy)methyl)azetidine (2.81 g, 15.79 mmol), Cs_2CO_3 (10.29 g, 31.59 mmol), Pd-PEPPSI-IPentCl (0.44 g, 0.53 mmol) in DMF (60 ml) was degassed under reduced pressure and purged with N_2 for five times, and stirred under N_2 at 100 °C for 5 hrs. After cooled to rt, the mixture was poured into EA (100 mL), and washed with brine (100 mL), water (3' 100 mL), brine (100 mL) in turn, then dried over anhydrous Na_2SO_4 , concentrated in vacuum. The residue was purified by silica column chromatography PE/EA (6:1) to afford 2',6'-bis(benzyloxy)-5-(3-((benzyloxy)methyl)azetidin-1-yl)-4,6-dimethyl-2,3'-bipyridine (3.7 g, 61.4%). $[\text{M}+\text{H}]^+ = 572$.

[0198] Step 2: 3-(5-(3-(hydroxymethyl)azetidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



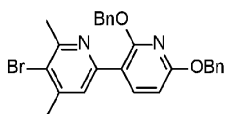
A 250 mL round bottom flask equipped with a magnetic stirrer, were charged with 2',6'-bis(benzyloxy)-5-(3-((benzyloxy)methyl)azetidin-1-yl)-4,6-dimethyl-2,3'-bipyridine (3.7 g, 6.49 mmol), THF (50 mL), and Pd/C (10 wt%, 3.7 g). The resulting mixture was degassed under reduced pressure and purged with H_2 for five times, then stirred at 50 °C for overnight. The mixture was diluted with THF (100 mL), then sonicated in an ultrasonic washer for 5 minutes, followed by filtration through a pad of celite. The filtrate was concentrated under vacuum. The residue was triturated with PE to afford 3-(5-(3-(hydroxymethyl)azetidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione (1.03 g, 52.6%). $[\text{M}+\text{H}]^+ = 304$.

[0199] Step 3: (1-(6-(2,6-dioxopiperidin-3-yl)-2,4-dimethylpyridin-3-yl)azetidin-3-yl)methyl methanesulfonate

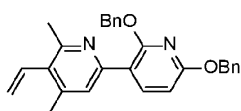


The compound was prepared in a manner similar to that in Intermediate 19 step 5.

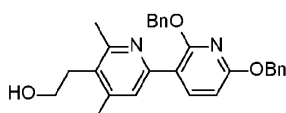
[0200] Intermediate 19: 2-(6-(2,6-dioxopiperidin-3-yl)-2,4-dimethylpyridin-3-yl)ethyl methanesulfonate

[0201] Step 1: 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine

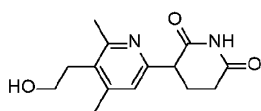
To a solution of 3-bromo-6-chloro-2,4-dimethylpyridine (9 g, 40.9 mmol) in dioxane/H₂O (100/20 mL) were added 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (17.1 g, 40.9 mmol), Pd(PPh₃)₄ (4.64 g, 4.10 mmol), and K₂CO₃ (16.94 g, 122.73 mmol). The resulting solution was stirred for 5 h at 100°C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc, the combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product purified by silica column chromatography (EA/PE = 0-50%) to afford 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine (12 g, 62.2 %). [M+H]⁺ = 475.1.

[0202] Step 2: 2',6'-bis(benzyloxy)-4,6-dimethyl-5-vinyl-2,3'-bipyridine

To a stirred mixture of 2',6'-bis(benzyloxy)-5-bromo-4,6-dimethyl-2,3'-bipyridine (3 g, 6.31 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.17 g, 7.58 mmol), and K₂CO₃ (2.61 g, 18.93 mmol) in 1,4-dioxane (30 mL) and H₂O (6 mL) was added Pd(dppf)Cl₂ (514.1 mg, 0.63 mmol). The resulting solution was stirred for 5 h at 100°C under N₂ atmosphere. After cooling to rt, diluted with H₂O and extracted with EtOAc, the combined organic layer was washed with brine, dried by Na₂SO₄ and concentrated. The filtrate was concentrated under reduced pressure. The crude product purified by silica column chromatography (EA/PE = 0-20%) to afford 2',6'-bis(benzyloxy)-4,6-dimethyl-5-vinyl-2,3'-bipyridine (1.7 g, 63.9 %). [M+H]⁺ = 423.0

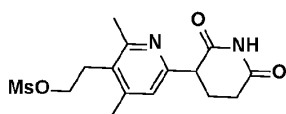
[0203] Step 3: 2-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)ethan-1-ol

To a stirred mixture of 2',6'-bis(benzyloxy)-4,6-dimethyl-5-vinyl-2,3'-bipyridine (1.7 g, 4.01 mmol) in THF (20 mL) was added 9-BBN (0.5 M in THF, 40 mL, 20.0 mmol) dropwise at 0°C. The reaction mixture was stirred overnight at rt, then NaOH (2M in water, 4 mL, 8.03 mmol) and H₂O₂ (30%, 40.2 mL, 12.1 mmol) were added at 0°C. The reaction mixture was stirred at rt for 2 h. The mixture was diluted with H₂O and extracted with EA, and the residue was purified by column chromatography (EA/PE = 0-35%) to afford 2-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)ethan-1-ol (1.4 g, 79.5%). [M+H]⁺ = 441.2

[0204] Step 4: 3-(5-(2-hydroxyethyl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione

To a stirred solution 2-(2',6'-bis(benzyloxy)-4,6-dimethyl-[2,3'-bipyridin]-5-yl)ethan-1-ol (1.4 g, 8.31 mmol) in THF (50 mL) was added Pd/C (10 wt%, 1.5 g). The resulting mixture was degassed under reduced pressure and purged with H₂ for five times, then stirred overnight at 50°C. The resulting mixture was filtered, the filter cake was washed with THF. The filtrate was concentrated under reduced pressure. And the residue was purified by column chromatography (EA/PE = 30-50%) to afford 3-(5-(2-hydroxyethyl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione (855.7 mg, 83.0%). $[M+H]^+ = 263.1$. ¹H NMR (300 MHz, DMSO) δ 10.80 (s, 1H), 6.96 (s, 1H), 4.83 – 4.74 (m, 1H), 3.83 (m, 1H), 3.52 (m, 2H), 2.78 (t, $J = 9$ Hz, 2H), 2.64 – 2.54 (m, 3H), 2.44 (s, 3H), 2.29 (s, 3H), 2.26 – 2.02 (m, 1H).

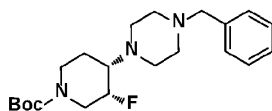
[0205] Step 5: 2-(6-(2,6-dioxopiperidin-3-yl)-2,4-dimethylpyridin-3-yl)ethyl methanesulfonate



To a solution of 3-(5-(2-hydroxyethyl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione (300 mg, 1.15 mmol) and Et₃N (347 mg, 3.44 mmol) in DCM (6 mL) and THF (6 mL), MsCl (172 mg, 1.49 mmol) was slowly added at 0 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was quenched with water (10 mL). The organic phase was separated and concentrated in vacuum. The residue was purified by prep-TLC (DCM:MeOH=20:1) to afford product (220 mg, 56.5% yield). $[M+H]^+ = 341.5$.

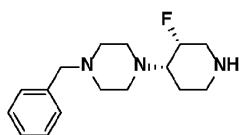
[0206] **Intermediate 20:** 3-(3-fluoro-5-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

[0207] Step 1: tert-butyl (3R,4S)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidine-1-carboxylate



The solution of tert-butyl (3R,4S)-4-amino-3-fluoropiperidine-1-carboxylate (2.5 g, 11.46 mmol) N-benzyl-2-chloro-N-(2-chloroethyl)ethan-1-amine hydrochloride (3 g, 11.46 mmol) and NaHCO₃ (3.85 g, 45.84 mmol) in 50 mL EtOH was stirred at 80°C for 16 hours. The mixture was concentrated, diluted with water and extracted by DCM. The organic layer was separated and concentrated. The mixture was purified by silica column chromatography (MeOH : DCM = 0 - 4%) to afford tert-butyl (3R,4S)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidine-1-carboxylate (2 g, 5.3 mmol, 46.3%). $[M+H]^+ = 378.6$.

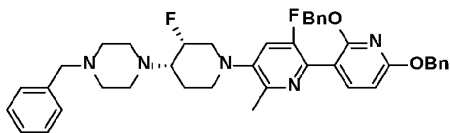
[0208] Step 2: 1-benzyl-4-((3R,4S)-3-fluoropiperidin-4-yl)piperazine



To a solution of tert-butyl (3R,4S)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidine-1-carboxylate (5 g, 13.2 mmol) in DCM (20 mL) was added TFA (10 mL). The reaction was stirred at room temperature for 2 hr and then concentrated in vacuo. The residue was dissolved in DCM (200 mL), washed with sat. NaHCO₃

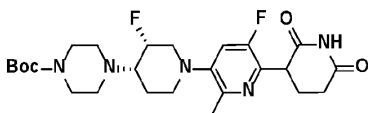
solution (3 x 100 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the product (3 g, 81.7%). [M+H]⁺ = 278.4.

[0209] Step 3: 2',6'-bis(benzyloxy)-5-((3R,4S)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-3-fluoro-6-methyl-2,3'-bipyridine



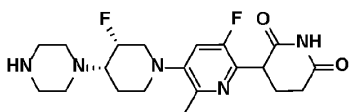
To a stirred solution of intermediate 11 (0.95 g, 1.8 mmol) in dioxane (20 mL) were added Cs₂CO₃ (1.2 g, 3.6 mmol), 1-benzyl-4-((3R,4S)-3-fluoropiperidin-4-yl)piperazine (0.5 g, 1.8 mmol) and Pd-Ruphos-G3 (0.3 g, 0.4 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 12 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (0-5%) to afford the product (0.95 g, 78%). [M+H]⁺ = 676.7.

[0210] Step 4: tert-butyl 4-((3R,4S)-1-(6-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylpyridin-3-yl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate



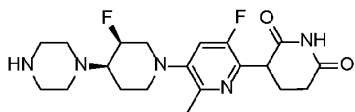
To a stirred mixture of 2',6'-bis(benzyloxy)-5-((3R,4S)-4-(4-benzylpiperazin-1-yl)-3-fluoropiperidin-1-yl)-3-fluoro-6-methyl-2,3'-bipyridine (0.95 g, 1.4 mmol), di-tert-butyl dicarbonate (1.5 g, 7 mmol) in i-PrOH (40 mL) and DMF (40 mL) was added Pd on carbon (1 g, wet, 10 wt %). The resulting mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 24 hr. Then the mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-7%) to afford the product (0.46 g, 64.5%). [M+H]⁺ = 508.4.

[0211] Step 5: 3-(3-fluoro-5-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



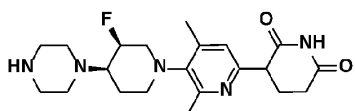
To a solution of tert-butyl 4-((3R,4S)-1-(6-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylpyridin-3-yl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate (460 mg, 0.9 mmol) in DCM (10 mL) was added TFA (5 mL). The reaction was stirred at room temperature for 2 hr and then concentrated in vacuo. The residue was dissolved in DCM (50 mL), washed with sat. NaHCO₃ solution (3 x 20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the product (260 mg, 70.4 %). [M+H]⁺ = 408.5.

[0212] **Intermediate 21:** 3-(3-fluoro-5-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



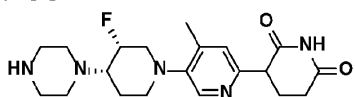
The title compound was prepared in a manner similar to that in Intermediate 20.

[0213] **Intermediate 22:** 3-(5-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



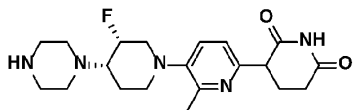
The title compound was prepared in a manner similar to that in Intermediate 20.

[0214] **Intermediate 23:** 3-(5-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione



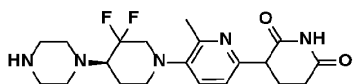
The title compound was prepared in a manner similar to that in Intermediate 20.

[0215] **Intermediate 24:** 3-(5-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



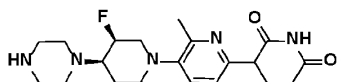
The title compound was prepared in a manner similar to that in Intermediate 20.

[0216] **Intermediate 25:** 3-(5-((R)-3,3-difluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a procedure similar to that in intermediate 20.

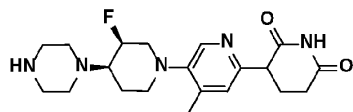
[0217] **Intermediate 26:** 3-(5-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a procedure similar to that in intermediate 20.

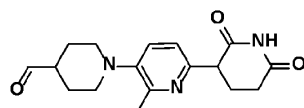
[0218] **Intermediate 27:** 3-(5-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione

yl)piperidine-2,6-dione



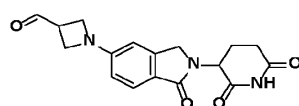
The title compound was prepared in a manner similar to that in intermediate 20.

[0219] Intermediate 28: 1-(6-(2,6-dioxopiperidin-3-yl)-2-methylpyridin-3-yl)piperidine-4-carbaldehyde

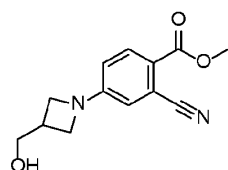


The title compound was prepared in a manner similar to that in intermediate 14.

[0220] Intermediate 29: 1-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)azetidine-3-carbaldehyde

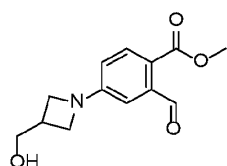


[0221] Step 1: Methyl 2-cyano-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate



To a stirred mixture of methyl 2-cyano-5-fluorobenzoate (20 g, 112 mmol) and azetidin-3-ylmethanol (hydrogen chloride) (14 g, 112 mmol) in DMSO (100 mL) was added DIEA (29 g, 223 mmol) in 3 h at 60 °C. The resulting mixture was extracted with EtOAc (500 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. Methyl 2-cyano-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate (18 g, 66.7%) was obtained. [M+H]⁺ = 247.0.

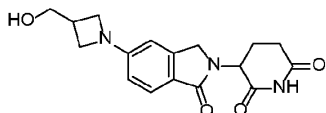
[0222] Step 2: Methyl 2-formyl-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate



To a stirred mixture of methyl 2-cyano-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate (18 g, 72.9 mmol) in AcOH (150 mL) and H₂O (75 mL) was added Raney-Ni (15 g) in portions for 4 h at 40 °C under air atmosphere. The resulting mixture was filtered, the filter cake was washed with DCM and MeOH (300 mL). The filtrate was concentrated under reduced pressure. The filtrate was extracted with EtOAc (500 mL). The combined

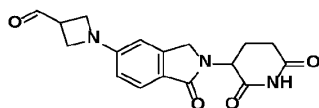
organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (9:1). Methyl 2-formyl-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate (10 g, 55.6%) was obtained. $[\text{M}+\text{H}]^+ = 250.1$.

[0223] Step 3: 3-(5-(3-(hydroxymethyl) azetidin-1-yl)-1-oxoisindolin-2-yl) piperidine-2,6-dione



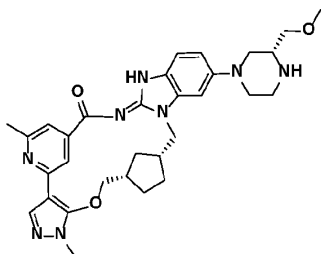
A mixture of 3-aminopiperidine-2,6-dione (hydrogen chloride) (9.9 g, 60.2 mmol) and DIEA (10.4 g, 80.3 mmol) in DMF (90 mL) was stirred for 5 h at room temperature. The mixture was acidified to pH <7 with AcOH (12 g, 201 mmol) followed by the addition of methyl 2-formyl-4-(3-(hydroxymethyl) azetidin-1-yl) benzoate (10 g, 40.2 mmol) in DMF (10 mL) at room temperature. The resulting mixture was stirred overnight at room temperature. To the above mixture was added NaBH_3CN (7.5 g, 119.35 mmol) in portions at room temperature. The resulting mixture was stirred for additional 2 h at room temperature. The reaction was quenched with water at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford crude product. The residue was purified by trituration with DCM. This resulted in 3-(5-(3-(hydroxymethyl) azetidin-1-yl)-1-oxoisindolin-2-yl) piperidine-2,6-dione (4 g, 30.8%). ^1H NMR (300 MHz, DMSO) δ 10.94 (s, 1H), 7.48 (d, $J = 8$ Hz, 1H), 6.52 – 6.42 (m, 2H), 5.04 (m, 1H), 4.81 (t, $J = 8$ Hz, 1H), 4.30 (d, $J = 16$ Hz, 1H), 4.18 (d, $J = 20$ Hz, 1H), 3.93 (m, 2H), 3.65 (m, 2H), 3.59 (t, $J = 8$ Hz, 2H), 2.97 – 2.76 (m, 2H), 2.64 – 2.53 (m, 1H), 2.35 (m, 1H), 1.95 (m, 1H). $[\text{M}+\text{H}]^+ = 330.1$.

[0224] Step 4: 1-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)azetidine-3-carbaldehyde



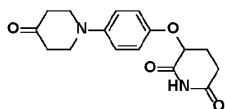
The title compound was prepared in a manner similar to that in Intermediate 33 step 2. $[\text{M}+\text{H}]^+ = 328.1$

[0225] Intermediate 30: (7¹R,7³S,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

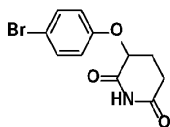


The title compound was prepared in a manner similar to that in Intermediate 2. $[\text{M}+\text{H}]^+ = 571.5$

[0226] Intermediate 31: 3-(4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione

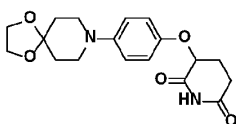


[0227] Step 1: 3-(4-bromophenoxy)piperidine-2,6-dione



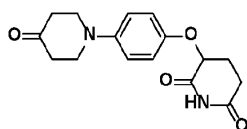
The solution of 4-bromophenol (2 g, 11.6 mmol), 3-bromopiperidine-2,6-dione (4.4 g, 23.1 mmol) and Cs_2CO_3 (11.3 g, 34.7 mmol) in DMF (50 mL) was stirred at 60 °C for 5 hr and then diluted with EtOAc (400 mL) and washed with brine (3 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/EA (0-30%) to afford the product (1 g, 30.5%); $[\text{M}+\text{H}]^+ = 284.2$.

[0228] Step 2: 3-(4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenoxy)piperidine-2,6-dione



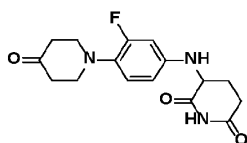
To a stirred solution of 3-(4-bromophenoxy)piperidine-2,6-dione (900 mg, 3.2 mmol) and 1,4-dioxo-8-azaspiro[4.5]decan-8-yl (544 mg, 1.3 mmol) in DMA (20 mL) were added Cs_2CO_3 (2 g, 6.3 mmol), Ruphos (591 mg, 0.24 mmol) and $\text{Pd}_2(\text{dba})_3$ (580 mg, 0.6 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (25: 1) to afford the product (130 mg, 11.9%); $[\text{M}+\text{H}]^+ = 347.3$.

[0229] Step 3: 3-(4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione

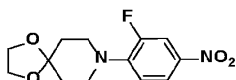


The solution of 3-(4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenoxy)piperidine-2,6-dione (130 mg, 0.4 mmol) in HCl aq. (8 N, 5 mL) was stirred at r.t. for 2 hr and DCM (100 mL) was added. The resulting mixture was adjusted to pH = 7 with NaHCO_3 aq. and the organic layer was separated and dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product (100 mg, 88.1%); $[\text{M}+\text{H}]^+ = 303.2$.

[0230] **Intermediate 32:** 3-((3-fluoro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione

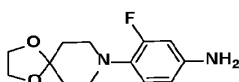


[0231] Step 1: 8-(2-fluoro-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane



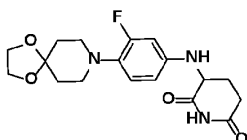
To the solution of 1,2-difluoro-4-nitrobenzene (3.0 g, 18.9 mmol) and 1,4-dioxo-8-azaspiro[4.5]decane (4.0 g, 28.3 mmol) in 60 mL DMF were added K_2CO_3 (5.2 g, 37.8 mmol). The resulting mixture was stirred at 80 °C for 16 hours. The reaction was poured into water (150 mL), and the precipitate was filtered, washed with water and dried under air to afford the crude product (5.3 g, 96.2%). $[M+H]^+ = 283.5$.

[0232] Step 2: 3-fluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline



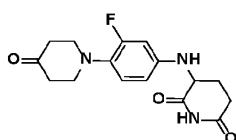
To the solution of 8-(2-fluoro-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane (5.1 g, 18.0 mmol) in 40 mL DCM and 40 mL MeOH was added Pd/C (2.5 g, 10 wt. %, wet). The mixture was stirred at RT for 12 hours under hydrogen atmosphere (balloon). The mixture was filtered through a celite pad and washed with DCM. The filtrate was concentrated in vacuum to afford the crude product (4.4 g, 96.5%). $[M+H]^+ = 253.5$.

[0233] Step 3: 3-((3-fluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione



To the solution of 3-fluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline (700 mg, 2.8 mmol) and 3-bromopiperidine-2,6-dione (525 mg, 2.8 mmol) in 10 mL DMF were added Na_2CO_3 (595 mg, 5.6 mmol). The resulting mixture was heated at 70 °C for 16 hours. The mixture was quenched with water and extracted with EA (2 x 50 mL). The combined organic phase was washed with brine (2 x 30 mL), concentrated in vacuum and purified with combiflash (DCM: EA= 1:2) to afford the title compound (345 mg, 34.5%). $[M+H]^+ = 364.5$.

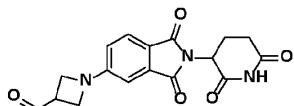
[0234] Step 4: 3-((3-fluoro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione



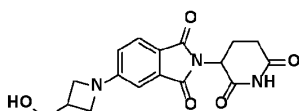
3-((3-fluoro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione (345 mg, 0.95 mmol) was placed in 100 mL round bottom flask with a magnetic stir bar. Then 10 mL 8N HCl aqueous was added. The mixture was stirred at room temperature for 2 hours. The mixture was added dropwise to sat. aq. $NaHCO_3$

solution and finally pH=6-7. The liquid was extracted with DCM (2 x 50 mL). The combined organic phase was concentrated in vacuum and purified with combiflash (DCM:MeOH= 25:1) to afford the title compound (300 mg, 99.0%). $[M+H]^+ = 320.5$.

[0235] Intermediate 33: 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)azetidine-3-carbaldehyde

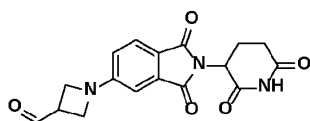


[0236] Step 1: 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione



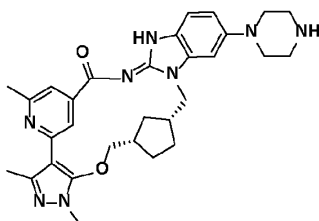
A mixture of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (2.76 g, 1 mmol), azetidin-3-ylmethanol (870 mg, 1 mmol) and DIEA (2.85 g, 2 mmol) in DMSO (30 mL) was stirred in a round bottom flask at 100 °C for 12 hours under N₂. The mixture was diluted with H₂O and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (10:1). 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione (3 g, 87%) was obtained. $[M+H]^+ = 344.3$

[0237] Step 2: 1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)azetidine-3-carbaldehyde



A mixture of 2-(2,6-dioxopiperidin-3-yl)-5-(3-(hydroxymethyl)azetidin-1-yl)isoindoline-1,3-dione (1.71 g, 0.5 mmol), 2-Iodoxybenzoic acid (2.8 g, 1 mmol) in DMSO (15 mL) was stirred in a round bottom flask at 25 °C for 12 hours under N₂. The mixture was diluted with H₂O and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH₂Cl₂ / MeOH (10:1) to afford the title compound (1.5 g, 88%). $[M+H]^+ = 342.3$

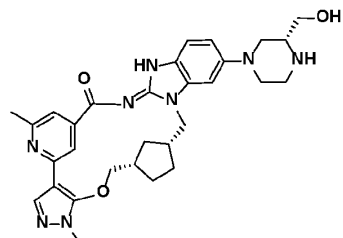
[0238] Intermediate 34: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in Intermediate 40 with intermediate 39.

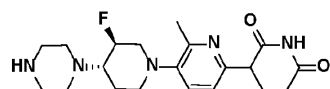
$[M+H]^+ = 541.5$.

[0239] Intermediate 35: (7¹R,7³S,E)-5⁶-((R)-3-(hydroxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



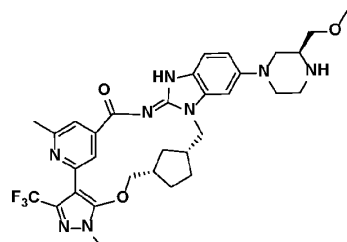
The title compound was prepared in a manner similar to that in Intermediate 2. $[M+H]^+ = 557.5$.

[0240] Intermediate 36: 3-(5-((3S,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



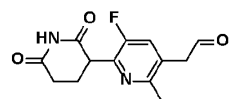
The title compound was prepared in a manner similar to that in intermediate 20. $[M+H]^+ = 390.3$.

[0241] Intermediate 37: (7¹R,7³S,E)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-1³-(trifluoromethyl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

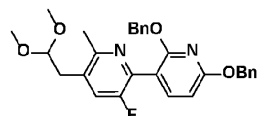


The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+ = 639.5$.

[0242] Intermediate 38: 2-(6-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylpyridin-3-yl)acetaldehyde



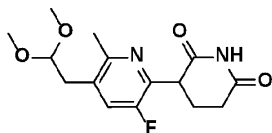
[0243] Step 1: 2',6'-bis(benzyloxy)-5-(2,2-dimethoxyethyl)-3-fluoro-6-methyl-2,3'-bipyridine



To a mixture of 2',6'-bis(benzyloxy)-5-bromo-3-fluoro-6-methyl-2,3'-bipyridine (700 mg, 1.5 mmol, obtained from the same way of WO2023098656 A1), 3-bromo-1,1-dimethoxypropane (400 mg, 2.2 mmol), NiI₂ (91 mg, 0.3 mmol), HCl salt of picolinimidamide (46 mg, 0.3 mmol), NaI (87 mg, 0.58 mmol), Mn (160 mg, 3 mmol)

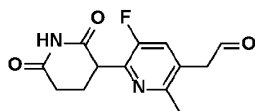
in DMA (15 mL) was added TFA (25 mg, 0.25 mmol) under N₂. The resulting mixture was heated to 100 °C for 3 hrs under N₂. After cooling to r.t, the reaction was diluted with EA (60 mL) and then washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column (PE:EA=5:1) to afford the product (560 mg, 78.5%); [M+H]⁺ = 489.6.

[0244] Step 2: 3-(5-(2,2-dimethoxyethyl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



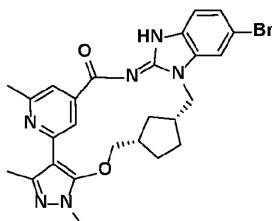
Under N₂, to a solution of 2',6'-bis(benzyloxy)-5-(2,2-dimethoxyethyl)-3-fluoro-6-methyl-2,3'-bipyridine (560 mg, 1.15 mmol) in DMF (10 mL)/i-PrOH (10 mL) was added 10% Pd/C (500 mg) at 25 °C. Then the mixture was exchanged with H₂ twice and stirred under H₂ atmosphere at 50 °C for 12 hours. The mixture was filtered through a pad of Celite and washed with MeOH (50 mL). The filtrate was concentrated under vacuum to afford the crude product (120 mg, 33.7%). [M+H]⁺ = 311.4.

[0245] Step 3: 2-(6-(2,6-dioxopiperidin-3-yl)-5-fluoro-2-methylpyridin-3-yl)acetaldehyde

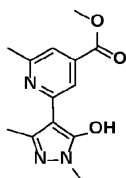


The solution of 3-(5-(2,2-dimethoxyethyl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione (120 mg, 0.4 mmol) in HCl aq. (8 N, 5 mL) was stirred at r.t. for 2 hr and DCM(100 mL) was added. The resulting mixture was adjusted to pH = 7 with NaHCO₃ aq. and the organic layer was separated and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the product (100 mg, 97.8%); [M+H]⁺ = 265.2.

[0246] **Intermediate 39:** (7¹R,7³S,E)-5⁶-bromo-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



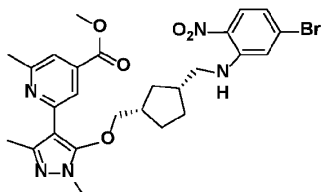
[0247] Step 1: methyl 2-(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate



To the solution of methyl 2-chloro-6-methylisonicotinate (1.85g, 10 mmol), 1,3-dimethyl-1H-pyrazol-5-ol (2.24 g, 20 mmol) and Na₂CO₃ (2.12 g, 20 mmol) in 50 mL anisole, Pd(dppf)Cl₂ (1.46 g, 2 mmol) was added at N₂ atmosphere. The mixture was stirred at 130°C for 16 hours at N₂ atmosphere. The mixture was filtered

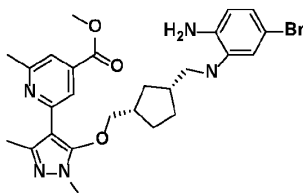
and the filtrate was concentrated in vacuum. The residue was purified by silica column chromatography (MeOH:DCM=0-7%) to afford methyl 2-(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (990 mg, 3.79 mmol, 37.9% yield). $[M+H]^+ = 262.2$.

[0248] Step 2: methyl 2-(5-(((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate



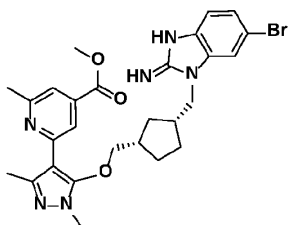
To the solution of methyl 2-(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (990 mg, 3.79 mmol), ((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methanol (1.24 g, 3.79 mmol) and PPh_3 (1.19 g, 4.55 mmol) in 30 mL THF, DIAD (920 mg, 4.55 mmol) was added at 0°C . The mixture was stirred at room temperature for 4 hours. The mixture was concentrated in vacuum and purified by silica column chromatography (MeOH:DCM=0-5%) to afford methyl 2-(5-(((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (2.6 g crude with PPh_3O). $[M+H]^+ = 572.2$.

[0249] Step 3: methyl 2-(5-(((1S,3R)-3-(((2-amino-5-bromophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate



To the solution of methyl 2-(5-(((1S,3R)-3-(((5-bromo-2-nitrophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (2.6 g crude with PPh_3O) in 50 mL THF, Raney Ni was added. The mixture was stirred at room temperature for 1 hour at H_2 atmosphere. The mixture was filtered by celite and the filtrate was concentrated in vacuum to afford methyl 2-(5-(((1S,3R)-3-(((2-amino-5-bromophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (2.5 g crude). $[M+H]^+ = 542.2$.

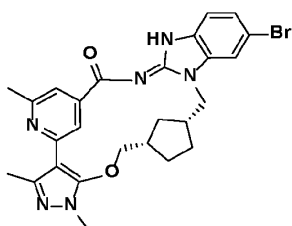
[0250] Step 4: methyl 2-(5-(((1S,3R)-3-(((6-bromo-2-imino-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate



To the solution of methyl 2-(5-(((1S,3R)-3-(((2-amino-5-bromophenyl)amino)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate

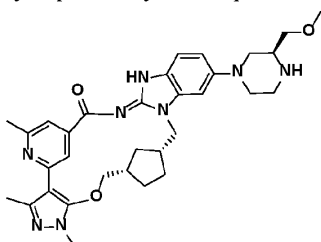
1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (2.5 g crude) in 30 mL MeOH, BrCN (630 mg, 6 mmol) was added. The mixture was stirred at room temperature for 4 hours. The mixture was concentrated in vacuum. The residue was dissolved in DCM (100 mL) and washed with sat. aq. K_2CO_3 (50 mL x 3) and separated. The organic layer was dried and concentrated and purified by silica column chromatography (MeOH:DCM=0-8%) to afford methyl 2-(5-(((1S,3R)-3-((6-bromo-2-imino-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (1.6 g, 2.83 mmol). $[M+H]^+=567.2$.

[0251] Step 5: (7¹R,7³S,E)-5⁶-bromo-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



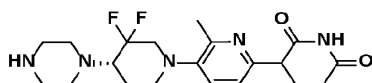
To the solution of methyl 2-(5-(((1S,3R)-3-((6-bromo-2-imino-2,3-dihydro-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (1.6 g, 2.83 mmol) in 30 mL THF, 5 mL 1N LiHMDS in THF was added. The mixture was stirred at room temperature for 1 hour. The mixture was quenched with sat. aq. NH_4Cl (30 mL) and concentrated. The residue was dissolved in DCM (70 mL) and washed with brine (40 mL x 3). The organic layer was separated and concentrated and purified by silica column chromatography (MeOH:DCM=0-4%) to afford (7¹R,7³S,E)-5⁶-bromo-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one (780 mg, 1.46 mmol, 51.6% yield). $[M+H]^+=535.2$.

[0252] Intermediate 40: (7¹R,7³S,E)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



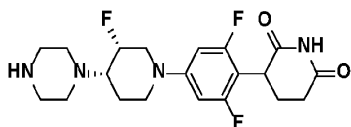
The title compound was prepared in a manner similar to that in Intermediate 2 with intermediate 39. $[M+H]^+=585.1$.

[0253] Intermediate 41: 3-(5-((S)-3,3-difluoro-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

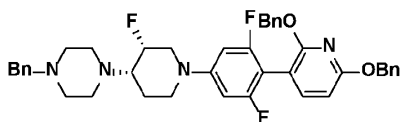


The title compound was prepared in a procedure similar to that in intermediate 20. $[M+H]^+=408.1$.

[0254] **Intermediate 42:** 3-(2,6-difluoro-4-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione

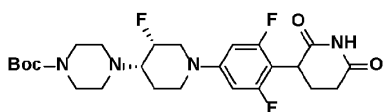


[0255] Step 1: 1-benzyl-4-((3R,4S)-1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)-3-fluoropiperidin-4-yl)piperazine



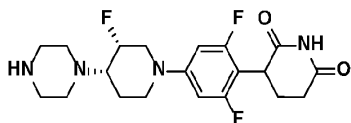
To the solution of 2,6-bis(benzyloxy)-3-(4-bromo-2,6-difluorophenyl)pyridine (1.0 g, 2.1 mmol), 1-benzyl-4-((3R,4S)-3-fluoropiperidin-4-yl)piperazine (694 mg, 2.5 mmol) and Cs_2CO_3 (2.0 g, 6.3 mmol) in 20 mL 1,4-dioxane, were added Pd-G3 RuPhos (351 mg, 0.42 mmol) and RuPhos (392 mg, 0.84 mmol). The mixture was stirred at 100 °C for 16 hours under N_2 . The mixture was filtered through a celite pad and washed with DCM. The filtrate was concentrated under reduced pressure to give the crude residue, which was purified by silica column chromatography (DCM : MeOH = 100:1-20:1) to afford the product (1.1 g, 78.0%). $[\text{M}+\text{H}]^+ = 679.5$.

[0256] Step 2: tert-butyl 4-((3R,4S)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate



To the solution of 1-benzyl-4-((3R,4S)-1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)-3-fluoropiperidin-4-yl)piperazine (1.1 g, 1.6 mmol) and $(\text{Boc})_2\text{O}$ (1.0 g, 4.8 mmol) in 20 mL DMF and 20 mL iPrOH was added Pd/C (0.8 g, 10 wt. %, wet). The mixture was stirred at 50 °C for 16 hours under hydrogen atmosphere (balloon). The mixture was cooled to room temperature and filtered by celite. The filtrate was concentrated in vacuum to give the crude residue, which was purified by silica gel column chromatography (DCM : MeOH = 100:0-20:1) to afford the product (790 mg, 95.5%). $[\text{M}+\text{H}]^+ = 511.5$.

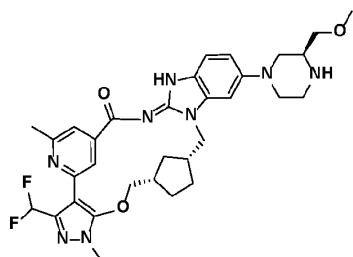
[0257] Step 3: 3-(2,6-difluoro-4-((3R,4S)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



To a solution of 4-((3R,4S)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate (790 mg, 1.5 mmol) in DCM (6 mL) was added TFA (2mL). The mixture was stirred at room temperature for 1 h. The mixture was concentrated and basified with sat. aq. NaHCO_3 . The liquid was extracted with DCM/ $\text{CF}_3\text{CH}_2\text{OH}$ (3 x 30 mL). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated in vacuum to afford the title product (600 mg, 94.5%). $[\text{M}+\text{H}]^+ = 411.5$.

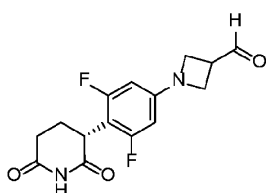
[0258] **Intermediate 43:** (7¹R,7³S,E)-1³-(difluoromethyl)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-

dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

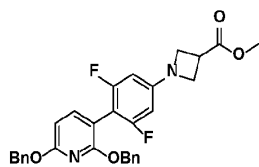


The title compound was prepared in a manner similar to that in Intermediate 40. $[M+H]^+ = 621.3$.

[0259] Intermediate 44: (R)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)azetidine-3-carbaldehyde



[0260] Step 1: methyl 1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylate



A mixture of 2,6-bis(benzyloxy)-3-(4-bromo-2,6-difluorophenyl)pyridine (3.00 g, 6.22 mmol), methyl azetidine-3-carboxylate hydrochloride (1.41 g, 9.33 mmol), Cs_2CO_3 (6.06 g, 18.7 mmol) and RuPhos Pd G3 (520.7 mg, 0.62 mmol) in toluene (50 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with brine (300 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford the product (1.7 g, 53 %). $[M+H]^+ = 517.1$.

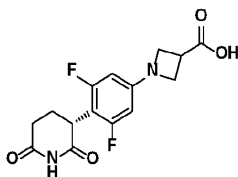
[0261] Step 2: 1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylic acid



To a stirred mixture of methyl 1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylate (1.7 g, 3.29 mmol) in THF (20 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (168 mg, 4 mmol) in 10 mL water dropwise at room temperature. Then the mixture was stirred for 2 hours. The resulting mixture was concentrated in vacuum. The water layer was adjusted to pH<5 with 1N HCl and then extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to afford the product (1.4 g, 85%), which was

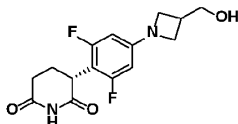
used in next step without further purification. $[M+H]^+ = 503.2$.

[0262] Step 3: (R)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylic acid



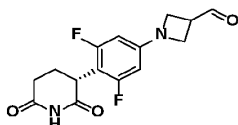
To a solution of 1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylic acid (1.40 g, 2.79 mmol) in iPrOH (20 mL) and DCM (20 mL) was added Pd/C (1.0 g, 10% wt), and the mixture was stirred at room temperature under hydrogen atmosphere for 48 hours. The resulting mixture was filtered, the filter cake was washed with MeOH (20 mL). The filtrate was concentrated under reduced pressure and purified by chiral HPLC (analytical method: CHIRALPAK AD-3 3.0*100 mm, 3 μ m, MeOH (0.1%DEA)), and the title compound corresponded to peak A @ 1.849 min/254 nm (190 mg, 22%). $[M+H]^+ = 325.3$.

[0263] Step 4: (R)-3-(2,6-difluoro-4-(3-(hydroxymethyl)azetidin-1-yl)phenyl)piperidine-2,6-dione



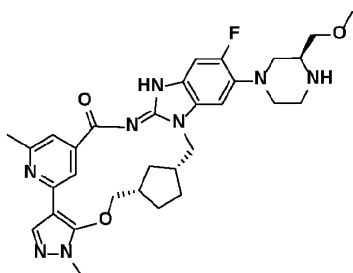
To the solution of (R)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)azetidine-3-carboxylic acid (6.5 g, 20 mmol) in THF was added $BH_3 \cdot THF$ (30 mL, 1 M in THF) dropwise at 0 $^{\circ}C$. The reaction mixture was stirred at room temperature overnight. Then the mixture was quenched with MeOH (20 mL) and diluted with DCM (150 mL), washed with sat. aq. $NaHCO_3$ (3 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography, eluted with DCM/MeOH (30:1 to 15:1) to afford the title product (3.8 g, 61.2 %). $[M+H]^+ = 311.2$.

[0264] Step 5: (R)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)azetidine-3-carbaldehyde



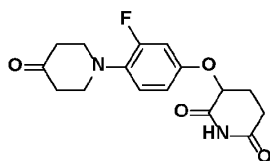
A mixture of (R)-3-(2,6-difluoro-4-(3-(hydroxymethyl)azetidin-1-yl)phenyl)piperidine-2,6-dione (3.8 g, 12.3 mmol) and IBX (6.8 g, 24.6 mmol) in DMSO (80 mL) was stirred in a flask at room temperature overnight. The reaction was quenched with water and the mixture was extracted with DCM (60 mL x 3). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (100 mL), sat. aq. $NaHCO_3$ (100 mL x 2), sat. aq. $NaCl$ (100 mL x 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under vacuum to afford the product (2.3 g, 70.1%), which was used without further purification. $[M+H]^+ = 309.1$.

[0265] **Intermediate 45:** (7¹R,7³S,E)-5⁵-fluoro-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one



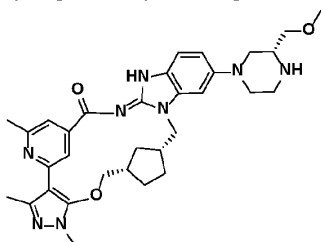
The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+ = 589.3$.

[0266] **Intermediate 46:** 3-(3-fluoro-4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione

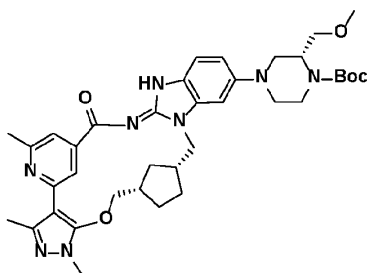


The title compound was prepared in a manner similar to that in Intermediate 31. $[M+H]^+ = 321.2$

[0267] **Intermediate 47:** (7¹R,7³S,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



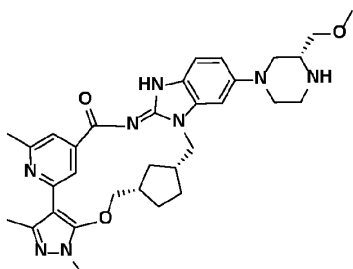
[0268] Step 1: tert-butyl (R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate



To the solution of intermediate 39 (150 mg, 0.28 mmol), tert-butyl (R)-2-(methoxymethyl)piperazine-1-carboxylate (129 mg, 0.56 mmol) and tBuONa (135 mg, 1.4 mmol) in 5 mL DMA was added Pd₂(dba)₃ (51 mg, 0.056 mmol) and RuPhos (52 mg, 0.12 mmol). The mixture was stirred at 90°C for 1 hour. The mixture was concentrated in vacuum and purified by silica column chromatography (MeOH:DCM=0-4%) to afford the title compound (180 mg, 93.8%). $[M+H]^+ = 685.2$.

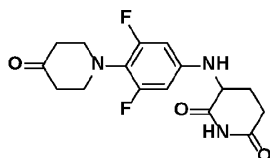
[0269] Step 2: (7¹R,7³S,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-

1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



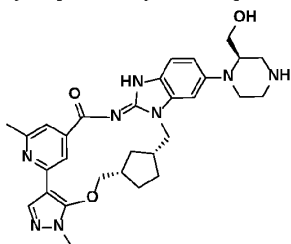
To the solution of tert-butyl (R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate (180 mg, 0.26 mmol) in 2 mL DCM was added 2 mL TFA. The mixture was stirred at room temperature for 15 minutes. The mixture was concentrated and dissolved in DCM (20 mL). The residue was washed with sat. aq. NaHCO₃ (10 mL x 3) and separated. The organic layer was concentrated and purified by silica column chromatography ((MeOH+2% NH₃.H₂O):DCM=0-15%) to afford the title compound (130 mg, 84.6%). [M+H]⁺=585.2.

[0270] Intermediate 48: 3-((3,5-difluoro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione



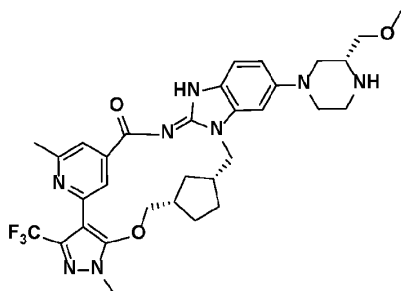
The title compound was prepared in a manner similar to that in Intermediate 32. [M+H]⁺=338.2.

[0271] Intermediate 49: (7¹R,7³S,E)-5⁶-((R)-2-(hydroxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



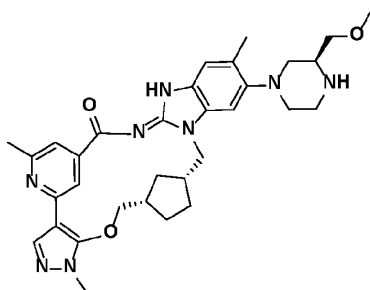
The title compound was prepared in a manner similar to that in Intermediate 2. [M+H]⁺=557.2.

[0272] Intermediate 50: (7¹R,7³S,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-1³-(trifluoromethyl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



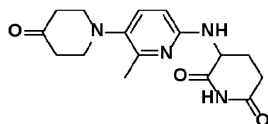
The title compound was prepared in a manner similar to that in Intermediate 47 $[M+H]^+=639.3$.

[0273] Intermediate 51: (7¹R,7³S,E)-5⁶-(S)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶,5⁵-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



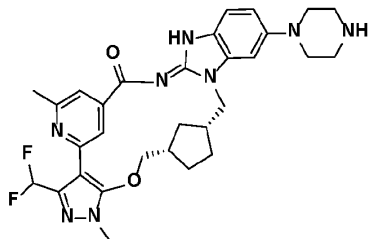
The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+=585.3$.

[0274] Intermediate 52: 3-((6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)amino)piperidine-2,6-dione



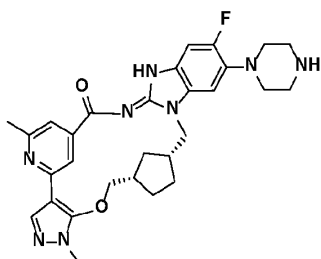
The title compound was prepared in a manner similar to that in Intermediate 32. $[M+H]^+=317.2$.

[0275] Intermediate 53: (7¹R,7³S,E)-1³-(difluoromethyl)-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



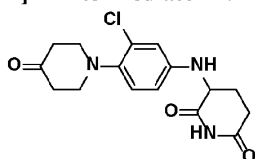
The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+=577.3$.

[0276] Intermediate 54: (7¹R,7³S,E)-5⁵-fluoro-1¹,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

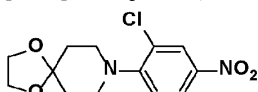


The title compound was prepared in a manner similar to that in Intermediates 1 and 2. $[M+H]^+ = 545.3$.

[0277] **Intermediate 55:** 3-((3-chloro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione

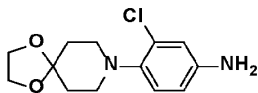


[0278] Step 1: 8-(2-chloro-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane



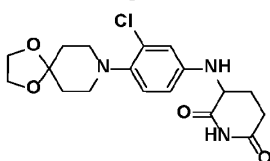
To a stirred solution 2-chloro-1-fluoro-4-nitrobenzene (2 g, 11.5 mmol) in DMF (30 mL) were added 1,4-dioxo-8-azaspiro[4.5]decane (2.0 g, 13.8 mmol) and K_2CO_3 (3.2 g, 23 mmol). The resulting mixture was stirred for 12 hours at 80 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (50 mL), filtered and the filter cake was washed with water to afford the product (3 g, 87%). $[M+H]^+ = 299.3$.

[0279] Step 2: 3-chloro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline



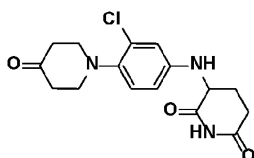
To a stirred solution 8-(2-chloro-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane (3 g, 10.1 mmol) in THF (40 mL) were added Raney Ni (1 g). The resulting mixture was stirred for 1 hour at rt under H_2 . The mixture was filtered and concentrated in vacuum to afford the product (2.6 g, 95%). $[M+H]^+ = 269.3$.

[0280] Step 3: 3-((3-chloro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione



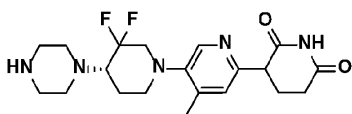
To a solution of 3-chloro-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline (2.6 g, 9.7 mmol) in DMF (40 mL) were added 3-bromopiperidine-2,6-dione (3.7 g, 19.4 mmol), and Na_2CO_3 (3.1 g, 29.1 mmol). The resulting mixture was stirred for 12 hours at 70 °C. The mixture was poured into water and extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine (1 x 15 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude residue, which was purified by silica column chromatography (DCM: MeOH = 100:1- 10:1) to afford the product (1.8 g, 49%). $[M+H]^+ = 380.3$.

[0281] Step 4: 3-((3-chloro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione



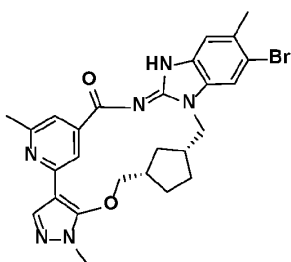
The solution of 3-((3-chloro-4-((1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione (1 g, 2.6 mmol) in HCl (8 M, 10 mL) was stirred for 2 hours at rt. To the mixture was added sat. aq. NaHCO₃ dropwise and the pH was adjusted to 6-7. The liquid was extracted with DCM (30 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to afford the title compound (800 mg, 92%). [M+H]⁺ = 336.2.

[0282] Intermediate 56: 3-(5-((S)-3,3-difluoro-4-(piperazin-1-yl)piperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione



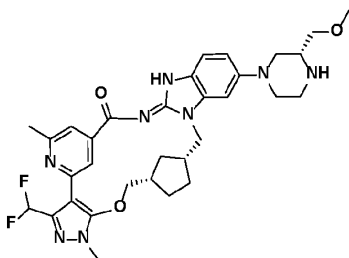
The title compound was prepared in a procedure similar to that in intermediate 20. [M+H]⁺ = 408.2.

[0283] Intermediate 57: (7¹R,7³S,E)-5⁶-bromo-1¹,2⁶,5⁵-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one



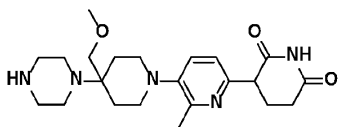
The title compound was prepared in a procedure similar to that in intermediate 1. [M+H]⁺ = 535.2.

[0284] Intermediate 58: (7¹R,7³S,E)-1³-(difluoromethyl)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one



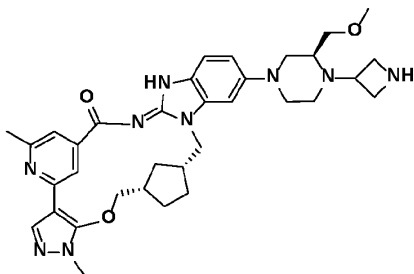
The title compound was prepared in a manner similar to that in Intermediates 1 and 2. [M+H]⁺ = 621.2.

[0285] Intermediate 59: 3-(5-(4-(methoxymethyl)-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

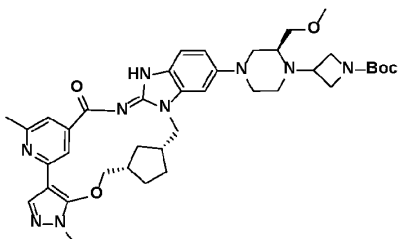


The title compound was prepared in a manner similar to that in Intermediate 20. $[M+H]^+ = 416.5$.

[0286] Intermediate 61: (7¹R,7³S,E)-5⁶-((S)-4-(azetidin-3-yl)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

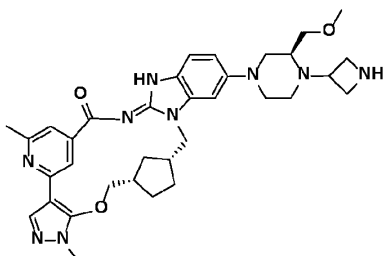


[0287] Step 1: tert-butyl 3-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)azetidine-1-carboxylate



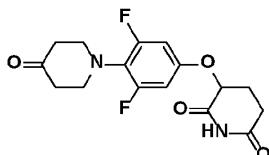
To a solution of intermediate 3 (80 mg, 0.14 mmol) and tert-butyl 3-oxoazetidine-1-carboxylate (50 mg, 0.28 mmol) in DCE (6 mL) was added STAB (89 mg, 0.42 mmol). Then the mixture was stirred at RT overnight. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 20:1) to afford the title product (95 mg, 93.1%). $[M+H]^+ = 726.6$.

[0288] Step 2: (7¹R,7³S,E)-5⁶-((S)-4-(azetidin-3-yl)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one



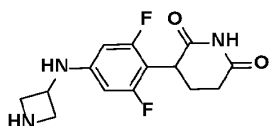
To a solution of tert-butyl 3-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)azetidine-1-carboxylate (95 mg, 0.13 mmol) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 60 minutes. The mixture was concentrated and basified with sat. aq. NaHCO₃. The liquid was extracted with DCM/MeOH (3 x 20 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum to afford the title product (78 mg, 95.1%). $[M+H]^+ = 626.6$.

[0289] Intermediate 62: 3-(3,5-difluoro-4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione

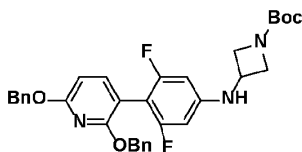


The title compound was prepared in a manner similar to that in Intermediate 31. $[M+H]^+ = 339.3$.

[0290] Intermediate 63: 3-(4-(azetidin-3-ylamino)-2,6-difluorophenyl)piperidine-2,6-dione

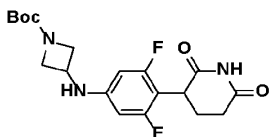


[0291] Step 1: tert-butyl 3-((4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)amino)azetidine-1-carboxylate



To the solution of intermediate 6 (3.0 g, 6.2 mmol), tert-butyl 3-aminoazetidine-1-carboxylate (2.1 g, 12.4 mmol) and Cs₂CO₃ (4.0 g, 12.4 mmol) in 80 mL 1,4-dioxane, were added Pd₂(dba)₃ (1.1 g, 1.24 mmol) and XantPhos (1.4 g, 2.48 mmol). The mixture was stirred at 100 °C for 16 hours under N₂. The mixture was filtered through a celite pad and washed with DCM (50 mL). The filtrate was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (PE : EA = 100:1-2:1) to afford the product (3.4 g, 95.0%). $[M+H]^+ = 574.5$.

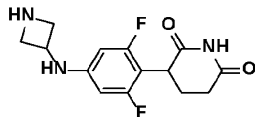
[0292] Step 2: tert-butyl 3-((4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)amino)azetidine-1-carboxylate



To the solution of tert-butyl 3-((4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)amino)azetidine-1-carboxylate (3.4 g, 5.9 mmol) in 40 mL DMF and 40 mL iPrOH was added Pd/C (2.0 g, 10 wt. %, wet). The mixture was stirred at 50 °C for 48 hours under hydrogen atmosphere (balloon). The mixture was cooled to room temperature and filtered by celite directly. The filtrate was concentrated in vacuum to give the crude

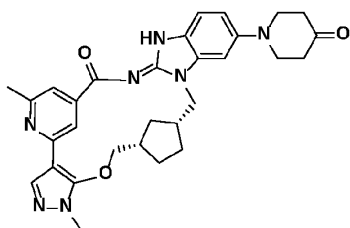
residue, which was purified by silica gel column chromatography (DCM : MeOH = 100:0-20:1) to afford the product (1.8 g, 76.9%). $[M+H]^+ = 396.5$.

[0293] Step 3: 3-(4-(azetidin-3-ylamino)-2,6-difluorophenyl)piperidine-2,6-dione

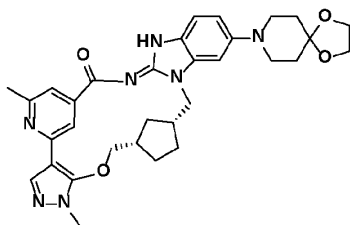


To a solution of tert-butyl 3-((4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)amino)azetidine-1-carboxylate (530 mg, 1.3 mmol) in DCM (6 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 60 minutes. The mixture was concentrated in vacuum to afford the title product as TFA salt (395 mg, 99.5%). $[M+H]^+ = 296.5$.

[0294] Intermediate 64: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(4-oxopiperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

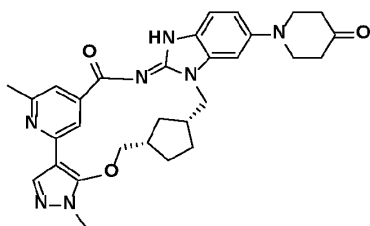


[0295] Step 1: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



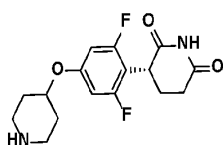
To the solution of intermediate 1 (1 g, 1.92 mmol), 1,4-dioxo-8-azaspiro[4.5]decan-8-yl (549 mg, 3.84 mmol) and t-BuONa (369 mg, 3.84 mmol) in 20 mL DMA were added Pd₂(dba)₃ (348 mg, 0.38 mmol) and RuPhos (177 mg, 0.38 mmol). The mixture was stirred at 80°C for 0.5 hour under N₂. The reaction was quenched with NH₄Cl/H₂O (15 mL) and extracted by DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 15 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column (DCM : CH₃OH = 15:1) to give the title product (1 g, 88.5%). $[M+H]^+ = 584.3$.

[0296] Step 2: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(4-oxopiperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

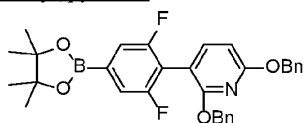


The solution of (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-5²,5³-dihydro-11H,51H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one (1 g, 2.6 mmol) in HCl (8 M, 10 mL) was stirred for 2 hours at rt. To the mixture was added sat. aq. NaHCO₃ dropwise and the pH was adjusted to 6-7. The liquid was extracted with DCM (20 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (800 mg, 87%). [M+H]⁺ = 540.3.

[0297] **Intermediate 65:** (R)-3-(2,6-difluoro-4-(piperidin-4-yloxy)phenyl)piperidine-2,6-dione

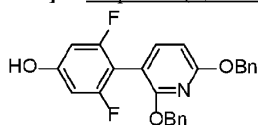


[0298] Step 1: 2,6-bis(benzyloxy)-3-(2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine



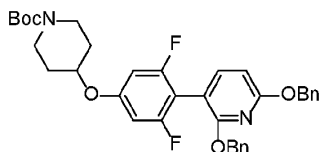
To a solution of intermediate 6 (35 g, 72.8 mmol) in dioxane (300 mL) were added B(pin)₂ (37.0 g, 146 mmol), Pd(dppf)Cl₂ (5.28 g, 7.30 mmol), and K₂CO₃ (30.1 g, 218 mmol). The resulting solution was stirred overnight at 100°C under N₂ atmosphere. After cooled to room temperature and filtered, the filter cake was washed with EA (100 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by silica column chromatography (EA:PE=0-10%) to afford 2,6-bis(benzyloxy)-3-(2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (30 g, 77.9%). [M+H]⁺ = 530.4.

[0299] Step 2: 4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenol



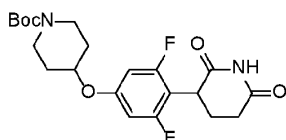
To a stirred mixture of 2,6-bis(benzyloxy)-3-(2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (30 g, 56.7 mmol) in AcOH (100 mL) and THF (100 mL) were added H₂O₂ (100 mL) in portions at 0 °C. The mixture was stirred overnight at rt. Then sat. aq. Na₂S₂O₃ (150 mL) was added and then the mixture was extracted with EA (50 mL x 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure and purified by silica column chromatography (EA:PE=0-30%) to afford 4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenol (21 g, 88.48%). [M+H]⁺ = 420.43.

[0300] Step 3: tert-butyl 4-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate



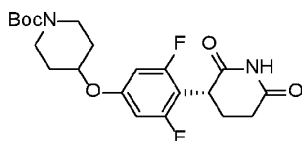
A 500 mL round-bottomed flask equipped with a magnetic stirrer were charged with 4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenol (20.5 g, 48.9 mmol), tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (20.5 g, 73.4 mmol), Cs_2CO_3 (47.8 g, 146.6 mmol), and DMF (210 mL). The resulting mixture was degassed under reduced pressure and purged with N_2 for three times, then stirred at 110 °C for 2 hours. After cooled to room temperature, the reaction was quenched with water (400 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EA/PE, 12-16%) to afford tert-butyl 4-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate (14 g, 47.6%). $[\text{M}+\text{H}]^+ = 603.3$.

[0301] Step 4: tert-butyl 4-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate



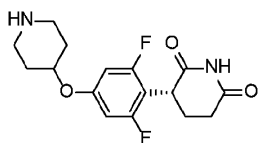
A 500 mL round-bottomed flask equipped with a magnetic stirrer, were charged with tert-butyl 4-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate (14 g, 23.3 mmol), dry THF (240 mL), and Pd/C (10 wt %, 27 g). The resulting mixture was degassed under reduced pressure and purged with H_2 for five times, then stirred overnight at 50°C under H_2 atmosphere. The mixture was diluted with THF/DCM/MeOH (200 mL/200 mL/200 mL), then sonicated in an ultrasonic washer for 5 minutes, followed by filtration through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by column chromatography (EA/PE, 40-50%) to afford tert-butyl 4-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate (6.9 g, 70.0%). $[\text{M}+\text{H}]^+ = 425.3$.

[0302] Step 5: tert-butyl (R)-4-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate



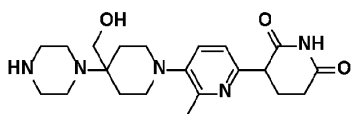
The crude product (6.7 g) was purified by Prep-SFC with the following conditions (column: CHIRALPAK IC 5*25 cm, 5 μm , Mobile phase A: CO_2 , mobile phase B: MeOH (1% 2mM NH_3 -MeOH), Gradient A:B = 40:60, Flow rate 130 mL/min, column temp 30 °C) to afford tert-butyl (R)-4-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate, which corresponds to peak A @ 8.45 min. $[\text{M}+\text{H}]^+ = 425.3$.

[0303] Step 6: (R)-3-(2,6-difluoro-4-(piperidin-4-yloxy)phenyl)piperidine-2,6-dione



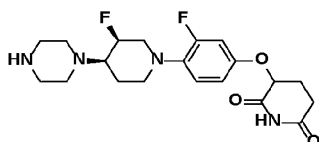
To a solution of tert-butyl (R)-4-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenoxy)piperidine-1-carboxylate (500 mg, 1.18 mmol) in DCM (10 mL) was added HCl (4 M in dioxane, 3 mL). The mixture was stirred in a flask at room temperature for 2 h. The mixture was evaporated in vacuum to afford the crude product (350 mg, 91.6%), which was used for next step without further purification. $[M+H]^+ = 325.2$.

[0304] Intermediate 66: 3-(5-(4-(hydroxymethyl)-4-(piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

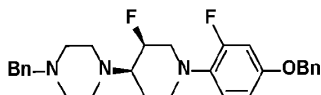


The title compound was prepared in a manner similar to that in Intermediate 20. $[M+H]^+ = 402.3$.

[0305] Intermediate 67: 3-(3-fluoro-4-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)phenoxy)piperidine-2,6-dione

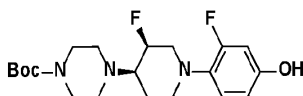


[0306] Step 1: 1-benzyl-4-((3S,4R)-1-(4-(benzyloxy)-2-fluorophenyl)-3-fluoropiperidin-4-yl)piperazine



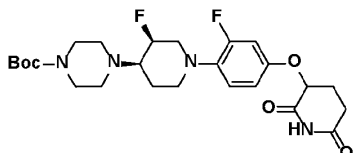
To a stirred solution of 4-(benzyloxy)-1-bromo-2-fluorobenzene (1 g, 3.6 mmol) and 1-benzyl-4-((3S,4R)-3-fluoropiperidin-4-yl)piperazine (986 mg, 3.6 mmol), prepared in a manner similar to steps 1-2 in intermediate 20) in dioxane (20 mL) were added Cs_2CO_3 (2.2 g, 7.1 mmol), Ruphos (663 mg, 1.42 mmol) and $\text{Pd}_2(\text{dba})_3$ (651 mg, 0.7 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 6 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (15: 1) to afford the product (700 mg, 41.2%); $[M+H]^+ = 478.3$.

[0307] Step 2: tert-butyl 4-((3S,4R)-3-fluoro-1-(2-fluoro-4-hydroxyphenyl)piperidin-4-yl)piperazine-1-carboxylate



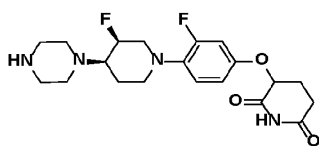
Under N₂, to a solution of 1-benzyl-4-((3S,4R)-1-(4-(benzyloxy)-2-fluorophenyl)-3-fluoropiperidin-4-yl)piperazine (700 mg, 1.5 mmol) and di-tert-butyl dicarbonate (640 mg, 2.9 mmol) in DMF (10 mL)/i-PrOH (10 mL) was added 10% Pd/C (700 mg) at 25 °C. Then the mixture was exchanged with H₂ twice and stirred under H₂ atmosphere at 50 °C for 12 hours. The mixture was filtered through a pad of Celite and washed with MeOH (50 mL). The filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (20: 1) to afford the product (460 mg, 79%); [M+H]⁺ = 398.4.

[0308] Step 3: tert-butyl 4-((3S,4R)-1-(4-((2,6-dioxopiperidin-3-yl)oxy)-2-fluorophenyl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate



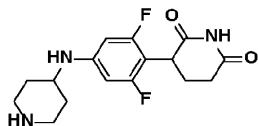
The solution of tert-butyl 4-((3S,4R)-3-fluoro-1-(2-fluoro-4-hydroxyphenyl)piperidin-4-yl)piperazine-1-carboxylate (450 mg, 1.1 mmol), 3-bromopiperidine-2,6-dione (434 mg, 2.3 mmol) and Cs₂CO₃ (1.1 g, 3.4 mmol) in DMSO (15 mL) was stirred at 50 °C for 5 hr and diluted with EtOAc (400 mL), washed with brine (3 x 150 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1) to afford the product (210 mg, 36.5%); [M+H]⁺ = 509.6.

[0309] Step 4: 3-(3-fluoro-4-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)phenoxy)piperidine-2,6-dione



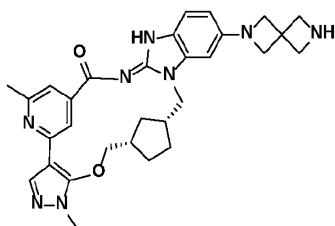
To a solution of tert-butyl 4-((3S,4R)-1-(4-((2,6-dioxopiperidin-3-yl)oxy)-2-fluorophenyl)-3-fluoropiperidin-4-yl)piperazine-1-carboxylate (210 mg, 0.4 mmol) in DCM (5 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 2 hr and then concentrated in vacuo. The residue was dissolved in DCM (100 mL), washed with sat. aq. NaHCO₃ (3 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the product (130 mg, 77%); [M+H]⁺ = 409.5.

[0310] Intermediate 68: 3-(2,6-difluoro-4-(piperidin-4-ylamino)phenyl)piperidine-2,6-dione



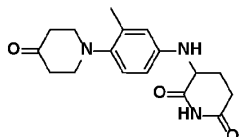
The title compound was prepared in a manner similar to that in Intermediate 63. [M+H]⁺ = 324.2.

[0311] Intermediate 69: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(2,6-diazaspiro[3.3]heptan-2-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

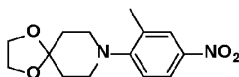


The title compound was prepared in a manner similar to that in Intermediate 2. $[M+H]^+ = 539.5$.

[0312] Intermediate 70: 3-((3-methyl-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione

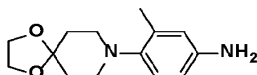


[0313] Step1: 8-(2-methyl-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane



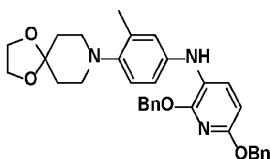
To a stirred solution 1-fluoro-2-methyl-4-nitrobenzene (2 g, 12.9 mmol) in DMF (30 mL) were added 1,4-dioxo-8-azaspiro[4.5]decane (2.2 g, 15.5 mmol) and K_2CO_3 (3.6 g, 25.8 mmol). The resulting mixture was stirred for 12 hours at 80 °C. The mixture was allowed to cool down to room temperature. The resulting mixture was poured into water (30 mL), filtered and the filter cake was washed with water (30 mL) to afford the product (3.2 g, 89%). $[M+H]^+ = 279.3$.

[0314] Step2: 3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline

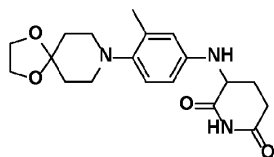


To a stirred solution 8-(2-methyl-4-nitrophenyl)-1,4-dioxo-8-azaspiro[4.5]decane (3.2 g, 11.5 mmol) in THF (40 mL) was added Raney Ni (1 g). The resulting mixture was stirred for 1 hour at rt under H_2 . The mixture was filtered and concentrated in vacuum to afford the product (2.7 g, 95%). $[M+H]^+ = 249.3$.

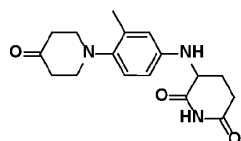
[0315] Step 3: 2,6-bis(benzyloxy)-N-(3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)pyridin-3-amine



To the solution of 3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)aniline (2 g, 8.1 mmol) in dioxane (40 mL) were added 2,6-bis(benzyloxy)-3-bromopyridine (3.3 g, 8.9 mmol), $Pd_2(dba)_3$ (1.5 g, 1.6 mmol), RuPhos (745 mg, 1.6 mmol) and Cs_2CO_3 (5.3 g, 16.2 mmol). The mixture was stirred at 100 °C for 12 hours under N_2 . The mixture was diluted with water (60 mL) and extracted by EtOAc (40 mL x 3). The organic layer was washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The resulting mixture was purified by silica column chromatography (PE:EA=10:1-5:1) to afford the product (3.5 g, 80%). $[M+H]^+ = 538.4$.

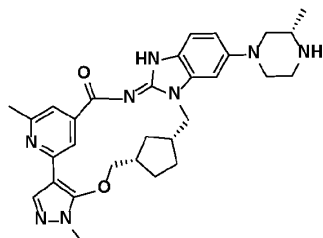
[0316] Step4: 3-((3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione

To a stirred solution 2,6-bis(benzyloxy)-N-(3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)pyridin-3-amine (3.5 g, 6.5 mmol) in DMF/i-PrOH (100 mL/40 mL) were added Pd/C (3.5 g, 10 wt %, wet). The resulting mixture was stirred for 16 hour at 50 °C under H₂. The mixture was filtered and concentrated in vacuum to afford the product (2.0 g, 86%). [M+H]⁺ = 360.3.

[0317] Step5: 3-((3-methyl-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione

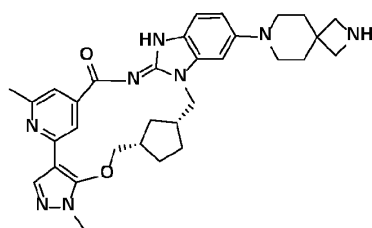
The solution of 3-((3-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)phenyl)amino)piperidine-2,6-dione (1 g, 2.8 mmol) in HCl (8 M, 10 mL) was stirred for 2 hours at rt. To the mixture was added sat. aq. NaHCO₃ dropwise and the pH was adjusted to 6-7. The liquid was extracted with DCM (20 mL x 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford the title compound (800 mg, 89%). [M+H]⁺ = 316.2.

[0318] Intermediate 71: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-((S)-3-methylpiperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



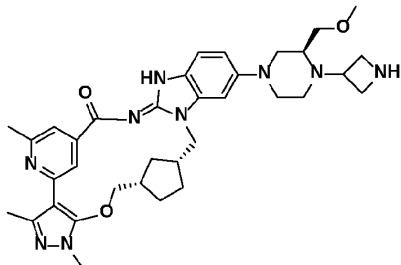
The title compound was prepared in a manner similar to that in Intermediate 2. [M+H]⁺ = 541.2.

[0319] Intermediate 72: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(2,7-diazaspiro[3.5]nonan-7-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



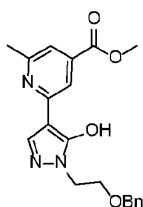
The title compound was prepared in a manner similar to that in Intermediate 2. [M+H]⁺ = 567.5.

[0320] **Intermediate 73:** (7¹R,7³S,E)-5⁶-((S)-4-(azetidin-3-yl)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

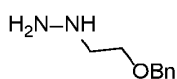


The title compound was prepared in a manner similar to that in Intermediate 61. $[M+H]^+ = 640.5$.

[0321] **Intermediate 74:** methyl 2-(1-(2-(benzyloxy)ethyl)-5-hydroxy-1H-pyrazol-4-yl)-6-methylisonicotinate

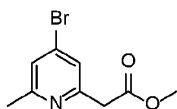


[0322] Step 1: (2-(benzyloxy)ethyl)hydrazine

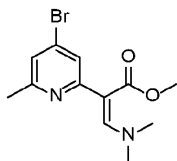


To a stirred mixture of ((2-bromoethoxy)methyl)benzene (10 g, 46.7 mmol) in EtOH (100 mL) was added hydrazine hydrate (58 mL, 467 mmol) dropwise at 0°C. The resulting mixture was stirred overnight at rt. The resulting mixture was concentrated under reduced pressure, and extracted with EA. The combined organic layers were washed with brine, and dried over anhydrous Na₂SO₄. The crude product (10 g) was used in the next step directly without further purification. $[M+H]^+ = 167.1$.

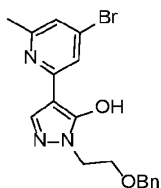
[0323] Step 2: methyl 2-(4-bromo-6-methylpyridin-2-yl)acetate



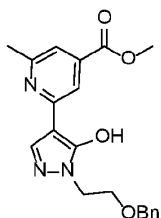
To a stirred mixture of 4-bromo-2,6-dimethylpyridine (20 g, 108.1 mmol) in THF (200 mL) was added LDA (108.1 mL, 2 M in THF) dropwise at -78 °C. The resulting mixture was stirred for 30 min at -78 °C under N₂ atmosphere. To the above mixture was added dimethyl carbonate (9.73g, 108.1 mmol) dropwise over 10 min at -78 °C. The resulting mixture was stirred for additional 2 h at rt. The reaction mixture was quenched with NH₄Cl (aq.), and extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford methyl 2-(4-bromo-6-methylpyridin-2-yl)acetate (9 g, 34%). $[M+H]^+ = 244.1$.

[0324] Step 3: methyl (Z)-2-(4-bromo-6-methylpyridin-2-yl)-3-(dimethylamino)acrylate

A mixture of methyl 2-(4-bromo-6-methylpyridin-2-yl)acetate (9 g, 37.0 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (5.29g, 44.4mmol) in DMF (100 mL) was stirred overnight at 80 °C. The resulting mixture was concentrated under reduced pressure. The crude product (11g) was used in the next step directly without further purification. $[M+H]^+ = 299.2$.

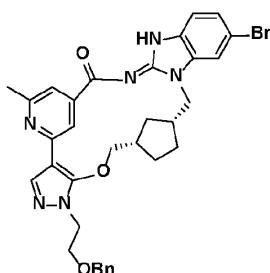
[0325] Step 4: 1-(2-(benzyloxy)ethyl)-4-(4-bromo-6-methylpyridin-2-yl)-1H-pyrazol-5-ol

A mixture of methyl (Z)-2-(4-bromo-6-methylpyridin-2-yl)-3-(dimethylamino)acrylate (11 g crude, 36.9 mmol) and (2-(benzyloxy)ethyl)hydrazine (9.1 g crude, 55.35 mmol) in MeOH was stirred overnight at rt. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 1-(2-(benzyloxy)ethyl)-4-(4-bromo-6-methylpyridin-2-yl)-1H-pyrazol-5-ol (3.8 g, 27.1%). $[M+H]^+ = 388.3$.

[0326] Step 5: methyl 2-(1-(2-(benzyloxy)ethyl)-5-hydroxy-1H-pyrazol-4-yl)-6-methylisonicotinate

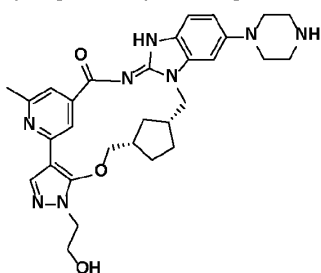
A mixture of 1-(2-(benzyloxy)ethyl)-4-(4-bromo-6-methylpyridin-2-yl)-1H-pyrazol-5-ol (3.4 g, 8.78mmol), Pd(dppf)Cl₂ (0.72 g, 0.88 mmol) and DIEA (5.65g, 43.8mmol) in MeOH (30mL) was stirred for 3 h at 100 °C under CO (20 atm.) atmosphere. The mixture was allowed to cool down to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford methyl 2-(1-(2-(benzyloxy)ethyl)-5-hydroxy-1H-pyrazol-4-yl)-6-methylisonicotinate (3 g, 93.8%). $[M+H]^+ = 368.2$. ¹H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.91 (s, 1H), 7.52 (s, 1H), 7.35 – 7.21 (m, 5H), 4.47 (s, 2H), 4.04 (t, *J* = 4 Hz, 2H), 3.91 (s, 3H), 3.73 (t, *J* = 4 Hz, 2H), 2.56 (s, 3H).

[0327] Intermediate 75: (7¹R,7³S,E)-1¹-(2-(benzyloxy)ethyl)-5⁶-bromo-2⁶-methyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphan-3-one

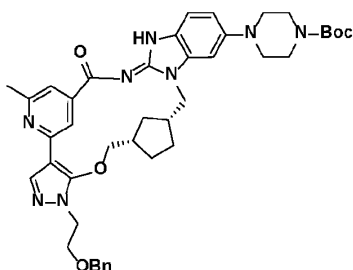


The title compound was prepared in a manner similar to that in Intermediate 1 with intermediate 74.

[0328] Intermediate 76: (7¹R,7³S,E)-1¹-(2-hydroxyethyl)-2⁶-methyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

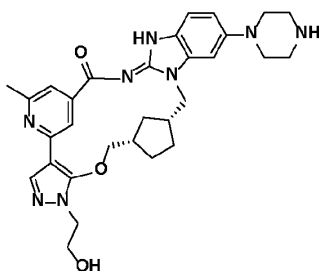


[0329] Step 1: tert-butyl 4-((7¹R,7³S,E)-1¹-(2-(benzyloxy)ethyl)-2⁶-methyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate



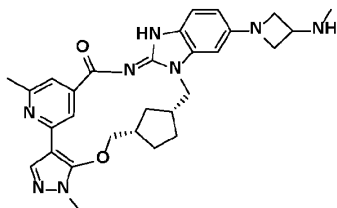
To the solution of intermediate 75 (300 mg, 0.47 mmol), tert-butyl piperazine-1-carboxylate (175 mg, 0.94 mmol) and t-BuONa (135 mg, 1.41 mmol) in 8 mL DMA were added Pd₂(dba)₃ (86 mg, 0.09 mmol) and RuPhos (84 mg, 0.18 mmol). The resulting mixture was stirred at 90 °C for 1 hour under N₂. The mixture was concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (DCM: MeOH = 100:1- 20:1) to afford the product (265 mg, 75.7%). [M+H]⁺ = 747.5.

[0330] Step 2: (7¹R,7³S,E)-1¹-(2-hydroxyethyl)-2⁶-methyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



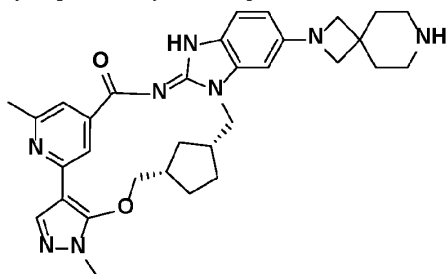
To the solution of tert-butyl 4-((7¹R,7³S,E)-1¹-(2-(benzyloxy)ethyl)-2⁶-methyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazine-1-carboxylate (265 mg, 0.35 mmol) in 10 mL DCM was added BBr₃ in DCM (1 M, 1.0 mL). After stirring at room temperature for 1 hour, the reaction mixture was quenched with aq. NaHCO₃, extracted with DCM (3 x 30 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated in vacuum to give the crude residue, which was purified by silica gel column chromatography (DCM: MeOH = 100:1- 5:1) to afford the product (90 mg, 45.7%). [M+H]⁺ = 557.5.

[0331] **Intermediate 77:** (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(3-(methylamino)azetidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



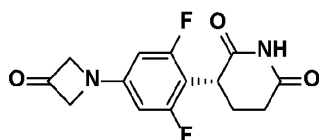
The title compound was prepared in a manner similar to that in Intermediate 2. [M+H]⁺ = 527.5.

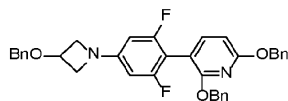
[0332] **Intermediate 78:** (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-(2,7-diazaspiro[3.5]nonan-2-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



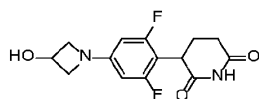
The title compound was prepared in a manner similar to that in Intermediate 2. [M+H]⁺ = 567.5

[0333] **Intermediate 79:** (R)-3-(2,6-difluoro-4-(3-oxoazetidin-1-yl)phenyl)piperidine-2,6-dione

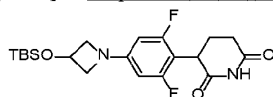


[0334] Step 1: 2,6-bis(benzyloxy)-3-(4-(3-(benzyloxy)azetidin-1-yl)-2,6-difluorophenyl)pyridine

A solution of intermediate 6 (20 g, 41.49 mmol), 3-(benzyloxy)azetidine hydrochloride (9.96 g, 49.79 mmol), $\text{Pd}_2(\text{dba})_3$ (3.79 g, 4.15 mmol), RuPhos (3.88 g, 8.3 mmol) and Cs_2CO_3 (40.58 g, 124.47 mmol) in dioxane (400 mL) was stirred at 100 °C for 3 h under nitrogen atmosphere. After cooled to room temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (10:1) to afford 2,6-bis(benzyloxy)-3-(4-(3-(benzyloxy)azetidin-1-yl)-2,6-difluorophenyl)pyridine (17 g, 72.6 %). $[\text{M}+\text{H}]^+ = 565.6$.

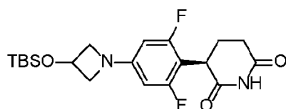
[0335] Step 2: 3-(2,6-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl)piperidine-2,6-dione

To a solution of 2,6-bis(benzyloxy)-3-(4-(3-(benzyloxy)azetidin-1-yl)-2,6-difluorophenyl)pyridine (17 g, 30.09 mmol) in DCM/THF (200 mL/200 mL), was added Pd/C (10 wt %, wet, 34 g). The mixture was stirred for 2 days at 65 °C under hydrogen atmosphere. After cooled to room temperature. The resulting mixture was filtered, the filter cake was washed with iPrOH. The filtrate was concentrated under reduced pressure and purified by trituration with DCM/MeOH (10/1) to afford 3-(2,6-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl)piperidine-2,6-dione (8 g, 89.9%). $[\text{M}+\text{H}]^+ = 297.1$

[0336] Step 3: 3-(4-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione

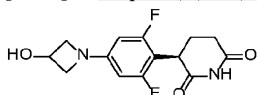
The solution of 3-(2,6-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl)piperidine-2,6-dione (11 g, 37.16 mmol), TBSCl (11.15 g, 74.32 mmol) and imidazole (7.58 g, 111.49 mmol) in DMF (200 mL) was stirred for 2h at rt. The resulting mixture was diluted with sat. aq. NaHCO_3 (500 mL) and extracted with EA (200 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 3-(4-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione (11 g, 72.4 %). $[\text{M}+\text{H}]^+ = 411.2$

[0337] Step 4: (R)-3-(4-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



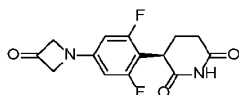
The crude product (11 g) was purified by Prep-SFC and the title compound corresponds to (CHIRALPAK IF-3, 4.6*50 mm, 3 μ m, MtBE(0.1%DEA):(MeOH:DCM=1:1)=80:20, peak A @1.084 min). (4 g, 36%, ee=100%). $[M+H]^+ = 411.2$

[0338] Step 5: (R)-3-(2,6-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl)piperidine-2,6-dione



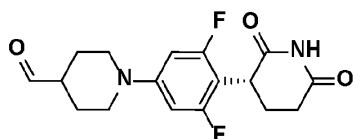
(R)-3-(4-(3-((tert-butyldimethylsilyl)oxy)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione (2.6 g, 6.3 mmol) was placed in a 250 mL round bottom flask with a magnetic stir bar. Then, 60 mL THF and 60 mL 1M HCl were added at 0 °C. The mixture was stirred at room temperature for 3 hours. The mixture was added dropwise to sat. aq. NaHCO_3 and pH was adjusted to 6-7. The liquid was extracted with DCM (50 mL x 3) and separated. The combined organic phase was concentrated in vacuum and purified with combiflash (DCM : MeOH= 20:1) to afford the title compound (1.8 g, 95% yield). $[M+H]^+ = 297.2$.

[0339] Step 6: (R)-3-(2,6-difluoro-4-(3-oxoazetidin-1-yl)phenyl)piperidine-2,6-dione



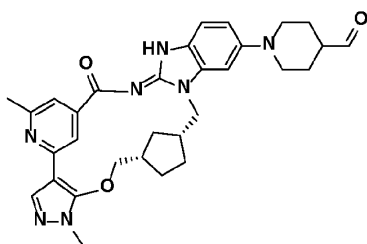
To a stirred solution of (R)-3-(2,6-difluoro-4-(3-hydroxyazetidin-1-yl)phenyl)piperidine-2,6-dione (1.8 g, 6.0 mmol) in DCM (60 mL) were added Dess-Martin periodinane (3.8 g, 9.0 mmol) at room temperature. The resulting mixture was stirred for 2 h at room temperature. Then the mixture was diluted with DCM (100 mL), washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL), sat. aq. NaHCO_3 (3 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product (2.0 g), which was used without further purification. $[M+H]^+ = 295.2$.

[0340] Intermediate 80: (R)-1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)piperidine-4-carbaldehyde



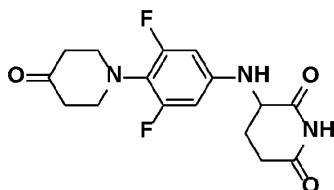
The title compound was prepared in a manner similar to that in Intermediate 7. $[M+H]^+ = 337.2$

[0341] Intermediate 82: 1-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-56-yl)piperidine-4-carbaldehyde



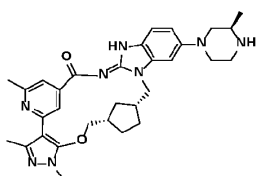
The title compound was prepared in a manner similar to that in Intermediate 64. $[M+H]^+ = 554.5$

[0342] Intermediate 83: 3-((3,5-difluoro-4-(4-oxopiperidin-1-yl)phenyl)amino)piperidine-2,6-dione



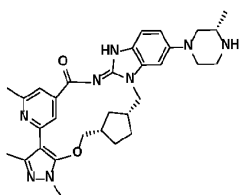
The title compound was prepared in a manner similar to that in Intermediate 32. $[M+H]^+ = 338.2$

[0343] Intermediate 84: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-((R)-3-methylpiperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



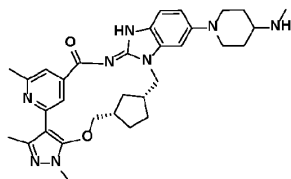
The title compound was prepared in a manner similar to that in intermediate 2 with intermediate 39. $[M+H]^+ = 555.3$

[0344] Intermediate 85: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-((S)-3-methylpiperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



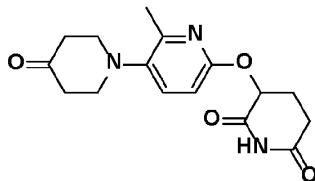
The title compound was prepared in a manner similar to that in intermediate 2 with intermediate 39. $[M+H]^+ = 555.3$

[0345] Intermediate 86: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(4-(methylamino)piperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

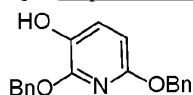


The title compound was prepared in a manner similar to that in intermediate 2 with intermediate 39. $[M+H]^+ = 569.3$

[0346] Intermediate 87: 3-((6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)oxy)piperidine-2,6-dione



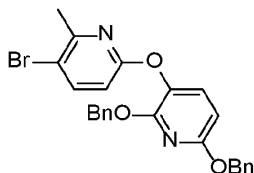
[0347] Step 1: 2,6-bis(benzyloxy)pyridin-3-ol



To a solution of 2,6-bis(benzyloxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (20.0 g, 47.96 mmol) and NaOH (3.8 g, 95.92 mmol) in DCM (200 mL) was added H_2O_2 (40 mL). The reaction mixture was stirred for 2h at rt. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA = 0-6%) to afford 2,6-bis(benzyloxy)pyridin-3-ol (10.0g, 68.02% yield).

$[M+H]^+ = 308.12$

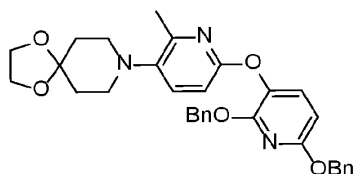
[0348] Step 2: 2,6-bis(benzyloxy)-3-((5-bromo-6-methylpyridin-2-yl)oxy)pyridine



To a solution of 2,6-bis(benzyloxy)pyridin-3-ol (10.0 g, 32.57mmol) and 3-bromo-6-fluoro-2-methylpyridine (6.1 g, 32.57 mmol) in DMSO (100 mL) was added CS_2CO_3 (31.7 g, 97.71 mmol). The reaction mixture was stirred for overnight at 80°C. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE = 0-3%) to afford 2,6-bis(benzyloxy)-3-((5-bromo-6-methylpyridin-2-yl)oxy)pyridine (13.0g, 83.87% yield).

$[M+H]^+ = 477.07$

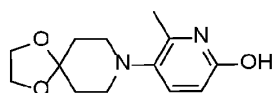
[0349] Step 3: 8-((2,6-bis(benzyloxy)pyridin-3-yl)oxy)-2-methylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane



A mixture of 2,6-bis(benzyloxy)-3-((5-bromo-6-methylpyridin-2-yl)oxy)pyridine (13 g, 27.31 mmol), 1,4-dioxo-8-azaspiro[4.5]decane (5.85 g, 41.0 mmol), $\text{Pd}_2(\text{dba})_3$ (2.49 g, 2.73 mmol), Ruphos (2.59 g, 5.46 mmol) and Cs_2CO_3 (26.6 g, 81.9 mmol) in dioxane (130 mL) was stirred at 100 °C for overnight under nitrogen atmosphere. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE = 0-20%) to afford 8-(6-((2,6-bis(benzyloxy)pyridin-3-yl)oxy)-2-methylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane (6.0g, 40.8% yield).

$[\text{M}+\text{H}]^+ = 540.24$

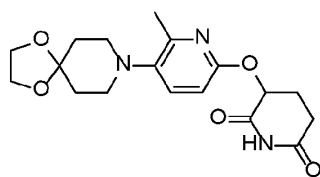
[0350] Step 4: 6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-ol



A 250 mL round bottom flask equipped with a magnetic stirrer, were charged with 8-(6-((2,6-bis(benzyloxy)pyridin-3-yl)oxy)-2-methylpyridin-3-yl)-1,4-dioxo-8-azaspiro[4.5]decane (6.0 g, 11.1 mmol), THF (60.0 mL) and Pd/C (60 wt %, 6.0 g). The resulting mixture was degassed under reduced pressure and purged with H_2 for five times, then stirred at 50°C for overnight. The mixture was filtration through a pad of celite. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM = 0-10%) to afford 6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-ol (2.1g, 75.5%).

$[\text{M}+\text{H}]^+ = 251.13$

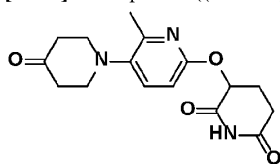
[0351] Step 5: 3-((6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)oxy)piperidine-2,6-dione



To a solution of 6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-ol (2.1 g, 8.39 mmol) and 3-bromopiperidine-2,6-dione (2.0 g, 10.5 mmol) in THF (21 mL) was added NaH (671.6 mg, 16.78 mmol). The reaction mixture was stirred for overnight at rt. The reaction mixture was diluted with aq. sat. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE = 0-60%) to afford 3-((6-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-2-yl)oxy)piperidine-2,6-dione (1.25g, 41.6%).

$[M+H]^+ = 362.2$

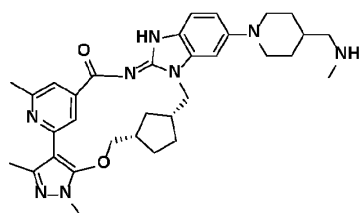
[0352] Step 6: 3-((6-methyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)oxy)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in intermediate 7 step 4.

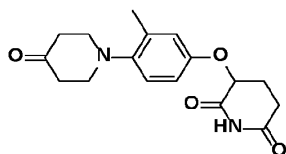
$[M+H]^+ = 318.2$

[0353] Intermediate 88: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(4-((methylamino)methyl)piperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



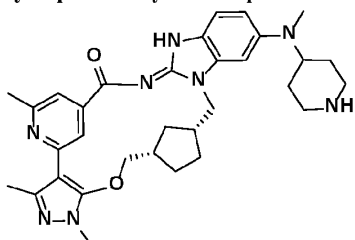
The title compound was prepared in a manner similar to that in intermediate 2 with intermediate 39. $[M+H]^+ = 583.5$

[0354] Intermediate 89: 3-(3-methyl-4-(4-oxopiperidin-1-yl)phenoxy)piperidine-2,6-dione



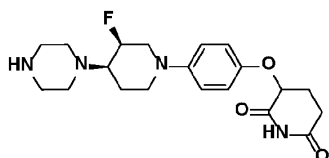
The title compound was prepared in a manner similar to that in intermediate 31. $[M+H]^+ = 317.2$

[0355] Intermediate 90: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(methyl(piperidin-4-yl)amino)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



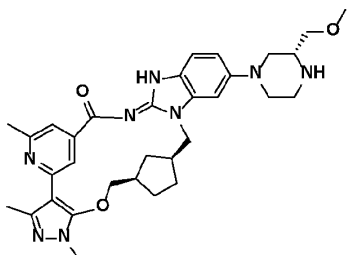
The title compound was prepared in a manner similar to that in intermediate 2. $[M+H]^+ = 569.5$

[0356] Intermediate 91: 3-(4-((3S,4R)-3-fluoro-4-(piperazin-1-yl)piperidin-1-yl)phenoxy)piperidine-2,6-dione



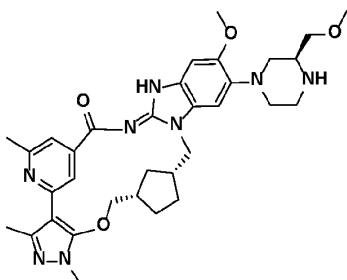
The title compound was prepared in a manner similar to that in intermediates 31 and 20. $[M+H]^+ = 391.3$

[0357] Intermediate 93: (7¹S,7³R,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



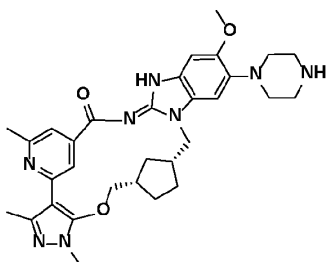
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 585.4$.

[0358] Intermediate 94: (7¹R,7³S,E)-5⁵-methoxy-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



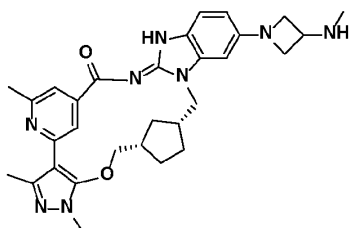
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 615.4$.

[0359] Intermediate 95: (7¹R,7³S,E)-5⁵-methoxy-1¹,1³,2⁶-trimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



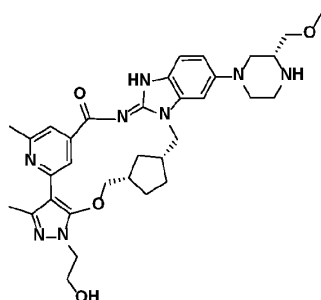
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 571.5$.

[0360] Intermediate 96: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(3-(methylamino)azetidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



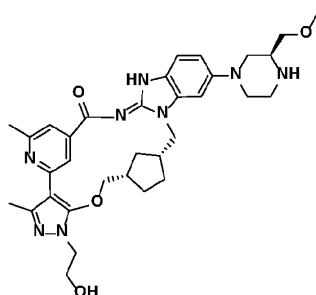
The title compound was prepared in a manner similar to that in intermediate 2. $[M+H]^+ = 541.5$.

[0361] Intermediate 98: (7¹R,7³S,E)-1¹-(2-hydroxyethyl)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1³,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



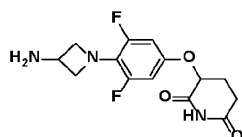
The title compound was prepared in a manner similar to that in intermediates 75 and 76. $[M+H]^+ = 615.5$.

[0362] Intermediate 99: (7¹R,7³S,E)-1¹-(2-hydroxyethyl)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1³,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



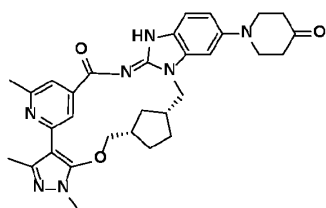
The title compound was prepared in a manner similar to that in intermediates 75 and 76. $[M+H]^+ = 615.5$.

[0363] Intermediate 100: 3-(4-(3-aminoazetidin-1-yl)-3,5-difluorophenoxy)piperidine-2,6-dione



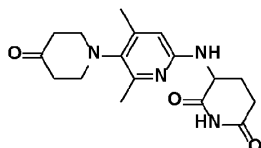
The title compound was prepared in a manner similar to that in intermediate 31 (steps 1) and 63 (steps 1 and 3). $[M+H]^+ = 312.5$.

[0364] Intermediate 101: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(4-oxopiperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



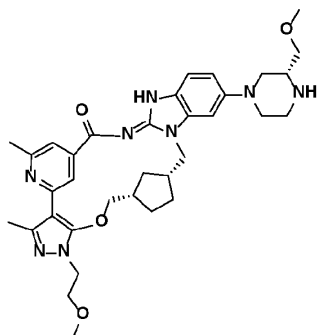
The title compound was prepared in a manner similar to that in intermediate 64. $[M+H]^+ = 554.3$.

[0365] Intermediate 102: 3-((4,6-dimethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)amino)piperidine-2,6-dione



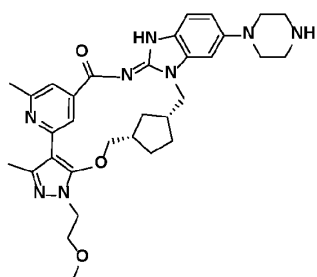
The title compound was prepared in a manner similar to that in intermediate 32. $[M+H]^+ = 331.3$.

[0366] Intermediate 103: (7¹R,7³S,E)-1¹-(2-methoxyethyl)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1³,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



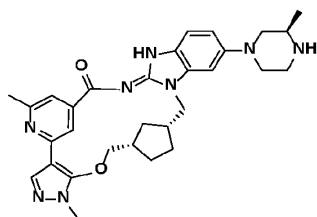
The title compound was prepared in a manner similar to that in intermediates 74, 75 and 2. $[M+H]^+ = 629.6$.

[0367] Intermediate 104: (7¹R,7³S,E)-1¹-(2-methoxyethyl)-1³,2⁶-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



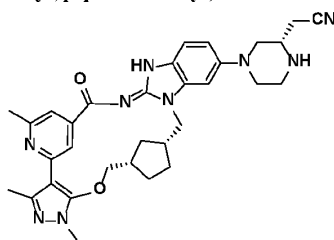
The title compound was prepared in a manner similar to that in intermediates 74, 75 and 2. $[M+H]^+ = 585.5$.

[0368] Intermediate 105: (7¹R,7³S,E)-1¹,2⁶-dimethyl-5⁶-((R)-3-methylpiperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



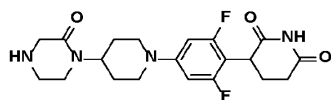
The title compound was prepared in a manner similar to that in intermediate 2. $[M+H]^+ = 541.5$.

[0369] Intermediate 106: 2-((S)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-56-yl)piperazin-2-yl)acetone nitrile

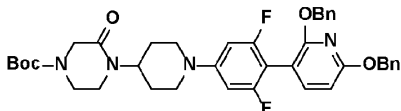


The title compound was prepared in a manner similar to that in intermediate 2. $[M+H]^+ = 580.4$.

[0370] Intermediate 107: 3-(2,6-difluoro-4-(4-(2-oxopiperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione

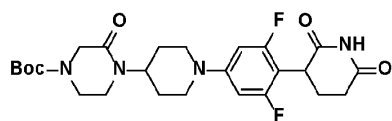


[0371] Step 1: tert-butyl 4-(1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)-3-oxopiperazine-1-carboxylate



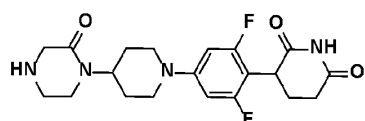
To a stirred solution of intermediate 6 (1.5 g, 3.1 mmol) and tert-butyl 3-oxo-4-(piperidin-4-yl)piperazine-1-carboxylate (1.2 g, 4.2 mmol) in DMA (30 mL) were added Cs_2CO_3 (3.17 g, 9.75 mmol), $\text{Pd}_2(\text{dba})_3$ (300 mg, 0.325 mmol) and Ruphos (300 mg, 0.65 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (200 mL), washed with water (3 x 100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (4:1) to afford the product (360 mg, 16.9%); $[M+H]^+ = 685.7$.

[0372] Step 2: tert-butyl 4-(1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)-3-oxopiperazine-1-carboxylate



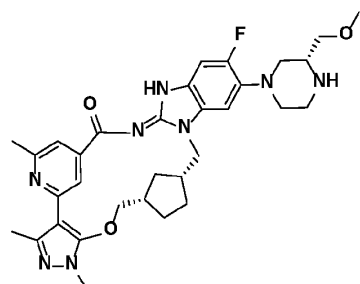
tert-butyl 4-(1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)-3-oxopiperazine-1-carboxylate (360 mg, 0.53 mmol) was dissolved in DMF (8 mL) and iPrOH (4 mL). Pd/C (350 mg, 10 wt. %, wet) was added to the solution in one portion. The resulting mixture was stirred under hydrogen atmosphere (1 atm) at 50 °C overnight. The solid was filtered off and the filtrate was concentrated to give the crude product. The crude was purified by silica gel column chromatography, eluted with DMC/MeOH (20:1) to afford the product (200 mg, 75.1%); $[M+H]^+ = 507.5$.

[0373] Step 3: 3-(2,6-difluoro-4-(4-(2-oxopiperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



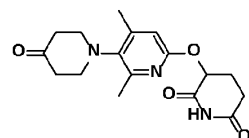
To a 100-mL round-bottomed flask equipped with a magnetic stir bar was added tert-butyl 4-(1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)-3-oxopiperazine-1-carboxylate (200 mg, 0.53 mmol), DCM (6 mL) and TFA (2 mL). After stirring for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford the product as TFA salt (270 mg), which was used without further purification. $[M+H]^+ = 407.4$.

[0374] **Intermediate 108:** (7¹R,7³S,E)-5⁵-fluoro-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 603.5$.

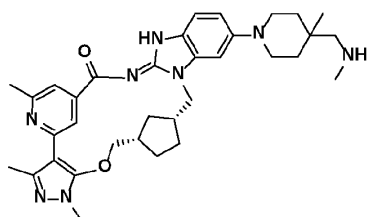
[0375] **Intermediate 109:** 3-((4,6-dimethyl-5-(4-oxopiperidin-1-yl)pyridin-2-yl)oxy)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in intermediate 87. $[M+H]^+ = 332.2$.

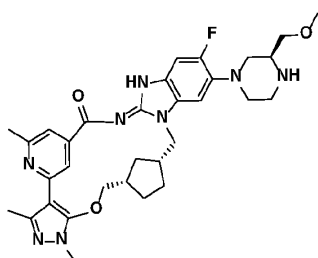
[0376] **Intermediate 110:** (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-(4-methyl-4-

((methylamino)methyl)piperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



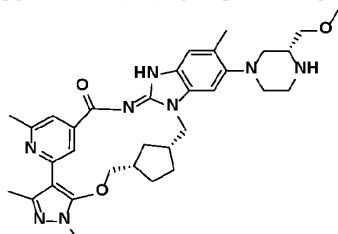
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 597.6$.

[0377] Intermediate 111: (7¹R,7³S,E)-5⁵-fluoro-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



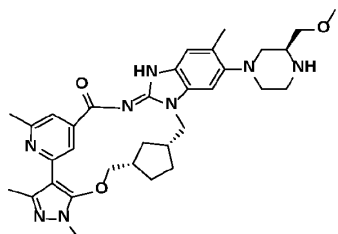
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 603.5$.

[0378] Intermediate 112: (7¹R,7³S,E)-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶,5⁵-tetramethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 599.5$.

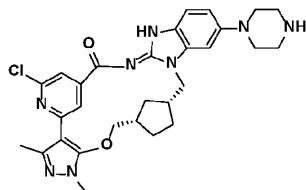
[0379] Intermediate 113: (7¹R,7³S,E)-5⁶-((S)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶,5⁵-tetramethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 599.5$.

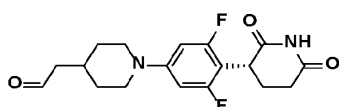
[0380] Intermediate 114: (7¹R,7³S,E)-2⁶-chloro-1¹,1³-dimethyl-5⁶-(piperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-

cyclopentanacyclononaphan-3-one



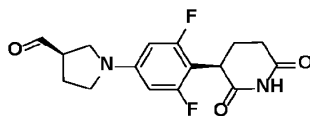
The title compound was prepared in a manner similar to that in intermediates 1 and 2. $[M+H]^+ = 561.3$.

[0381] Intermediate 115: (R)-2-(1-(4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)acetaldehyde

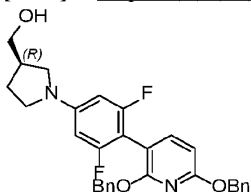


The title compound was prepared in a manner similar to that in intermediate 44. $[M+H]^+ = 350.2$.

[0382] Intermediate 116: (R)-1-(4-((R)-2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)pyrrolidine-3-carbaldehyde

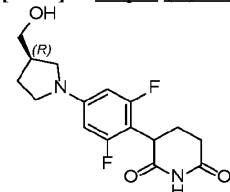


[0383] Step 1: (R)-1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)pyrrolidin-3-yl)methanol



To a solution of (R)-pyrrolidin-3-ylmethanol (9.2 g, 91.0 mmol) in dioxane (600 mL) were added intermediate 6 (52.5 g, 109 mmol), $Pd_2(dba)_3$ (8.3 g, 9.0 mmol), Johnphos (5.39 g, 18.0 mmol) and K_3PO_4 (57.8 g, 272 mmol). The resulting mixture was stirred overnight at 110°C under N_2 atmosphere. After cooled to room temperature and filtered, the filter cake was washed with EA. The filtrate was concentrated under reduced pressure. The crude product was purified by silica column chromatography (EA/PE=0-25%) to afford (R)-1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)pyrrolidin-3-yl)methanol (33.5 g, 73.1%). $[M+H]^+ = 503.21$

[0384] Step2: (R)-3-(2,6-difluoro-4-((R)-3-(hydroxymethyl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione



A 1000 mL round bottom flask equipped with a magnetic stirrer, was charged with (R)-1-(4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluorophenyl)pyrrolidin-3-yl)methanol (33.5 g, 66.7 mmol), dry THF (400 mL) and Pd/C (10 wt %, 34 g). The resulting mixture was degassed under reduced pressure and purged with H_2 for three times, then stirred overnight at 40°C. The mixture was diluted with THF/EA (1/1), then sonicated in an ultrasonic washer for 10 minutes, followed by filtration through a pad of celite. The filtrate was concentrated under vacuum. The residue was purified by trituration (PE/EA=1/1) to afford 3-(2,6-difluoro-4-((R)-3-

(hydroxymethyl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione (16.5g, 76.7%).

The title compound was purified by prep-chiral-SFC and analyzed by the following conditions corresponding to peak A @ 0.999 min. $[M+H]^+ = 325.0$

Injection Volume (μL) : 1.00

Column Name : (S,S)WHELK-01 4.6*50 mm, 3.5 μm

Solvent A: CO_2

Solvent B: MeOH (0.1% DEA)

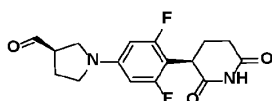
Temperature ($^\circ\text{C}$) : 35

Flow (mL/min) : 4

Gradient (B%): 10% to 50% in 2.0 min, hold 1.0 min at 50%

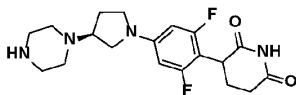
Back Pressure (psi): 1500

[0385] Step 3: (R)-1-(4-((R)-2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)pyrrolidine-3-carbaldehyde

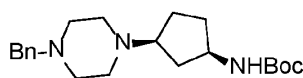


The title compound was prepared in a manner similar to that in intermediate 33 step 2. $[M+H]^+ = 323.0$.

[0386] Intermediate 117: 3-(2,6-difluoro-4-((S)-3-(piperazin-1-yl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione

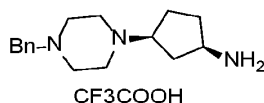


[0387] Step 1: tert-butyl ((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)carbamate



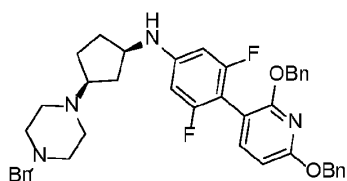
A mixture of tert-butyl ((1R,3S)-3-aminocyclopentyl)carbamate (7 g, 35 mmol), benzyl-bis(2-chloroethyl)amine hydrochloride (9.38 g, 35 mmol), KI (581 mg, 3.5 mmol) and K_2CO_3 (24.2 g, 175 mmol) in acetonitrile (140 mL) was stirred at 80°C for overnight. After the reaction mixture had cooled, it was diluted with dichloromethane and extracted with 1N HCl. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by reverse phase column (ACN/water(0.05%TFA)=0-30%) to afford tert-butyl ((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)carbamate (5.3 g, 42.0%). $[M+H]^+ = 360.3$

[0388] Step 2: (1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentan-1-amine trifluoroacetate



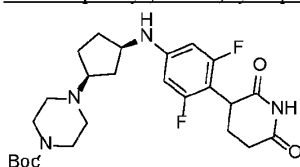
To a solution of tert-butyl ((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)carbamate (5.3 g, 14.8 mmol) in dichloromethane (40 mL) was added trifluoroacetic acid (20 mL). The reaction mixture was stirred at rt for overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by trituration (PE/EA = 10/1) to afford (1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentan-1-amine trifluoroacetate (5.4 g, 98.1%). $[M+H]^+ = 260.11$

[0389] Step 3: N-((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)-4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluoroaniline



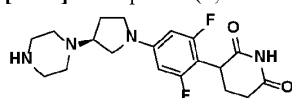
A mixture of intermediate 6 (6.0 g, 12.5 mmol), (1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentan-1-amine trifluoroacetate (5.5 g, 15.0 mmol), $\text{Pd}_2(\text{dba})_3$ (1.1 g, 1.24 mmol), Ruphos (593.7 mg, 1.24 mmol) and Cs_2CO_3 (12.1 g, 37.4 mmol) in dioxane (60 mL) was stirred at 100°C for overnight under nitrogen atmosphere. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE = 50%-100%) to afford crude solid. Then, the residue was purified by reverse phase column (ACN/water(0.05%TFA) = 0-50%) to afford N-((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)-4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluoroaniline (5.3 g, 64.3%). $[\text{M}+\text{H}]^+ = 661.33$.

[0390] Step 4: tert-butyl 4-((1S,3R)-3-((4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)amino)cyclopentyl)piperazine-1-carboxylate



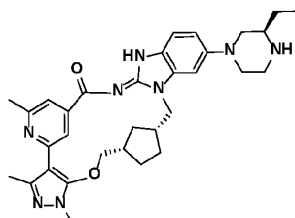
A mixture of N-((1R,3S)-3-(4-benzylpiperazin-1-yl)cyclopentyl)-4-(2,6-bis(benzyloxy)pyridin-3-yl)-3,5-difluoroaniline (5.0 g, 7.57 mmol), Boc_2O (2.0 g, 9.08 mmol) and Pd/C (5.0 g) in THF (80 mL) was stirred at 50°C for overnight under H_2 atmosphere. After the reaction mixture had cooled, it was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM = 0-5%) to afford tert-butyl 4-((1S,3R)-3-((4-(2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)amino)cyclopentyl)piperazine-1-carboxylate (2.64 g, 71.3%). $[\text{M}+\text{H}]^+ = 493.25$

[0391] Step 5: 3-(2,6-difluoro-4-((S)-3-(piperazin-1-yl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione



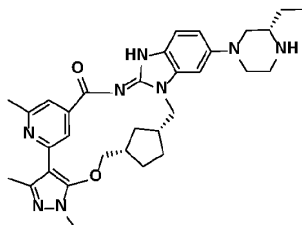
The title compound was prepared in a manner similar to that in intermediate 2 step 2. $[\text{M}+\text{H}]^+ = 379.2$.

[0392] Intermediate 118: (7¹R,7³S,E)-5⁶-((R)-3-ethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5⁴H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



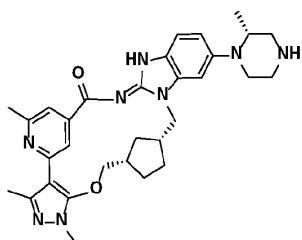
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

[0393] Intermediate 119: (7¹R,7³S,E)-5⁶-((S)-3-ethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



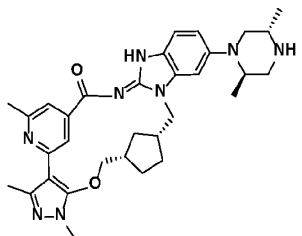
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

[0394] Intermediate 120: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-((R)-2-methylpiperazin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



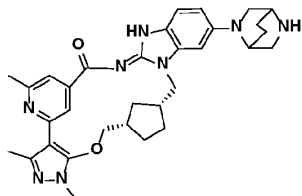
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 555.2$.

[0395] Intermediate 121: (7¹R,7³S,E)-5⁶-((2R,5S)-2,5-dimethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

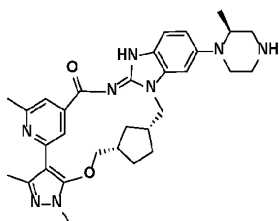
[0396] Intermediate 122: (7¹R,7³S,E)-5⁶-(2,5-diazabicyclo[2.2.2]octan-2-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 567.4$

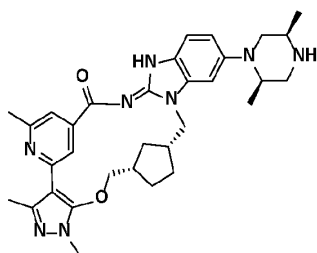
[0397] Intermediate 123: (7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-5⁶-((S)-2-methylpiperazin-1-yl)-5²,5³-dihydro-

1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



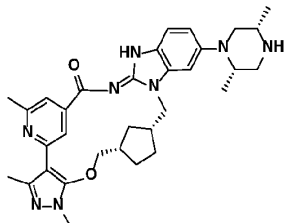
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 555.3$

[0398] Intermediate 124: (7¹R,7³S,E)-5⁶-((2R,5R)-2,5-dimethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



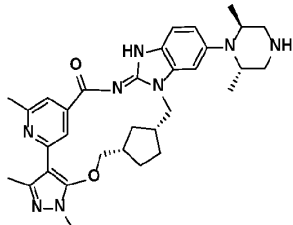
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

[0399] Intermediate 125: (7¹R,7³S,E)-5⁶-((2S,5S)-2,5-dimethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

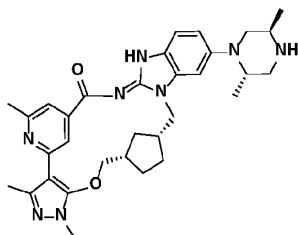
[0400] Intermediate 126: (7¹R,7³S,E)-5⁶-((2S,6S)-2,6-dimethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

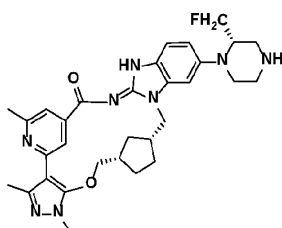
[0401] Intermediate 127: (7¹R,7³S,E)-5⁶-((2S,5R)-2,5-dimethylpiperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one

cyclopentanacyclononaphan-3-one



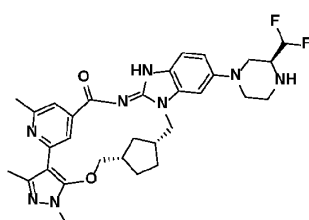
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 569.2$.

[0402] Intermediate 128: (7¹R,7³S,E)-5⁶-(S)-2-(fluoromethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



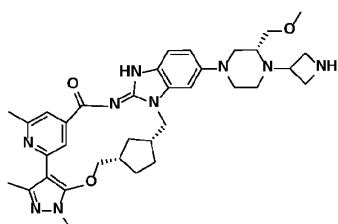
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 573.6$.

[0403] Intermediate 129: (7¹R,7³S,E)-5⁶-(S)-3-(difluoromethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



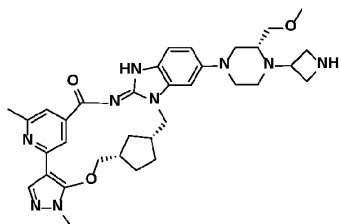
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 591.5$.

[0404] Intermediate 130: (7¹R,7³S,E)-5⁶-((R)-4-(azetidin-3-yl)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



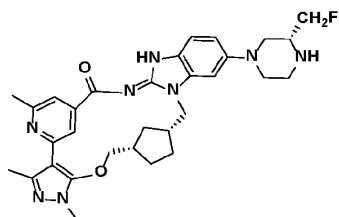
The title compound was prepared in a manner similar to that in intermediate 61. $[M+H]^+ = 640.5$.

[0405] Intermediate 131: (7¹R,7³S,E)-5⁶-((R)-4-(azetidin-3-yl)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



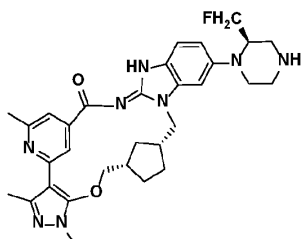
The title compound was prepared in a manner similar to that in intermediate 61. $[M+H]^+ = 626.6$

[0406] Intermediate 132: (7¹R,7³S,E)-5⁶-(*(R)*-3-(fluoromethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



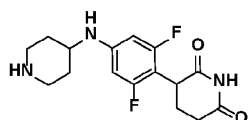
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 573.5$.

[0407] Intermediate 133: (7¹R,7³S,E)-5⁶-(*(R)*-2-(fluoromethyl)piperazin-1-yl)-1¹,1³,2⁶-trimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



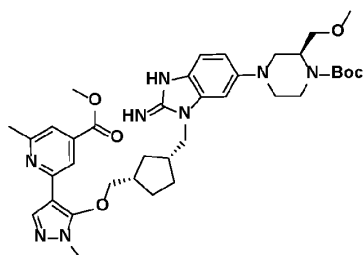
The title compound was prepared in a manner similar to that in intermediate 1 and 2. $[M+H]^+ = 573.6$.

[0408] Intermediate 134: (*(R)*)-3-(2,6-difluoro-4-(piperidin-4-ylamino)phenyl)piperidine-2,6-dione

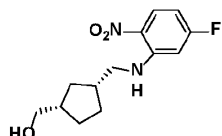


The title compound was prepared in a manner similar to that in intermediate 63. $[M+H]^+ = 324.2$.

[0409] Intermediate 135: tert-butyl (S)-4-(2-imino-3-(((1*R*,3*S*)-3-(((4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-1-carboxylate

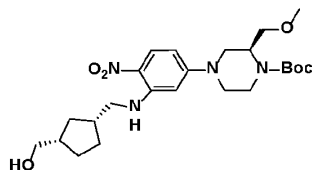


[0410] Step 1: ((1S,3R)-3-(((5-fluoro-2-nitrophenyl)amino)methyl)cyclopentyl)methanol



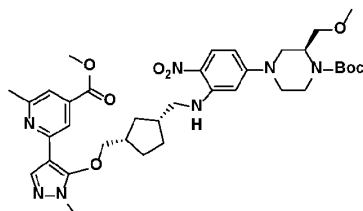
2,4-difluoronitrobenzene (1.15 g, 7.26 mmol, 1.1 equiv.) was added to a 50 mL 3-neck round-bottom flask and toluene (10 mL, 10 vol) was added. TEA (1.40 g, 13.9 mmol, 2.1 equiv.) was then added, followed by ((1S,3R)-3-(aminomethyl)cyclopentyl)methanol hydrochloride (1.1 g, 6.6 mmol, 1.0 equiv.). The mixture was heated to 75 °C and stirred at 75 °C overnight. The reaction mixture was cooled to rt and washed with water (~2 x 10 vol). The organic layer was collected and solvent was swapped from toluene to acetonitrile. The compound in acetonitrile (5 vol) was directly used for next step. $[M+H]^+ = 269.2$

[0411] Step 2: tert-butyl (S)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate



To ((1S,3R)-3-(((5-fluoro-2-nitrophenyl)amino)methyl)cyclopentyl)methanol in acetonitrile was added TEA (1.0 g, 9.9 mmol, 1.5 equiv.) and tert-butyl (S)-2-(methoxymethyl)piperazine-1-carboxylate (1.27 g, 8.0 mmol, 1.2 equiv.) was then added. The mixture was heated to 75 °C and stirred at 75 °C for 24 hours. The reaction mixture was cooled to rt and diluted with DCM (10-15 vol) to dissolve the product. The mixture was washed with water (~2 x 10 vol). The organic layer was concentrated and purified by silica column chromatography (EA/DCM=0-30%) to afford tert-butyl (S)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate. $[M+H]^+ = 479.3$

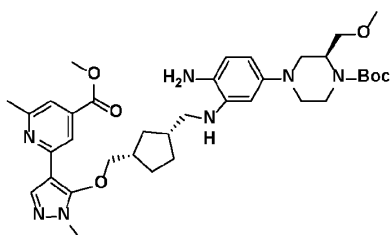
[0412] Step 3: tert-butyl (S)-4-(3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate



To a 50 mL flask, were added tert-butyl (S)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-

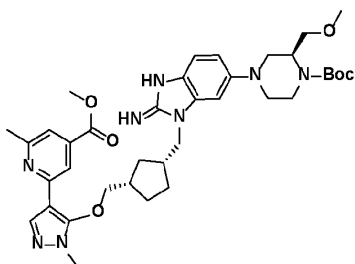
nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.14 g, 2.38 mmol, 1.0 equiv.) and methyl 2-(5-hydroxy-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (588 mg, 2.38 mmol, 1.0 equiv.). THF (10 mL, 10 vol) was then added to afford a slurry. Triphenylphosphine (750 mg, 2.86 mmol, 1.2 equiv.) was then added. After that DIAD (578 mg, 2.86 mmol, 1.2 equiv.) was added slowly using a syringe and stirred at R.T for 1h. The reaction mixture was concentrated and purified by silica column chromatography (EA/DCM=0-30%) to afford tert-butyl (S)-4-(3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.55 g, 92.0% yield). $[M+H]^+=708.4$

[0413] Step 4: tert-butyl (S)-4-(4-amino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate



To a stainless steel reactor was charged with tert-butyl (S)-4-(3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.55 g, 2.2 mmol, 1.00 eq.) and (5 % Wt. Pt, 62.5% H₂O, Kaili Catalyst & New Materials Co.,Ltd) Pt/V/C (826 mg, 0.13 mmol, 0.06 eq.). The reactor was evacuated and filled with N₂ three cycles. 25 ml (15 V) anhydrous THF was transferred to the reactor. The reactor was purged with N₂ three times and H₂ three times. The reactor was pressurized with 0.4 MPa of hydrogen and stirred at 40 °C for 24 h. The mixture was filtered, and the solvent was concentrated to afford tert-butyl (S)-4-(4-amino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.35 g, 90.9% yield). $[M+H]^+=678.4$

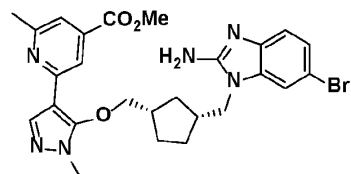
[0414] Step 5: tert-butyl (S)-4-(2-imino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-1-carboxylate



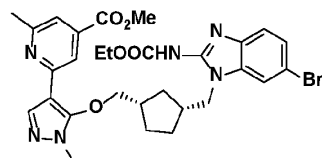
To the solution of tert-butyl (S)-4-(4-amino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.35 g, 2.0 mmol) and BrCN (0.25 g, 2.4 mmol) in 30 mL MeOH was stirred at room temperature for 2 hrs. The mixture was extracted with DCM, washed with aq. sat. NaHCO₃ and separated. The organic layer was concentrated and purified by silica column chromatography (EA/DCM=0-30%) to afford tert-butyl (S)-4-(2-imino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1-methyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-

1-carboxylate (1.30 g, 92.9% yield). $[M+H]^+ = 703.4$

[0415] Intermediate 136: methyl 2-(5-(((1S,3R)-3-((2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate

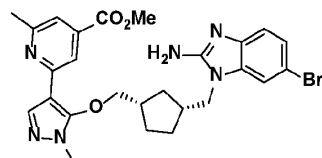


[0416] Step 1: methyl 2-(5-(((1S,3R)-3-((6-bromo-2-((ethoxycarbonyl)amino)-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate



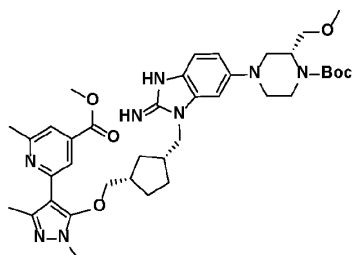
To a solution of methyl 2-(5-(((1S,3R)-3-((2-amino-5-bromophenyl)amino)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (4.2 g, 8.07 mmol, 1 eq.) (product of intermediate 1 step 8) in THF (40 ml, 10 vol) was added O-ethyl carbonisothiocyanatide (1.05 eq) in two batches to the reactor, and stirred at 30° C for 30 minutes after each addition. The reaction was stirred at rt for 1 h to afford an intermediate ($[M+H]^+ = 659.6$). Then, DIPEA (1.56 g, 12.1 mmol, 1.5 eq.) and EDCI (1.86 g, 9.68 mmol, 1.2 eq.) were added. The resulting reaction mixture was stirred at rt for 12 h. The reaction was quenched by H₂O and extracted by DCM. DCM was removed and the crude product was purified by column chromatography (5% MeOH/DCM) to give methyl 2-(5-(((1S,3R)-3-((6-bromo-2-((ethoxycarbonyl)amino)-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (4.6 g, 93% yield). $[M+H]^+ = 625.5$.

[0417] Step 2: methyl 2-(5-(((1S,3R)-3-((2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate

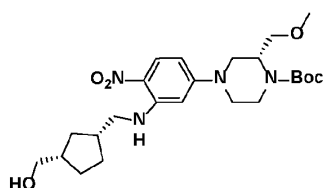


The solution of methyl 2-(5-(((1S,3R)-3-((6-bromo-2-((ethoxycarbonyl)amino)-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (4.6 g, 7.37 mmol) in CH₃CN (46 ml, 10 vol) and H₂O (4.6 ml, 1 vol) was stirred at 80 °C for 20 h. The mixture was concentrated to afford methyl 2-(5-(((1S,3R)-3-((2-amino-6-bromo-1H-benzo[d]imidazol-1-yl)methyl)cyclopentyl)methoxy)-1-methyl-1H-pyrazol-4-yl)-6-methylisonicotinate (3.9 g, 95.8% yield). $[M+H]^+ = 553.5$.

[0418] Intermediate 137: tert-butyl (R)-4-(2-imino-3-(((1R,3S)-3-(((4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-1-carboxylate

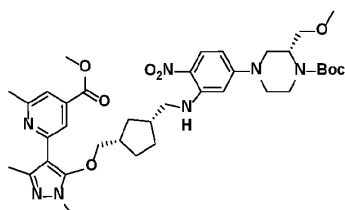


[0419] Step 1: tert-butyl (R)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate



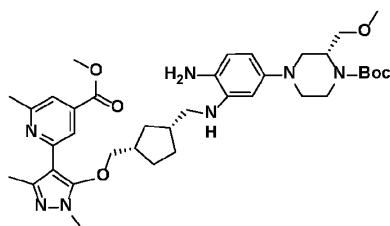
To ((1S,3R)-3-((5-fluoro-2-nitrophenyl)amino)methyl)cyclopentyl)methanol in acetonitrile was added TEA (1.0 g, 9.9 mmol, 1.5 equiv.) and tert-butyl (R)-2-(methoxymethyl)piperazine-1-carboxylate (1.27 g, 8.0 mmol, 1.2 equiv.) was then added. The mixture was heated to 75 °C and stirred at 75 °C for 24 hours. The reaction mixture was cooled to rt and diluted with DCM (10-15 vol) to dissolve the product. The mixture was washed with water (~2 x 10 vol). The organic layer was concentrated and purified by silica column chromatography (EA/DCM=0-30%) to afford tert-butyl (R)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate. $[M+H]^+=479.3$

[0420] Step 2: tert-butyl (R)-4-(3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate



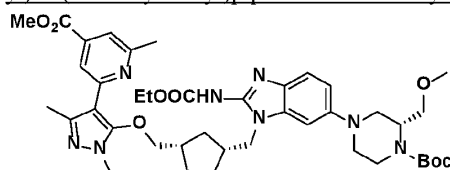
To a 50 mL flask, were added tert-butyl (R)-4-(3-(((1R,3S)-3-(hydroxymethyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.14 g, 2.38 mmol, 1.0 equiv.) and methyl 2-(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)-6-methylisonicotinate (588 mg, 2.38 mmol, 1.0 equiv.). THF (10 mL, 10 vol) was then added to afford a slurry. Triphenylphosphine (750 mg, 2.86 mmol, 1.2 equiv.) was then added. After that DIAD (578 mg, 2.86 mmol, 1.2 equiv.) was added slowly using a syringe and stirred at rt for 1h. The reaction mixture was concentrated and purified by silica column chromatography (EA/DCM=0-30%) to afford tert-butyl (R)-4-(3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.55 g, 92.0% yield). $[M+H]^+=722.4$

[0421] Step 3: tert-butyl (R)-4-(4-amino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate



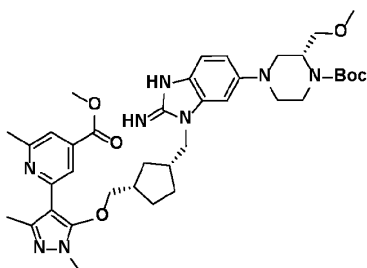
To a stainless steel reactor was charged with tert-butyl (R)-4-(3-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)-4-nitrophenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.55 g, 2.2 mmol, 1.00 eq.) and (5 % Wt. Pt, 62.5% H₂O, Kaili Catalyst & New Materials Co.,Ltd) Pt/V/C (826 mg, 0.13 mmol, 0.06 eq.). The reactor was evacuated and filled with N₂ three cycles. 25 ml (15 V) anhydrous THF was transferred to the reactor. The reactor was purged with N₂ three times and H₂ three times. The reactor was pressurized with 0.4 MPa of hydrogen and stirred at 40 °C for 24 h. The mixture was filtered, and the solvent was concentrated to afford tert-butyl (R)-4-(4-amino-3-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.35 g, 90.9% yield). [M+H]⁺=692.4

[0422] Step 4: tert-butyl (R)-4-(2-((ethoxycarbonyl)amino)-1-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-1H-benzo[d]imidazol-6-yl)-2-(methoxymethyl)piperazine-1-carboxylate



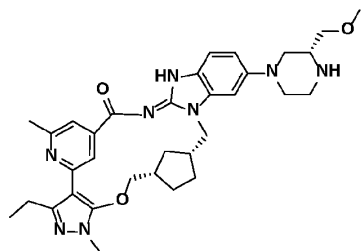
[0423] To a solution of tert-butyl (R)-4-(4-amino-3-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)amino)phenyl)-2-(methoxymethyl)piperazine-1-carboxylate (1.35 g, 1.95 mmol, 1 eq.) in THF (15 ml, 10 vol) was added O-ethyl carbonisothiocyanatide (1.05 eq) in two batches to the reactor, and stirred at 30° C for 30 minutes after each addition. The reaction was stirred at rt for 1 h to afford an intermediate ([M+H]⁺=823.4). Then, DIPEA (377 mg, 2.9 mmol, 1.5 eq.) and EDCI (450 mg, 2.34 mmol, 1.2 eq.) were added. The resulting reaction mixture was stirred at rt for 12 h. The reaction was quenched by H₂O and extracted by DCM. DCM was removed and the crude product was purified by column chromatography (5% MeOH/DCM) to give tert-butyl (R)-4-(2-(((ethoxycarbonyl)amino)-1-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-1H-benzo[d]imidazol-6-yl)-2-(methoxymethyl)piperazine-1-carboxylate (1.38 g, 89% yield). [M+H]⁺=789.4

[0424] Step 5: tert-butyl (R)-4-(2-imino-3-((((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-1-carboxylate



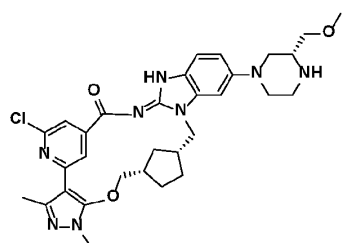
The solution of tert-butyl (R)-4-(2-((ethoxycarbonyl)amino)-1-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-1H-benzo[d]imidazol-6-yl)-2-(methoxymethyl)piperazine-1-carboxylate (1.38 g, 1.75 mmol) in CH₃CN (14 ml, 10 vol) and H₂O (1.5 ml, 1 vol) was stirred at 80 °C for 20 h. The mixture was concentrated to afford tert-butyl (R)-4-(2-imino-3-(((1R,3S)-3-(((4-(4-(methoxycarbonyl)-6-methylpyridin-2-yl)-1,3-dimethyl-1H-pyrazol-5-yl)oxy)methyl)cyclopentyl)methyl)-2,3-dihydro-1H-benzo[d]imidazol-5-yl)-2-(methoxymethyl)piperazine-1-carboxylate (1.15 g, 91.7% yield). [M+H]⁺=717.4

[0425] Intermediate 138: (7¹R,7³S,E)-1³-ethyl-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,2⁶-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



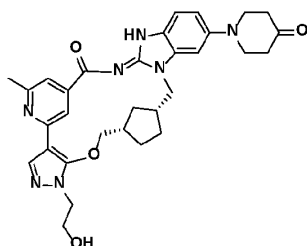
The title compound was prepared in a manner similar to that in intermediates 1 and 2. [M+H]⁺ = 599.5.

[0426] Intermediate 139: (7¹R,7³S,E)-2⁶-chloro-5⁶-((R)-3-(methoxymethyl)piperazin-1-yl)-1¹,1³-dimethyl-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediates 1 and 2. [M+H]⁺ = 605.3.

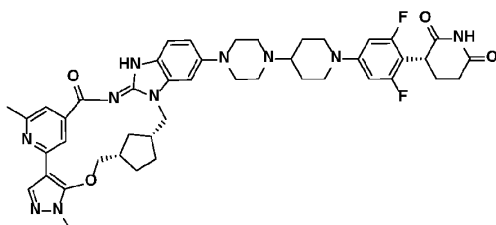
[0427] Intermediate 140: (7¹R,7³S,E)-1¹-(2-hydroxyethyl)-2⁶-methyl-5⁶-(4-oxopiperidin-1-yl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphan-3-one



The title compound was prepared in a manner similar to that in intermediates 64 with intermediate 75. $[M+H]^+ = 570.3$.

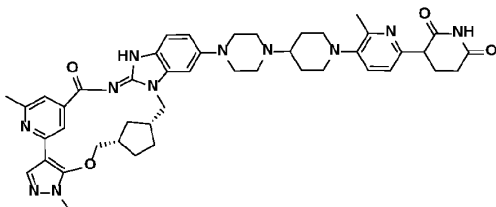
Compound synthesis

[0428] Example 1: (R)-3-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



To a solution of intermediate 2 (80 mg, 0.15 mmol) and intermediate 7 (68 mg, 0.21 mmol) in DCE (8 mL) was added STAB (95 mg, 0.45 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO₃ and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column (DCM : CH₃OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (33 mg, 26.1%). ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.01 (s, 1H), 6.90 (d, $J = 8.7$ Hz, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 4.30 (s, 1H), 4.19 (s, 1H), 4.05 (dd, $J = 12.5, 5.0$ Hz, 3H), 3.81 (d, $J = 12.1$ Hz, 2H), 3.74 (s, 3H), 3.16 (s, 4H), 2.77 (dd, $J = 15.1, 7.7$ Hz, 3H), 2.68 (s, 4H), 2.65 – 2.57 (m, 2H), 2.55 (s, 3H), 2.53 (d, $J = 4.0$ Hz, 2H), 2.49 – 2.40 (m, 2H), 2.09 (qd, $J = 13.4, 4.9$ Hz, 1H), 1.99 – 1.79 (m, 6H), 1.67 (s, 1H), 1.54 – 1.43 (m, 2H). $[M+H]^+ = 833.7$

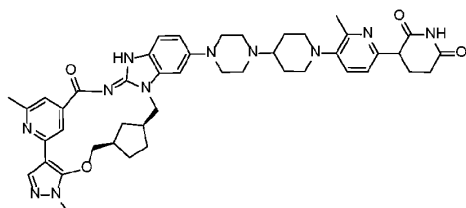
[0429] Example 2: 3-(5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 15. ¹H NMR (500 MHz, DMSO) δ 12.56 (s, 1H), 10.88 (s, 1H), 8.64 (s, 1H), 8.02 (s, 1H), 7.60 (s, 1H), 7.56 (d, $J =$

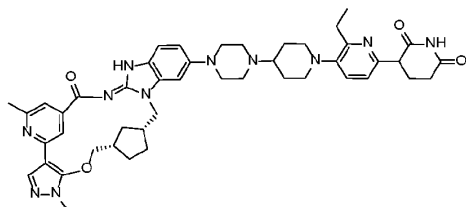
8.1 Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 7.27 (d, $J = 7.9$ Hz, 1H), 7.17 (s, 1H), 7.01 (d, $J = 8.3$ Hz, 1H), 4.33 (s, 1H), 4.22 (s, 1H), 4.13 (s, 2H), 4.00 (dd, $J = 9.8, 5.2$ Hz, 1H), 3.95 (d, $J = 11.6$ Hz, 2H), 3.77 (s, 3H), 3.72 (d, $J = 10.9$ Hz, 2H), 3.41 – 3.39 (m, 2H), 3.29 (d, $J = 10.7$ Hz, 4H), 3.08 (d, $J = 11.8$ Hz, 2H), 2.74 (t, $J = 11.4$ Hz, 2H), 2.67 – 2.58 (m, 7H), 2.48 (s, 3H), 2.25 (d, $J = 10.1$ Hz, 3H), 2.09 (dd, $J = 13.3, 5.2$ Hz, 1H), 1.96 – 1.80 (m, 6H), 1.68 (s, 1H). $[M+H]^+ = 812.7$

[0430] Example 3: 3-(5-(4-(4-((7¹S,7³R,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



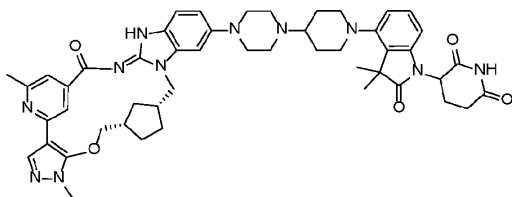
The title compound was prepared in a manner similar to that in Example 1 with intermediates 5 and 15. ¹H NMR (500 MHz, DMSO) δ 12.56 (s, 1H), 10.88 (s, 1H), 8.64 (s, 1H), 8.02 (s, 1H), 7.60 (s, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 7.27 (d, $J = 7.9$ Hz, 1H), 7.17 (s, 1H), 7.01 (d, $J = 8.3$ Hz, 1H), 4.33 (s, 1H), 4.22 (s, 1H), 4.13 (s, 2H), 4.00 (dd, $J = 9.8, 5.2$ Hz, 1H), 3.95 (d, $J = 11.6$ Hz, 2H), 3.77 (s, 3H), 3.72 (d, $J = 10.9$ Hz, 2H), 3.41 – 3.39 (m, 2H), 3.29 (d, $J = 10.7$ Hz, 4H), 3.08 (d, $J = 11.8$ Hz, 2H), 2.74 (t, $J = 11.4$ Hz, 2H), 2.67 – 2.58 (m, 7H), 2.48 (s, 3H), 2.25 (d, $J = 10.1$ Hz, 3H), 2.09 (dd, $J = 13.3, 5.2$ Hz, 1H), 1.96 – 1.79 (m, 6H), 1.68 (s, 1H). $[M+H]^+ = 812.6$

[0431] Example 4: 3-(5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-ethylpyridin-2-yl)piperidine-2,6-dione



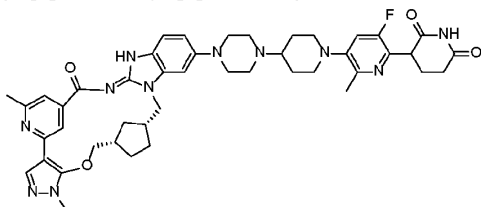
The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 17. ¹H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 10.79 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 7.02 (s, 1H), 6.91 (dd, $J = 8.8, 1.7$ Hz, 1H), 4.30 (s, 1H), 4.19 (t, $J = 8.0$ Hz, 1H), 4.09 (s, 2H), 3.91 (dd, $J = 7.7, 5.6$ Hz, 1H), 3.75 (d, $J = 5.0$ Hz, 3H), 3.18 (s, 4H), 3.07 (s, 2H), 2.80 (td, $J = 14.8, 7.4$ Hz, 1H), 2.75 – 2.52 (m, 15H), 2.43 – 2.34 (m, 1H), 2.23 – 2.09 (m, 2H), 1.99 – 1.75 (m, 6H), 1.70 – 1.57 (m, 3H), 1.18 (t, $J = 7.4$ Hz, 3H). $[M+H]^+ = 826.6$

[0432] Example 5: 3-(4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione



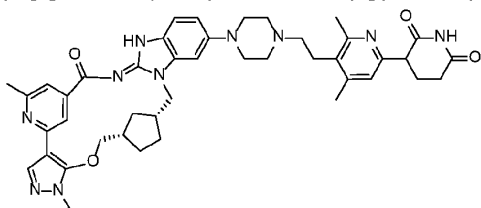
The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 10. ^1H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 11.06 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H), 6.92 (d, J = 9.0 Hz, 1H), 6.80 (s, 1H), 5.31 – 5.09 (m, 1H), 4.32 (ddd, J = 14.6, 11.5, 5.9 Hz, 1H), 4.19 (t, J = 7.7 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.74 (s, 3H), 3.23 – 3.13 (m, 4H), 2.94 – 2.86 (m, 3H), 2.85 – 2.77 (m, 3H), 2.72 (s, 4H), 2.67 – 2.57 (m, 4H), 2.55 (s, 3H), 2.52 (d, J = 1.4 Hz, 1H), 2.41 (t, J = 10.7 Hz, 1H), 1.96 – 1.90 (m, 4H), 1.87 – 1.79 (m, 2H), 1.68 – 1.57 (m, 3H), 1.42 (s, 3H), 1.41 (s, 3H). $[\text{M}+\text{H}]^+ = 880.7$.

[0433] Example 6: 3-(5-(4-(4-((7 ^1R ,7 ^3S ,E)-1 1 ,2 6 -dimethyl-3-oxo-5 2 ,5 3 -dihydro-1 ^1H ,5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5 6 -yl)piperazin-1-yl)piperidin-1-yl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 12. ^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 11.6 Hz, 1H), 7.03 (s, 1H), 6.92 (dd, J = 8.8, 1.9 Hz, 1H), 4.39 – 4.25 (m, 1H), 4.23 – 4.17 (m, 1H), 4.14 (dd, J = 11.2, 5.3 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.74 (s, 3H), 3.23 – 3.14 (m, 7H), 2.76 – 2.71 (m, 5H), 2.68 (d, J = 5.2 Hz, 1H), 2.66 (s, 1H), 2.64 – 2.62 (m, 1H), 2.59 – 2.56 (m, 1H), 2.55 (s, 3H), 2.54 – 2.52 (m, 2H), 2.44 – 2.35 (m, 5H), 2.28 – 2.19 (m, 1H), 2.08 – 2.01 (m, 1H), 1.94 (d, J = 11.3 Hz, 3H), 1.87 – 1.79 (m, 2H), 1.70 – 1.58 (m, 3H). $[\text{M}+\text{H}]^+ = 830.7$.

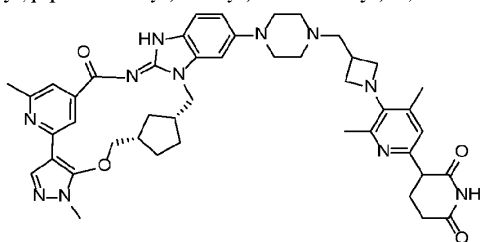
[0434] Example 7: 3-(5-(2-(4-((7 ^1R ,7 ^3S ,E)-1 1 ,2 6 -dimethyl-3-oxo-5 2 ,5 3 -dihydro-1 ^1H ,5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5 6 -yl)piperazin-1-yl)ethyl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



To the solution of intermediate 2 (90 mg, 0.17 mmol), intermediate 19 (70 mg, 0.21 mmol) and KI (65 mg, 0.35 mmol) in MeCN (5 mL) and DIEA (67 mg, 0.52 mmol) in DMSO (2 mL) was added. The resulting mixture was heated at 80°C overnight under N_2 . The mixture was quenched with water and extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine (1 x 15 mL), dried over Na_2SO_4 , filtered

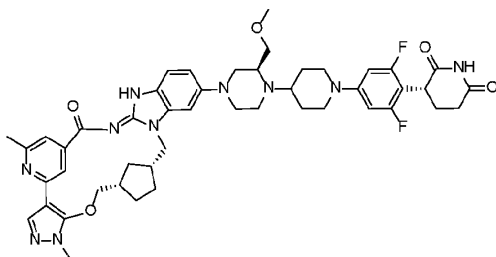
and concentrated under reduced pressure to give the crude residue, which was purified by silica column chromatography (DCM: MeOH = 100:1-10:1), followed by Prep-HPLC chromatography to afford the title product (21 mg, 16%). ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.79 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.98 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.19 (t, *J* = 7.9 Hz, 1H), 4.13 – 4.02 (m, 2H), 3.85 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.74 (s, 3H), 3.26 – 3.18 (m, 4H), 2.86 – 2.79 (m, 2H), 2.73 – 2.66 (m, 4H), 2.64 – 2.56 (m, 5H), 2.55 (s, 3H), 2.52 (s, 2H), 2.47 (s, 3H), 2.39 – 2.35 (m, 1H), 2.32 (s, 3H), 2.25 – 2.16 (m, 1H), 2.12 – 2.04 (m, 1H), 1.97 – 1.89 (m, 1H), 1.87 – 1.79 (m, 2H), 1.71 – 1.63 (m, 1H). [M+H]⁺ = 771.6.

[0435] Example 8: 3-(5-(3-((4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)azetidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 7 with intermediates 2 and 18. ¹H NMR (500 MHz, DMSO) δ 10.72 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 1.7 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.74 (s, 1H), 4.36 – 4.28 (m, 1H), 4.25 (t, *J* = 7.4 Hz, 2H), 4.19 (t, *J* = 8.1 Hz, 1H), 4.14 – 4.00 (m, 2H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.74 (s, 3H), 3.72 (d, *J* = 5.3 Hz, 1H), 3.17 (s, 4H), 2.79 (dt, *J* = 13.7, 6.7 Hz, 1H), 2.68 – 2.52 (m, 15H), 2.35 (s, 3H), 2.23 (s, 3H), 2.20 – 2.11 (m, 1H), 2.09 – 2.01 (m, 1H), 1.96 – 1.88 (m, 1H), 1.86 – 1.78 (m, 2H), 1.73 – 1.62 (m, 1H). [M+H]⁺ = 812.6.

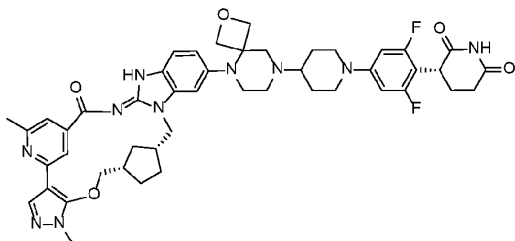
[0436] Example 9: (R)-3-(4-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 7. ¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.36 – 4.25 (m, 1H), 4.19 (t, *J* = 7.9 Hz, 1H), 4.13 – 4.08 (m, 1H), 4.05 (dd, *J* = 12.6, 5.2 Hz, 2H), 3.83 (d, *J* = 11.9 Hz, 2H), 3.74 (s, 3H), 3.57 (dd, *J* = 9.6, 4.3 Hz, 1H), 3.51 (dd, *J* = 9.7, 5.9 Hz, 1H), 3.30 (s, 3H), 3.28 (d, *J* = 3.0 Hz, 1H), 3.24 – 3.16 (m, 1H), 3.10 – 3.01 (m, 2H), 2.98 (dd, *J* = 11.1, 7.1 Hz, 1H), 2.94 – 2.86 (m, 1H), 2.86 – 2.68 (m, 7H), 2.67 – 2.57 (m, 3H), 2.55 (s, 3H), 2.09 (qd, *J* = 12.9, 3.8 Hz, 1H), 2.00 – 1.81 (m, 5H), 1.74 (d, *J* = 11.9 Hz, 1H), 1.68 – 1.57

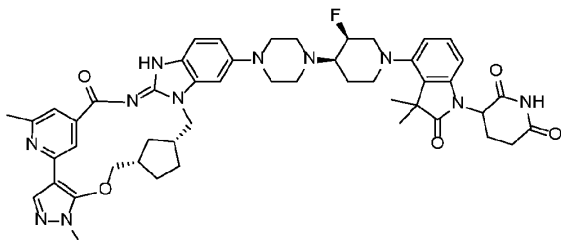
(m, 2H), 1.44 (ddd, $J = 15.2, 12.4, 3.6$ Hz, 1H). $[M+H]^+ = 877.6$.

[0437] Example 10: (R)-3-(4-(4-(5-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-oxa-5,8-diazaspiro[3.5]nonan-8-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



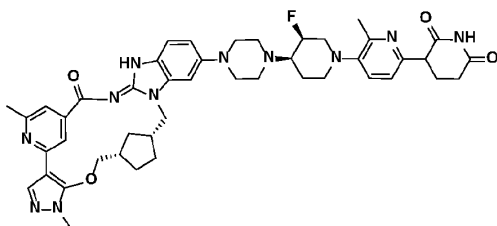
The title compound was prepared in a manner similar to that in Example 1 with intermediates 4 and 7. ¹H NMR (500 MHz, DMSO) δ 12.50 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.02 (s, 1H), 6.75 (dd, $J = 8.5, 1.6$ Hz, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 4.53 (d, $J = 6.1$ Hz, 2H), 4.38 (d, $J = 6.2$ Hz, 2H), 4.35 – 4.27 (m, 1H), 4.19 (t, $J = 8.2$ Hz, 1H), 4.10 (t, $J = 8.4$ Hz, 1H), 4.05 (dd, $J = 12.6, 5.1$ Hz, 2H), 3.80 (d, $J = 12.5$ Hz, 2H), 3.74 (s, 3H), 3.26 – 3.18 (m, 2H), 2.99 (s, 2H), 2.84 – 2.74 (m, 3H), 2.65 – 2.51 (m, 7H), 2.49 – 2.46 (m, 4H), 2.09 (qd, $J = 13.0, 3.7$ Hz, 1H), 2.00 – 1.89 (m, 2H), 1.83 (d, $J = 10.1$ Hz, 4H), 1.75 – 1.66 (m, 1H), 1.56 – 1.46 (m, 2H). $[M+H]^+ = 875.7$.

[0438] Example 11: 3-(4-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-3,3-dimethyl-2-oxoindolin-1-yl)piperidine-2,6-dione



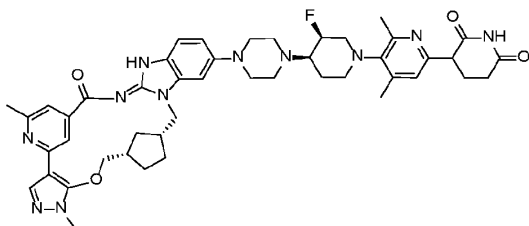
A mixture of intermediate 1 (104 mg, 0.2 mmol), intermediate 9 (137 mg, 0.3 mmol), Pd₂dba₃ (36.6 mg, 0.04 mmol), Ruphos (36.8 mg, 0.08 mmol) and ^tBuONa (76.8 mg, 0.8 mmol) in DMA (5 mL) was stirred in a round bottom flask at 90 °C for 1 hour under N₂. Water (10 mL) was added, and the mixture was extracted with DCM (20 mL $\times$ 3). The combined organic layer was dried over Na₂SO₄. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography to afford the product (40 mg, 22%). ¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 11.07 (s, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.25 (t, $J = 8.0$ Hz, 1H), 7.10 – 7.00 (m, 2H), 6.95 – 6.90 (m, 1H), 6.83 (s, 1H), 5.25 – 5.21 (m, 1H), 5.15 – 5.06 (m, 1H), 4.38 – 4.25 (m, 1H), 4.22 – 4.16 (m, 1H), 4.14 – 4.02 (m, 2H), 3.74 (s, 3H), 3.24 – 3.17 (m, 4H), 3.15 – 2.97 (m, 2H), 2.96 – 2.80 (m, 7H), 2.64 – 2.54 (m, 9H), 2.09 – 1.99 (m, 1H), 1.98 – 1.76 (m, 6H), 1.69 – 1.65 (m, 1H), 1.43 (dd, $J = 8.3, 3.8$ Hz, 6H). $[M+H]^+ = 898.6$.

[0439] Example 12: 3-(5-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



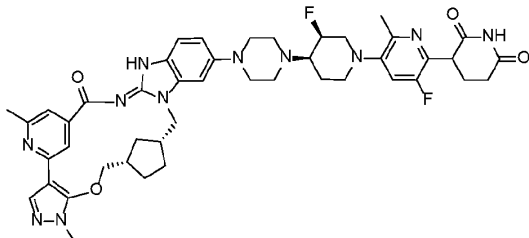
The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 26. ^1H NMR (500 MHz, DMSO) δ 12.36 (s, 1H), 10.79 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.40 (s, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 5.16-5.06 (m, 1H), 4.38 – 4.26 (m, 1H), 4.23 – 4.16 (m, 1H), 4.14 – 4.01 (m, 2H), 3.90 (dd, $J = 9.5, 5.3$ Hz, 1H), 3.74 (s, 3H), 3.19 (d, $J = 4.4$ Hz, 5H), 2.92 – 2.79 (m, 6H), 2.65 – 2.63 (m, 1H), 2.62 – 2.56 (m, 4H), 2.54 (dd, $J = 6.1, 2.4$ Hz, 5H), 2.44 – 2.42 (m, 3H), 2.26 – 2.17 (m, 1H), 2.12 – 2.00 (m, 2H), 1.96 – 1.75 (m, 5H), 1.72 – 1.62 (m, 1H). $[\text{M}+\text{H}]^+ = 830.6$.

[0440] Example 13: 3-(5-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 22. ^1H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.79 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.07 – 6.90 (m, 3H), 5.07-4.97 (m, 1H), 4.37 – 4.25 (m, 1H), 4.19 (t, $J = 7.5$ Hz, 1H), 4.14 – 4.02 (m, 2H), 3.85 (dd, $J = 8.1, 5.8$ Hz, 1H), 3.74 (s, 3H), 3.25 – 3.07 (m, 6H), 3.01-2.94 (m, 1H), 2.88 – 2.78 (m, 4H), 2.66 – 2.53 (m, 10H), 2.47 – 2.35 (m, 3H), 2.28 (d, $J = 13.9$ Hz, 3H), 2.25 – 2.14 (m, 1H), 2.12 – 1.99 (m, 2H), 1.97 – 1.59 (m, 6H). $[\text{M}+\text{H}]^+ = 844.6$.

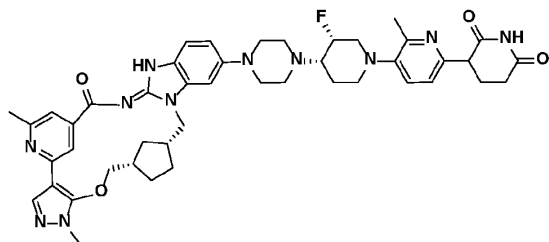
[0441] Example 14: 3-(5-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 21. ^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J =$

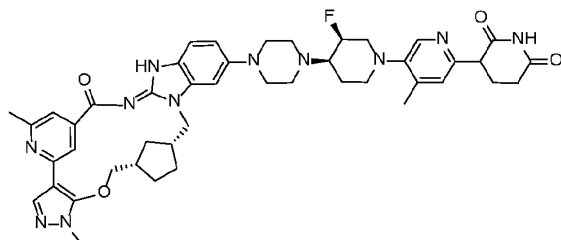
8.9 Hz, 1H), 7.34 (s, 1H), 7.04 (s, 1H), 6.93 (d, $J = 9.1$ Hz, 1H), 5.16–5.06 (m, 1H), 4.31 (s, 1H), 4.24 – 4.03 (m, 4H), 3.74 (s, 3H), 3.23 – 3.15 (m, 4H), 2.94 – 2.80 (m, 6H), 2.76 – 2.67 (m, 2H), 2.64 – 2.57 (m, 5H), 2.54 (d, $J = 3.8$ Hz, 4H), 2.40 (s, 3H), 2.32 – 2.20 (m, 1H), 2.09 – 1.99 (m, 2H), 1.96 – 1.66 (m, 6H). $[M+H]^+ = 848.7$.

[0442] Example 15: 3-(5-((3R,4S)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



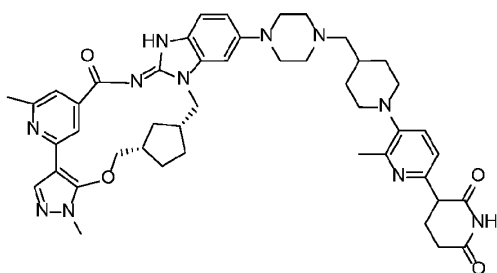
The titled compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 24. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.79 (s, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.38 (t, $J = 8.2$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 1H), 7.04 (s, 1H), 6.93 (d, $J = 9.1$ Hz, 1H), 4.31 (s, 1H), 4.19 (s, 1H), 4.10 (s, 1H), 3.90 (dd, $J = 9.4, 5.4$ Hz, 1H), 3.74 (s, 3H), 3.45 (s, 2H), 3.41 – 3.36 (m, 4H), 3.19 (s, 4H), 2.83 (s, 4H), 2.62 – 2.61 (m, 1H), 2.59 – 2.56 (m, 2H), 2.55 (s, 3H), 2.42 (s, 3H), 2.25 – 2.18 (m, 1H), 2.10 – 2.03 (m, 2H), 1.96 – 1.91 (m, 1H), 1.85 – 1.80 (m, 2H), 1.70 – 1.65 (m, 1H), 1.24 (s, 3H), 0.88 – 0.83 (m, 2H), $[M+H]^+ = 830.6$

[0443] Example 21: 3-(5-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione



The titled compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 27. ¹H NMR (500 MHz, DMSO) δ 12.36 (s, 1H), 10.80 (s, 1H), 8.52 (s, 1H), 8.16 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.15 (s, 1H), 7.04 (s, 1H), 6.93 (d, $J = 8.7$ Hz, 1H), 5.18 – 5.00 (m, 1H), 4.32 (dd, $J = 12.3, 10.5$ Hz, 1H), 4.19 (t, $J = 7.1$ Hz, 1H), 4.14 – 4.03 (m, 2H), 3.90 (dd, $J = 8.8, 5.4$ Hz, 1H), 3.74 (s, 3H), 3.29 – 3.17 (m, 6H), 3.01 – 2.79 (m, 7H), 2.65 – 2.56 (m, 6H), 2.55 (s, 3H), 2.28 (s, 3H), 2.23 – 2.16 (m, 1H), 2.13 – 2.08 (m, 1H), 2.04 – 1.98 (m, 1H), 1.95 – 1.90 (m, 1H), 1.87 – 1.79 (m, 3H), 1.71 – 1.61 (m, 1H). $[M+H]^+ = 830.7$.

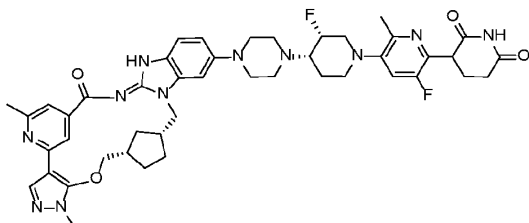
[0444] Example 23: 3-(5-(4-((4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 28.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.78 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (dd, $J = 8.4, 2.5$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 1H), 7.03 (s, 1H), 6.92 (d, $J = 8.9$ Hz, 1H), 4.36 – 4.27 (m, 1H), 4.20 (dd, $J = 12.3, 8.2$ Hz, 1H), 4.11 – 4.07 (m, 2H), 3.89 (dd, $J = 9.3, 5.3$ Hz, 1H), 3.74 (s, 4H), 3.18 (s, 4H), 3.08 (d, $J = 11.1$ Hz, 3H), 2.60 – 2.58 (m, 5H), 2.57 – 2.51 (m, 7H), 2.39 (s, 3H), 2.28 (d, $J = 7.2$ Hz, 2H), 2.23 – 2.19 (m, 1H), 2.12 – 2.07 (m, 1H), 1.97 – 1.78 (m, 6H), 1.74 – 1.64 (m, 2H), 1.34 – 1.29 (m, 2H); $[\text{M}+\text{H}]^+ = 826.7$.

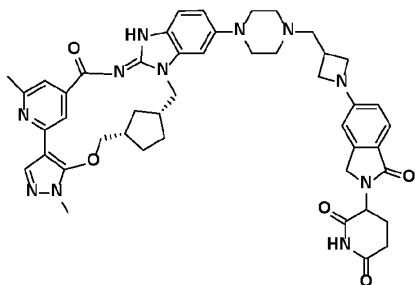
[0445] Example 27: 3-(5-((3R,4S)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 20.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (dd, $J = 12.3, 10.2$ Hz, 2H), 7.04 (s, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 5.18 – 5.04 (m, 1H), 4.38 – 4.01 (m, 5H), 3.74 (s, 3H), 3.43 (s, 1H), 3.26 – 3.16 (m, 5H), 2.94 – 2.78 (m, 6H), 2.75 – 2.54 (m, 9H), 2.40 (s, 3H), 2.26 (dd, $J = 20.2, 11.4$ Hz, 1H), 2.05 (dd, $J = 11.6, 7.1$ Hz, 2H), 1.97 – 1.62 (m, 6H). $[\text{M}+\text{H}]^+ = 848.6$.

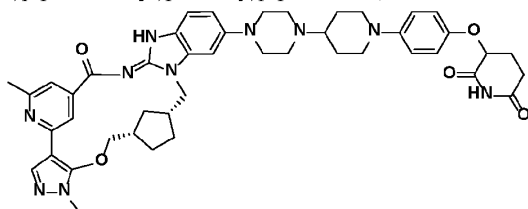
[0446] Example 35: 3-(5-(3-((4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)azetidin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 29.

^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.93 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.52 (s, 1H), 6.49 (d, J = 8.3 Hz, 1H), 5.03 – 4.99 (m, 1H), 4.35 – 4.26 (m, 2H), 4.18 – 4.15 (m, 2H), 4.06 – 4.02 (m, 4H), 3.74 – 3.71 (m, 3H), 3.60 – 3.56 (m, 2H), 3.18 – 3.15 (m, 4H), 3.06 – 3.01 (m, 1H), 2.96 – 2.84 (m, 1H), 2.67 – 2.64 (m, 2H), 2.62 – 2.59 (m, 6H), 2.57 – 2.54 (m, 3H), 2.53 – 2.49 (m, 3H), 2.35 – 2.32 (m, 1H), 1.95 – 1.92 (m, 2H), 1.84 – 1.79 (m, 2H), 1.71 – 1.66 (m, 1H); $[\text{M}+\text{H}]^+ = 838.7$.

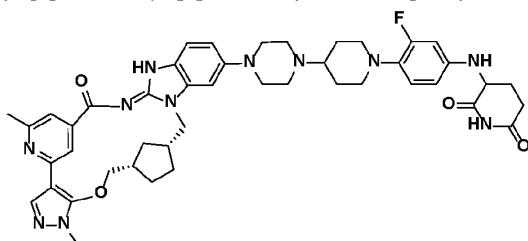
Example 57: 3-(4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenoxy)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 31.

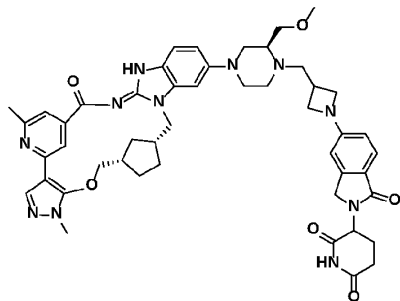
^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.88 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.02 (s, 1H), 6.95 – 6.85 (m, 5H), 5.02 – 4.49 (m, 1H), 4.30 (s, 1H), 4.18 (d, J = 8.0 Hz, 1H), 4.09 (s, 2H), 3.74 (s, 3H), 3.61 – 3.58 (m, 2H), 3.17 (s, 4H), 2.78 – 2.63 (m, 6H), 2.62 – 2.56 (m, 5H), 2.55 (s, 3H), 2.51 (s, 1H), 2.38 – 2.34 (m, 1H), 2.20 – 2.14 (m, 1H), 2.13 – 2.05 (m, 1H), 1.91 – 1.98 (m, 3H), 1.83 (s, 2H), 1.67 (s, 1H), 1.60 – 1.53 (m, 2H). $[\text{M}+\text{H}]^+ = 813.6$.

[0447] Example 59: 3-((4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3-fluorophenyl)amino)piperidine-2,6-dione



To a solution of intermediate 2 (60 mg, 0.11 mmol) and intermediate 32 (50 mg, 0.16 mmol) in DCE (6 mL) was added STAB (72 mg, 0.33 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO_3 (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH_3OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (31 mg, 33.1%). ^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.78 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 7.02 (s, 1H), 6.91 (dd, J = 8.9, 1.9 Hz, 1H), 6.84 (t, J = 9.4 Hz, 1H), 6.51 (dd, J = 15.0, 2.4 Hz, 1H), 6.42 (dd, J = 8.7, 2.1 Hz, 1H), 5.79 (d, J = 7.6 Hz, 1H), 4.35 – 4.16 (m, 3H), 4.10 (s, 2H), 3.74 (s, 3H), 3.23 – 3.14 (m, 6H), 2.76 – 2.66 (m, 5H), 2.65 – 2.52 (m, 9H), 2.39 – 2.32 (m, 1H), 2.12 – 2.05 (m, 1H), 1.95 – 1.75 (m, 7H), 1.73 – 1.54 (m, 3H). $[\text{M}+\text{H}]^+ = 830.6$.

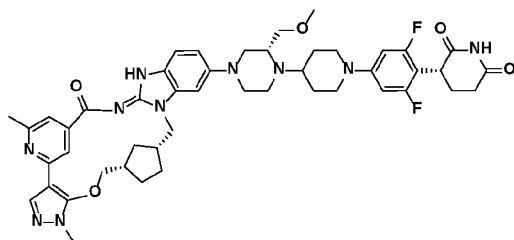
[0448] Example 63: 3-(5-(3-(((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)methyl)azetidin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 29.

¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.93 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.01 (s, 1H), 6.89 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.52 (s, 1H), 6.48 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.04 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.35 – 4.25 (m, 2H), 4.21 – 4.14 (m, 2H), 4.12 – 3.97 (m, 4H), 3.74 (s, 3H), 3.63 – 3.54 (m, 3H), 3.51 – 3.44 (m, 1H), 3.43 – 3.37 (m, 1H), 3.32 (s, 5H), 3.11 – 2.81 (m, 7H), 2.73 – 2.69 (m, 1H), 2.65 – 2.58 (m, 3H), 2.57 (s, 3H), 2.46 – 2.41 (m, 1H), 2.40 – 2.30 (m, 2H), 1.98 – 1.88 (m, 2H), 1.87 – 1.80 (m, 2H), 1.72 – 1.61 (m, 1H); [M+H]⁺ = 882.7.

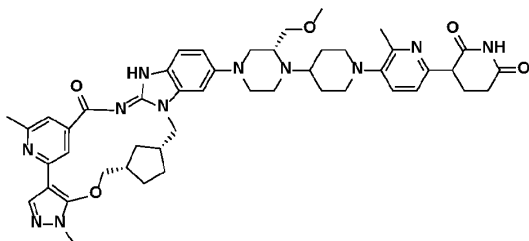
[0449] Example 64: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



To a solution of intermediate 30 (85 mg, 0.15 mmol) and intermediate 7 (67 mg, 0.21 mmol) in DCE (6 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (30 mg, 23.0%).

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.97 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.35 – 4.25 (m, 1H), 4.23 – 4.15 (m, 1H), 4.11 – 3.96 (m, 3H), 3.82 (d, *J* = 12.4 Hz, 2H), 3.74 (s, 3H), 3.61 – 3.55 (m, 1H), 3.53 – 3.48 (m, 1H), 3.32 (s, 5H), 3.27 (d, *J* = 9.6 Hz, 1H), 3.23 – 3.16 (m, 1H), 3.09 – 2.96 (m, 3H), 2.90 (t, *J* = 9.9 Hz, 1H), 2.85 – 2.70 (m, 5H), 2.69 – 2.64 (m, 1H), 2.59 (d, *J* = 6.9 Hz, 1H), 2.55 (s, 3H), 2.16 – 2.03 (m, 1H), 2.00 – 1.79 (m, 6H), 1.75 – 1.71 (m, 1H), 1.69 – 1.55 (m, 2H), 1.50 – 1.39 (m, 1H); [M+H]⁺ = 877.7.

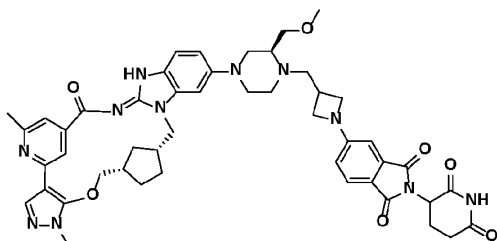
[0450] Example 65: 3-(5-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 30 and 15.

¹H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.78 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.38 (dd, J = 8.4, 3.8 Hz, 2H), 7.11 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 9.7 Hz, 1H), 4.37 – 4.25 (m, 1H), 4.22 – 4.18 (m, 1H), 4.11 – 4.07 (m, 2H), 3.91 – 3.87 (m, 1H), 3.74 (s, 3H), 3.61 – 3.55 (m, 1H), 3.52 – 3.49 (m, 1H), 3.28 – 3.22 (m, 1H), 3.19 – 3.11 (m, 2H), 3.09 – 3.05 (m, 2H), 3.01 – 2.97 (m, 1H), 2.94 – 2.80 (m, 2H), 2.72 – 2.69 (m, 2H), 2.65 – 2.51 (m, 14H), 2.41 (s, 3H), 2.25 – 2.15 (m, 1H), 2.13 – 2.04 (m, 1H), 1.99 – 1.89 (m, 2H), 1.86 – 1.73 (m, 4H), 1.73 – 1.64 (m, 1H), 1.63 – 1.53 (m, 1H); $[M+H]^+ = 856.7$.

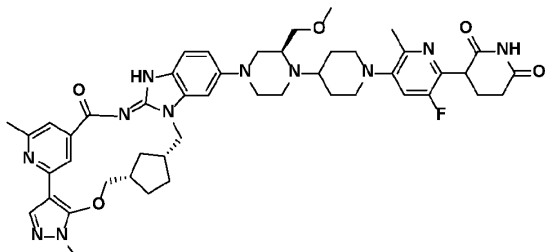
[0451] Example 69: 5-(3-(((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)methyl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione



To a solution of intermediate 3 (85 mg, 0.15 mmol) and intermediate 33 (72 mg, 0.21 mmol) in DCE (6 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at room temperature overnight. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (60 mg, 45%).

¹H NMR (500 MHz, DMSO) δ 12.55 (s, 1H), 11.08 (s, 1H), 8.61 (s, 1H), 7.99 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 17.3 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.71 (dd, J = 8.4, 1.9 Hz, 1H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.37 – 4.18 (m, 5H), 4.15 – 4.04 (m, 3H), 3.88 – 3.81 (m, 10H), 3.76 – 3.72 (m, 3H), 3.69 – 3.62 (m, 2H), 3.58 – 3.51 (m, 1H), 3.48 – 3.42 (m, 1H), 3.32 – 3.21 (m, 2H), 3.09 – 2.99 (m, 2H), 2.94 – 2.84 (m, 1H), 2.64 – 2.55 (m, 6H), 2.06 – 1.99 (m, 1H), 1.93 – 1.88 (m, 1H), 1.84 – 1.79 (m, 2H), 1.68 – 1.59 (m, 1H); $[M+H]^+ = 896.7$.

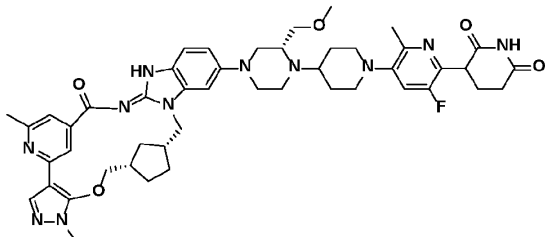
[0452] Example 70: 3-(5-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 12.

¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.86 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 11.6 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.36 – 4.26 (m, 1H), 4.23 – 4.19 (m, 1H), 4.16 – 4.04 (m, 3H), 3.74 (s, 3H), 3.60 – 3.55 (m, 1H), 3.53 – 3.49 (m, 1H), 3.27 – 3.24 (m, 1H), 3.21 – 3.16 (m, 2H), 3.09 – 3.03 (m, 2H), 3.01 – 2.96 (m, 1H), 2.92 – 2.82 (m, 3H), 2.76 – 2.67 (m, 6H), 2.65 – 2.60 (m, 5H), 2.55 (s, 4H), 2.38 (s, 3H), 2.29 – 2.20 (m, 1H), 2.06 – 1.99 (m, 1H), 1.98 – 1.91 (m, 2H), 1.87 – 1.72 (m, 5H), 1.63 – 1.59 (m, 1H); [M+H]⁺ = 874.7.

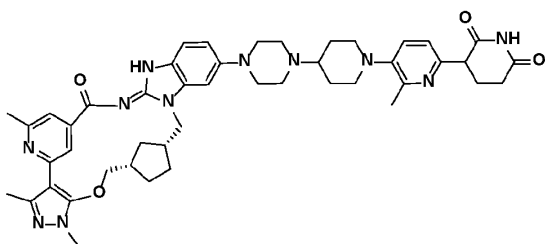
[0453] Example 71: 3-(5-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediate 30 and 12.

¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.86 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 11.6 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.36 – 4.26 (m, 1H), 4.23 – 4.19 (m, 1H), 4.16 – 4.05 (m, 3H), 3.74 (s, 3H), 3.60 – 3.55 (m, 1H), 3.53 – 3.49 (m, 1H), 3.27 – 3.24 (m, 1H), 3.21 – 3.16 (m, 2H), 3.11 – 3.03 (m, 2H), 3.01 – 2.96 (m, 1H), 2.92 – 2.82 (m, 3H), 2.76 – 2.67 (m, 6H), 2.65 – 2.61 (m, 5H), 2.55 (s, 4H), 2.38 (s, 3H), 2.29 – 2.20 (m, 1H), 2.06 – 1.99 (m, 1H), 1.98 – 1.91 (m, 2H), 1.88 – 1.72 (m, 5H), 1.63 – 1.59 (m, 1H); [M+H]⁺ = 874.7.

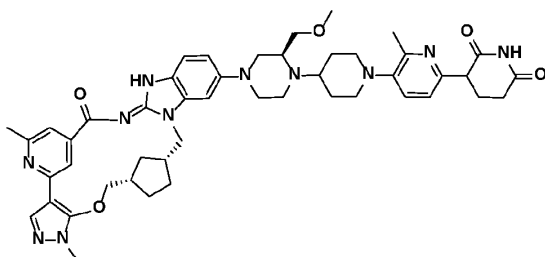
[0454] Example 72: 3-(6-methyl-5-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)pyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 34 and 15.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.78 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.9 Hz, 2H), 7.11 (d, J = 8.2 Hz, 1H), 7.03 (s, 1H), 6.95 – 6.89 (m, 1H), 4.35 – 3.98 (m, 4H), 3.89 (dd, J = 9.4, 5.3 Hz, 1H), 3.67 (s, 3H), 3.22 – 3.11 (m, 7H), 2.76 – 2.70 (m, 4H), 2.68 – 2.53 (m, 10H), 2.48 (s, 2H), 2.42 – 2.35 (m, 4H), 2.25 – 2.17 (m, 1H), 2.08 (dd, J = 12.8, 6.0 Hz, 1H), 1.97 – 1.76 (m, 6H), 1.69 – 1.57 (m, 3H). $[\text{M}+\text{H}]^+ = 826.6$.

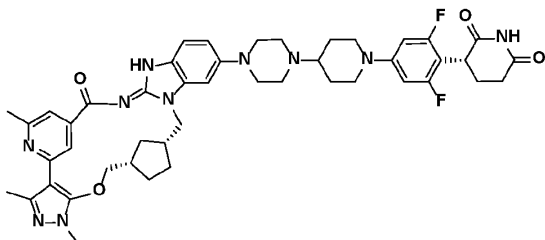
[0455] Example 73: 3-(5-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 15.

^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.78 (s, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.39 (d, J = 3.1 Hz, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 8.7 Hz, 1H), 4.39 – 4.25 (m, 1H), 4.19 (t, J = 8.0 Hz, 1H), 4.15 – 4.00 (m, 2H), 3.89 (dd, J = 9.4, 5.3 Hz, 1H), 3.74 (s, 3H), 3.61 – 3.54 (m, 1H), 3.54 – 3.47 (m, 1H), 3.36 – 3.33 (m, 1H), 3.31 – 3.28 (m, 4H), 3.28 – 3.22 (m, 1H), 3.18 – 3.10 (m, 2H), 3.10 – 3.02 (m, 2H), 3.01 – 2.94 (m, 1H), 2.93 – 2.80 (m, 2H), 2.74 – 2.54 (m, 10H), 2.41 (s, 3H), 2.26 – 2.17 (m, 1H), 2.12 – 2.04 (m, 1H), 1.99 – 1.53 (m, 9H). $[\text{M}+\text{H}]^+ = 856.7$.

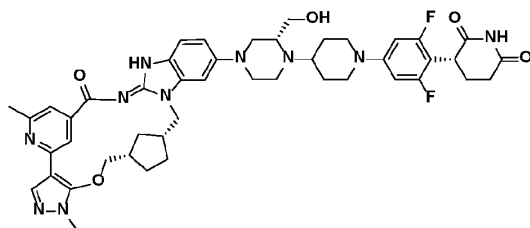
[0456] Example 74: (R)-3-(2,6-difluoro-4-(4-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



To a solution of intermediate 34 (80 mg, 0.15 mmol) and intermediate 7 (67 mg, 0.21 mmol) in DCE (6 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO_3 (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase

was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (35 mg, 28.0%). ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.02 (s, 1H), 6.90 (dd, *J* = 8.9, 1.9 Hz, 1H), 6.64 (d, *J* = 12.7 Hz, 2H), 4.36 – 3.97 (m, 5H), 3.81 (d, *J* = 12.6 Hz, 2H), 3.67 (s, 3H), 3.19 – 3.13 (m, 4H), 2.83 – 2.63 (m, 9H), 2.58 – 2.54 (m, 4H), 2.48 – 2.42 (m, 5H), 2.09 (dt, *J* = 12.8, 9.5 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.91 – 1.61 (m, 7H), 1.55 – 1.44 (m, 2H). [M+H]⁺ = 847.6.

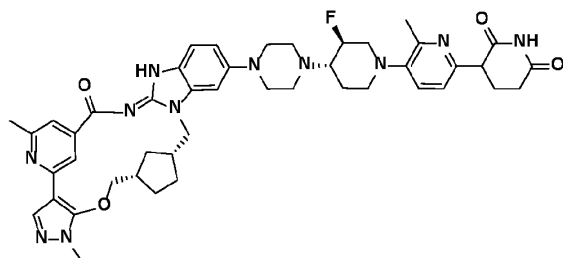
[0457] Example 75: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(hydroxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



To a solution of intermediate 35 (83 mg, 0.15 mmol) and intermediate 7 (67 mg, 0.21 mmol) in DCE (6 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (10 mg, 7.7%).

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.97 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.67 – 4.58 (m, 1H), 4.33 – 4.28 (m, 1H), 4.24 – 4.16 (m, 1H), 4.11 – 4.06 (m, 3H), 3.88 – 3.80 (m, 2H), 3.74 (s, 3H), 3.71 – 3.66 (m, 1H), 3.64 – 3.59 (m, 1H), 3.07 – 2.95 (m, 3H), 2.90 – 2.71 (m, 7H), 2.67 – 2.62 (m, 3H), 2.59 – 2.51 (m, 5H), 2.13 – 2.03 (m, 1H), 2.00 – 1.89 (m, 3H), 1.85 – 1.78 (m, 2H), 1.77 – 1.71 (m, 1H), 1.68 – 1.57 (m, 2H), 1.52 – 1.41 (m, 1H); [M+H]⁺ = 863.7.

[0458] Example 76: 3-(5-((3S,4S)-4-(4-((7¹R,7³S,E)-11,26-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

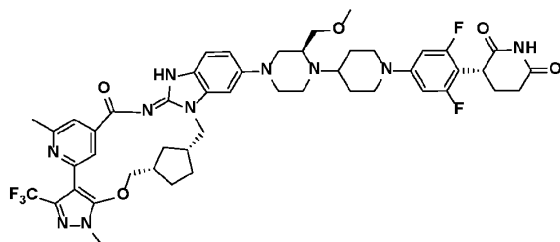


The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 36.

¹H NMR (500 MHz, DMSO) δ 12.33 (s, 1H), 10.79 (s, 1H), 8.54 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.38 (dd,

$J = 8.4, 4.6$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 5.18 – 5.03 (m, 1H), 4.40 – 3.99 (m, 4H), 3.90 (dd, $J = 9.5, 5.3$ Hz, 1H), 3.67 (s, 3H), 3.24 – 3.14 (m, 6H), 2.92 – 2.75 (m, 7H), 2.65 – 2.53 (m, 9H), 2.48 (s, 2H), 2.27 – 2.17 (m, 1H), 2.13 – 1.98 (m, 2H), 1.90 – 1.55 (m, 6H). $[M+H]^+ = 830.5$.

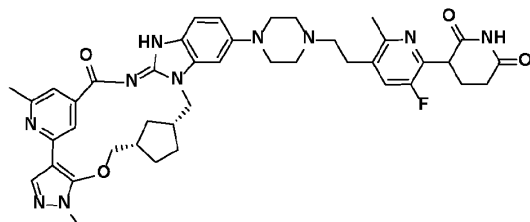
[0459] Example 77: (R)-3-(4-(4-((S)-4-((¹R,⁷S,E)-1¹,2⁶-dimethyl-3-oxo-1³-(trifluoromethyl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl) piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 37 and 7.

¹H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.87 (s, 1H), 8.61 (s, 1H), 7.59 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.99 (s, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.64 (d, $J = 12.7$ Hz, 2H), 4.41 – 4.24 (m, 2H), 4.22 – 4.10 (m, 2H), 4.05 (dd, $J = 12.6, 4.7$ Hz, 1H), 3.85 (s, 3H), 3.58 – 3.48 (m, 2H), 3.30 (s, 3H), 3.28 (s, 1H), 3.24 – 3.18 (m, 1H), 3.09 – 3.03 (m, 2H), 3.01 – 2.96 (m, 1H), 2.93 – 2.91 (m, 1H), 2.85 – 2.73 (m, 6H), 2.71 – 2.61 (m, 7H), 2.54 (s, 3H), 2.17 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.91 – 1.85 (m, 2H), 1.82 – 1.73 (m, 2H), 1.63 – 1.61 (m, 2H), 1.50 – 1.39 (m, 1H). $[M+H]^+ = 945.4$.

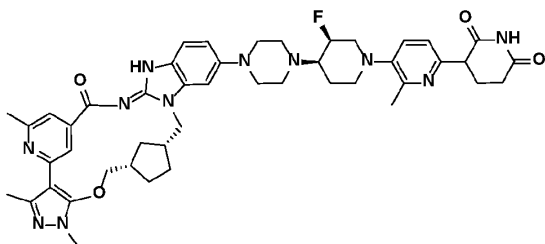
[0460] Example 78: 3-(5-(2-(4-((¹R,⁷S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)ethyl)-3-fluoro-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 38.

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.89 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.58 (d, $J = 10.7$ Hz, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.92 (d, $J = 8.6$ Hz, 1H), 4.30 (s, 1H), 4.21 – 4.17 (m, 2H), 4.09 (s, 2H), 3.74 (s, 3H), 3.19 (s, 4H), 2.83 – 2.79 (m, 2H), 2.76 – 2.69 (m, 2H), 2.66 (s, 4H), 2.63 – 2.59 (m, 4H), 2.55 (s, 4H), 2.45 (s, 3H), 2.31 – 2.24 (m, 1H), 2.12 – 2.01 (m, 1H), 1.93 – 1.67 (m, 5H). $[M+H]^+ = 775.6$.

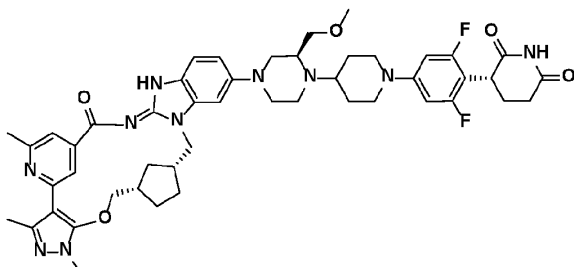
[0461] Example 79: 3-(5-((3S,4R)-3-fluoro-4-(4-((¹R,⁷S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediate 39 and 26.

^1H NMR (500 MHz, DMSO) δ 12.33 (s, 1H), 10.79 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (dd, $J = 8.4, 4.6$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 5.18 – 5.03 (m, 1H), 4.40 – 3.99 (m, 4H), 3.90 (dd, $J = 9.5, 5.3$ Hz, 1H), 3.67 (s, 3H), 3.24 – 3.14 (m, 6H), 2.92 – 2.75 (m, 7H), 2.65 – 2.53 (m, 9H), 2.48 (s, 2H), 2.42 (s, 3H), 2.27 – 2.17 (m, 1H), 2.13 – 1.98 (m, 2H), 1.90 – 1.55 (m, 6H). $[\text{M}+\text{H}]^+ = 844.6$.

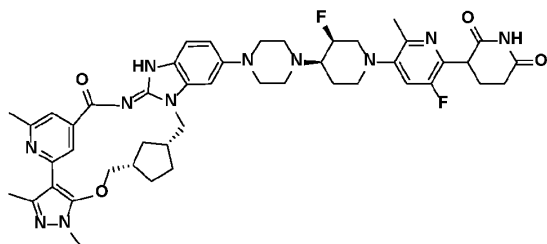
[0462] Example 80: (R)-3-(2,6-difluoro-4-(4-((S)-2-(methoxymethyl)-4-((^1R , ^7S , $^{\text{E}}$)-1 1 ,1 3 ,2 6 -trimethyl-3-oxo-5 2 ,5 3 -dihydro-1 ^1H ,5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5 6 -yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



To a solution of intermediate 40 (85 mg, 0.15 mmol) and intermediate 7 (67 mg, 0.21 mmol) in DCM (6 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at RT for 48 hours. The reaction was quenched with sat. aq. NaHCO_3 (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: $\text{CH}_3\text{OH} = 15:1$), followed by Prep-HPLC chromatography to afford the title product (28 mg, 21.7%).

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.98 (s, 1H), 6.87 (d, $J = 8.7$ Hz, 1H), 6.64 (d, $J = 12.8$ Hz, 2H), 4.31 – 4.03 (m, 5H), 3.82 (d, $J = 11.7$ Hz, 2H), 3.67 (s, 3H), 3.57 – 3.52 (m, 2H), 3.31 – 3.27 (m, 4H), 3.20 (s, 1H), 3.08 – 2.88 (m, 4H), 2.83 – 2.54 (m, 12H), 2.48 (s, 3H), 2.13 – 2.04 (m, 1H), 1.97 – 1.71 (m, 7H), 1.62 (d, $J = 8.7$ Hz, 2H), 1.45 (d, $J = 11.9$ Hz, 1H). $[\text{M}+\text{H}]^+ = 891.6$.

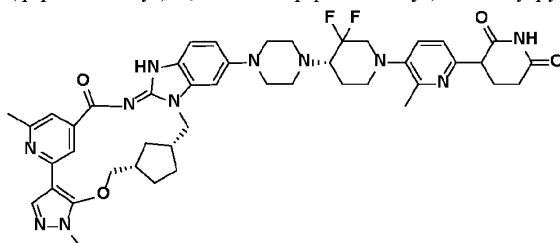
[0463] Example 82: 3-(3-fluoro-5-((3S,4R)-3-fluoro-4-(4-((^1R , ^7S , $^{\text{E}}$)-1 1 ,1 3 ,2 6 -trimethyl-3-oxo-5 2 ,5 3 -dihydro-1 ^1H ,5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5 6 -yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 39 and 21.

^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.34 (s, 1H), 7.05 (s, 1H), 6.92 (d, J = 8.0 Hz, 1H), 5.23 – 5.04 (m, 1H), 4.39 – 4.00 (m, 5H), 3.67 (s, 3H), 3.48 – 3.35 (m, 2H), 3.30 – 3.22 (m, 2H), 3.19 (d, J = 2.6 Hz, 2H), 2.95 – 2.78 (m, 6H), 2.76 – 2.65 (m, 2H), 2.61 – 2.53 (m, 8H), 2.48 (s, 3H), 2.40 (s, 3H), 2.30 – 2.20 (m, 1H), 2.08 – 1.99 (m, 2H), 1.91 – 1.78 (m, 4H), 1.70 – 1.60 (m, 1H). $[\text{M}+\text{H}]^+ = 862.7$.

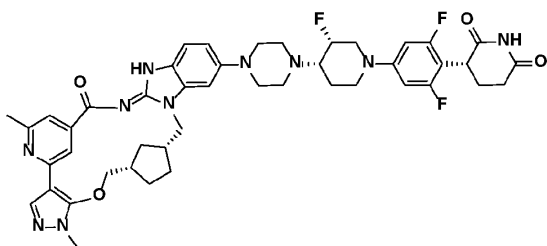
[0464] Example 83: 3-(5-((S)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3,3-difluoropiperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



To a stirred solution of intermediate 1 (60 mg, 0.1 mmol) in DMA (5 mL) were added intermediate 41 (47 mg, 0.1 mmol), *t*-BuONa (44 mg, 0.5 mmol), Ruphos (21 mg, 0.05 mmol) and $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.02 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 15 min at 100 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with DCM (50 mL), washed with water (3 x 20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by pre-HPLC to afford the title compound (8.97 mg, 9.2%).

^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.80 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.48 – 7.40 (m, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.04 (s, 1H), 6.92 (d, J = 8.7 Hz, 1H), 4.31 (s, 1H), 4.19 (s, 1H), 4.09 (s, 2H), 3.92 (dd, J = 9.5, 5.4 Hz, 1H), 3.74 (s, 3H), 3.17 (s, 5H), 3.12 – 2.90 (m, 7H), 2.87 – 2.83 (m, 1H), 2.64 – 2.56 (m, 4H), 2.55 – 2.53 (m, 4H), 2.43 (s, 3H), 2.26 – 2.17 (m, 1H), 2.12 – 1.99 (m, 2H), 1.95 – 1.93 (m, 2H), 1.83 – 1.68 (m, 4H). $[\text{M}+\text{H}]^+ = 848.7$.

[0465] Example 84: (R)-3-(4-((3R,4S)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



To the solution of intermediate 1 (100 mg, 0.19 mmol), intermediate 42 (94 mg, 0.23 mmol) and t-BuONa (73 mg, 0.76 mmol) in 6 mL DMA were added Pd₂(dba)₃ (35 mg, 0.038 mmol) and RuPhos (35 mg, 0.076 mmol). The mixture was stirred at 80 °C for 0.5 hour under N₂. The reaction was quenched with NH₄Cl/H₂O (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 15 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column (DCM : CH₃OH = 15:1) to give the racemate, which was further purified by Prep chiral-HPLC to afford the title product (35 mg, 21.7%).

Chiral HPLC method: Column: CHIRALPAK IE, 2cm x 25cm, 5μm

Mobile Phase A: MTBE

Mobile Phase B: MeOH: DCM = 50:50

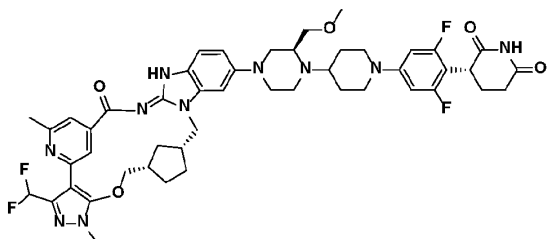
Flow rate: 20 mL/min

Gradient: 10% to 50% in 2.0 min, hold 1.0 min at 50%,

The title compound corresponds to peak A @ 4.083 min

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.03 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 12.8 Hz, 2H), 5.20 – 5.05 (m, 1H), 4.35 – 4.01 (m, 6H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.74 (s, 3H), 3.22 – 3.13 (m, 4H), 3.04 – 2.74 (m, 8H), 2.70 – 2.55 (m, 7H), 2.15 – 2.04 (m, 1H), 1.99 – 1.65 (m, 8H). [M+H]⁺ = 851.6.

[0466] Example 85: (R)-3-(4-(4-((S)-4-((7¹R,7³S,E)-1³-(difluoromethyl)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione

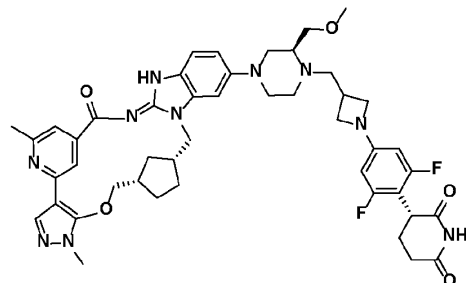


The title compound was prepared in a manner similar to that in Example 1 with intermediates 43 and 7.

¹H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.87 (s, 1H), 8.61 (s, 1H), 7.77 (t, *J* = 54.5 Hz, 1H), 7.53 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.38 – 4.22 (m, 2H), 4.17 – 4.01 (m, 3H), 3.86 – 3.78 (m, 5H), 3.60 – 3.55 (m, 1H), 3.53 – 3.48 (m, 1H), 3.30 (s, 3H), 3.28 – 3.16 (m, 3H), 3.09 – 2.96 (m, 3H), 2.94 – 2.86 (m, 1H), 2.85 – 2.68 (m, 5H), 2.67 – 2.52 (m, 7H), 2.15 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.91 – 1.80 (m, 4H), 1.76 – 1.70 (m, 1H), 1.69 – 1.57 (m, 2H), 1.49 – 1.40 (m,

1H). $[M+H]^+ = 927.7$.

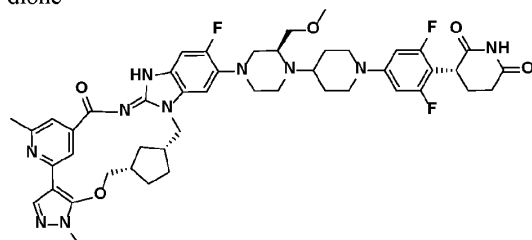
[0467] Example 86: (R)-3-(4-(3-(((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)methyl)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 44.

¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.85 (s, 1H), 8.52 (s, 1H), 7.88 (d, $J = 6.0$ Hz, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.01 (s, 1H), 6.89 (d, $J = 8.6$ Hz, 1H), 6.13 (s, 1H), 6.11 (s, 1H), 4.37 – 4.25 (m, 1H), 4.23 – 4.15 (m, 1H), 4.14 – 3.99 (m, 3H), 3.94 (q, $J = 7.8$ Hz, 2H), 3.74 (s, 3H), 3.59 (dd, $J = 9.8, 4.2$ Hz, 1H), 3.55 – 3.43 (m, 3H), 3.40 – 3.35 (m, 1H), 3.28 (s, 3H), 3.07 – 3.00 (m, 1H), 3.00 – 2.89 (m, 3H), 2.88 – 2.66 (m, 4H), 2.65 – 2.57 (m, 3H), 2.55 (s, 3H), 2.51 (s, 2H), 2.49 – 2.40 (m, 2H), 2.13 – 2.02 (m, 1H), 1.97 – 1.90 (m, 2H), 1.87 – 1.78 (m, 2H), 1.72 – 1.62 (m, 1H). $[M+H]^+ = 863.7$.

[0468] Example 87: (R)-3-(2,6-difluoro-4-(4-((S)-4-((7¹R,7³S,E)-5⁵-fluoro-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione

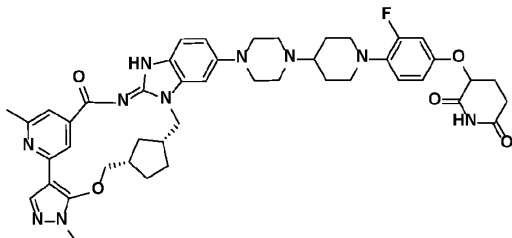


To a solution of intermediate 45 (60 mg, 0.1 mmol) and intermediate 7 (64 mg, 0.2 mmol) in DCE (6 mL) was added STAB (64 mg, 0.3 mmol). Then the mixture was stirred at RT for 48 hours. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 15:1), followed by Prep-HPLC chromatography to afford the title product (17 mg, 19%).

¹H NMR (500 MHz, DMSO) δ 12.55 (s, 1H), 10.87 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.29 (d, $J = 11.5$ Hz, 1H), 7.17 (d, $J = 7.2$ Hz, 1H), 6.64 (d, $J = 12.8$ Hz, 2H), 4.37 – 4.26 (m, 1H), 4.19 (d, $J = 8.0$ Hz, 1H), 4.10 – 4.06 (m, 3H), 3.81 (d, $J = 11.9$ Hz, 2H), 3.74 (s, 3H), 3.64 – 3.53 (m, 2H), 3.29 (s, 3H), 3.06 (dd, $J = 14.5, 10.1$ Hz, 2H), 3.01 (s, 2H), 2.92 – 2.89 (m, 2H), 2.79 – 2.75 (m, 4H), 2.72 – 2.66 (m, 1H), 2.65 –

2.62 (m, 2H), 2.55 (s, 3H), 2.54 – 2.50 (m, 3H), 2.15 – 2.04 (m, 1H), 1.99 – 1.86 (m, 3H), 1.85 – 1.72 (m, 3H), 1.63 – 1.60 (m, 2H), 1.49 – 1.45 (m, 1H). $[M+H]^+ = 895.2$.

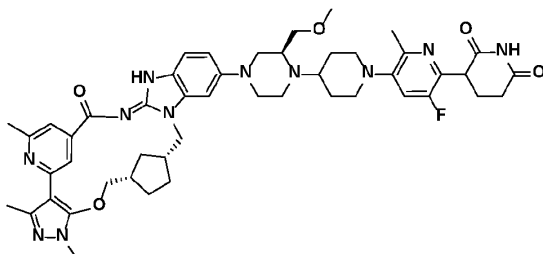
[0469] Example 88: 3-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3-fluorophenoxy)piperidine-2,6-dione



To a solution of intermediate 2 (50 mg, 0.1 mmol), intermediate 46 (61 mg, 0.2 mmol) in DCE (5 mL) was added STAB (60 mg, 0.3 mmol). Then the mixture was stirred at 50 °C for 1hr. H₂O (10 mL) was added and the resulting mixture was extracted with DCM (10 mL x 3). The combined organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound (3.7 mg, 4.7%).

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.92 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.94 – 6.86 (m, 2H), 6.78 – 6.77 (m, 1H), 5.14 – 5.11 (m, 1H), 4.30 (s, 1H), 4.19 (s, 1H), 4.10 (s, 2H), 3.74 (s, 3H), 3.18 (s, 4H), 2.76 – 2.67 (m, 5H), 2.67 – 2.57 (m, 6H), 2.55 (s, 5H), 2.38 – 2.36 (m, 1H), 2.21 – 2.08 (m, 2H), 1.95 – 1.75 (m, 6H), 1.70 – 1.57 (m, 3H). $[M+H]^+ = 831.7$.

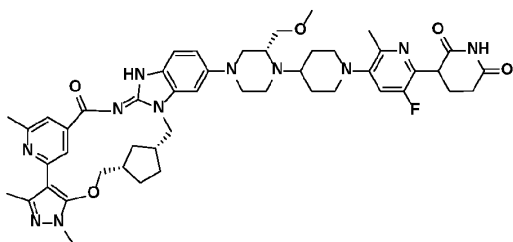
[0470] Example 89: 3-(3-fluoro-5-(4-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 40 and 12.

¹H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 11.6 Hz, 1H), 6.99 (s, 1H), 6.92 – 6.86 (m, 1H), 4.35 – 3.96 (m, 5H), 3.67 (s, 3H), 3.59 – 3.48 (m, 2H), 3.31 – 3.16 (m, 8H), 3.07 – 2.85 (m, 5H), 2.75 – 2.53 (m, 11H), 2.48 (s, 2H), 2.38 (s, 3H), 2.30 – 2.20 (m, 1H), 2.08 – 2.01 (m, 1H), 1.97 – 1.54 (m, 9H). $[M+H]^+ = 888.6$.

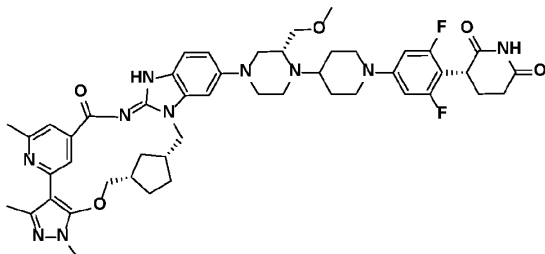
[0471] Example 90: 3-(3-fluoro-5-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 47 and 12.

^1H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 11.6 Hz, 1H), 6.99 (s, 1H), 6.92 – 6.86 (m, 1H), 4.35 – 3.96 (m, 5H), 3.67 (s, 3H), 3.59 – 3.48 (m, 2H), 3.31 – 3.16 (m, 8H), 3.07 – 2.85 (m, 5H), 2.75 – 2.53 (m, 11H), 2.48 (s, 2H), 2.38 (s, 3H), 2.30 – 2.20 (m, 1H), 2.08 – 2.01 (m, 1H), 1.97 – 1.54 (m, 9H). $[\text{M}+\text{H}]^+ = 888.6$.

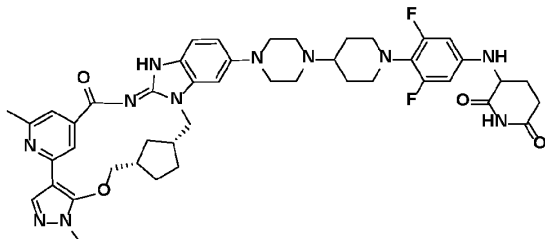
[0472] Example 91: (R)-3-(2,6-difluoro-4-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



To the solution of intermediate 47 (65 mg, 0.11 mmol) and intermediate 7 (72 mg, 0.22 mmol) in 2 mL DCE was added STAB (71 mg, 0.33 mmol). The mixture was stirred at 70 °C for 4 days. The mixture was concentrated and purified by silica column chromatography (MeOH: DCM=0-10%) to afford the crude product. The crude product was purified by prep-HPLC to afford title compound (7.0 mg, 0.008 mmol, 7.1%).

^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 6.86 (dd, J = 8.8, 1.8 Hz, 1H), 6.64 (d, J = 12.7 Hz, 2H), 4.38 – 3.97 (m, 5H), 3.82 (d, J = 12.4 Hz, 2H), 3.67 (s, 3H), 3.61 – 3.55 (m, 1H), 3.54 – 3.48 (m, 1H), 3.31 – 3.17 (m, 6H), 3.06 – 2.97 (m, 3H), 2.93 – 2.87 (m, 1H), 2.84 – 2.63 (m, 6H), 2.61 – 2.51 (m, 6H), 2.48 (s, 3H), 2.14 – 2.05 (m, 1H), 1.99 – 1.93 (m, 1H), 1.91 – 1.70 (m, 6H), 1.65 – 1.60 (m, 1H), 1.49 – 1.40 (m, 1H). $[\text{M}+\text{H}]^+ = 891.2$.

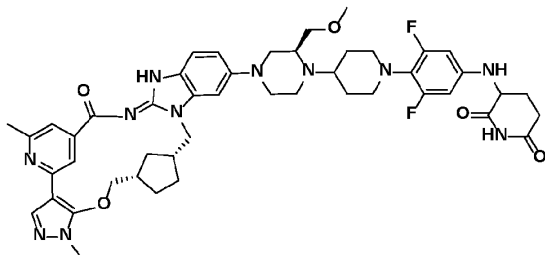
[0473] Example 92: 3-((4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3,5-difluorophenyl)amino)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 48.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.81 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.02 (s, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.33 (s, 1H), 6.31 (s, 1H), 6.24 (d, J = 7.9 Hz, 1H), 4.37 – 4.03 (m, 5H), 3.74 (s, 3H), 3.18 (s, 4H), 3.07 – 2.95 (m, 4H), 2.78 – 2.57 (m, 8H), 2.55 (s, 3H), 2.43 – 2.36 (m, 1H), 2.10 – 2.03 (m, 1H), 2.02 – 1.97 (m, 1H), 1.96 – 1.79 (m, 6H), 1.72 – 1.63 (m, 1H), 1.63 – 1.53 (m, 2H), 1.52 – 1.40 (m, 1H). $[\text{M}+\text{H}]^+ = 848.7$.

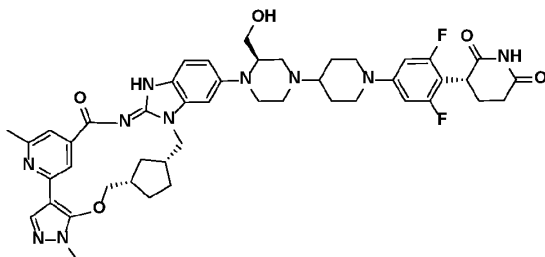
[0474] Example 93: 3-((4-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-3,5-difluorophenyl)amino)piperidine-2,6-dione



To a solution of intermediate 3 (80.0 mg, 0.14 mmol) and intermediate 48 (70.9 mg, 0.21 mmol) in DCE (5 mL) was added STAB (59.4 mg, 0.28 mmol) at 50 °C. The mixture was stirred at 50°C for 16 hr. Water (10 mL) was poured into the mixture. Then the mixture was extracted with DCM/MeOH (10:1, 20 mL). The organic phase was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (C-18 column chromatography (0.1% FA in water: acetonitrile = 90: 10 ~ 60: 40 gradient elution) to afford the product (28.0 mg, 22.4%).

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.81 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 6.98 (s, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.33 (s, 1H), 6.31 (s, 1H), 6.23 (d, J = 7.8 Hz, 1H), 4.37 – 4.26 (m, 2H), 4.23 – 4.16 (m, 1H), 4.15 – 3.98 (m, 2H), 3.74 (s, 3H), 3.56 (dd, J = 9.5, 4.1 Hz, 1H), 3.48 (dd, J = 9.6, 5.9 Hz, 1H), 3.38 – 3.32 (m, 6H), 3.05 – 2.92 (m, 6H), 2.92 – 2.87 (m, 2H), 2.83 – 2.63 (m, 4H), 2.62 – 2.57 (m, 2H), 2.55 (s, 3H), 2.12 – 2.03 (m, 1H), 2.00 – 1.63 (m, 9H), 1.56 – 1.45 (m, 1H). $[\text{M}+\text{H}]^+ = 892.7$.

[0475] Example 94: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-3-(hydroxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione

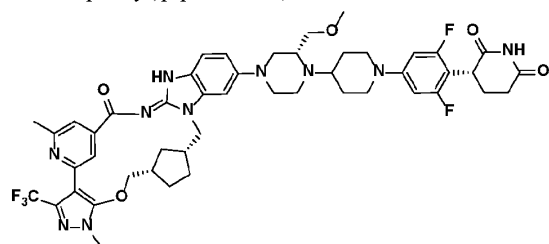


The titled compound was prepared in a manner similar to that in Example 1 with intermediates 49 and 7.

^1H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 4.36 – 4.27 (m, 1H), 4.21 – 4.18 (m, 1H), 4.08 – 4.02 (m, 3H), 3.81 (s, 1H), 3.79 (s, 1H), 3.74 (s, 4H), 3.69 – 3.66 (s, 1H), 3.25 – 3.21 (m,

2H), 3.10 (d, $J = 8.8$ Hz, 1H), 2.99 – 2.97 (m, 1H), 2.96 – 2.92 (m, 1H), 2.82 – 2.79 (m, 3H), 2.76 – 2.74 (m, 1H), 2.64 (s, 1H), 2.59 (s, 2H), 2.55 (s, 5H), 2.46 – 2.42 (m, 2H), 2.36 (s, 1H), 2.10 – 2.07 (m, 1H), 1.99 – 1.95 (m, 2H), 1.87 – 1.83 (m, 4H), 1.68 – 1.63 (m, 1H), 1.53 – 1.50 (m, 2H); $[M+H]^+ = 863.5$.

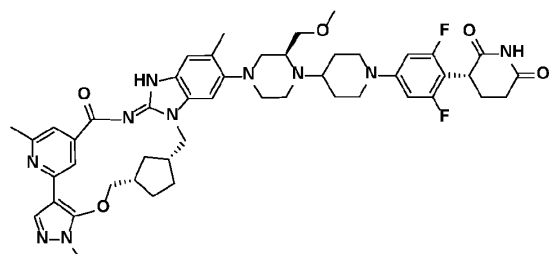
[0476] Example 95: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-1³-(trifluoromethyl)-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The titled compound was prepared in a manner similar to that in Example 1 with intermediates 50 and 7.

¹H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.87 (s, 1H), 8.61 (s, 1H), 7.59 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.99 (s, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.64 (d, $J = 12.7$ Hz, 2H), 4.41 – 4.24 (m, 2H), 4.22 – 4.10 (m, 2H), 4.05 (dd, $J = 12.6, 4.7$ Hz, 1H), 3.85 (s, 3H), 3.58 – 3.48 (m, 2H), 3.30 (s, 3H), 3.28 (s, 1H), 3.24 – 3.18 (m, 1H), 3.09 – 3.03 (m, 2H), 3.01 – 2.96 (m, 1H), 2.93 – 2.91 (m, 1H), 2.85 – 2.73 (m, 6H), 2.71 – 2.61 (m, 7H), 2.54 (s, 3H), 2.17 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.91 – 1.85 (m, 2H), 1.82 – 1.73 (m, 2H), 1.63 – 1.61 (m, 2H), 1.50 – 1.39 (m, 1H). $[M+H]^+ = 945.4$.

[0477] Example 96: (R)-3-(2,6-difluoro-4-(4-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,2⁶,5⁵-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



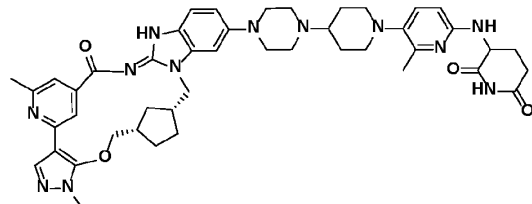
To a solution of intermediate 51 (80 mg, 0.14 mmol) and intermediate 7 (57 mg, 0.18 mmol) in DCE (6 mL) was added sodium triacetoxyborohydride (72 mg, 0.34 mmol) at room temperature. The resulting mixture was stirred at 50 °C overnight. The reaction was quenched with saturated aq. NaHCO₃ (20 mL) and extracted with DCM (2 x 30 mL). The combined organic layer was washed with brine (2 x 30 mL), dried over Na₂SO₄ and concentrated under vacuum to afford the crude residue, which was purified by silica gel column chromatography (DCM: MeOH = 100: 0~90: 10 gradient elution) to give the crude product, which was purified by Prep-HPLC to afford the title compound (15.2 mg, 12.3%).

The titled compound was prepared in a manner similar to that in Example 1 with intermediates 51 and 7.

¹H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.32 (s, 1H), 7.22 (s, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 4.30 (s, 1H), 4.18 (d, $J = 8.2$ Hz, 1H), 4.12 – 4.06 (m, 3H), 3.80

(d, $J = 12.0$ Hz, 2H), 3.74 (s, 3H), 3.67 – 3.61 (m, 2H), 3.32 – 3.31 (m, 2H), 3.28 (s, 3H), 3.06 (s, 1H), 2.88 (s, 4H), 2.81 – 2.76 (m, 5H), 2.72 – 2.69 (m, 1H), 2.59 (s, 2H), 2.55 (s, 3H), 2.33 (s, 3H), 2.08 (t, $J = 11.1$ Hz, 1H), 1.97 (d, $J = 5.5$ Hz, 1H), 1.91 (s, 2H), 1.83 (s, 2H), 1.77 (s, 2H), 1.67 (s, 1H), 1.59 (d, $J = 9.9$ Hz, 1H), 1.47 (d, $J = 11.0$ Hz, 1H); $[M+H]^+ = 891.5$

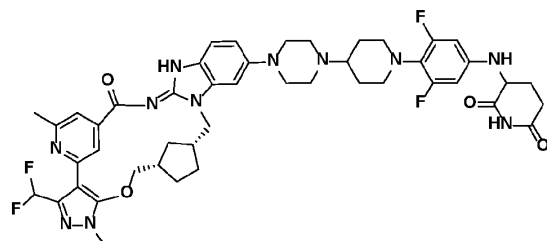
[0478] Example 98: 3-((5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)amino)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 52.

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.73 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.24 (d, $J = 8.7$ Hz, 1H), 7.02 (s, 1H), 6.91 (dd, $J = 8.8, 1.7$ Hz, 1H), 6.40 (dd, $J = 19.4, 8.2$ Hz, 2H), 4.70 – 4.62 (m, 1H), 4.35 – 4.04 (m, 4H), 3.74 (s, 3H), 3.20 – 3.15 (m, 4H), 2.93 (d, $J = 10.4$ Hz, 2H), 2.79 – 2.68 (m, 5H), 2.65 – 2.53 (m, 9H), 2.40 – 2.32 (m, 1H), 2.27 (s, 3H), 2.11 – 1.76 (m, 8H), 1.59 (d, $J = 9.3$ Hz, 3H). $[M+H]^+ = 827.6$.

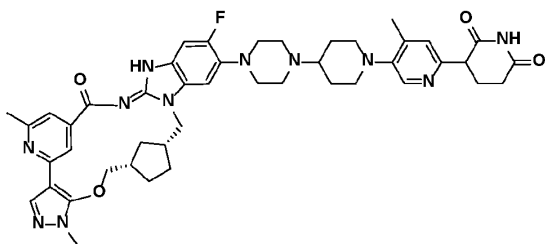
[0479] Example 99: 3-((4-(4-(4-((7¹R,7³S,E)-1³-(difluoromethyl)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3,5-difluorophenyl)amino)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 53 and 48.

¹H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.81 (s, 1H), 8.61 (s, 1H), 7.77 (t, $J = 54.6$ Hz, 1H), 7.54 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 6.33 (s, 1H), 6.31 (s, 1H), 6.24 (d, $J = 8.0$ Hz, 1H), 4.40 – 4.21 (m, 3H), 4.21 – 4.00 (m, 2H), 3.82 (s, 3H), 3.22 – 3.13 (m, 4H), 3.05 – 2.95 (m, 4H), 2.79 – 2.54 (m, 12H), 2.41 – 2.34 (m, 1H), 2.09 – 2.01 (m, 1H), 1.97 – 1.71 (m, 7H), 1.71 – 1.62 (m, 1H), 1.61 – 1.51 (m, 2H). $[M+H]^+ = 898.7$.

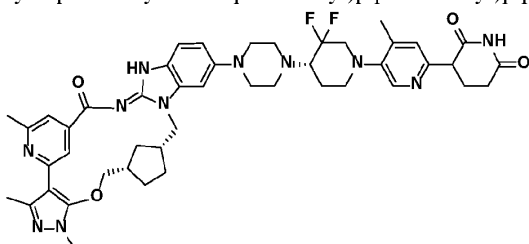
[0480] Example 100: 3-(5-(4-(4-((7¹R,7³S,E)-5⁵-fluoro-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 54 and 14.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.73 (s, 1H), 8.45 (s, 1H), 8.08 (s, 1H), 7.82 (s, 1H), 7.38 (s, 1H), 7.23 (d, J = 11.3 Hz, 1H), 7.12 (d, J = 5.6 Hz, 1H), 7.07 (s, 1H), 4.41 – 4.24 (m, 2H), 4.22 – 4.10 (m, 2H), 4.05 (dd, J = 12.6, 4.7 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.30 (s, 3H), 3.28 (s, 1H), 3.24 – 3.18 (m, 1H), 3.09 – 3.03 (m, 2H), 3.01 – 2.96 (m, 1H), 2.93 – 2.91 (m, 1H), 2.85 – 2.73 (m, 6H), 2.71 – 2.61 (m, 6H), 2.54 (s, 3H), 2.21 (s, 3H), 2.17 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.91 – 1.85 (m, 2H), 1.82 – 1.73 (m, 2H), 1.63 – 1.61 (m, 2H), 1.50 – 1.39 (m, 1H). $[\text{M}+\text{H}]^+ = 830.2$.

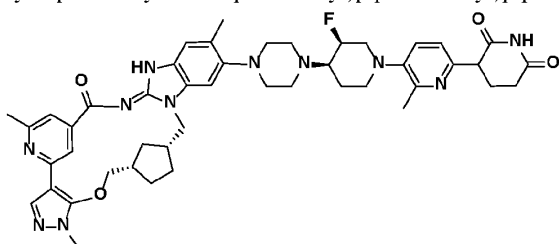
[0481] Example 101: 3-(5-((S)-3,3-difluoro-4-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(4,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 39 and 56.

^1H NMR (500 MHz, DMSO) δ 12.31 (s, 1H), 10.81 (s, 1H), 8.54 (s, 1H), 8.19 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.18 (s, 1H), 7.04 (s, 1H), 6.95 – 6.89 (m, 1H), 4.35 – 3.98 (m, 4H), 3.92 (dd, J = 9.0, 5.4 Hz, 1H), 3.67 (s, 3H), 3.24 – 3.05 (m, 8H), 3.02 – 2.90 (m, 6H), 2.65 – 2.53 (m, 8H), 2.48 (s, 2H), 2.29 (s, 3H), 2.20 (dd, J = 9.0, 4.5 Hz, 1H), 2.10 (dd, J = 13.5, 5.8 Hz, 1H), 2.03 – 1.58 (m, 7H). $[\text{M}+\text{H}]^+ = 862.6$.

[0482] Example 102: 3-(5-((3S,4R)-3-fluoro-4-(4-((7¹R,7³S,E)-1¹,2⁶,5⁵-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(4,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

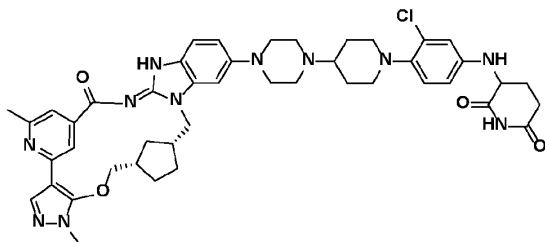


The titled compound was prepared in a manner similar to that in Example 11 with intermediates 57 and 26.

^1H NMR (500 MHz, DMSO) δ 12.45 (s, 1H), 10.79 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 4.32 (s, 1H), 4.19 (t, J = 8.0 Hz, 1H), 4.10

(s, 2H), 3.90 (dd, $J = 9.5, 5.2$ Hz, 1H), 3.74 (s, 3H), 3.39 – 3.36 (m, 2H), 3.31 – 3.29 (m, 2H), 3.19 (d, $J = 10.8$ Hz, 1H), 2.93 (d, $J = 4.5$ Hz, 4H), 2.86 – 2.81 (m, 5H), 2.66 – 2.62 (m, 1H), 2.60 – 2.57 (m, 4H), 2.55 (s, 4H), 2.43 (s, 3H), 2.34 (s, 3H), 2.29 – 2.18 (m, 1H), 2.11 – 2.01 (m, 2H), 1.96 – 1.87 (m, 1H), 1.85 – 1.83 (s, 3H), 1.69 (s, 1H); $[M+H]^+ = 844.5$

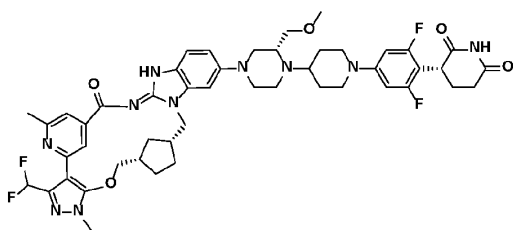
[0483] Example 103: 3-((3-chloro-4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)amino)piperidine-2,6-dione



To a solution of intermediate 2 and intermediate 55 (74 mg, 0.22 mmol) in DCE (6 mL) was added STAB (70 mg, 0.33 mmol). Then the mixture was stirred at 50°C for 16 hours. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 15:1), followed by Prep-HPLC chromatography to afford the title product (15 mg, 16%).

¹H NMR (500 MHz, DMSO) δ 12.38 (s, 1H), 10.77 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.96 – 6.89 (m, 2H), 6.76 (d, $J = 2.5$ Hz, 1H), 6.60 (dd, $J = 8.8, 2.4$ Hz, 1H), 5.85 (d, $J = 7.7$ Hz, 1H), 4.36 – 4.26 (m, 2H), 4.19 (t, $J = 8.4$ Hz, 1H), 4.09 (s, 2H), 3.74 (s, 3H), 3.22 – 3.10 (m, 6H), 2.78 – 2.67 (m, 6H), 2.64 – 2.59 (m, 4H), 2.58 – 2.54 (m, 5H), 2.36 (s, 1H), 2.14 – 2.03 (m, 1H), 1.98 – 1.82 (m, 6H), 1.72 – 1.56 (m, 3H). $[M+H]^+ = 846.2$.

[0484] Example 104: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1¹-(difluoromethyl)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione

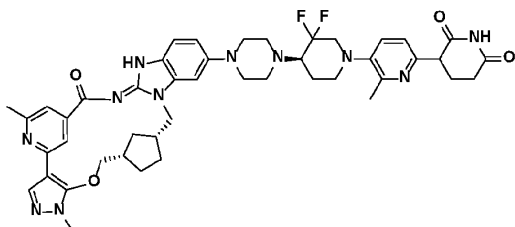


The title compound was prepared in a manner similar to that in Example 1 with intermediates 58 and 7.

¹H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 10.87 (s, 1H), 8.61 (s, 1H), 7.77 (t, $J = 54.6$ Hz, 1H), 7.53 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.98 (s, 1H), 6.92 – 6.84 (m, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.31 (dt, $J = 46.5, 14.9$ Hz, 2H), 4.17 – 4.00 (m, 3H), 3.87 – 3.78 (m, 5H), 3.57 (dd, $J = 9.5, 4.0$ Hz, 1H), 3.51 (dd, $J = 9.5, 5.5$ Hz, 1H), 3.30 (s, 3H), 3.30 – 3.24 (m, 2H), 3.23 – 3.17 (m, 1H), 3.10 – 2.96 (m, 3H), 2.94 – 2.85 (m, 1H), 2.85

– 2.51 (m, 11H), 2.15 – 2.04 (m, 1H), 1.99 – 1.57 (m, 9H), 1.50 – 1.39 (m, 1H). $[M+H]^+ = 927.7$.

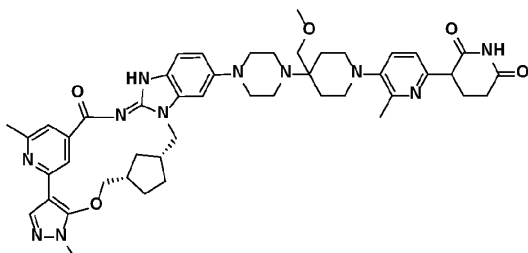
[0485] Example 105: 3-(5-((R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3,3-difluoropiperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 25.

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.80 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.43 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.92 (dd, $J = 8.8, 1.8$ Hz, 1H), 4.38 – 4.24 (m, 1H), 4.23 – 4.15 (m, 1H), 4.13 – 4.00 (m, 2H), 3.92 (dd, $J = 9.6, 5.3$ Hz, 1H), 3.74 (s, 3H), 3.23 – 3.14 (m, 5H), 3.12 – 2.92 (m, 6H), 2.89 – 2.81 (m, 1H), 2.69 – 2.51 (m, 10H), 2.43 (s, 3H), 2.27 – 2.17 (m, 1H), 2.12 – 1.90 (m, 4H), 1.87 – 1.77 (m, 2H), 1.73 – 1.61 (m, 1H). $[M+H]^+ = 848.7$.

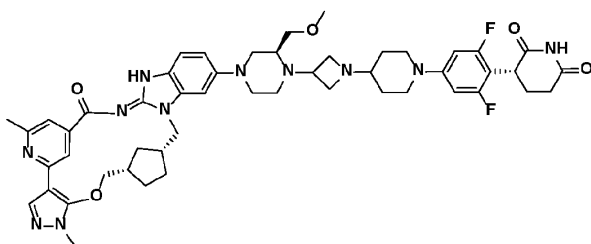
[0486] Example 106: 3-(5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-4-(methoxymethyl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 59.

¹H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.77 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.39 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.09 (d, $J = 8.2$ Hz, 1H), 7.00 (s, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 4.37 – 4.25 (m, 1H), 4.24 – 4.16 (m, 1H), 4.15 – 3.99 (m, 2H), 3.88 (dd, $J = 9.4, 5.3$ Hz, 1H), 3.74 (s, 3H), 3.41 (s, 2H), 3.29 (s, 3H), 3.18 – 3.10 (m, 4H), 3.05 – 2.97 (m, 2H), 2.91 – 2.83 (m, 4H), 2.79 – 2.74 (m, 2H), 2.65 – 2.52 (m, 9H), 2.39 (s, 3H), 2.24 – 2.16 (m, 1H), 2.10 – 2.03 (m, 1H), 1.97 – 1.89 (m, 3H), 1.87 – 1.79 (m, 2H), 1.78 – 1.68 (m, 3H). $[M+H]^+ = 856.7$.

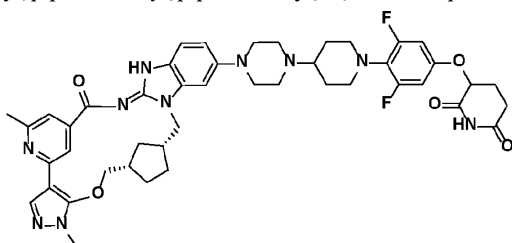
[0487] Example 108: (R)-3-(4-(4-(3-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)azetidin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 61 and 7.

^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.98 (s, 1H), 6.88 (dd, J = 8.8, 1.7 Hz, 1H), 6.62 (d, J = 12.8 Hz, 2H), 4.34 – 4.01 (m, 5H), 3.74 (s, 3H), 3.60 (s, 2H), 3.51 – 3.39 (m, 4H), 3.28 – 3.16 (m, 7H), 3.13 – 2.98 (m, 2H), 2.90 – 2.74 (m, 6H), 2.72 – 2.53 (m, 8H), 2.36 (s, 1H), 2.25 – 2.04 (m, 2H), 2.00 – 1.61 (m, 9H). $[\text{M}+\text{H}]^+ = 932.6$.

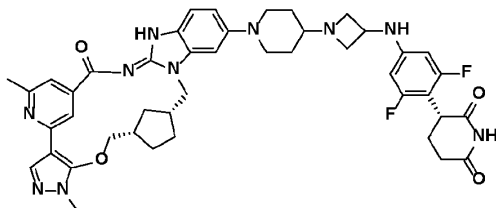
[0488] Example 111: 3-(4-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3,5-difluorophenoxy)piperidine-2,6-dione



The titled compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 62.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.96 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.77 (s, 1H), 5.23 – 5.19 (m, 1H), 4.30 (s, 1H), 4.18 (d, J = 7.6 Hz, 1H), 4.10 (s, 2H), 3.74 (s, 3H), 3.17 (s, 4H), 3.12 – 3.11 (m, 2H), 3.05 – 3.00 (m, 2H), 2.77 – 2.67 (m, 5H), 2.67 – 2.57 (m, 4H), 2.55 (s, 3H), 2.43 – 2.36 (m, 1H), 2.23 – 2.08 (m, 2H), 1.91 (s, 1H), 1.85 – 1.83 (m, 5H), 1.67 (s, 1H), 1.63 – 1.53 (m, 2H). $[\text{M}+\text{H}]^+ = 849.7$.

[0489] Example 112: (R)-3-(4-((1-(1-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperidin-4-yl)azetidin-3-yl)amino)-2,6-difluorophenyl)piperidine-2,6-dione



The racemate compound was prepared in a manner similar to that in Example 1 with intermediates 63 and 64.

Prep chiral-HPLC method:

Column: CHIRALPAK IE, 20*250 mm 5 μm

Mobile Phase A: MTBE

Mobile Phase B: MeOH: DCM = 50:50 (0.2% FA+0.2% DEA)

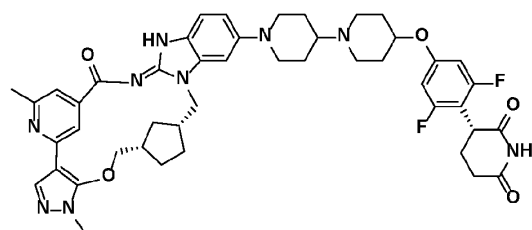
Flow rate: 18 mL/min

Gradient: Mobile Phase A: Mobile Phase B=10:90(v/v)

The title compound corresponds to peak A @ 11.3 min.

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.84 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.01 (s, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 6.8 Hz, 1H), 6.20 (d, *J* = 11.7 Hz, 2H), 4.33 – 3.93 (m, 7H), 3.74 (s, 3H), 3.66 (s, 2H), 3.56 – 3.52 (m, 2H), 2.85 – 2.73 (m, 6H), 2.63 – 2.53 (m, 5H), 2.19 (s, 1H), 2.10 – 2.00 (m, 1H), 1.93 – 1.65 (m, 8H), 1.39 – 1.33 (m, 2H). [M+H]⁺ = 819.6.

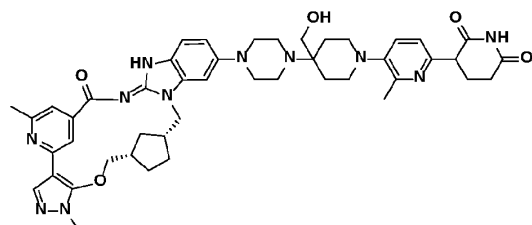
[0490] Example 113: (R)-3-(4-((1'-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-[1,4'-bipiperidin]-4-yl)oxy)-2,6-difluorophenyl)piperidine-2,6-dione



To a solution of intermediate 64 (60 mg, 0.11 mmol) and intermediate 65 (71 mg, 0.22 mmol) in DCE (6 mL) was added STAB (70 mg, 0.33 mmol). Then the mixture was stirred at 50°C for 16 hours. The reaction was quenched with sat. aq. NaHCO₃ (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography (DCM: CH₃OH = 15:1), followed by Prep-HPLC chromatography to afford the title product (15 mg, 16%).

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.92 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.02 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.78 (d, *J* = 10.9 Hz, 2H), 4.44 (d, *J* = 6.3 Hz, 2H), 4.35 – 4.24 (m, 2H), 4.23 – 4.06 (m, 4H), 3.74 (s, 3H), 2.85 – 2.80 (m, 3H), 2.69 (t, *J* = 11.4 Hz, 3H), 2.59 (s, 2H), 2.55 (s, 4H), 2.47 – 2.35 (m, 3H), 2.13 – 2.10 (m, 1H), 2.03 – 1.91 (m, 4H), 1.89 – 1.77 (m, 4H), 1.69 – 1.52 (m, 6H). [M+H]⁺ = 848.2.

[0491] Example 114: 3-(5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-4-(hydroxymethyl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione

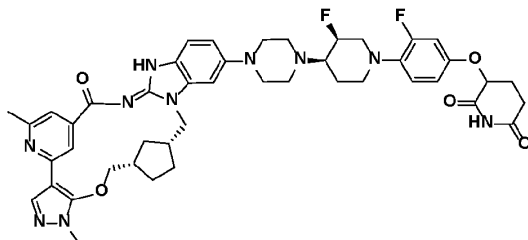


The title compound was prepared in a manner similar to that in Example 11 with intermediates 1 and 66.

¹H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.77 (s, 1H), 9.27 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s,

1H), 7.39 (d, $J = 8.3$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.09 (d, $J = 8.2$ Hz, 1H), 7.00 (s, 1H), 6.92 (d, $J = 8.7$ Hz, 1H), 4.37 – 4.25 (m, 1H), 4.24 – 4.16 (m, 1H), 4.15 – 3.99 (m, 2H), 3.88 (dd, $J = 9.4, 5.3$ Hz, 1H), 3.74 (s, 3H), 3.41 (s, 2H), 3.18 – 3.10 (m, 4H), 3.05 – 2.97 (m, 2H), 2.91 – 2.83 (m, 4H), 2.79 – 2.74 (m, 2H), 2.65 – 2.52 (m, 9H), 2.39 (s, 3H), 2.24 – 2.16 (m, 1H), 2.10 – 2.03 (m, 1H), 1.97 – 1.89 (m, 3H), 1.87 – 1.79 (m, 2H), 1.78 – 1.68 (m, 3H). $[M+H]^+ = 842.7$.

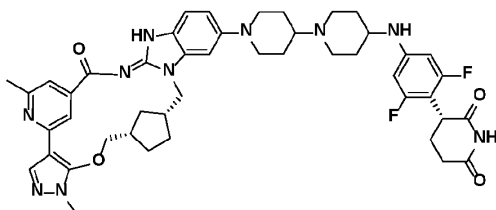
[0492] Example 115: 3-(4-((3S,4R)-4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)-3-fluoropiperidin-1-yl)-3-fluorophenoxy)piperidine-2,6-dione



To a stirred solution of intermediate 1 (60 mg, 0.1 mmol) in DMA (5 mL) were added intermediate 67 (47 mg, 0.1 mmol), t-BuONa (44 mg, 0.5 mmol), Ruphos (21 mg, 0.05 mmol) and Pd₂(dba)₃ (46 mg, 0.02 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 50 °C under nitrogen atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was concentrated under reduced pressure. The residue was diluted with DCM (50 mL), washed with water (3 x 20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the title compound (8.13 mg, 8.3%).

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.93 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.04 (s, 1H), 6.99 (t, $J = 9.6$ Hz, 1H), 6.93 (d, $J = 2.2$ Hz, 1H), 6.92 – 6.89 (m, 1H), 6.78 (d, $J = 8.7$ Hz, 1H), 5.15 – 5.12 (m, 2H), 4.31 (s, 1H), 4.19 (s, 1H), 4.09 (s, 2H), 3.74 (s, 3H), 3.52 – 3.48 (m, 1H), 3.37 (s, 1H), 3.19 – 3.18 (m, 4H), 2.93 – 2.76 (m, 5H), 2.74 – 2.56 (m, 6H), 2.55 (s, 3H), 2.21 – 2.17 (m, 1H), 2.16 – 1.96 (m, 3H), 1.91 (s, 1H), 1.82 – 1.79 (m, 4H), 1.68 (s, 1H). $[M+H]^+ = 849.7$.

[0493] Example 116: (R)-3-(4-((1'-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-[1,4'-bipiperidin]-4-yl)amino)-2,6-difluorophenyl)piperidine-2,6-dione

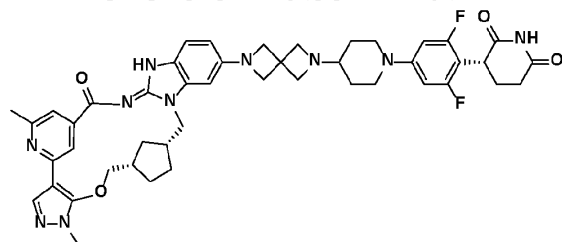


To a solution of intermediate 64 (80 mg, 0.15 mmol), intermediate 68 (59 mg, 0.18 mmol) and DIEA (58 mg, 0.45 mmol) in DCE (6 mL)/DMSO (2 mL) was added STAB (96 mg, 0.45 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO₃ (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phase was washed with brine (1 x 15 mL), dried over Na₂SO₄, filtered and

concentrated in vacuum. The residue was purified by silica gel column (DCM : CH₃OH = 15:1) to give the racemate, which was further purified by Prep chiral-HPLC with following condition: (Column: CHIRALPAK IE, 20*250 mm 5 μ m; Mobile Phase A: MTBE(0.1%FA), Mobile Phase B: MeOH: DCM = 50:50; Flow rate: 20 mL/min; Gradient: Mobile Phase A: Mobile Phase B=40:60(v/v), Injection Volume: 5 μ L; Wave Length: UV 254 nm and 220 nm; retention time: peak A 2.235 min, peak B 3.711 min) to give the peak A as the desired product (14 mg, 11.2%).

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.83 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.25 (d, J = 12.1 Hz, 2H), 6.15 (d, J = 6.8 Hz, 1H), 4.35 – 4.03 (m, 4H), 3.97 (dd, J = 12.5, 4.9 Hz, 1H), 3.79 – 3.72 (m, 5H), 3.26 – 3.22 (m, 2H), 2.97 (s, 2H), 2.80 – 2.54 (m, 11H), 2.10 – 1.78 (m, 11H), 1.64 (d, J = 10.8 Hz, 3H), 1.46 – 1.35 (m, 2H). [M+H]⁺ = 847.6.

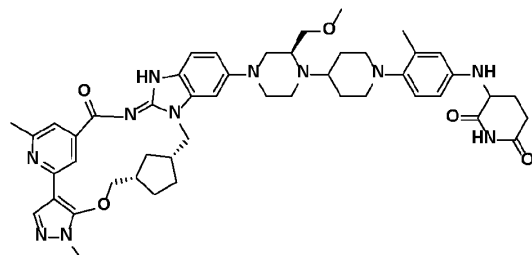
[0494] Example 117: (R)-3-(4-(4-(6-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2,6-diazaspiro[3.3]heptan-2-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 69 and 7.

¹H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 10.87 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 12.3 Hz, 2H), 6.49 (s, 1H), 6.37 (d, J = 8.3 Hz, 1H), 4.34 – 3.87 (m, 10H), 3.77 – 3.60 (m, 6H), 2.88 – 2.74 (m, 4H), 2.65 – 2.51 (m, 8H), 2.22 – 2.03 (m, 2H), 1.99 – 1.60 (m, 10H). [M+H]⁺ = 845.6.

[0495] Example 118: 3-((4-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-3-methylphenyl)amino)piperidine-2,6-dione

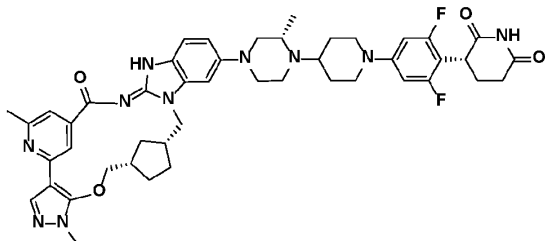


The title compound was prepared in a manner similar to that in Example 1 with intermediates 3 and 70.

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.75 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 6.52 (s, 1H), 6.46 (d, J = 8.4 Hz, 1H), 5.44 (d, J = 7.3 Hz, 1H), 4.38 – 4.27 (m, 1H), 4.26 – 4.17 (m, 2H), 4.14 – 4.03 (m, 2H), 3.74 (s, 3H), 3.57 – 3.54 (m, 2H), 3.27 – 3.21 (m, 4H), 3.05 (t, J = 7.4 Hz, 2H), 2.98 – 2.96 (m, 3H), 2.89 (m, 2H), 2.84 – 2.68 (m, 4H), 2.62 – 2.58 (m, 6H), 2.55 (s, 3H), 2.16 (s, 3H), 2.10 – 2.08 (m, 1H), 1.97 – 1.80 (m, 6H), 1.74

(d, $J = 9.0$ Hz, 2H), 1.60 – 1.49 (m, 1H). $[M+H]^+ = 870.2$.

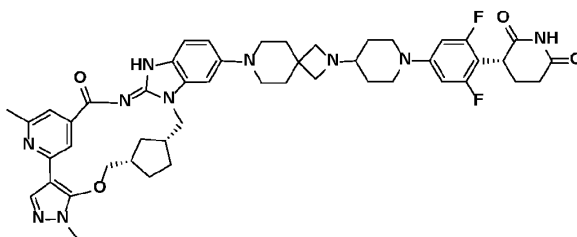
[0496] Example 119: (R)-3-(4-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-methylpiperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 71 and 7.

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 6.99 (s, 1H), 6.90 (d, $J = 8.9$ Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.29 (s, 1H), 4.19 (s, 1H), 4.11 – 4.02 (m, 3H), 3.84 (d, $J = 11.9$ Hz, 2H), 3.74 (s, 3H), 3.43 – 3.37 (m, 2H), 3.30 (s, 2H), 2.97 – 2.93 (m, 2H), 2.89 – 2.82 (m, 3H), 2.81 – 2.72 (m, 3H), 2.64 (t, $J = 9.8$ Hz, 2H), 2.55 (s, 4H), 2.12 – 2.07 (m, 1H), 1.99 – 1.90 (m, 2H), 1.88 – 1.74 (m, 4H), 1.68 – 1.65 (m, 3H), 1.43 (d, $J = 10.0$ Hz, 1H), 1.13 (d, $J = 6.1$ Hz, 3H); $[M+H]^+ = 847.5$

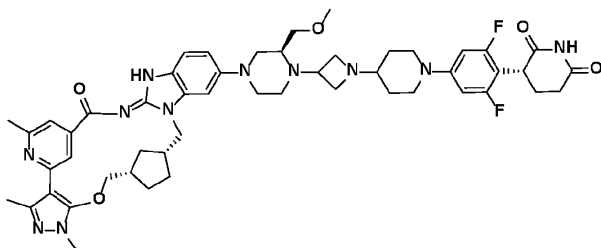
[0497] Example 120: (R)-3-(4-(4-(7-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2,7-diazaspiro[3.5]nonan-2-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 72 and 7.

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.02 (s, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 4.29 (s, 1H), 4.18 (d, $J = 7.9$ Hz, 1H), 4.09 (s, 1H), 4.05 (d, $J = 4.9$ Hz, 1H), 4.03 (d, $J = 4.9$ Hz, 1H), 3.74 (s, 3H), 3.63 (d, $J = 12.5$ Hz, 2H), 3.10 (s, 4H), 2.98 (s, 4H), 2.84 (t, $J = 10.7$ Hz, 2H), 2.79 – 2.74 (m, 1H), 2.64 – 2.57 (m, 2H), 2.55 (s, 3H), 2.52 – 2.47 (m, 3H), 2.25 (s, 1H), 2.12 – 2.04 (m, 1H), 1.97 – 1.91 (m, 2H), 1.81 (s, 6H), 1.69 (d, $J = 10.3$ Hz, 3H), 1.23 – 1.19 (m, 2H); $[M+H]^+ = 873.5$

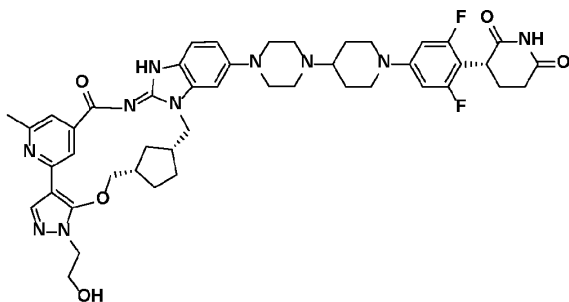
[0498] Example 121: (R)-3-(2,6-difluoro-4-(4-(3-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)azetidin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 73 and 7.

^1H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.99 (s, 1H), 6.87 (dd, J = 9.0, 1.0 Hz, 1H), 6.61 (d, J = 12.8 Hz, 2H), 4.38 – 3.98 (m, 5H), 3.67 (s, 3H), 3.62 – 3.52 (m, 2H), 3.50 – 3.38 (m, 8H), 3.28 – 3.18 (m, 7H), 3.11 – 2.99 (m, 2H), 2.90 – 2.73 (m, 6H), 2.70 – 2.51 (m, 8H), 2.38 – 2.33 (m, 1H), 2.22 – 2.15 (m, 1H), 2.13 – 2.04 (m, 1H), 1.97 – 1.92 (m, 1H), 1.89 – 1.77 (m, 3H), 1.72 – 1.65 (m, 2H), 1.27 – 1.17 (m, 2H). $[\text{M}+\text{H}]^+ = 946.2$.

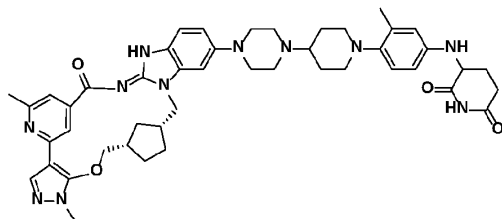
[0499] Example 122: (R)-3-(2,6-difluoro-4-(4-(4-((^7R , $^7^3\text{S}$, E)-1 1 -(2-hydroxyethyl)-2 6 -methyl-3-oxo-5 2 , 5 3 -dihydro-1 ^1H , 5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5 6 -yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



To a solution of intermediate 76 (90 mg, 0.16 mmol) and intermediate 7 (73 mg, 0.23 mmol) in DCE (6 mL) was added STAB (102 mg, 0.48 mmol). Then the mixture was stirred at 50 °C overnight. The reaction was quenched with sat. aq. NaHCO_3 (15 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with brine (1 x 10 mL), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by silica gel column (DCM : CH_3OH = 10:1), followed by Prep-HPLC chromatography to afford the title product (9.0 mg, 6.5%).

^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.50 (s, 1H), 7.94 (s, 1H), 7.44 (s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.01 (s, 1H), 6.91 (d, J = 8.9 Hz, 1H), 6.64 (d, J = 12.7 Hz, 2H), 4.97 (t, J = 5.4 Hz, 1H), 4.34 – 4.01 (m, 7H), 3.86 – 3.78 (m, 4H), 3.19 – 3.13 (m, 4H), 2.81 – 2.74 (m, 3H), 2.71 – 2.54 (m, 11H), 2.45 – 2.35 (m, 1H), 2.14 – 2.03 (m, 1H), 1.99 – 1.66 (m, 8H), 1.49 (d, J = 8.9 Hz, 2H). $[\text{M}+\text{H}]^+ = 863.6$.

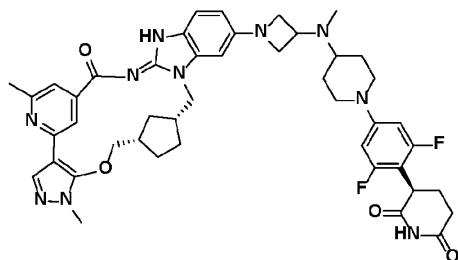
[0500] Example 123: 3-((4-(4-(4-((^7R , $^7^3\text{S}$, E)-1 1 , 2 6 -dimethyl-3-oxo-5 2 , 5 3 -dihydro-1 ^1H , 5 ^1H -9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5 6 -yl)piperazin-1-yl)piperidin-1-yl)-3-methylphenyl)amino)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 70.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.75 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 8.6 Hz, 1H), 5.44 (d, J = 7.4 Hz, 1H), 4.30 (s, 1H), 4.25 – 4.17 (m, 2H), 4.10 (s, 2H), 3.74 (s, 3H), 3.18 (s, 4H), 2.95 (s, 2H), 2.71 (d, J = 5.2 Hz, 5H), 2.59 (d, J = 4.8 Hz, 3H), 2.55 (s, 5H), 2.38 – 2.31 (m, 1H), 2.16 (s, 3H), 2.13 – 2.06 (m, 1H), 1.94 – 1.82 (m, 7H), 1.60 – 1.50 (m, 4H). $[\text{M}+\text{H}]^+ = 826.2$.

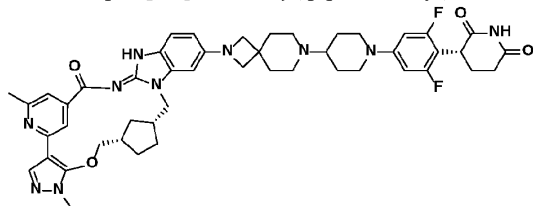
[0501] Example 124: (R)-3-(4-(4-((1-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)azetidin-3-yl)(methylamino)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 77 and 7.

^1H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 12.7 Hz, 2H), 6.52 (d, J = 1.7 Hz, 1H), 6.38 (dd, J = 8.6, 1.9 Hz, 1H), 4.34 – 4.24 (m, 1H), 4.19 (s, 1H), 4.10 (d, J = 8.7 Hz, 1H), 4.07 – 4.01 (m, 4H), 3.88 – 3.84 (m, 2H), 3.77 – 3.73 (m, 4H), 3.60 (t, J = 6.0 Hz, 2H), 2.84 – 2.67 (m, 4H), 2.65 – 2.57 (m, 4H), 2.54 (s, 4H), 2.15 (s, 3H), 2.10 – 2.02 (m, 1H), 2.00 – 1.89 (m, 2H), 1.88 – 1.84 (m, 2H), 1.72 – 1.62 (m, 3H), 1.57 – 1.46 (m, 2H); $[\text{M}+\text{H}]^+ = 833.7$.

[0502] Example 125: (R)-3-(4-(4-(2-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2,7-diazaspiro[3.5]nonan-7-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione

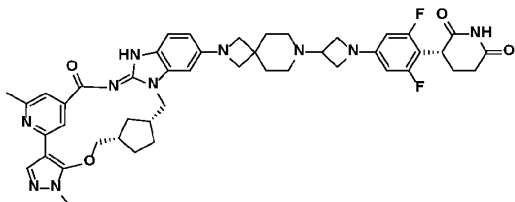


The title compound was prepared in a manner similar to that in Example 1 with intermediates 78 and 7.

^1H NMR (500 MHz, DMSO) δ 12.36 (s, 1H), 10.87 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 12.8 Hz, 2H), 6.48 (s, 1H), 6.35 (d, J = 8.6 Hz, 1H), 4.35 – 4.22 (m, 1H), 4.19 (t, J = 7.8 Hz, 1H), 4.11 (dd, J = 10.4, 2.7 Hz, 1H), 4.04 (dt, J = 12.7, 4.6 Hz, 1H), 3.99 (d, J = 5.6 Hz, 1H),

3.80 (d, $J = 12.1$ Hz, 2H), 3.74 (s, 3H), 3.57 (s, 4H), 2.83 – 2.68 (m, 4H), 2.65 – 2.52 (m, 7H), 2.43 – 2.41 (m, 4H), 2.14 – 2.02 (m, 1H), 1.98 – 1.88 (m, 2H), 1.84 – 1.81 (m, 2H), 1.79 – 1.70 (m, 7H), 1.69 – 1.61 (m, 1H), 1.52 – 1.42 (m, 2H). $[M+H]^+ = 873.7$.

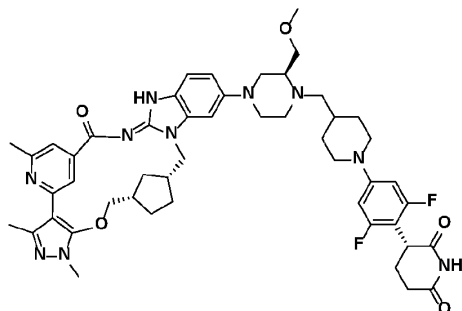
[0503] Example 126: (R)-3-(4-(3-(2-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2,7-diazaspiro[3.5]nonan-7-yl)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 78 and 79.

¹H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.86 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.33 (d, $J = 8.5$ Hz, 1H), 6.48 (s, 1H), 6.36 (dd, $J = 8.6, 1.7$ Hz, 1H), 6.13 (d, $J = 11.1$ Hz, 2H), 4.35 – 4.24 (m, 1H), 4.19 (dd, $J = 13.9, 7.0$ Hz, 1H), 4.12 – 4.10 (m, 1H), 4.03 (dd, $J = 12.3, 4.9$ Hz, 2H), 3.93 (t, $J = 7.3$ Hz, 2H), 3.74 (s, 3H), 3.66 – 3.61 (m, 2H), 3.59 (s, 4H), 3.29 (s, 1H), 3.22 (d, $J = 6.0$ Hz, 1H), 2.82 – 2.72 (m, 1H), 2.66 – 2.52 (m, 7H), 2.36 – 2.19 (m, 3H), 2.13 – 2.02 (m, 1H), 1.95 – 1.91 (m, 2H), 1.87 – 1.72 (m, 7H), 1.68 – 1.64 (m, 1H); $[M+H]^+ = 845.7$.

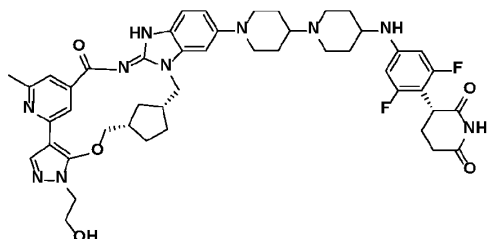
[0504] Example 127: (R)-3-(2,6-difluoro-4-(4-(((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 40 and 80.

¹H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.01 (s, 1H), 6.89 (d, $J = 8.7$ Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 4.39 – 3.95 (m, 5H), 3.76 (d, $J = 12.3$ Hz, 2H), 3.67 (s, 3H), 3.55 (dd, $J = 9.5, 4.1$ Hz, 1H), 3.44 (dd, $J = 9.5, 6.2$ Hz, 1H), 3.40 – 3.32 (m, 2H), 3.29 – 3.22 (m, 4H), 3.01 (t, $J = 8.4$ Hz, 1H), 2.96 – 2.91 (m, 1H), 2.90 – 2.83 (m, 1H), 2.83 – 2.70 (m, 3H), 2.69 – 2.56 (m, 4H), 2.55 (s, 3H), 2.51 (s, 1H), 2.49 – 2.45 (m, 4H), 2.45 – 2.38 (m, 1H), 2.20 (dd, $J = 12.5, 5.1$ Hz, 1H), 2.14 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.90 – 1.77 (m, 4H), 1.77 – 1.61 (m, 3H), 1.21 – 1.08 (m, 2H). $[M+H]^+ = 905.7$.

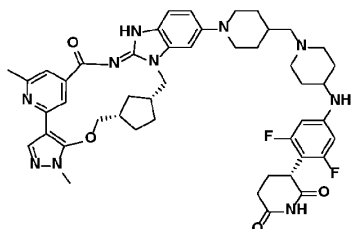
[0505] Example 129: (R)-3-(2,6-difluoro-4-(((1'-((7¹R,7³S,E)-1¹-(2-hydroxyethyl)-2⁶-methyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-[1,4'-bipiperidin]-4-yl)amino)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 140 and 68.

^1H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.82 (s, 1H), 8.50 (s, 1H), 7.94 (s, 1H), 7.44 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.02 (s, 1H), 6.92 (d, $J = 9.1$ Hz, 1H), 6.23 (d, $J = 12.1$ Hz, 2H), 6.12 (d, $J = 8.0$ Hz, 1H), 4.97 (t, $J = 5.4$ Hz, 1H), 4.28 – 3.95 (m, 8H), 3.85 – 3.71 (m, 5H), 3.19 (s, 2H), 2.87 – 2.58 (m, 10H), 2.41 – 2.29 (m, 5H), 2.05 (t, $J = 12.6$ Hz, 1H), 1.93 – 1.84 (m, 7H), 1.60 (d, $J = 12.3$ Hz, 2H), 1.34 (d, $J = 10.5$ Hz, 2H). $[\text{M}+\text{H}]^+ = 877.6$.

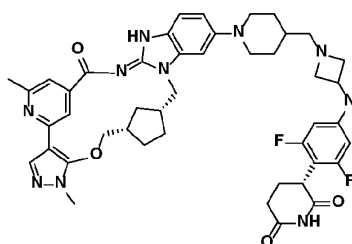
[0506] Example 131: (R)-3-(4-((1-((1-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperidin-4-yl)methyl)piperidin-4-yl)amino)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 82 and 68.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.83 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.01 (s, 1H), 6.93 (d, $J = 8.6$ Hz, 1H), 6.29 (d, $J = 11.4$ Hz, 3H), 4.35 – 4.28 (m, 1H), 4.22 – 4.17 (m, 1H), 4.12 – 4.06 (m, 2H), 4.00 – 3.97 (m, 1H), 3.74 (s, 3H), 3.72 – 3.68 (m, 3H), 3.10 – 2.97 (m, 2H), 2.82 – 2.67 (m, 4H), 2.64 – 2.58 (m, 3H), 2.55 (s, 3H), 2.51 – 2.45 (m, 3H), 2.11 – 2.02 (m, 3H), 1.94 – 1.82 (m, 8H), 1.68 (s, 2H), 1.40 – 1.32 (m, 2H), 1.23 – 1.19 (m, 2H). $[\text{M}+\text{H}]^+ = 861.5$.

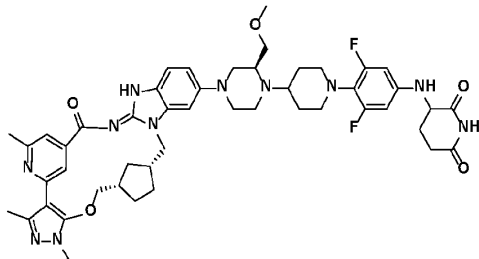
[0507] Example 132: (R)-3-(4-((1-((1-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperidin-4-yl)methyl)azetidin-3-yl)amino)-2,6-difluorophenyl)piperidine-2,6-dione



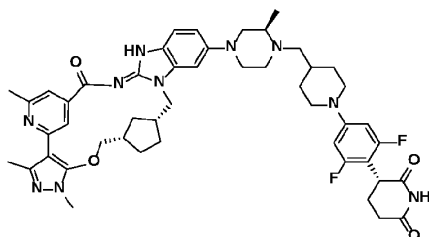
The title compound was prepared in a manner similar to that in Example 1 with intermediates 82 and 63.

^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.84 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.44 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.00 (s, 1H), 6.90 (d, $J = 8.8$ Hz, 1H), 6.70 (d, $J = 6.6$ Hz, 1H), 6.20 (s, 1H), 6.18 (s, 1H), 4.36 – 4.24 (m, 1H), 4.19 (t, $J = 7.8$ Hz, 1H), 4.14 – 3.93 (m, 4H), 3.81 – 3.59 (m, 7H), 3.43 – 3.34 (m, 2H), 2.90 – 2.53 (m, 10H), 2.48 – 2.38 (m, 2H), 2.10 – 2.01 (m, 1H), 1.96 – 1.89 (m, 2H), 1.87 – 1.75 (m, 4H), 1.69 – 1.62

[0508] **Example 133:** 3-((3,5-difluoro-4-((S)-2-(methoxymethyl)-4-((⁷R,⁷S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)amino)piperidine-2,6-dione

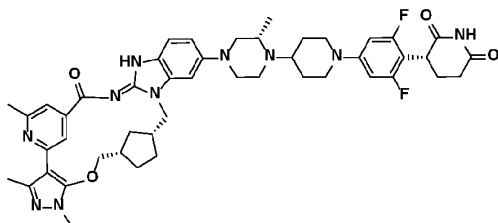

$$[\text{M}+\text{H}]^+ = 906.7$$

[0509] Example 134: (R)-3-(2,6-difluoro-4-(4-(((R)-2-methyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione



¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.02 (s, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 4.40 – 3.93 (m, 5H), 3.80 – 3.72 (m, 2H), 3.67 (s, 3H), 3.49 – 3.38 (m, 2H), 2.98 (d, *J* = 11.0 Hz, 1H), 2.88 (t, *J* = 9.7 Hz, 1H), 2.83 – 2.70 (m, 3H), 2.65 – 2.51 (m, 8H), 2.49 – 2.43 (m, 4H), 2.30 (t, *J* = 9.4 Hz, 1H), 2.14 – 1.60 (m, 11H), 1.27 – 1.09 (m, 3H), 1.07 (d, *J* = 5.9 Hz, 3H). [M+H]⁺ = 875.7

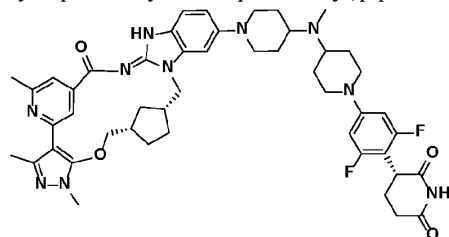
[0510] **Example 135:** (R)-3-(2,6-difluoro-4-(4-((S)-2-methyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentana-cyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 85 and 7.

¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 6.89 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 12.8 Hz, 2H), 4.37 – 4.24 (m, 1H), 4.22 – 4.15 (m, 1H), 4.13 – 3.93 (m, 3H), 3.91 – 3.85 (m, 1H), 3.81 – 3.78 (m, 2H), 3.66 (s, 3H), 3.22 – 3.20 (m, 1H), 3.03 – 2.99 (m, 1H), 2.89 – 2.73 (m, 4H), 2.72 – 2.51 (m, 9H), 2.49 – 2.34 (m, 6H), 2.11 – 2.07 (m, 1H), 2.00 – 1.93 (m, 1H), 1.85 – 1.64 (m, 6H), 1.54 – 1.47 (m, 2H), 0.96 – 0.95 (m, 3H); $[M+H]^+ = 861.7$.

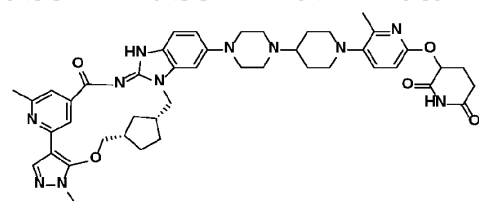
[0511] Example 136: (R)-3-(2,6-difluoro-4-(4-(methyl(1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperidin-4-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 86 and 7.

¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.01 (s, 1H), 6.90 (dd, J = 8.9, 1.9 Hz, 1H), 6.62 (d, J = 12.8 Hz, 2H), 4.36 – 4.25 (m, 1H), 4.22 (s, 1H), 4.13 – 3.96 (m, 3H), 3.81 (d, J = 13.1 Hz, 2H), 3.67 (s, 5H), 2.82 – 2.62 (m, 7H), 2.55 (s, 4H), 2.48 (s, 4H), 2.21 (s, 3H), 2.09 – 2.06 (m, 1H), 1.96 – 1.93 (m, 1H), 1.90 – 1.76 (m, 5H), 1.76 – 1.73 (m, 2H), 1.68 – 1.53 (m, 2H), 1.51 – 1.40 (m, 2H), 1.33 – 1.18 (m, 4H); $[M+H]^+ = 875.7$.

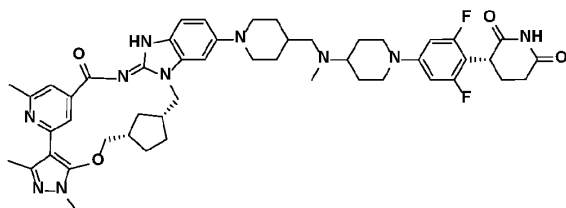
[0512] Example 137: 3-((5-(4-(4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)oxy)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in Example 1 with intermediates 2 and 87.

¹H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 5.87 – 5.76 (m, 1H), 4.37 – 4.24 (m, 1H), 4.19 (s, 1H), 4.10 (dd, J = 8.1, 5.6 Hz, 2H), 3.74 (s, 3H), 3.17 (t, J = 7.7 Hz, 4H), 3.03 – 3.01 (m, 2H), 2.85 – 2.81 (m, 1H), 2.75 – 2.71 (m, 4H), 2.64 – 2.61 (m, 6H), 2.55 (s, 3H), 2.40 – 2.34 (m, 4H), 2.19 – 2.16 (m, 2H), 2.00 – 1.76 (m, 6H), 1.66 – 1.62 (m, 3H); $[M+H]^+ = 828.7$.

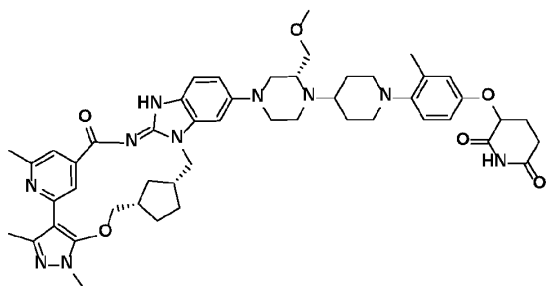
[0513] Example 138: (R)-3-(2,6-difluoro-4-(4-(methyl(1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 88 and 7.

^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.01 (s, 1H), 6.90 (dd, $J = 8.9, 1.9$ Hz, 1H), 6.62 (d, $J = 12.8$ Hz, 2H), 4.36 – 4.25 (m, 1H), 4.22 (s, 1H), 4.13 – 3.96 (m, 3H), 3.81 (d, $J = 13.1$ Hz, 2H), 3.67 (s, 5H), 2.82 – 2.62 (m, 7H), 2.55 (s, 4H), 2.48 (s, 4H), 2.29 (d, $J = 6.5$ Hz, 2H), 2.21 (s, 3H), 2.09 – 2.06 (m, 1H), 1.96 – 1.93 (m, 1H), 1.90 – 1.76 (m, 5H), 1.76 – 1.73 (m, 2H), 1.68 – 1.53 (m, 2H), 1.51 – 1.40 (m, 2H), 1.33 – 1.18 (m, 4H); $[\text{M}+\text{H}]^+ = 889.5$.

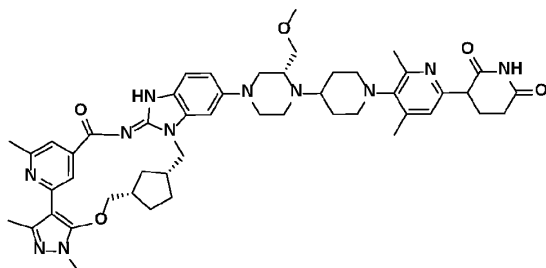
[0514] Example 140: 3-(4-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3-methylphenoxy)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 47 and 89.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.89 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 7.02 – 6.94 (m, 2H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 2.8$ Hz, 1H), 6.79 (dd, $J = 8.7, 2.8$ Hz, 1H), 5.07 (dd, $J = 10.6, 5.0$ Hz, 1H), 4.35 – 3.96 (m, 4H), 3.67 (s, 3H), 3.58 – 3.49 (m, 2H), 3.31 – 3.22 (m, 4H), 3.09 – 2.95 (m, 5H), 2.91 – 2.78 (m, 2H), 2.75 – 2.52 (m, 12H), 2.48 (s, 3H), 2.22 (s, 3H), 2.19 – 2.07 (m, 2H), 1.92 – 1.71 (m, 7H), 1.66 – 1.50 (m, 2H). $[\text{M}+\text{H}]^+ = 885.6$.

[0515] Example 141: 3-(5-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione

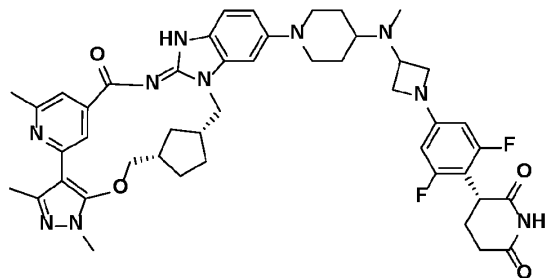


The title compound was prepared in a manner similar to that in example 1 with intermediates 47 and 13.

^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.78 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.03 – 6.84 (m, 3H), 4.38 – 3.95 (m, 4H), 3.84 (dd, $J = 9.1, 5.3$ Hz, 1H), 3.67 (s, 3H), 3.59 (dd, $J = 9.7$,

4.3 Hz, 1H), 3.51 (dd, $J = 9.5, 6.0$ Hz, 1H), 3.28 – 2.79 (m, 13H), 2.74 – 2.52 (m, 10H), 2.48 (s, 3H), 2.41 (d, $J = 6.9$ Hz, 3H), 2.28 (s, 3H), 2.22 – 2.15 (m, 1H), 2.07 (dd, $J = 13.2, 5.6$ Hz, 1H), 1.94 – 1.49 (m, 9H). $[M+H]^+ = 884.6$.

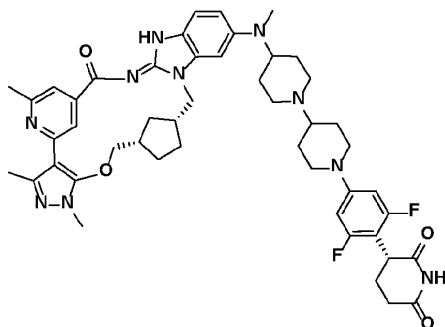
[0516] Example 142: (R)-3-(2,6-difluoro-4-(3-(methyl(1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperidin-4-yl)amino)azetidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 86 and 79.

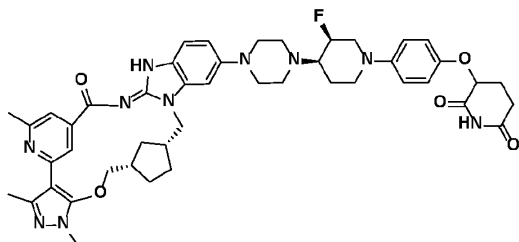
¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.35 (s, 1H), 7.03 (s, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 6.14 (d, $J = 11.1$ Hz, 2H), 4.36 – 3.99 (m, 5H), 3.95 (s, 2H), 3.84 – 3.71 (m, 3H), 3.68 – 3.62 (m, 5H), 2.83 – 2.73 (m, 1H), 2.67 (t, $J = 11.6$ Hz, 2H), 2.61 – 2.52 (m, 8H), 2.48 (s, 3H), 2.19 (s, 3H), 2.12 – 2.03 (m, 1H), 1.97 – 1.58 (m, 10H). $[M+H]^+ = 847.6$.

[0517] Example 143: (R)-3-(2,6-difluoro-4-(4-(methyl((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)amino)-[1,4'-bipiperidin]-1'-yl)phenyl)piperidine-2,6-dione



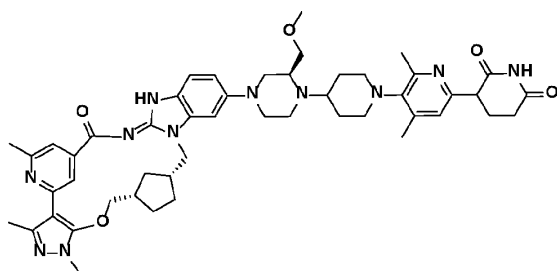
The title compound was prepared in a manner similar to that in example 1 with intermediates 90 and 7. ¹H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.34 (d, $J = 8.7$ Hz, 1H), 6.84 – 6.74 (m, 2H), 6.63 (d, $J = 12.8$ Hz, 2H), 4.36 – 3.97 (m, 5H), 3.81 (d, $J = 12.3$ Hz, 2H), 3.67 (s, 3H), 3.61 – 3.54 (m, 1H), 2.96 (d, $J = 9.7$ Hz, 2H), 2.81 – 2.70 (m, 6H), 2.65 – 2.52 (m, 8H), 2.48 (s, 3H), 2.31 – 2.23 (m, 2H), 2.13 – 2.03 (m, 1H), 1.99 – 1.59 (m, 12H), 1.52 – 1.42 (m, 2H). $[M+H]^+ = 875.6$.

[0518] Example 144: 3-(4-((3S,4R)-3-fluoro-4-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenoxy)piperidine-2,6-dione



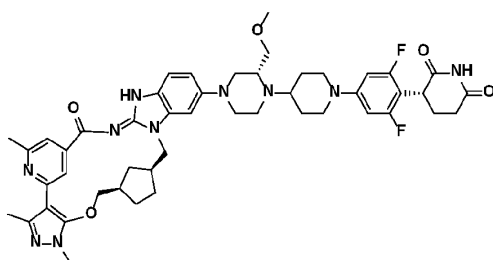
The title compound was prepared in a manner similar to that in example 11 with intermediates 39 and 91. ^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.88 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.04 (s, 1H), 6.96 – 6.83 (m, 5H), 5.16 – 5.06 (m, 1H), 5.02 (dd, J = 10.4, 4.9 Hz, 1H), 4.37 – 4.24 (m, 1H), 4.22 – 4.15 (m, 1H), 4.14 – 3.98 (m, 2H), 3.79 (t, J = 11.6 Hz, 1H), 3.67 (s, 4H), 3.18 (d, J = 4.1 Hz, 4H), 2.87 – 2.73 (m, 5H), 2.73 – 2.53 (m, 10H), 2.48 (s, 4H), 2.22 – 2.14 (m, 1H), 2.12 – 2.03 (m, 1H), 1.97 – 1.93 (m, 1H), 1.91 – 1.74 (m, 4H), 1.66 – 1.62 (m, 1H); $[\text{M}+\text{H}]^+ = 845.7$.

[0519] Example 147: 3-(5-(4-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4,6-dimethylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 40 and 13. ^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.78 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (dd, J = 8.7, 4.3 Hz, 1H), 7.03 – 6.86 (m, 3H), 4.38 – 3.95 (m, 4H), 3.84 (dd, J = 9.1, 5.4 Hz, 1H), 3.67 (s, 3H), 3.61 – 3.47 (m, 3H), 3.29 (d, J = 2.8 Hz, 4H), 3.18 – 2.78 (m, 9H), 2.74 – 2.52 (m, 10H), 2.48 (s, 3H), 2.44 – 2.35 (m, 3H), 2.28 (s, 3H), 2.18 (dt, J = 14.4, 7.1 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.92 – 1.48 (m, 8H). $[\text{M}+\text{H}]^+ = 884.6$.

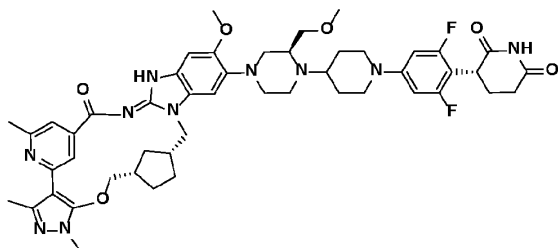
[0520] Example 150: (R)-3-(2,6-difluoro-4-(4-((R)-2-(methoxymethyl)-4-((7¹S,7³R,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 93 and 7. ^1H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.98 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.38 – 3.95 (m, 5H), 3.82 (d, J = 12.4 Hz, 2H), 3.67 (s, 3H), 3.57 (dd, J = 9.7, 4.3 Hz, 1H), 3.50 (dd, J = 9.6, 5.8 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 2H), 3.20

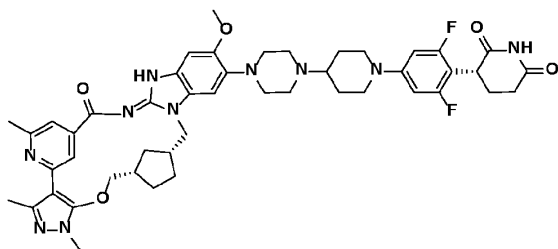
(s, 1H), 3.09 – 2.95 (m, 3H), 2.93 – 2.86 (m, 1H), 2.85 – 2.51 (m, 12H), 2.48 – 2.41 (m, 3H), 2.15 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.91 – 1.77 (m, 4H), 1.76 – 1.69 (m, 1H), 1.67 – 1.55 (m, 2H), 1.50 – 1.39 (m, 1H). $[M+H]^+ = 891.7$

[0521] Example 151: (R)-3-(2,6-difluoro-4-(4-((S)-4-((7¹R,7³S,E)-55-methoxy-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



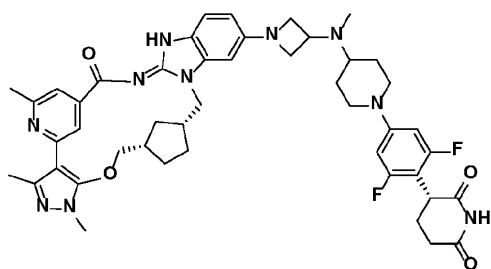
The title compound was prepared in a manner similar to that in example 1 with intermediates 94 and 7. ¹H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.16 (s, 1H), 7.04 (s, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.34 – 3.98 (m, 5H), 3.84 – 3.76 (m, 5H), 3.66 (s, 3H), 3.61 (d, *J* = 4.9 Hz, 2H), 3.30 (s, 3H), 3.05 – 2.66 (m, 12H), 2.62 – 2.52 (m, 6H), 2.48 (s, 3H), 2.13 – 2.04 (m, 1H), 1.99 – 1.71 (m, 7H), 1.63 – 1.41 (m, 3H). $[M+H]^+ = 921.6$.

[0522] Example 152: (R)-3-(2,6-difluoro-4-(4-(4-((7¹R,7³S,E)-5⁵-methoxy-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



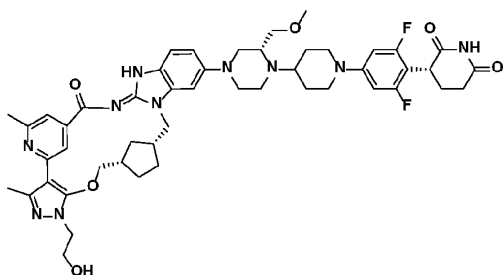
The title compound was prepared in a manner similar to that in example 1 with intermediates 95 and 7. ¹H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.34 – 3.98 (m, 5H), 3.84 – 3.76 (m, 5H), 3.66 (s, 3H), 3.06 – 2.95 (m, 4H), 2.83 – 2.73 (m, 3H), 2.70 – 2.51 (m, 12H), 2.48 – 2.41 (m, 4H), 2.14 – 2.03 (m, 1H), 2.00 – 1.70 (m, 7H), 1.49 (d, *J* = 10.6 Hz, 2H). $[M+H]^+ = 877.6$.

[0523] Example 153: (R)-3-(2,6-difluoro-4-(4-(methyl(1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)azetidin-3-yl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione



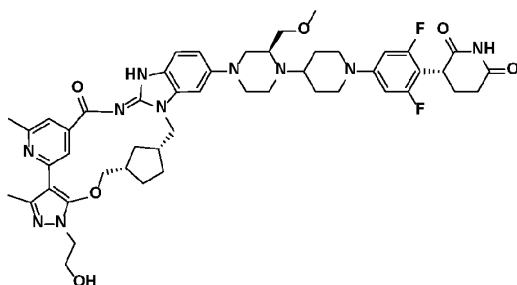
The title compound was prepared in a manner similar to that in example 1 with intermediates 96 and 7. ^1H NMR (500 MHz, DMSO) δ 12.38 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.33 (s, 1H), 6.64 (d, J = 12.7 Hz, 2H), 6.52 (s, 1H), 6.38 (dd, J = 8.6, 1.9 Hz, 1H), 4.34 – 3.97 (m, 7H), 3.85 (d, J = 12.1 Hz, 2H), 3.78 – 3.72 (m, 1H), 3.67 (s, 3H), 3.60 (t, J = 6.1 Hz, 2H), 2.81 – 2.52 (m, 12H), 2.47 (s, 3H), 2.14 (s, 3H), 2.12 – 2.03 (m, 1H), 1.99 – 1.64 (m, 7H), 1.55 – 1.45 (m, 2H). $[\text{M}+\text{H}]^+ = 847.6$.

[0524] Example 156: (R)-3-(2,6-difluoro-4-(4-((R)-4-((7^R,7^S,E)-1¹-(2-hydroxyethyl)-1³,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



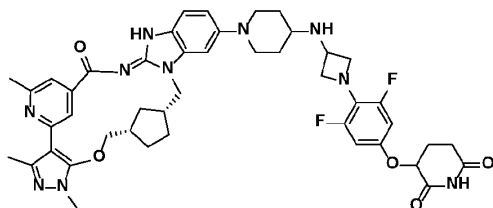
The title compound was prepared in a manner similar to that in example 1 with intermediates 98 and 7. ^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.44 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.98 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 12.7 Hz, 2H), 4.95 (t, J = 5.4 Hz, 1H), 4.36 – 4.21 (m, 2H), 4.11 – 4.00 (m, 3H), 4.00 – 3.93 (m, 2H), 3.85 – 3.81 (m, 4H), 3.59 – 3.46 (m, 2H), 3.29 (d, J = 9.0 Hz, 4H), 3.24 – 3.14 (m, 1H), 3.08 – 2.97 (m, 3H), 2.90 – 2.84 (m, 1H), 2.77 – 2.74 (m, 4H), 2.68 – 2.65 (m, 2H), 2.56 (d, J = 8.4 Hz, 4H), 2.51 (s, 4H), 2.13 – 2.03 (m, 1H), 1.99 – 1.69 (m, 7H), 1.68 – 1.56 (m, 2H), 1.51 – 1.39 (m, 1H). $[\text{M}+\text{H}]^+ = 921.7$.

[0525] Example 157: (R)-3-(2,6-difluoro-4-(4-((S)-4-((7^R,7^S,E)-1¹-(2-hydroxyethyl)-1³,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



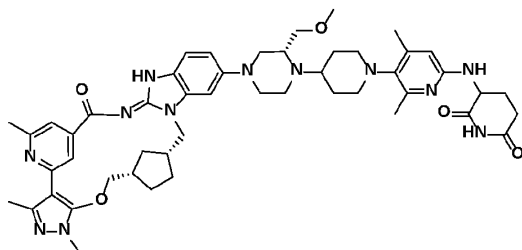
The title compound was prepared in a manner similar to that in example 1 with intermediates 99 and 7. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.52 (s, 1H), 7.44 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 12.7 Hz, 2H), 4.95 (t, *J* = 5.4 Hz, 1H), 4.36 – 4.21 (m, 2H), 4.11 – 4.00 (m, 3H), 4.00 – 3.93 (m, 2H), 3.85 – 3.81 (m, 4H), 3.59 – 3.46 (m, 2H), 3.29 (d, *J* = 9.0 Hz, 4H), 3.24 – 3.14 (m, 1H), 3.08 – 2.97 (m, 3H), 2.90 – 2.84 (m, 1H), 2.77 – 2.74 (m, 4H), 2.68 – 2.65 (m, 2H), 2.58 (d, *J* = 8.4 Hz, 4H), 2.51 (s, 4H), 2.13 – 2.03 (m, 1H), 1.99 – 1.69 (m, 7H), 1.68 – 1.57 (m, 2H), 1.51 – 1.40 (m, 1H). [M+H]⁺ = 921.7.

[0526] Example 158: 3-(3,5-difluoro-4-(3-((1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanaacyclononaphane-5⁶-yl)piperidin-4-yl)amino)azetidin-1-yl)phenoxy)piperidine-2,6-dione



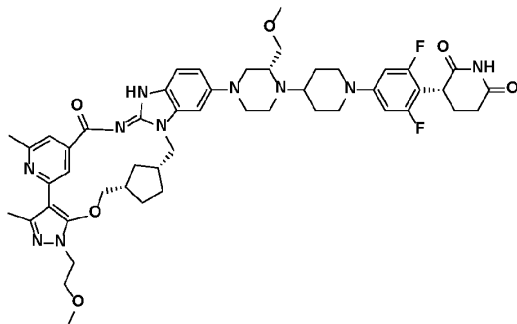
The title compound was prepared in a manner similar to that in example 1 with intermediates 101 and 100. ¹H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.92 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 5.09 (dd, *J* = 11.0, 5.1 Hz, 1H), 4.42 – 3.94 (m, 6H), 3.76 – 3.56 (m, 8H), 2.78 – 2.51 (m, 12H), 2.48 – 2.38 (m, 3H), 2.21 – 2.14 (m, 1H), 2.14 – 2.03 (m, 1H), 1.90 – 1.60 (m, 6H), 1.45 – 1.33 (m, 2H). [M+H]⁺ = 849.7

[0527] Example 159: 3-((5-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanaacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4,6-dimethylpyridin-2-yl)amino)piperidine-2,6-dione



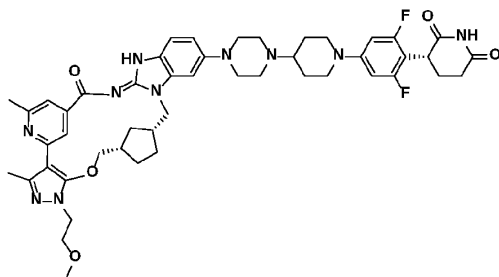
The title compound was prepared in a manner similar to that in example 1 with intermediates 47 and 102. ¹H NMR (500 MHz, DMSO) δ_H 12.43 (s, 1H), 10.72 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 6.42 – 6.35 (m, 1H), 6.25 – 6.12 (m, 1H), 4.65 (d, *J* = 8.6 Hz, 1H), 4.38 – 3.95 (m, 4H), 3.67 (s, 3H), 3.58 – 3.47 (m, 3H), 3.30 – 2.93 (m, 9H), 2.91 – 2.52 (m, 14H), 2.48 (s, 3H), 2.31 – 2.22 (m, 3H), 2.16 (d, *J* = 13.1 Hz, 3H), 2.05 – 1.95 (m, 2H), 1.90 – 1.46 (m, 8H). [M+H]⁺ = 899.6.

[0528] Example 160: (R)-3-(2,6-difluoro-4-(4-((R)-4-((7¹R,7³S,E)-1¹-(2-methoxyethyl)-1³,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanaacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



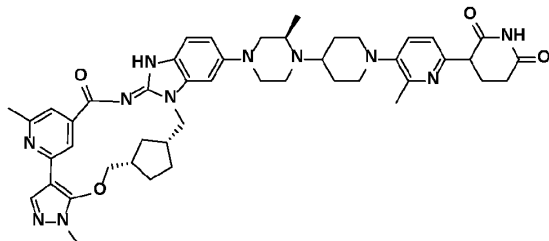
The title compound was prepared in a manner similar to that in example 1 with intermediates 103 and 7. ^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.51 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.40 – 3.99 (m, 7H), 3.87 – 3.79 (m, 2H), 3.78 – 3.70 (m, 2H), 3.60 – 3.54 (m, 1H), 3.54 – 3.48 (m, 1H), 3.31 – 3.17 (m, 9H), 3.09 – 2.97 (m, 3H), 2.93 – 2.86 (m, 1H), 2.85 – 2.53 (m, 12H), 2.49 – 2.47 (m, 2H), 2.15 – 2.04 (m, 1H), 2.00 – 1.94 (m, 1H), 1.92 – 1.70 (m, 6H), 1.68 – 1.56 (m, 2H), 1.50 – 1.39 (m, 1H). $[\text{M}+\text{H}]^+ = 935.7$

[0529] Example 161: (R)-3-(2,6-difluoro-4-(4-(4-((7R,7S,E)-1-(2-methoxyethyl)-1,3,2'-dimethyl-3-oxo-5,5'-dihydro-1H,5H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5'-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 104 and 7. ^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.51 (s, 1H), 7.45 (s, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.01 (s, 1H), 6.93 – 6.85 (m, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.40 – 4.17 (m, 2H), 4.14 – 3.95 (m, 5H), 3.85 – 3.69 (m, 4H), 3.57 – 3.27 (m, 7H), 3.20 – 3.09 (m, 4H), 2.83 – 2.53 (m, 13H), 2.48 – 2.39 (m, 2H), 2.14 – 2.03 (m, 1H), 1.99 – 1.93 (m, 1H), 1.90 – 1.76 (m, 5H), 1.72 – 1.59 (m, 1H), 1.53 – 1.43 (m, 2H). $[\text{M}+\text{H}]^+ = 891.7$

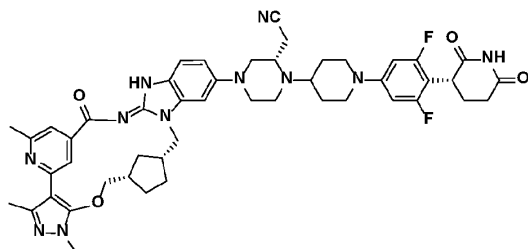
[0530] Example 162: 3-(5-(4-((R)-4-((7R,7S,E)-1-(2-methoxyethyl)-1,3,2'-dimethyl-3-oxo-5,5'-dihydro-1H,5H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5'-yl)-2-methylpiperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 105 and 15. ^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.78 (s, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (t, J =

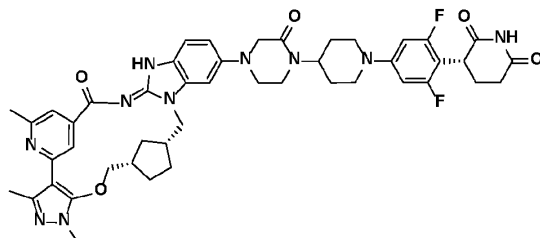
8.4 Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 1H), 7.01 (s, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 4.37 – 4.24 (m, 1H), 4.19 (dd, $J = 15.9, 6.3$ Hz, 1H), 4.14 – 4.01 (m, 2H), 3.89 (dd, $J = 9.3, 5.3$ Hz, 1H), 3.74 (s, 3H), 3.51 – 3.45 (m, 1H), 3.43 (dd, $J = 7.8, 5.5$ Hz, 1H), 3.14 (dd, $J = 15.4, 6.6$ Hz, 2H), 2.96 – 2.86 (m, 4H), 2.75 – 2.69 (m, 1H), 2.63 – 2.54 (m, 11H), 2.45 – 2.39 (m, 3H), 2.28 – 2.15 (m, 1H), 2.08 (dd, $J = 12.9, 6.2$ Hz, 1H), 1.98 – 1.75 (m, 6H), 1.71 – 1.66 (m, 2H), 1.63 – 1.57 (m, 1H), 1.13 (d, $J = 6.2$ Hz, 3H). $[M+H]^+ = 826.7$.

[0531] Example 163: 2-((S)-1-(1-(4-((R)-2,6-dioxopiperidin-3-yl)-3,5-difluorophenyl)piperidin-4-yl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanaacyclonaphane-5⁶-yl)piperazin-2-yl)acetonitrile



The title compound was prepared in a manner similar to that in example 1 with intermediates 106 and 7. ¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.90 (d, $J = 9.1$ Hz, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 4.35 – 4.29 (m, 1H), 4.23 – 4.15 (m, 1H), 4.13 – 3.98 (m, 3H), 3.87 – 3.78 (m, 2H), 3.67 (s, 3H), 3.27 (dd, $J = 7.9, 4.3$ Hz, 1H), 3.17 – 3.10 (m, 3H), 3.09 – 3.02 (m, 1H), 2.86 – 2.70 (m, 9H), 2.55 (s, 6H), 2.48 – 2.43 (m, 4H), 2.10 – 2.06 (m, 1H), 1.99 – 1.91 (m, 1H), 1.89 – 1.75 (m, 5H), 1.68 – 1.53 (m, 2H), 1.50 – 1.38 (m, 1H). $[M+H]^+ = 886.7$.

[0532] Example 164: (R)-3-(2,6-difluoro-4-(4-(2-oxo-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanaacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The racemate compound was prepared in a manner similar to that in example 11 with intermediates 107 and 39.

The title compound was purified by chiral HPLC and corresponds to the peak @ 15.858 min.

Inj. Volume: 2.0 μ L

Column: CHIRALPAK IE 4.6*250 mm 5 μ m

Flow Rate (mL/min): 1.0

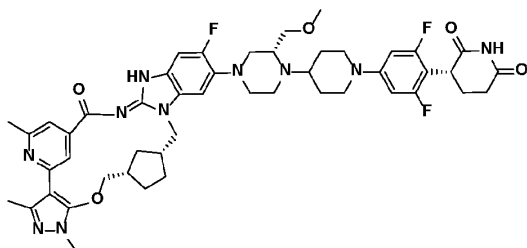
Gradient:

Time (min)	MtBE (0.1%DEA+0.1%FA)(%)	MeOH:DCM=50:50(%)
0	20	80
30	20	80

¹H NMR (500 MHz, DMSO) δ 12.44 (s, 1H), 10.88 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, $J = 8.7$ Hz, 1H), 7.07 (s, 1H), 6.90 (dd, $J = 8.9, 2.0$ Hz, 1H), 6.69 (s, 1H), 6.66 (s, 1H), 4.52 – 4.57 (m, 1H), 4.34 – 4.29 (m,

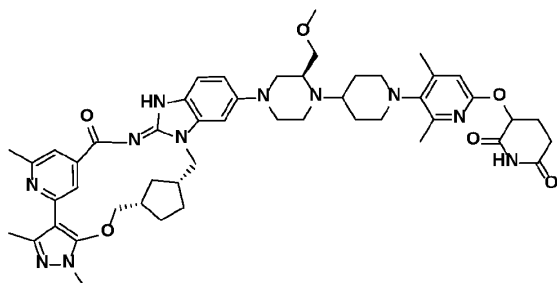
1H), 4.20 – 4.16 (m, 1H), 4.08 – 4.04 (m, 2H), 3.91 – 3.87 (m, 4H), 3.67 (s, 3H), 3.47 (d, $J = 3.9$ Hz, 2H), 3.40 (d, $J = 5.0$ Hz, 2H), 2.88 – 2.75 (m, 3H), 2.64 – 2.62 (m, 1H), 2.55 (s, 3H), 2.54 – 2.51 (m, 4H), 2.48 (s, 3H), 2.11 – 2.07 (m, 1H), 2.01 – 1.92 (m, 1H), 1.83 – 1.76 (m, 6H), 1.64 – 1.62 (m, 3H). $[M+H]^+ = 861.7$

[0533] Example 165: (R)-3-(2,6-difluoro-4-(4-((R)-4-((7¹R,7³S,E)-5⁵-fluoro-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



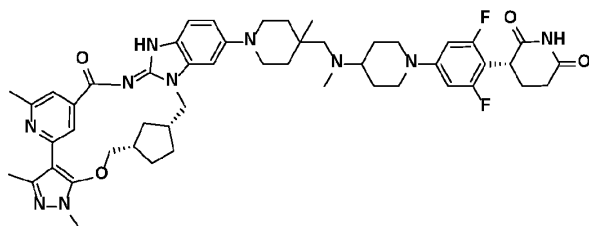
The title compound was prepared in a manner similar to that in example 1 with intermediates 108 and 7. ¹H NMR (500 MHz, DMSO) δ 12.56 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.29 (d, $J = 11.5$ Hz, 1H), 7.18 (d, $J = 7.3$ Hz, 1H), 6.64 (d, $J = 12.8$ Hz, 2H), 4.26 – 4.22 (m, 1H), 4.18 – 4.14 (m, 1H), 4.06 – 4.03 (m, 3H), 3.83 (d, $J = 11.5$ Hz, 2H), 3.70 (d, $J = 9.7$ Hz, 1H), 3.67 (s, 3H), 3.61 – 3.58 (m, 1H), 3.54 (dd, $J = 9.6, 4.3$ Hz, 1H), 3.42 – 3.39 (m, 1H), 3.28 – 3.26 (m, 6H), 2.95 – 2.87 (m, 2H), 2.79 – 2.73 (m, 4H), 2.64 – 2.60 (m, 2H), 2.55 (s, 4H), 2.51 – 2.47 (m, 5H), 2.13 – 2.05 (m, 1H), 1.99 – 1.92 (m, 1H), 1.90 – 1.79 (m, 4H), 1.73 (d, $J = 11.3$ Hz, 1H), 1.66 – 1.59 (m, 2H), 1.44 – 1.42 (m, 1H). $[M+H]^+ = 909.6$

[0534] Example 167: 3-((5-(4-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-4,6-dimethylpyridin-2-yl)oxy)piperidine-2,6-dione



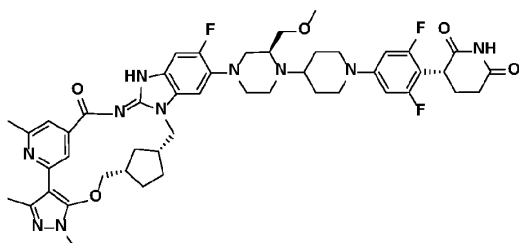
The title compound was prepared in a manner similar to that in example 1 with intermediates 40 and 109. ¹H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 6.99 (s, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 6.58 – 6.45 (m, 1H), 5.82 (t, $J = 8.5$ Hz, 1H), 4.38 – 3.95 (m, 4H), 3.67 (s, 3H), 3.60 – 3.48 (m, 2H), 3.28 – 3.01 (m, 7H), 2.99 – 2.54 (m, 15H), 2.48 (s, 3H), 2.40 – 2.31 (m, 4H), 2.29 – 2.23 (m, 3H), 2.17 – 2.11 (m, 2H), 1.92 – 1.47 (m, 9H). $[M+H]^+ = 900.6$

[0535] Example 168: (R)-3-(2,6-difluoro-4-(4-(methyl((4-methyl-1-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperidin-4-yl)methyl)amino)piperidin-1-yl)phenyl)piperidine-2,6-dione



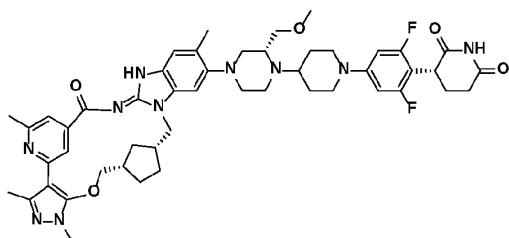
The title compound was prepared in a manner similar to that in example 1 with intermediates 110 and 7. ^1H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.02 (s, 1H), 6.92 (d, J = 6.9 Hz, 1H), 6.62 (d, J = 12.8 Hz, 2H), 4.36 – 3.97 (m, 5H), 3.84 (d, J = 12.6 Hz, 2H), 3.67 (s, 3H), 3.26 (s, 3H), 2.96 (t, J = 10.4 Hz, 2H), 2.82 – 2.53 (m, 11H), 2.39 – 2.22 (m, 6H), 2.11 – 1.93 (m, 3H), 1.90 – 1.58 (m, 9H), 1.53 – 1.36 (m, 4H), 0.95 (s, 3H). $[\text{M}+\text{H}]^+ = 903.6$.

[0536] Example 169: (R)-3-(2,6-difluoro-4-(4-((S)-4-((7¹R,7³S,E)-5⁵-fluoro-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 111 and 7. ^1H NMR (500 MHz, DMSO) δ 12.56 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.29 (d, J = 11.5 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 6.64 (d, J = 12.8 Hz, 2H), 4.26 – 4.22 (m, 1H), 4.18 – 4.14 (m, 1H), 4.06 – 4.03 (m, 3H), 3.83 (d, J = 11.5 Hz, 2H), 3.70 (d, J = 9.7 Hz, 1H), 3.67 (s, 3H), 3.61 – 3.58 (m, 1H), 3.54 (dd, J = 9.6, 4.3 Hz, 1H), 3.42 – 3.39 (m, 1H), 3.28 – 3.26 (m, 6H), 2.95 – 2.87 (m, 2H), 2.79 – 2.73 (m, 4H), 2.64 – 2.60 (m, 2H), 2.55 (s, 4H), 2.51 – 2.47 (m, 5H), 2.13 – 2.05 (m, 1H), 1.99 – 1.92 (m, 1H), 1.90 – 1.79 (m, 4H), 1.73 (d, J = 11.3 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.44 – 1.42 (m, 1H). $[\text{M}+\text{H}]^+ = 909.6$.

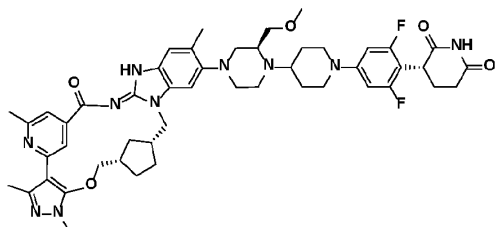
[0537] Example 172: (R)-3-(2,6-difluoro-4-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶,5⁵-tetramethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 112 and 7. ^1H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.32 (s, 1H), 7.22 (s, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.31 (dd, J = 7.3, 5.1 Hz, 1H), 4.18 (t, J = 7.3 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.80 (d, J = 12.0 Hz, 2H), 3.66 (s, 3H), 3.60 (d, J = 4.4 Hz, 1H), 3.26 (s, 3H), 3.05 (s, 1H), 2.93 – 2.73 (m, 10H), 2.72

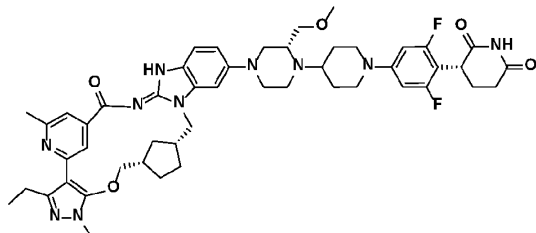
– 2.65 (m, 1H), 2.64 – 2.51 (m, 8H), 2.48 (s, 3H), 2.33 (s, 3H), 2.13 – 2.06 (m, 1H), 1.99 – 1.71 (m, 7H), 1.69 – 1.55 (m, 2H), 1.52 – 1.41 (m, 1H). $[M+H]^+ = 905.7$.

[0538] Example 173: (R)-3-(2,6-difluoro-4-(4-((S)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶,5⁵-tetramethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



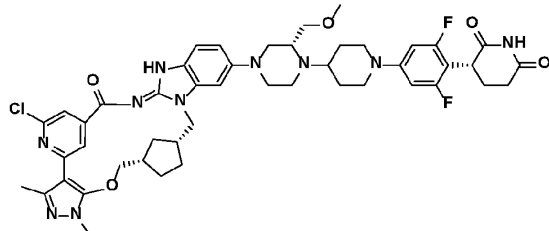
The title compound was prepared in a manner similar to that in example 1 with intermediates 113 and 7. ¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.32 (s, 1H), 7.22 (s, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.31 (dd, $J = 7.3, 5.1$ Hz, 1H), 4.20 (t, $J = 7.3$ Hz, 1H), 4.09 – 3.98 (m, 2H), 3.82 – 3.78 (m, 2H), 3.66 (s, 3H), 3.62 (d, $J = 4.4$ Hz, 1H), 3.26 (s, 3H), 3.05 (s, 1H), 2.93 – 2.73 (m, 10H), 2.72 – 2.65 (m, 1H), 2.64 – 2.51 (m, 8H), 2.48 (s, 3H), 2.33 (s, 3H), 2.13 – 2.06 (m, 1H), 1.99 – 1.71 (m, 7H), 1.69 – 1.55 (m, 2H), 1.51 – 1.40 (m, 1H). $[M+H]^+ = 905.7$.

[0539] Example 175: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-1³-ethyl-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



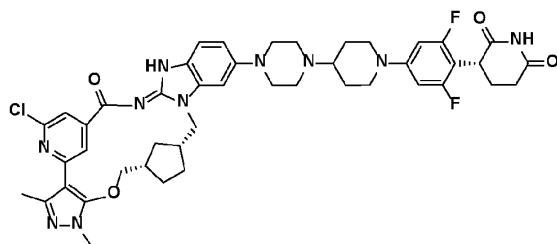
The title compound was prepared in a manner similar to that in example 1 with intermediates 138 and 7. ¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.98 (s, 1H), 6.87 (d, $J = 8.6$ Hz, 1H), 6.64 (d, $J = 13.0$ Hz, 2H), 4.34 – 3.98 (m, 5H), 3.83 (d, $J = 11.6$ Hz, 2H), 3.68 (s, 3H), 3.60 – 3.48 (m, 2H), 3.30 – 3.18 (m, 6H), 3.06 – 2.88 (m, 6H), 2.83 – 2.52 (m, 11H), 2.14 – 2.04 (m, 1H), 1.96 – 1.61 (m, 9H), 1.44 (d, $J = 12.8$ Hz, 1H), 1.21 – 1.16 (m, 3H). $[M+H]^+ = 905.6$.

[0540] Example 176: (R)-3-(4-(4-((R)-4-((7¹R,7³S,E)-2⁶-chloro-1¹,1³-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



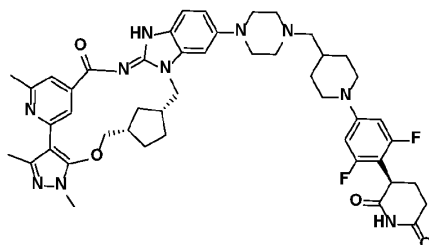
The title compound was prepared in a manner similar to that in example 1 with intermediates 139 and 7. ¹H NMR (500 MHz, DMSO) δ 12.52 (s, 1H), 10.87 (s, 1H), 8.69 (s, 1H), 7.55 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.31 (s, 1H), 4.24 – 4.16 (m, 1H), 4.14 – 4.00 (m, 3H), 3.84 – 3.78 (m, 2H), 3.68 (s, 3H), 3.57 (dd, *J* = 9.3, 3.8 Hz, 1H), 3.50 (dd, *J* = 6.2, 3.5 Hz, 1H), 3.30 (s, 5H), 3.24 – 3.16 (m, 1H), 3.03 – 2.99 (m, 3H), 2.92 – 2.86 (m, 1H), 2.85 – 2.71 (m, 4H), 2.70 – 2.51 (m, 5H), 2.44 (s, 3H), 2.12 – 2.07 (m, 1H), 1.96 – 1.93 (m, 1H), 1.91 – 1.78 (m, 4H), 1.73 – 1.69 (m, 1H), 1.63 – 1.59 (m, 2H), 1.49 – 1.40 (m, 1H). [M+H]⁺ = 911.7.

[0541] Example 179: (R)-3-(4-(4-(4-((7¹R,7³S,E)-2⁶-chloro-1¹,1³-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



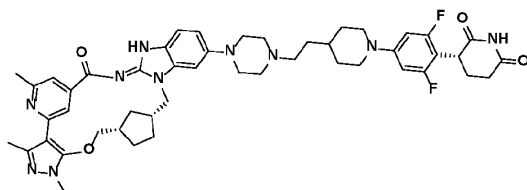
The title compound was prepared in a manner similar to that in example 1 with intermediates 114 and 7. ¹H NMR (500 MHz, DMSO) δ 12.50 (s, 1H), 10.87 (s, 1H), 8.69 (s, 1H), 7.55 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.33 – 4.28 (m, 1H), 4.24 – 4.15 (m, 1H), 4.14 – 4.00 (m, 3H), 3.82 (d, *J* = 11.7 Hz, 2H), 3.68 (s, 3H), 3.23 – 3.16 (m, 4H), 2.82 – 2.77 (m, 4H), 2.71 – 2.59 (m, 7H), 2.44 (s, 4H), 2.16 – 2.02 (m, 1H), 1.98 (d, *J* = 5.2 Hz, 1H), 1.91 – 1.72 (m, 6H), 1.66 – 1.62 (m, 1H), 1.55 – 1.44 (m, 2H). [M+H]⁺ = 867.7.

[0542] Example 182: (R)-3-(2,6-difluoro-4-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)methyl)piperidin-1-yl)phenyl)piperidine-2,6-dione



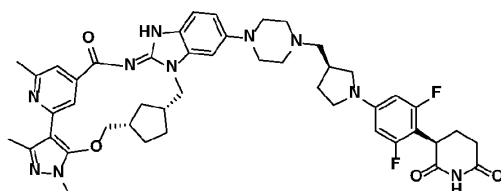
The title compound was prepared in a manner similar to that in example 1 with intermediates 34 and 80. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.03 (s, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 6.62 (d, *J* = 12.8 Hz, 2H), 4.24 (m, 2H), 4.04 (dd, *J* = 12.6, 5.1 Hz, 2H), 3.76 (d, *J* = 12.7 Hz, 2H), 3.67 (s, 3H), 3.17 (s, 4H), 2.75 (t, *J* = 11.8 Hz, 3H), 2.64 (s, 1H), 2.56 – 2.54 (m, 5H), 2.53 – 2.51 (m, 6H), 2.48 (s, 4H), 2.23 (d, *J* = 6.4 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.99 – 1.94 (m, 1H), 1.81 – 1.78 (m, 6H), 1.63 (s, 1H), 1.16 (d, *J* = 11.6 Hz, 2H). [M+H]⁺ = 861.6.

[0543] Example 183: (R)-3-(2,6-difluoro-4-(4-(2-(4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)ethyl)piperidin-1-yl)phenyl)piperidine-2,6-dione



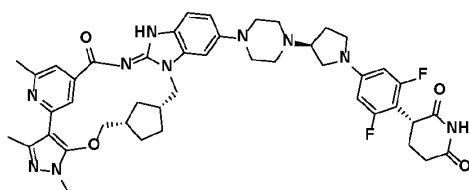
The title compound was prepared in a manner similar to that in example 1 with intermediates 34 and 115. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.02 (s, 1H), 6.90 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.61 (d, *J* = 12.8 Hz, 2H), 4.30 – 4.24 (m, 2H), 4.04 (dd, *J* = 12.5, 5.0 Hz, 2H), 3.75 (d, *J* = 12.8 Hz, 2H), 3.67 (s, 3H), 3.16 (s, 4H), 2.82 – 2.76 (m, 1H), 2.74 – 2.69 (m, 3H), 2.63 (d, *J* = 1.8 Hz, 1H), 2.57 – 2.52 (m, 9H), 2.48 (s, 4H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.12 – 2.03 (m, 1H), 1.98 – 1.93 (m, 1H), 1.81 (s, 3H), 1.74 (d, *J* = 11.1 Hz, 3H), 1.62 (s, 1H), 1.52 (s, 1H), 1.44 (dd, *J* = 14.0, 6.7 Hz, 2H), 1.23 – 1.17 (m, 2H). [M+H]⁺ = 875.7

[0544] Example 184: (R)-3-(2,6-difluoro-4-((S)-3-((4-((7^R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 34 and 116. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.84 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.93 – 6.89 (m, 1H), 6.20 (d, *J* = 12.2 Hz, 2H), 4.30 – 4.19 (m, 2H), 4.01 (dd, *J* = 12.4, 4.9 Hz, 2H), 3.67 (s, 3H), 3.38 (s, 1H), 3.29 (s, 1H), 3.22 (d, *J* = 8.3 Hz, 1H), 3.19 (s, 4H), 3.02 – 2.97 (m, 1H), 2.80 – 2.74 (m, 1H), 2.63 (dd, *J* = 3.7, 1.8 Hz, 2H), 2.61 (s, 3H), 2.58 (s, 2H), 2.55 (s, 3H), 2.52 (d, *J* = 1.9 Hz, 1H), 2.48 (s, 4H), 2.40 (d, *J* = 7.4 Hz, 2H), 2.37 – 2.35 (m, 1H), 2.09 (t, *J* = 9.6 Hz, 2H), 1.96 – 1.92 (m, 1H), 1.81 (s, 3H), 1.74 (dd, *J* = 11.8, 7.8 Hz, 2H), 1.63 (s, 1H). [M+H]⁺ = 847.7

[0545] Example 186: (R)-3-(2,6-difluoro-4-((S)-3-((4-((7^R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)pyrrolidin-1-yl)phenyl)piperidine-2,6-dione



The racemate compound was prepared in a manner similar to that in example 11 with intermediates 39 and 117.

The title compound was purified by chiral HPLC, and corresponds to peak A @ 1.773 min:

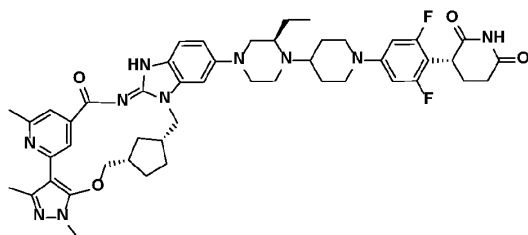
Column	CHIRALPAK IF
Column Size	4.6*50 mm, 3 μm
Mobile Phase A	MtBE(0.1%FA):(MeOH:DCM=1:1)=10:90
Flow rate	1.0 mL/min

Temperature 25 °C

¹H NMR (500 MHz, DMSO) δ 10.85 (s, 1H), 8.54 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 6.24 (s, 1H), 4.39 – 3.94 (m, 5H), 3.71 – 3.65 (m, 3H), 3.63 – 3.57 (m, 1H), 3.55 – 3.48 (m, 2H), 3.41 – 3.35 (m, 3H), 3.25 – 3.17 (m, 5H), 3.13 – 3.08 (m, 1H), 3.05 – 2.96 (m, 1H), 2.85 – 2.74 (m, 1H), 2.68 – 2.63 (m, 4H), 2.57 – 2.54 (m, 3H), 2.48 – 2.44 (m, 3H), 2.29 – 2.19 (m, 1H), 2.16 – 2.03 (m, 1H), 1.98 – 1.78 (m, 5H), 1.68 – 1.56 (m, 1H), 1.49 – 1.42 (m, 1H).

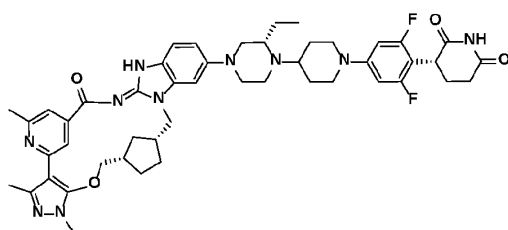
[M+H]⁺ = 833.7.

[0546] Example 188: (R)-3-(4-(4-((R)-2-ethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



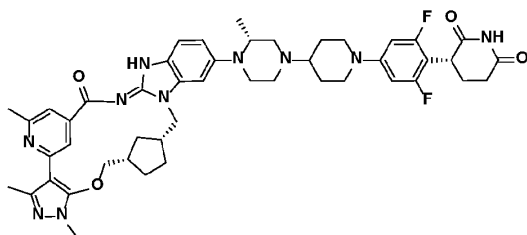
The title compound was prepared in a manner similar to that in example 1 with intermediates 118 and 7. ¹H NMR (500 MHz, DMSO) δ 12.38 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 1.4 Hz, 1H), 6.90 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.38 – 3.97 (m, 5H), 3.82 (d, *J* = 12.2 Hz, 2H), 3.67 (s, 3H), 3.31 – 3.22 (m, 3H), 2.99 (t, *J* = 8.4 Hz, 1H), 2.94 – 2.74 (m, 7H), 2.65 – 2.53 (m, 8H), 2.48 – 2.34 (m, 3H), 2.14 – 2.05 (m, 1H), 2.00 – 1.93 (m, 1H), 1.87 – 1.59 (m, 9H), 1.48 – 1.39 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H). [M+H]⁺ = 875.7

[0547] Example 189: (R)-3-(4-(4-((S)-2-ethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



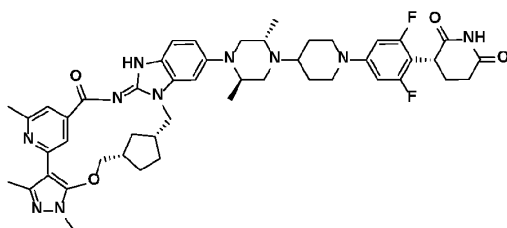
The title compound was prepared in a manner similar to that in example 1 with intermediates 119 and 7. ¹H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 4.41 – 3.97 (m, 5H), 3.82 (d, *J* = 12.4 Hz, 2H), 3.66 (s, 3H), 3.29 – 3.17 (m, 3H), 3.03 – 2.74 (m, 8H), 2.67 – 2.51 (m, 8H), 2.48 – 2.41 (m, 3H), 2.14 – 2.03 (m, 1H), 1.99 – 1.92 (m, 1H), 1.92 – 1.60 (m, 9H), 1.49 – 1.39 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H). [M+H]⁺ = 875.7

[0548] Example 190: (R)-3-(2,6-difluoro-4-(4-((R)-3-methyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



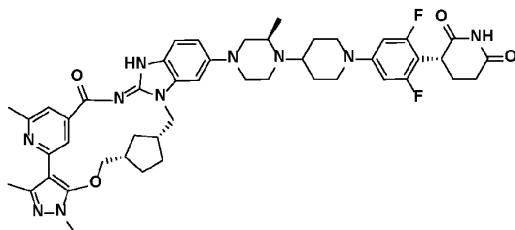
The title compound was prepared in a manner similar to that in example 1 with intermediates 120 and 7. ¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.01 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.37 – 3.97 (m, 5H), 3.88 (d, *J* = 5.5 Hz, 1H), 3.79 (d, *J* = 12.2 Hz, 2H), 3.66 (s, 3H), 3.21 (d, *J* = 11.6 Hz, 1H), 3.00 (t, *J* = 8.9 Hz, 1H), 2.89 – 2.73 (m, 4H), 2.68 – 2.52 (m, 8H), 2.48 – 2.38 (m, 6H), 2.15 – 2.03 (m, 1H), 2.00 – 1.93 (m, 1H), 1.91 – 1.58 (m, 7H), 1.55 – 1.41 (m, 2H), 0.96 (d, *J* = 6.3 Hz, 3H). [M+H]⁺ = 861.7

[0549] Example 191: (R)-3-(4-(4-((2S,5R)-2,5-dimethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



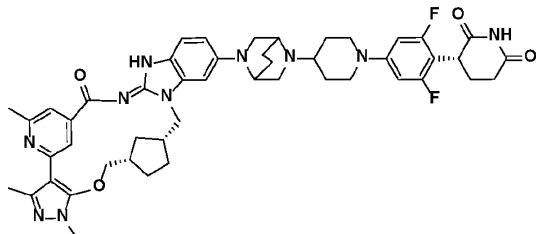
The title compound was prepared in a manner similar to that in example 1 with intermediates 121 and 7. ¹H NMR (500 MHz, DMSO) δ 12.48 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.40 – 3.96 (m, 5H), 3.81 (d, *J* = 11.8 Hz, 2H), 3.66 (s, 3H), 3.50 – 3.41 (m, 1H), 3.28 (s, 1H), 3.12 – 2.99 (m, 2H), 2.92 – 2.74 (m, 6H), 2.65 – 2.52 (m, 6H), 2.48 (s, 3H), 2.38 – 2.30 (m, 1H), 2.14 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.91 – 1.58 (m, 8H), 1.51 – 1.39 (m, 1H), 1.04 (d, *J* = 5.5 Hz, 3H), 0.88 (d, *J* = 6.1 Hz, 3H). [M+H]⁺ = 875.7

[0550] Example 192: (R)-3-(2,6-difluoro-4-(4-((R)-2-methyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



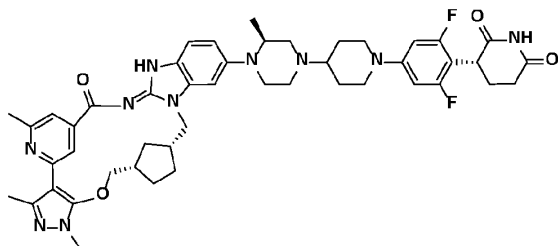
The title compound was prepared in a manner similar to that in example 1 with intermediates 84 and 7. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.99 (s, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 12.7 Hz, 2H), 4.29 – 4.19 (m, 2H), 4.05 (dd, *J* = 12.6, 4.8 Hz, 2H), 3.84 (d, *J* = 12.3 Hz, 2H), 3.67 (s, 3H), 3.40 (t, *J* = 11.2 Hz, 2H), 2.94 – 2.89 (m, 3H), 2.86 – 2.73 (m, 5H), 2.63 (t, *J* = 9.7 Hz, 2H), 2.55 (s, 4H), 2.53 – 2.49 (m, 2H), 2.47 (s, 4H), 2.12 – 2.05 (m, 1H), 1.98 – 1.94 (m, 1H), 1.86 – 1.76 (m, 5H), 1.71 – 1.60 (m, 3H), 1.42 (d, *J* = 9.7 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H); [M+H]⁺ = 861.7.

[0551] Example 193: (3R)-3-(2,6-difluoro-4-(4-(5-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2,5-diazabicyclo[2.2.2]octan-2-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



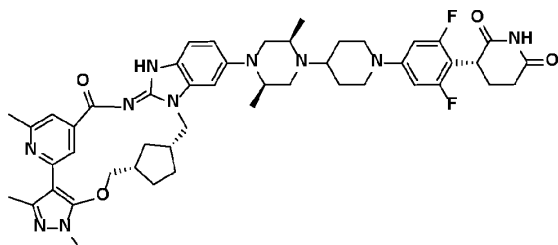
The title compound was prepared in a manner similar to that in example 1 with intermediates 122 and 7. ¹H NMR (500 MHz, DMSO) δ 12.32 (s, 1H), 10.86 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.65 (d, *J* = 10.6 Hz, 2H), 6.61 (s, 2H), 4.26 – 4.02 (m, 2H), 4.07 – 3.99 (m, 4H), 3.68 (s, 1H), 3.67 (s, 4H), 3.60 (s, 1H), 3.23 (s, 2H), 2.96 (s, 2H), 2.87 – 2.82 (m, 2H), 2.79 – 2.74 (m, 1H), 2.66 – 2.61 (m, 1H), 2.58 – 2.56 (m, 2H), 2.55 (s, 4H), 2.53 – 2.52 (m, 1H), 2.47 (s, 4H), 2.10 – 2.04 (m, 1H), 1.97 – 1.94 (m, 3H), 1.89 – 1.86 (m, 3H), 1.81 – 1.78 (m, 3H), 1.59 (s, 2H), 1.38 (d, *J* = 10.5 Hz, 2H). [M+H]⁺ = 873.7

[0552] Example 195: (R)-3-(2,6-difluoro-4-(4-((S)-3-methyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



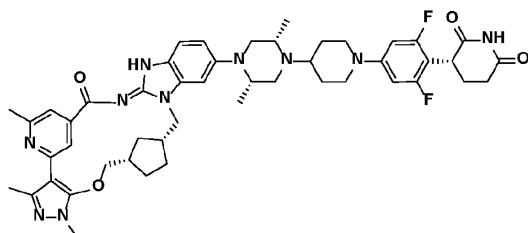
The title compound was prepared in a manner similar to that in example 1 with intermediates 123 and 7. ¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.46 (s, 1H), 7.46 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.03 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 4.26 – 4.20 (m, 2H), 4.07 – 4.03 (m, 2H), 3.82 (d, *J* = 12.4 Hz, 2H), 3.60 (s, 3H), 3.29 (s, 2H), 3.16 (s, 3H), 2.89 (s, 1H), 2.79 – 2.74 (m, 3H), 2.73 – 2.72 (m, 6H), 2.70 – 2.67 (m, 4H), 2.64 – 2.63 (m, 2H), 2.54 (s, 3H), 2.45 (s, 1H), 2.37 – 2.35 (m, 1H), 2.11 – 2.07 (m, 1H), 1.99 – 1.93 (m, 1H), 1.88 (d, *J* = 11.4 Hz, 3H), 1.75 (s, 2H), 1.49 (d, *J* = 10.1 Hz, 3H). [M+H]⁺ = 861.5.

[0553] Example 196: (R)-3-(4-(4-((2R,5R)-2,5-dimethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



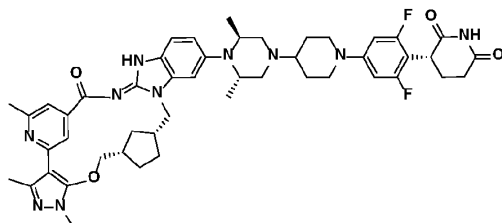
The title compound was prepared in a manner similar to that in example 1 with intermediates 124 and 7. ¹H NMR (500 MHz, DMSO) δ 12.48 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.40 – 3.96 (m, 5H), 3.81 (d, *J* = 11.8 Hz, 2H), 3.66 (s, 3H), 3.50 – 3.41 (m, 1H), 3.28 (s, 1H), 3.12 – 2.99 (m, 2H), 2.92 – 2.74 (m, 6H), 2.65 – 2.52 (m, 6H), 2.48 (s, 3H), 2.38 – 2.30 (m, 1H), 2.14 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.91 – 1.58 (m, 8H), 1.51 – 1.39 (m, 1H), 1.04 (d, *J* = 5.5 Hz, 3H), 0.88 (d, *J* = 6.1 Hz, 3H). [M+H]⁺ = 875.6.

[0554] Example 197: (R)-3-(4-(4-((2S,5S)-2,5-dimethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



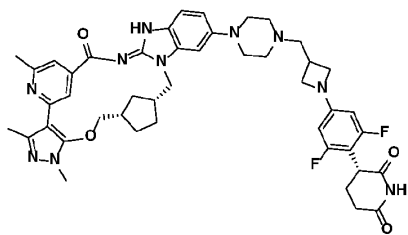
The title compound was prepared in a manner similar to that in example 1 with intermediates 125 and 7. ¹H NMR (500 MHz, DMSO) δ 12.47 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.15 (s, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.39 – 3.98 (m, 5H), 3.81 (d, *J* = 10.7 Hz, 2H), 3.67 (s, 3H), 3.54 – 3.45 (m, 1H), 3.28 (s, 1H), 3.12 – 3.00 (m, 2H), 2.87 – 2.74 (m, 6H), 2.59 – 2.52 (m, 7H), 2.48 (s, 3H), 2.15 – 2.04 (m, 1H), 2.00 – 1.94 (m, 1H), 1.90 – 1.62 (m, 8H), 1.51 – 1.41 (m, 1H), 1.04 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 6.0 Hz, 3H). [M+H]⁺ = 875.6.

[0555] Example 198: (R)-3-(4-(4-((3S,5S)-3,5-dimethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



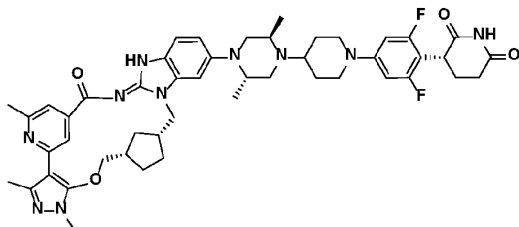
The title compound was prepared in a manner similar to that in example 1 with intermediates 126 and 7. ¹H NMR (500 MHz, DMSO) δ 12.43 (s, 1H), 10.87 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 12.8 Hz, 2H), 4.35 – 4.30 (m, 1H), 4.20 – 4.17 (m, 1H), 4.07 – 4.03 (m, 3H), 3.79 – 3.77 (m, 2H), 3.67 (s, 3H), 3.58 – 3.55 (m, 3H), 2.82 – 2.78 (m, 6H), 2.64 – 2.62 (m, 4H), 2.43 – 2.39 (m, 5H), 2.37 – 2.36 (m, 2H), 2.10 – 2.07 (m, 1H), 1.98 – 1.95 (m, 1H), 1.85 – 1.81 (m, 5H), 1.69 – 1.64 (m, 1H), 1.53 – 1.49 (m, 2H), 1.24 (s, 1H), 0.89 (d, *J* = 6.1 Hz, 6H). [M+H]⁺ = 875.6.

[0556] Example 199: (R)-3-(2,6-difluoro-4-(3-((4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)methyl)azetidin-1-yl)phenyl)piperidine-2,6-dione



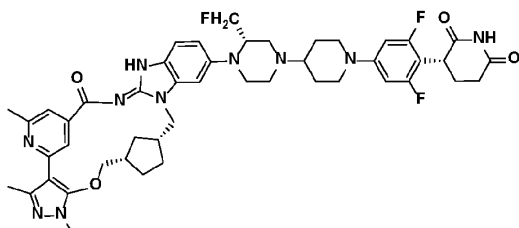
The title compound was prepared in a manner similar to that in example 1 with intermediates 34 and 44. ^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.85 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 6.91 (dd, J = 8.8, 1.8 Hz, 1H), 6.12 (d, J = 11.1 Hz, 2H), 4.32 – 4.24 (m, 2H), 4.03 (dd, J = 12.5, 4.9 Hz, 2H), 3.96 (t, J = 7.6 Hz, 2H), 3.67 (s, 3H), 3.51 (t, J = 5.9 Hz, 2H), 3.17 (s, 4H), 3.00 – 2.95 (m, 1H), 2.82 – 2.76 (m, 1H), 2.64 (d, J = 7.2 Hz, 2H), 2.58 – 2.57 (m, 3H), 2.56 – 2.55 (m, 6H), 2.53 – 2.52 (m, 2H), 2.48 (s, 4H), 2.09 – 2.03 (m, 1H), 1.94 (dd, J = 9.4, 3.9 Hz, 1H), 1.86 – 1.81 (m, 4H), 1.63 (s, 1H). $[\text{M}+\text{H}]^+ = 833.7$.

[0557] Example 200: (R)-3-(4-(4-((2R,5S)-2,5-dimethyl-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 127 and 7. ^1H NMR (500 MHz, DMSO) δ 12.47 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.15 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 4.39 – 3.98 (m, 5H), 3.81 (d, J = 10.7 Hz, 2H), 3.67 (s, 3H), 3.54 – 3.45 (m, 1H), 3.28 (s, 1H), 3.12 – 3.00 (m, 2H), 2.87 – 2.74 (m, 6H), 2.59 – 2.52 (m, 6H), 2.48 (s, 3H), 2.37–2.35 (m, 1H), 2.15 – 2.04 (m, 1H), 2.00 – 1.94 (m, 1H), 1.90 – 1.62 (m, 8H), 1.51 – 1.41 (m, 1H), 1.04 (d, J = 5.9 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H). $[\text{M}+\text{H}]^+ = 875.7$.

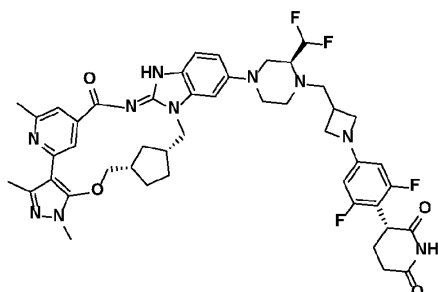
[0558] Example 202: (R)-3-(2,6-difluoro-4-(4-((S)-3-(fluoromethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 128 and 7. ^1H NMR (500 MHz, DMSO) δ 12.39 (s, 1H), 10.93 – 10.79 (m, 1H), 8.53 (s, 1H), 7.48 – 7.42 (m, 1H), 7.39 – 7.33 (m, 1H), 7.05 (s, 1H), 6.93 (d, J = 9.1 Hz, 1H), 6.66 (s, 1H), 6.63 (s, 1H), 4.74 – 4.58 (m, 1H), 4.45 – 4.33 (m, 1H), 4.32 – 4.24 (m, 1H), 4.23 – 3.99 (m, 5H), 3.80 (d, J = 11.8 Hz, 2H), 3.66 (s, 3H), 3.36 (d, J = 11.3 Hz, 1H), 3.28 (s, 1H), 3.12 – 2.91 (m, 3H), 2.84 – 2.74 (m, 3H), 2.62 – 2.52 (m, 8H), 2.48 – 2.39 (m, 5H), 2.15 – 2.04 (m, 1H), 2.00 – 1.93 (m, 1H), 1.91 – 1.75 (m, 5H), 1.68 – 1.58 (m, 1H), 1.56 – 1.45 (m, 2H). $[\text{M}+\text{H}]^+ = 875.7$.

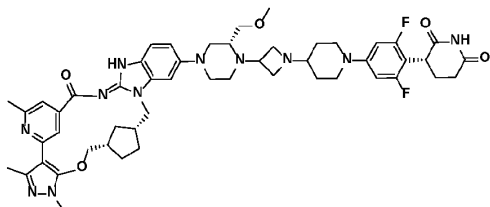
=879.7.

[0559] Example 205: (R)-3-(4-(3-(((S)-2-(difluoromethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)methyl)azetidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



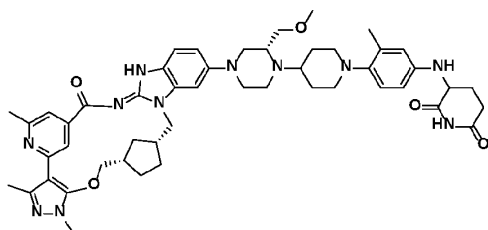
The title compound was prepared in a manner similar to that in example 1 with intermediates 129 and 44. ¹H NMR (500 MHz, DMSO) δ 12.46 (s, 1H), 10.85 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.04 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.13 (s, 1H), 6.11 (s, 1H), 4.31 (s, 1H), 4.19 (s, 1H), 4.03 (dd, *J* = 12.5, 4.9 Hz, 2H), 3.93 (t, *J* = 7.4 Hz, 2H), 3.67 (s, 3H), 3.54 – 3.51 (m, 2H), 3.24 (s, 3H), 3.11 (d, *J* = 10.8 Hz, 2H), 3.08 – 3.02 (m, 3H), 3.00 – 2.96 (m, 1H), 2.88 – 2.84 (m, 1H), 2.79 – 2.76 (m, 2H), 2.69 – 2.63 (m, 2H), 2.56 – 2.55 (m, 6H), 2.48 (s, 4H), 2.11 – 2.04 (m, 1H), 1.96 – 1.92 (m, 1H), 1.82 (s, 3H), 1.64 (s, 1H). [M+H]⁺ = 883.6.

[0560] Example 206: (R)-3-(2,6-difluoro-4-(4-(3-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)azetidin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



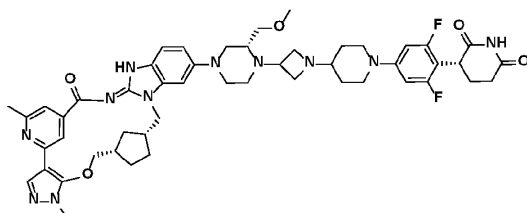
The title compound was prepared in a manner similar to that in example 1 with intermediates 130 and 7. ¹H NMR (500 MHz, DMSO) δ 12.41 (s, 1H), 10.87 (s, 1H), 8.53 (s, 1H), 7.45 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.61 (d, *J* = 12.9 Hz, 2H), 4.29 – 4.01 (m, 6H), 3.67 (s, 2H), 3.63 – 3.55 (m, 3H), 3.50 – 3.39 (m, 5H), 3.28 – 3.18 (m, 5H), 3.12 – 2.99 (m, 2H), 2.88 – 2.73 (m, 7H), 2.69 – 2.62 (m, 3H), 2.55 (s, 3H), 2.48 (s, 3H), 2.37 – 2.34 (m, 1H), 2.23 – 2.16 (m, 1H), 2.11 – 2.01 (m, 1H), 1.99 – 1.93 (m, 1H), 1.90 – 1.76 (m, 4H), 1.69 – 1.67 (m, 3H), 1.22 – 1.21 (m, 2H). [M+H]⁺ = 946.5.

[0561] Example 207: 3-((4-(4-((R)-2-(methoxymethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)-3-methylphenyl)amino)piperidine-2,6-dione



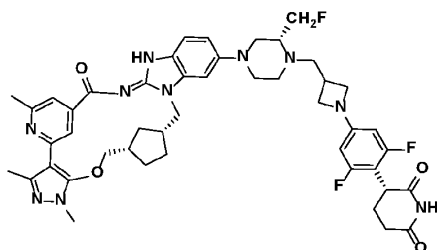
The title compound was prepared in a manner similar to that in example 1 with intermediates 47 and 70. ^1H NMR (500 MHz, DMSO) δ 12.32 (s, 1H), 10.75 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.99 (s, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 6.83 (d, $J = 8.6$ Hz, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 6.46 (dd, $J = 8.6, 2.4$ Hz, 1H), 5.44 (d, $J = 7.5$ Hz, 1H), 4.44 – 3.96 (m, 5H), 3.67 (s, 3H), 3.58 – 3.49 (m, 2H), 3.31 – 3.27 (m, 7H), 3.06 – 2.92 (m, 5H), 2.90 – 2.86 (m, 1H), 2.80 – 2.68 (m, 3H), 2.63 – 2.58 (m, 3H), 2.53 – 2.51 (m, 2H), 2.55 (s, 3H), 2.48 (s, 3H), 2.16 (s, 3H), 2.13 – 2.07 (m, 1H), 1.93 – 1.80 (m, 5H), 1.75 – 1.71 (m, 2H), 1.55 – 1.53 (m, 2H). $[\text{M}+\text{H}]^+ = 884.7$.

[0562] Example 208: (R)-3-(4-(4-(3-((R)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)-2-(methoxymethyl)piperazin-1-yl)azetidin-1-yl)piperidin-1-yl)-2,6-difluorophenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 131 and 7. ^1H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.86 (s, 1H), 8.52 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.98 (s, 1H), 6.87 (d, $J = 9.0$ Hz, 1H), 6.61 (d, $J = 12.9$ Hz, 2H), 4.33 – 4.30 (m, 1H), 4.20 – 4.17 (m, 1H), 4.13 – 3.94 (m, 4H), 3.74 (s, 3H), 3.60 – 3.57 (m, 3H), 3.48 – 3.40 (m, 6H), 3.27 (s, 3H), 3.26 – 3.21 (m, 4H), 3.09 – 3.01 (m, 3H), 2.92 – 2.77 (m, 4H), 2.69 – 2.63 (m, 5H), 2.55 (s, 3H), 2.20 – 2.16 (m, 1H), 2.10 – 2.06 (m, 1H), 1.97 – 1.93 (m, 1H), 1.84 – 1.80 (m, 2H), 1.70 – 1.66 (m, 2H), 1.23 – 1.21 (m, 2H). $[\text{M}+\text{H}]^+ = 932.5$.

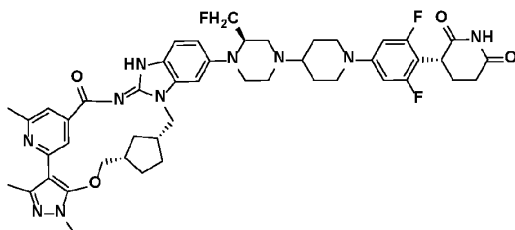
[0563] Example 210: (R)-3-(2,6-difluoro-4-(3-((R)-2-(fluoromethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclonaphane-5⁶-yl)piperazin-1-yl)methyl)azetidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 132 and 44. ^1H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.84 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.38 (d, $J = 8.7$ Hz, 1H), 7.04 (s, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 6.13 (s, 1H), 6.11 (s, 1H), 4.78 – 4.69 (m, 1H), 4.68 – 4.58 (m, 1H), 4.35 – 3.91 (m, 7H), 3.67 (s, 3H), 3.57 – 3.49 (m, 2H), 3.42 (d, $J = 10.0$ Hz, 1H), 3.32 (s, 2H), 3.10 – 2.73 (m, 8H),

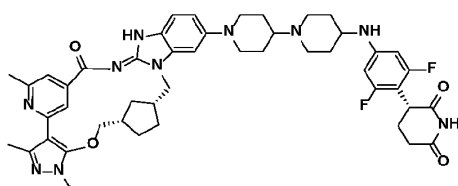
2.70 – 2.53 (m, 7H), 2.48 – 2.41 (m, 4H), 2.13 – 2.02 (m, 1H), 1.97 – 1.76 (m, 4H), 1.69 – 1.52 (m, 1H). $[M+H]^+ = 865.7$.

[0564] Example 211: (R)-3-(2,6-difluoro-4-(4-((R)-3-(fluoromethyl)-4-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)piperazin-1-yl)piperidin-1-yl)phenyl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 133 and 7. ¹H NMR (500 MHz, DMSO) δ 12.40 (s, 1H), 10.86 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.05 (s, 1H), 6.92 (d, $J = 7.7$ Hz, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 4.74 – 4.58 (m, 1H), 4.45 – 4.25 (m, 2H), 4.23 – 4.15 (m, 2H), 4.12 – 3.95 (m, 3H), 3.80 (d, $J = 9.6$ Hz, 2H), 3.67 (s, 3H), 3.41 – 3.31 (m, 2H), 3.10 – 2.91 (m, 3H), 2.83 – 2.74 (m, 3H), 2.65 – 2.52 (m, 8H), 2.48 – 2.38 (m, 5H), 2.14 – 2.03 (m, 1H), 1.99 – 1.93 (m, 1H), 1.90 – 1.77 (m, 5H), 1.70 – 1.58 (m, 1H), 1.56 – 1.42 (m, 2H). $[M+H]^+ = 879.7$.

[0565] Example 213: (R)-3-(2,6-difluoro-4-((1'-((7¹R,7³S,E)-1¹,1³,2⁶-trimethyl-3-oxo-5²,5³-dihydro-1¹H,^{51H}-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-[1,4'-bipiperidin]-4-yl)amino)phenyl)piperidine-2,6-dione



The racemate compound was prepared in a manner similar to that in example 1 with intermediates 101 and 134.

The title product was purified by chiral HPLC and corresponds to peak A @ 4.377 min.

Inj. Volume: 3.0 μ L

Column: CHIRALPAK IF 4.6*150 mm 5 μ m

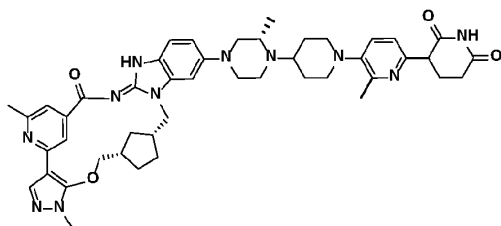
Flow Rate (mL/min): 1.0

Gradient:

Time (min)	MtBE (0.1%FA+0.1%DEA)(%)	MeOH:DCM=50:50(%)
0	30	70
15	30	70

¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.82 (s, 1H), 8.54 (s, 1H), 7.45 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.03 (s, 1H), 6.92 (d, $J = 8.8$ Hz, 1H), 6.24 (d, $J = 12.0$ Hz, 2H), 6.14 (d, $J = 7.2$ Hz, 1H), 4.39 – 3.91 (m, 5H), 3.77 – 3.72 (m, 2H), 3.67 (s, 3H), 3.25 – 3.22 (m, 6H), 2.95 – 2.88 (m, 2H), 2.83 – 2.62 (m, 5H), 2.55 (s, 3H), 2.48 (s, 3H), 2.38 – 2.35 (m, 2H), 2.11 – 2.01 (m, 1H), 1.93 – 1.88 (m, 8H), 1.66 – 1.60 (m, 2H), 1.38 – 1.36 (m, 2H). $[M+H]^+ = 861.4$.

[0566] Example 214: 3-(5-(4-((S)-4-((7¹R,7³S,E)-1¹,2⁶-dimethyl-3-oxo-5²,5³-dihydro-1¹H,5¹H-9-oxa-4-aza-5(2,1)-benzo[d]imidazola-2(2,4)-pyridina-1(4,5)-pyrazola-7(1,3)-cyclopentanacyclononaphane-5⁶-yl)-2-methylpiperazin-1-yl)piperidin-1-yl)-6-methylpyridin-2-yl)piperidine-2,6-dione



The title compound was prepared in a manner similar to that in example 1 with intermediates 71 and 14. ¹H NMR (500 MHz, DMSO) δ 12.42 (s, 1H), 10.78 (s, 1H), 8.53 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.37 (t, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.01 (s, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.30 (s, 1H), 4.19 (s, 1H), 4.10 (s, 1H), 3.89 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.74 (s, 3H), 3.45 (d, *J* = 9.5 Hz, 2H), 3.15 (d, *J* = 9.4 Hz, 3H), 2.95 – 2.88 (m, 5H), 2.72 (t, *J* = 11.8 Hz, 1H), 2.63 (s, 3H), 2.61 – 2.59 (m, 2H), 2.58 – 2.56 (m, 2H), 2.55 (s, 3H), 2.54 – 2.52 (m, 1H), 2.41 (s, 3H), 2.24 – 2.18 (m, 1H), 2.12 – 2.07 (m, 1H), 1.97 – 1.90 (m, 1H), 1.85 – 1.81 (m, 4H), 1.73 – 1.68 (m, 2H), 1.58 (d, *J* = 8.6 Hz, 1H), 1.14 (d, *J* = 6.2 Hz, 3H). [M+H]⁺ = 826.7.

Cell line

[0567] H1975-clone#8 (L858R/C797S): EGFR-L858R/C797S were stably expressed in H1975 cell lines by lentivirus-mediated over-expression, respectively. The EGFR over-expressed cells then underwent knockout, in which the EGFR targeting sgRNA was designed to only target the endogenous EGFR copies and preserve the exogenous EGFR copies. Followed by the knockout, the edited H1975 cells were seeded in 96 well plates at the concentration of 1 cell/cell, cultured for about 2 weeks to allow single clones formation. The formed clones were screened by DNA sequencing and whole exon sequencing analysis for the desired edition. H1975-clone#8 were finally confirmed as homozygous L858R/C797S EGFR clones.

[0568] H1975-clone#23 (Del19/C797S): EGFR- Del19/C797S were stably expressed in H1975 cell lines by lentivirus-mediated over-expression, respectively. The EGFR over-expressed cells then underwent knockout, in which the EGFR targeting sgRNA was designed to only target the endogenous EGFR copies and preserve the exogenous EGFR copies. Followed by the knockout, the edited H1975 cells were seeded in 96 well plates at the concentration of 1 cell/well, cultured for about 2 weeks to allow single clones formation. The formed clones were screened by DNA sequencing and whole exon sequencing analysis for the desired edition. H1975-clone#23 were finally confirmed as homozygous Del19/C797S EGFR clones.

[0569] BaF3-L858R (abbv. L858R) cell were purchased from Kangyuan Bochuang Biotechnology (Beijing) Co., Ltd.

Cell Degradation

Cell treatment

[0570] On day 1, H1975-clone#8 (L858R/C797S) cells are seeded at 5000 cells/well in cell culture medium [RPMI1640(Gibco, Cat#72400-047), 10% heat-inactive FBS, 1%PS(Gibco, Cat#10378)] in Corning 96 well plate (Cat#3599) .

[0571] On day 2, BaF3-L858R cells are seeded at 50000 cells/well at a volume of 54μl/well in cell culture medium [RPMI1640(Gibco, phenol red free, Cat#11835-030), 10% heat-inactive FBS, 1%PS(Gibco, Cat#10378)] in Corning 96 well plate (Cat#3799).

[0572] H1975-#8 and BaF3-L858R cells are treated with compounds diluted in 0.1%DMSO cell culture medium on day 2, incubate for 16h, 37°C, 5%CO₂. the final concentration of compounds in all assay is start with 10uM, 5-fold dilution, total 8 doses were included.

HTRF assay

[0573] After 16h treatment, for H1975-#8 cells, add 100ul HTRF 1X lysis buffer to each well ; for BaF3-L858R cells ,add 20ul 4xlysis buffer to each well ; seal the plate and incubate 1 hour at room temperature on a plate shaker; Once the cells are lysed, 16 µL of cell lysate are transferred to a PE 384-well HTRF detection plate; 4 µL of pre-mixed HTRF antibodies are added to each well ; Cover the plate with a plate sealer, spin 1000 rpm for 1 min, Incubate overnight at room temperature; Read on BMG PheraStar with HTRF protocol (337nm-665nm-620nm).

[0574] The inhibition (degradation) percentage of the compound was calculated by the following equation: Inhibition percentage of Compound = $100 - 100 \times (\text{Signal-low control}) / (\text{High control-low control})$, wherein signal = each test compound group

Low control = only lysis buffer without cells, indicating that EGFR is completely degraded;

High control = Cell group with added DMSO and without compound, indicating microplate readings without EGFR degradation;

[0575] Dmax is the maximum percentage of inhibition (degradation).

[0576] The IC₅₀ (DC₅₀) value of a compound can be obtained by fitting the following equation

$$Y = \text{Bottom} + (\text{TOP} - \text{Bottom}) / (1 + ((\text{IC}_{50} / X) ^ \text{hillslope}))$$

[0577] Wherein, X and Y are known values, and IC₅₀, Hillslope, Top and Bottom are the parameters obtained by fitting with software. Y is the inhibition percentage (calculated from the equation), X is the concentration of the compound; IC₅₀ is the concentration of the compound when the 50% inhibition is reached. The smaller the IC₅₀ value is, the stronger the inhibitory ability of the compound is. Vice versa, the higher the IC₅₀ value is, the weaker the ability the inhibitory ability of the compound is; Hillslope represents the slope of the fitted curve, generally around 1 *; Bottom represents the minimum value of the curve obtained by data fitting, which is generally 0% ± 20%; Top represents the maximum value of the curve obtained by data fitting, which is generally 100% ± 20%. The experimental data were fitted by calculating and analyzing with Dotmatics data analysis software.

Cell p-EGFR Inhibition assay

Cell treatment

[0578] On day 1, H1975-clone#23 (DEL19/C797S) cells are seeded at 3×10^4 cells/well in cell culture medium [RPMI1640(Gibco, Cat#72400-047), 10% heat-inactive FBS, 1%PS(Gibco, Cat#10378)] in Corning 96 well plate (Cat#3599) .

[0579] On day 2, BaF3-L858R cells are seeded at 2×10^5 cells/well at a volume of 54µl/well in cell culture medium [RPMI1640(Gibco, phenol red free, Cat#11835-030), 10% heat-inactive FBS, 1%PS(Gibco, Cat#10378)] in Corning 96 well plate (Cat#3799).

[0580] H1975-#23 and BaF3-L858R cells are treated with compounds diluted in 0.1%DMSO cell culture medium on day 2, incubate for 16h, 37°C, 5%CO₂. the final concentration of compounds in all assay is start with 10uM, 5-fold dilution, total 8 doses were included.

HTRF assay

[0581] After 16h treatment, for H1975-#23 cells, add 50ul HTRF 1× lysis buffer to each well ; for BaF3-L858R cells ,add 20ul 4× lysis buffer to each well ; seal the plate and incubate 1 hour at room temperature on a plate shaker; Once the cells are lysed, 16 µL of cell lysate are transferred to a PE 384-well HTRF detection plate; 4 µL of pre-mixed HTRF antibodies are added to each well ; Cover the plate with a plate sealer, spin 1000 rpm for 1 min, Incubate overnight at room temperature; Read on BMG PheraStar with HTRF protocol (337nm-665nm-620nm).

[0582] The inhibition percentage of the compound was calculated by the following equation: Inhibition percentage of Compound = $100 - 100 \times (\text{Signal-low control}) / (\text{High control-low control})$, wherein signal = each test compound group

Low control = only lysis buffer without cells, indicating that p-EGFR is completely inhibited.

High control = Cell group with added DMSO and without compound, indicating microplate readings without p-EGFR inhibited.

[0583] Imax is the maximum percentage of inhibition.

[0584] The IC₅₀ value of a compound can be obtained by fitting the following equation.

$$Y = \text{Bottom} + (\text{TOP} - \text{Bottom}) / (1 + ((\text{IC}_{50} / X)^{\text{Hillslope}}))$$

[0585] Wherein, X and Y are known values, and IC₅₀, Hillslope, Top and Bottom are the parameters obtained by fitting with software. Y is the inhibition percentage (calculated from the equation), X is the concentration of the compound; IC₅₀ is the concentration of the compound when the 50% inhibition is reached. The smaller the IC₅₀ value is, the stronger the inhibitory ability of the compound is. Vice versa, the higher the IC₅₀ value is, the weaker the ability the inhibitory ability of the compound is Hillslope represents the slope of the fitted curve, generally around 1 *; Bottom represents the minimum value of the curve obtained by data fitting, which is generally 0% ± 20%; Top represents the maximum value of the curve obtained by data fitting, which is generally 100% ± 20%. The experimental data were fitted by calculating and analyzing with Dotmatics data analysis software.

Table 1. Degradation (BaF3-L858R and H1975-clone#8 (L858R/C797S)) result for Examples

Example No	BaF3-L858R		H1975-clone#8 (L858R/C797S)	
	DC ₅₀ (nM)	D _{max} (%)	DC ₅₀ (nM)	D _{max} (%)
1	3.25	89.7	1.41	79.19
2	0.879	87.15	1.38	72.6
3	20.09	72.72	16.35	43.95
4	1.23	87.59	2.34	75.42
5	1.01	84.37	0.856	75.68
6	3.1	100.63	1.2	86.64
7	0.631	99.39	2.0316	45.4
8	3.2	64.04	3.18	74.17
9	6.11	86.6	4.28	71.65
10	4.07	73.02	3.15	66.8

11	0.834	84.59	3.75	61.52
12	0.493	90	0.774	88.41
13	0.307	91.5	1.4	65.47
14	0.552	83.99	0.616	90.93
15	7.6	94.19	11.11	85.15
21	2.99	98.96	0.782	83.18
23	12.82	86.05	0.608	54.98
27	1.75	91.12	3.19	90.21
35	0.49	91.75	0.6	58.02
57	3.84	82.6	3.14	58.49
59	3.18	85.1	2.87	68.95
63	0.55	90.04	0.61	60.89
64	1.07	83.31	1.87	69.97
65	0.94	88.69	0.87	78.56
69	3.2	89.35	5.24	62.39
70	3.78	87.66	4.11	73.46
71	3.63	84.61	3.3	80.16
72	0.4	91.61	0.64	76.57
73	2.02	87.22	2.24	78.37
74	0.99	90.43	1	86.22
75	1.6	82.72	0.97	61.33
76	3.23	84.83	3.87	79.39
77	3.4	89.47	5.5	85.66
78	3.68	87.78	4.18	65.49
79	0.41	92.61	0.48	91.69
80	1.73	88.11	5.24	82.36
82	0.31	74.12	0.8	89.18
83	4.08	69.13	5.64	81.8
84	4.01	79.65	2.1	64.66
85	4.23	77.98	4.91	82.96
86	2.74	70.33	3.22	65.99
87	2.86	64.11	8.71	70.8
88	16.41	95.81	1.63	82.92
89	1.75	73.86	1.64	87.47
90	3.21	80.57	2.06	87.4
91	2.04	81.49	2.28	88.66
92	1.97	85.77	3.12	79.85
93	9.09	77.38	7.66	83.77

94	3.37	71.57	0.83	73.9
95	8.5	86.55	12.13	78.96
96	3.41	86.61	3.15	82.66
98	2.6	80.59	2.49	75
99	1.06	82.32	6	85.62
100	3.34	72.3	3.07	87.33
101	2.22	81.78	1.58	90.21
102	0.59	85.75	0.76	91.52
103	3.38	81.62	2.53	83.31
104	4.1	83.17	3.7	86.92
105	3.68	82.74	4.09	85.25
106	6.69	82.51	2.45	83.27
108	3.32	87.31	0.75	76.98
111	3.18	80.74	1.92	85.67
112	2.2	72.83	0.41	67.55
113	3.49	70.53	2.69	77.35
114	3.11	75.67	1.09	81.96
115	1.6	81.91	2.84	81.08
116	1.25	85.38	0.61	83.42
117	1.11	78.04	0.92	80.56
118	2.64	79.03	5.97	73.74
119	2.47	77.02	2.3	74.58
120	3.14	70.84	0.55	65.65
121	1.06	82.19	0.98	88.32
122	4.53	70.68	3.24	52.22
123	3.37	77.06	2.14	81.58
124	3.58	71.14	2.3	67.53
125	1.37	77.11	2.61	67.41
126	2.04	83.28	1.49	73.72
127	9.26	88.84	6.07	81.87
129	16.21	71.91	1.45	69.35
131	4.84	69.11	0.867	72
132	3.22	81.02	2.05	65.95
133	2.36	85.73	2.94	86.47
134	1.89	85.87	4.97	79.89
135	3.08	89.06	1.91	86.89
136	3.52	81.06	0.152	76.08
137	2.37	83.34	3.35	78.23

138	3.61	85.49	1.27	83.42
140	3.04	93.28	1.94	85.59
141	1.13	87.5	0.804	66.08
142	7.26	80.29	0.748	87.35
143	5.23	74.32	1.51	81.95
144	3.1	73.64	0.938	84.77
147	1.04	87.63	2.02	63.2
150	8.77	90.48	7.29	84.98
151	1.68	90.59	2.62	88.52
152	1.19	86.64	1.28	88.69
153	2.8	84.4	2.92	86.96
156	2.11	87.41	2.73	87.98
157	2.03	85.83	1.88	87.96
158	3.75	79.81	4.39	77.26
159	9.56	77.55	3.75	81.28
160	3.08	76.5	3.01	88.21
161	7.2	91.43	2.96	89.3
162	4.86	88.6	3.14	85.43
163	4.4	88.11	2.97	82.53
164	2.79	92.71	1.19	88.71
165	3.32	91.08	4.45	88.72
167	4.72	83.25	4.33	88.56
168	2.96	80.9	3.07	81.06
169	2.62	86.46	2.81	91.64
172	5.09	84.83	0.909	85.56
173	4.28	95.16	4.31	91.39
175	4.07	88.67	7.25	83.91
176	8.27	89.05	10.66	85.37
179	5.38	90.75	10.57	89.58
182	21.77	89.15	1.39	79.84
183	5.3	91.58	5.83	91.15
184	4.99	90.13	3.16	89.28
186	3.82	80.04	2.92	80.4
188	4.2	93.16	3.78	84.89
189	4.4	87.56	2.38	90.22
190	3.11	88.2	1.69	94.92
191	2.94	89.33	0.73	88.66
192	2.42	87.87	1.01	88.8

193	7.4	76.16	0.76	70.78
195	1.83	90.93	1.13	93.91
196	1.61	91.87	3.21	88.79
197	8.79	73.99	7.24	89.7
198	7.56	89.74	4.41	100.08
199	6.02	82.45	2.28	91.82
200	2.1	85.73	1.87	94.58
202	1.06	92.5	4.8	87.91
205	5.75	90.35	3.05	85.78
206	1.1	92.06	0.54	90.68
207	1.04	91.91	1.7	87.5
208	0.67	91.62	1.01	70.65
210	0.74	90.25	3.72	86.86
211	0.73	91.28	3.07	88.78
213	2.18	88.29	0.63	82.54
214	0.65	82.61	0.61	77.32

Table 2. pEGFR inhibition (BaF3-L858R and H1975-clone#23 (DEL19/C797S)) result for Examples

Example No	BaF3-L858R		H1975-clone#23 (DEL19/C797S)	
	IC ₅₀ (nM)	I _{max} (%)	IC ₅₀ (nM)	I _{max} (%)
35	1.3	91.6	0.5	101.1
57	10.5	101	1.2	97.9
59	7	102.5	0.7	99.6
63	0.2	103	0.2	100.6
64	3.2	101.9	0.7	101.2
65	2.8	103	0.3	101.5
69	5.7	99.9	1.8	100.1
70	11	102.1	1.4	99.2
71	6.4	99.7	1.1	99.8
72	3.2	92.8	0.6	101.7
73	10.2	93.5	1	101.1
74	3.2	93.3	1.7	101.2
75	7.9	92.6	0.6	101.1
76	7.8	94.9	0.7	101
77	10.9	91.3	9.5	99.2
78	16.9	92.5	1.2	100.6
79	1.1	92.7	0.3	101.4

80	3.8	91.7	1.6	99.9
82	3.1	91.9	1.1	101.1
83	18	96.5	1	100.7
84	6	109.3	0.5	100.5
85	11.6	97.5	3.1	99.7
86	17.2	97.1	3	100.2
87	13.8	96.2	1.5	100.3
88	6.1	108.3	3	100.7
89	8	99.7	1.9	101.2
90	6.3	98.4	2.5	101.7
91	3.5	97.1	2.2	100.8
92	10	97.2	1	100.1
93	19.6	96.9	2	100.3
94	6.1	99.6	0.8	101.2
95	10.8	99.3	4.5	101
96	6.3	100.3	0.8	100.9
98	4.7	110.3	1.4	101.3
99	8	100.3	2.2	99.2
100	6.7	107.3	0.5	101
101	3.5	106.4	1	101
102	1.5	95	0.6	100.5
103	16.3	95.6	0.8	102
104	4.4	95	2	100.5
105	10.1	93.9	0.7	100.1
106	16	97.6	0.8	99.8
108	7.7	95.9	0.6	100.3
111	16.1	97.6	1	100.1
112	15.4	104.4	0.4	98.9
113	17.1	94.6	0.7	99
114	7.3	98.4	0.4	100.5
115	3.9	97.7	1.3	99.8
116	7.9	98.5	0.8	99.4
117	14.9	97.1	0.6	100
118	7.3	98.5	1.3	100.2
119	18.2	94.3	0.6	100.8
120	15.6	94.2	1.1	99.1
121	6	96.6	0.7	100.8
122	11	96.8	0.5	98.9

123	16.3	95.3	0.7	100.4
124	17.1	94.6	0.9	99.6
125	20.65	98.6	2.2	101.9
126	13.3	99.16	1.44	102.92
127	4.89	101.7	4.06	100.85
131	6.4	102.8	0.796	103.08
132	62.72	97.32	0.63	100.62
133	2.88	96.88	1.45	99.55
134	2.49	98.27	1.76	92.81
135	2.32	104.33	1.4	104.78
136	8.91	104.73	1.44	103.49
137	14.62	96.47	0.528	98.8
138	7.09	104.27	1.37	102.96
140	6.86	96.47	1.03	101.57
141	7.7	98.22	0.825	100.38
142	4.77	97.8	1.42	102.03
143	7.8	98.2	1.15	101.28
144	5.5	98.7	0.97	100.78
150	72.06	91.27	2.16	100.12
151	5.03	95.95	1.02	99.54
152	15.03	95.61	2.46	100.06
153	11.1	97.42	1.56	100.23
156	4.81	95.16	0.789	100.92
157	2.87	96.89	1.1	100.52
158	72.63	95.45	3.65	100.46
160	3.02	94.19	0.59	95.87
161	4.51	93.23	0.49	95.04
162	3.68	93.37	0.21	95.16
163	2.24	94.53	0.6	96.05
164	1.85	94.91	0.254	96.95
165	4.83	93.3	1.34	94.62
167	6.86	98.09	3.01	102.84
168	8.76	100.64	2.56	102.22
169	8.76	100.12	2.5	102.95
172	6.2	100	2.74	103.44
173	11.51	98.39	3.94	103.01
175	2.83	98.51	1.28	100.72
176	15.22	94.16	3.6	101.78

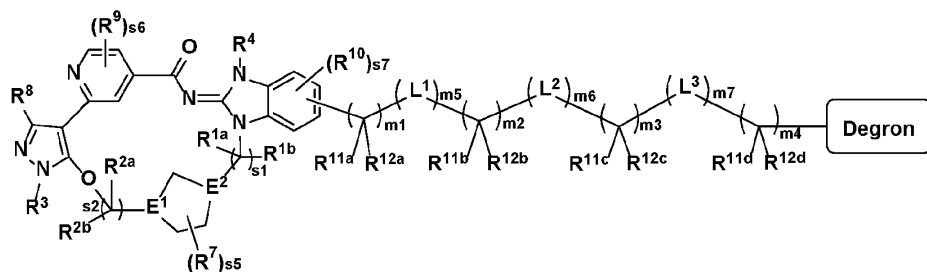
179	14.4	99.14	2.85	100.7
182	2.2069	100.38	2.3787	99.73
183	5.3205	98.21	7.3233	99.41
184	1.2488	91.67	2.4765	100.52
186	4.7712	92	2.3748	100.56
188	<0.1280	90.67	1.9541	99.79
189	<0.1280	92.5	2.1098	100.03
190	0.58	91.5	1.1958	100.67
191	0.5282	90.84	0.7695	99.88
192	1.5333	89.34	1.3897	99.96
193	2.351	101.04	2.743	100.43
195	<0.1280	90.34	1.4427	99.96
196	3.0921	85.84	2.8068	99.76
197	9.1633	101.23	3.3803	103.49
198	6.6611	101.37	3.1816	102.48
199	<0.1280	99.05	2.9212	102.91
200	<0.1280	98.42	1.7943	102.89
202	9.2508	92	2.4765	100.52
205	1.2176	92.5	0.5395	99.83
206	1.1741	94.08	0.8513	99.52
207	1.5018	88.5	1.3976	100.67
208	1.2132	91.5	3.0245	99.76
210	1.0438	89.17	1.5556	99.96
211	2.0494	89.34	1.5954	99.96
213	0.8707	88.33	1.6939	98.77
214	3.32	100.54	0.604	100.03

[0586] The foregoing examples and description of certain embodiments should be taken as illustrating, rather than as limiting, the present disclosure. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present disclosure as set forth in the claims. All such variations are intended to be included within the scope of the present disclosure. All references cited are incorporated herein by reference in their entireties.

[0587] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in any country.

What is claimed is:

1. A compound of Formula (I):



(I)

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof,

wherein:

E^1 is N or CR^5 ;

E^2 is N or CR^6 ;

R^{1a} , R^{1b} , R^{2a} and R^{2b} are each independently absent, hydrogen, halogen, $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl or $-CN$; wherein each said $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, or $-C_{3-8}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl and $-CN$;

R^3 and R^4 are each independently hydrogen, $-C_{1-6}$ alkyl, or $-C_{3-8}$ cycloalkyl; wherein each said $-C_{1-6}$ alkyl or $-C_{3-8}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, hydroxy, halogen, and $-C_{1-6}$ alkoxy;

R^5 and R^6 are each independently absent, hydrogen, halogen, $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl or $-CN$; wherein each said $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, or $-C_{3-8}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl and $-CN$; or

R^5 and R^6 with the carbon atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and $-C_{1-8}$ alkyl;

R^7 is each independently absent, hydrogen, halogen, $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl or $-CN$; wherein each said $-C_{1-8}$ alkyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, $-C_{1-8}$ alkoxy, or $-C_{3-8}$ cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, $-C_{1-8}$ alkoxy, $-C_{3-8}$ cycloalkyl and $-CN$; or

two R^7 with the carbon atom(s) to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and $-C_{1-8}$ alkyl;

R^8 and R^9 are each independently selected from hydrogen, halogen, $-C_{1-6}$ alkyl and C_{3-8} cycloalkyl; wherein each of $-C_{1-6}$ alkyl or C_{3-8} cycloalkyl is optionally substituted with at least one substituent selected from

hydrogen, halogen, hydroxy, and -C₁₋₆alkoxy;

R¹⁰ is each independently selected from hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, 5- to 12-membered heteroaryl, -NR^{10a}R^{10b}, -OR^{10a}, -SR^{10a}, -C(O)R^{10a}, -CO₂R^{10a}, -C(O)NR^{10a}R^{10b}, -NR^{10a}COR^{10b}, -NR^{10a}CO₂R^{10b}, -NR^{10a}SO₂R^{10b}, and -CN; wherein each of -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one R^{10c};

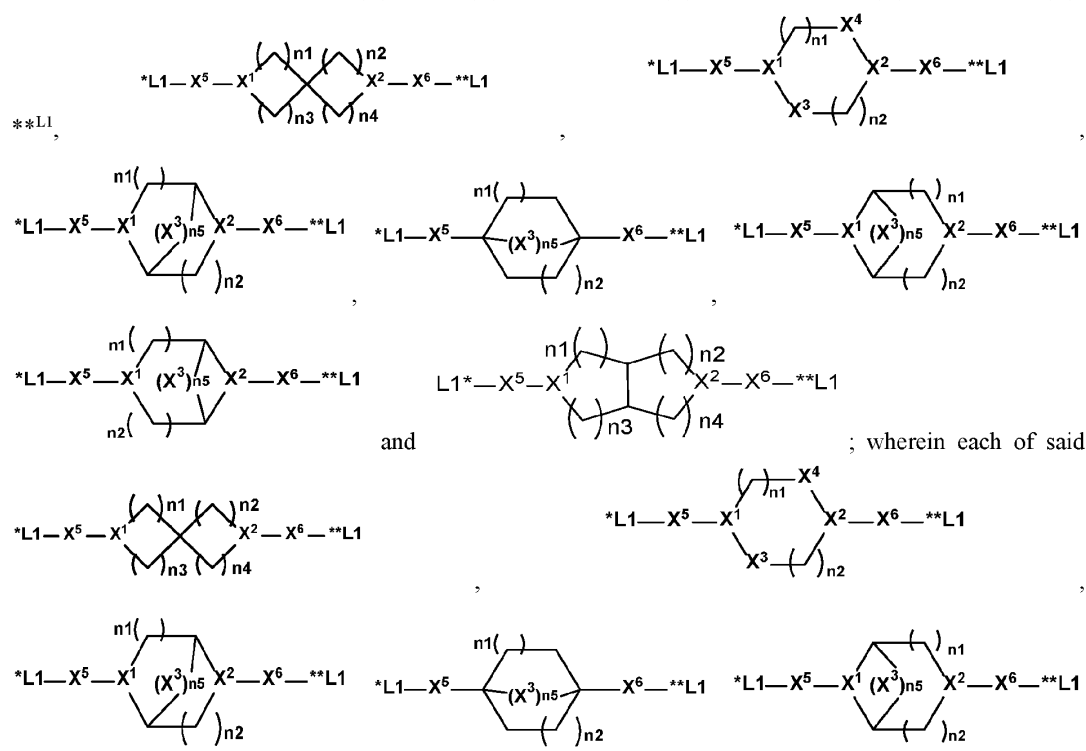
R^{10a} and R^{10b} are each independently selected from hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, and 5- to 12-membered heteroaryl; wherein each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{10d};

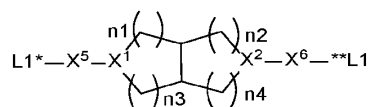
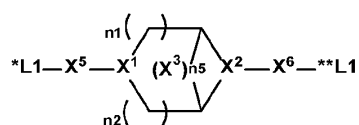
R^{10c} and R^{10d} are each independently selected from halogen, hydrogen, -C₁₋₈alkyl, -C₁₋₈alkoxy, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, 5- to 12-membered heteroaryl, oxo (=O), -NR^{10e}R^{10f}, -OR^{10e}, -SR^{10e}, -SO₂R^{10e}, -SO₂NR^{10e}R^{10f}, -C(O)R^{10e}, -CO₂R^{10e}, -C(O)NR^{10e}R^{10f}, -NR^{10e}COR^{10f}, -NR^{10e}CO₂R^{10f}, -NR^{10e}SO₂R^{10f}, and -CN;

R^{10e} and R^{10f} are each independently selected from hydrogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₂aryl, or 5- to 12-membered heteroaryl;

R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, R^{12c} and R^{12d} are each independently absent, oxo, hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, or -C₃₋₈cycloalkyl; wherein each of said -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy or -C₃₋₈cycloalkyl is optionally substituted with at least one substituent selected from hydrogen, halogen, -C₁₋₈alkyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, -C₁₋₈alkoxy, and -CN;

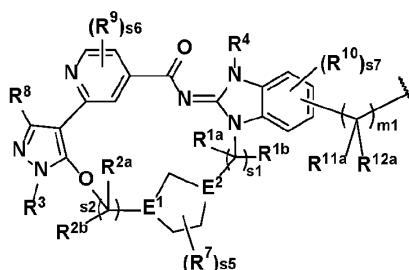
L¹ is selected from -O-, -NR^a-, -C(O)-, ^{*L1}-C(O)NR^a-**L1, ^{*L1}-C(O)O-**L1, ^{*L1}-NR^aC(O)-**L1, ^{*L1}-OC(O)-





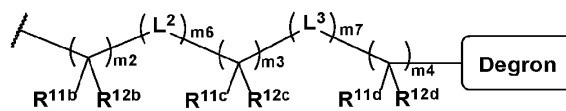
with at least one R^{Llc} ;

is optionally substituted



wherein *L¹ refers to the position attached to the

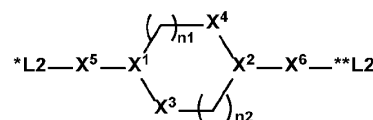
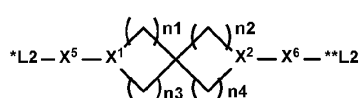
moiety, and **L1



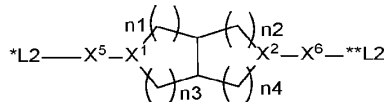
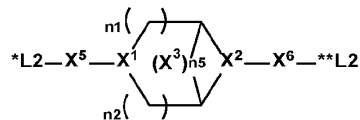
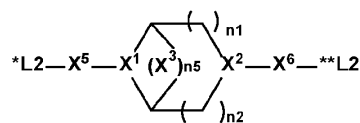
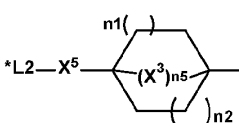
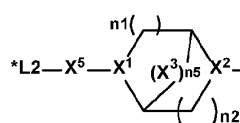
refers to the position attached to the

moiety;

L^2 is selected from -O-, -NR^a-, -C(O)-, $^{*L^2}$ -C(O)NR^a- $^{**L^2}$, $^{*L^2}$ -C(O)O- $^{**L^2}$, $^{*L^2}$ -NR^aC(O)- $^{**L^2}$, $^{*L^2}$ -OC(O)-

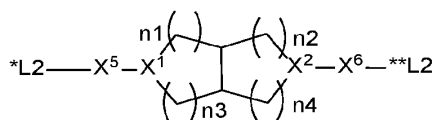
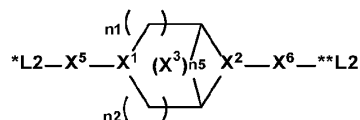
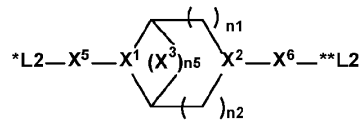
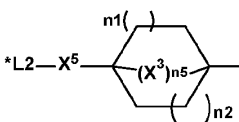
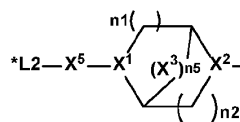
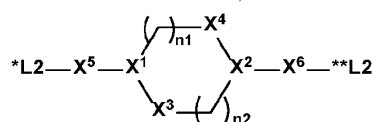
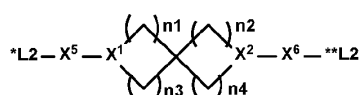


**L2



and

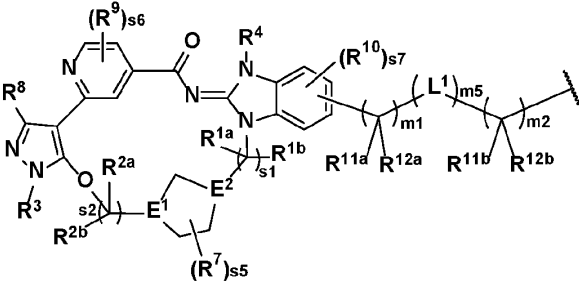
; wherein each of said



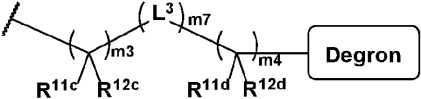
and

is optionally

substituted with at least one R^{L2c};



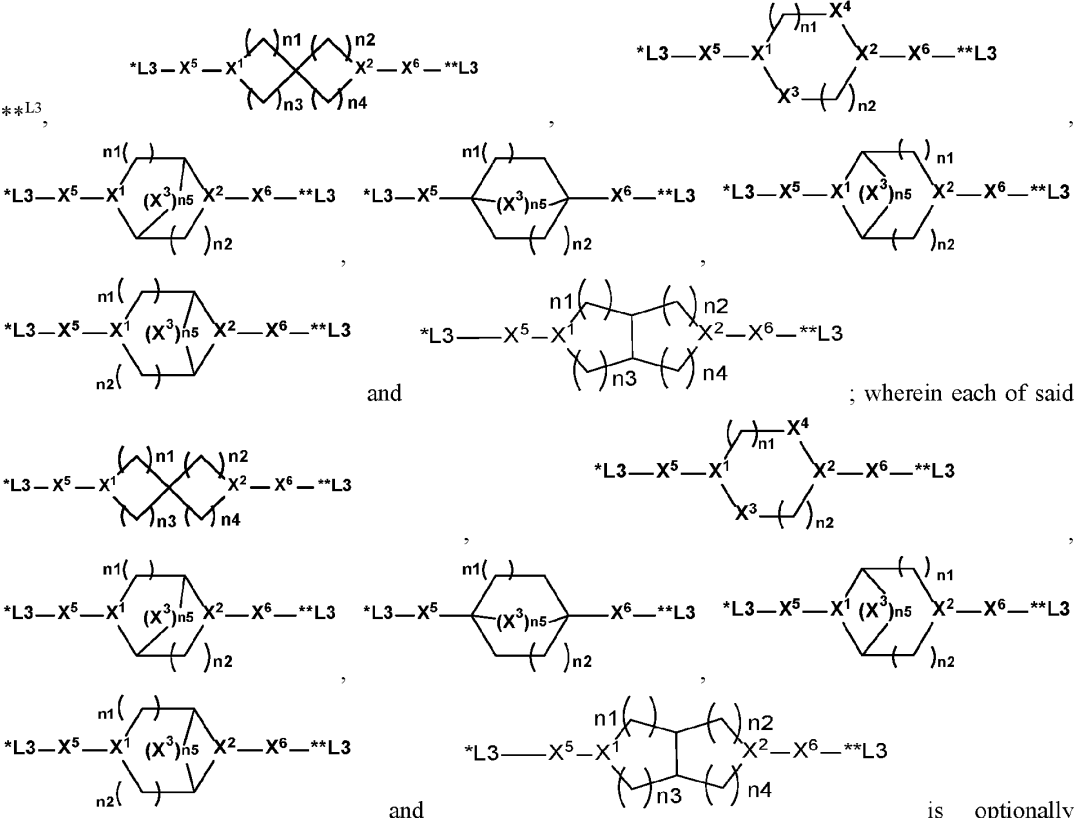
wherein *L2 refers to the position attached to the



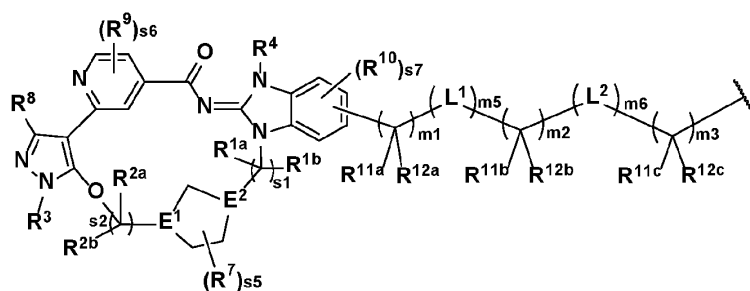
moiety, and **L2 refers to the position attached to the

moiety;

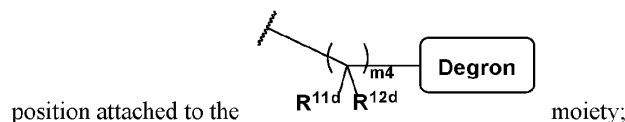
L^3 is selected from $-O-$, $-NR^a-$, $-C(O)-$, $^{*L3}-C(O)NR^a-^{**L3}$, $^{*L3}-C(O)O-^{**L3}$, $^{*L3}-NR^aC(O)-^{**L3}$, $^{*L3}-OC(O)-$



substituted with at least one R^{L3c} ,
wherein *L3 refers to the position attached to the



moiety, and $**L^3$ refers to the



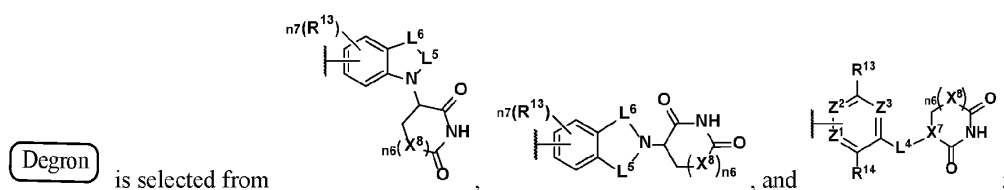
each of said R^{L1c} , R^{L2c} and R^{L3c} are independently absent, oxo (=O), halogen, hydroxy, -CN, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl, or 5- to 12-membered heteroaryl; wherein each of said -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ,

R^{Lca} is independently absent, oxo (=O), halogen, hydroxy, -CN, -C₁-C₈alkyl, -C₁-C₈alkoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, C₆-C₁₂aryl or 5- to 12-membered heteroaryl; or

two R^{L1c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;

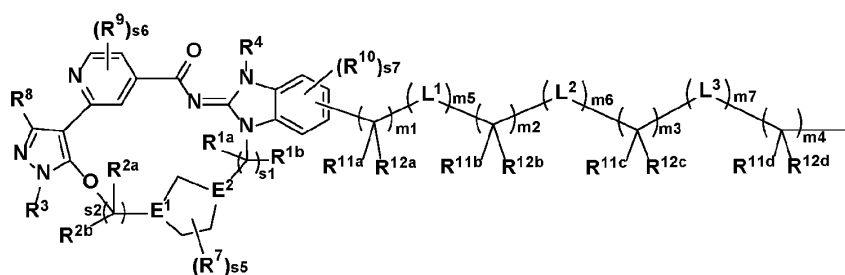
two R^{L2c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;

two R^{L3c} together with the atoms to which they are attached, form a 3- to 12-membered ring, said ring comprising 0-3 heteroatoms independently selected from nitrogen, oxygen and sulfur; said ring is optionally substituted with at least one substituent selected from halogen, hydroxy, and -C₁-C₈alkyl;



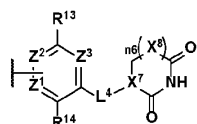
Z^1 , Z^2 and Z^3 are each independently N or CR^z, provided that Z^1 , Z^2 and Z^3 are not N at the same time;

R^z, at each occurrence, is independently absent, hydrogen, halogen, -C₁-alkyl, -NR^{za}R^{zb}, -OR^{za}, -SR^{za}, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl, or CN; wherein each of -C₁-alkyl, C₃-C₈cycloalkyl, 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{zc};



wherein the

moiety



is linked to the moiety via any one of Z^1 or Z^2 which is CR^z and R^z is absent;

R^{Za} and R^{Zb} are each independently absent, hydrogen, $-C_1$ - C_8 alkyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_6 - C_{12} aryl, or 5- to 12-membered heteroaryl; wherein each of said $-C_1$ - C_8 alkyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_6 - C_{12} aryl, or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{Zd} ;

R^{Zc} and R^{Zd} are each independently halogen, hydroxy, $-C_1$ - C_8 alkyl, $-C_1$ - C_8 alkoxy, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_6 - C_{12} aryl, or 5- to 12-membered heteroaryl;

R^{13} and R^{14} are each independently absent, hydrogen, halogen, $-C_1$ - C_8 alkyl, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_1$ - C_8 alkoxy, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, $-C_6$ - C_{12} aryl, 5- to 12-membered heteroaryl, $-CN$, $-SO_2R^{13a}$, $-SO_2NR^{13a}R^{13b}$, $-COR^{13a}$, $-CO_2R^{13a}$, $-CONR^{13a}R^{13b}$, $-NR^{13a}R^{13b}$, $-NR^{13a}COR^{13b}$, $-NR^{13a}CO_2R^{13b}$, or $-NR^{13a}SO_2R^{13b}$; wherein each of $-C_1$ - C_8 alkyl, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_1$ - C_8 alkoxy, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, $-C_6$ - C_{12} aryl or 5- to 12-membered heteroaryl is optionally substituted with halogen, $-C_1$ - C_8 alkyl, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_6 - C_{12} aryl, 5- to 12-membered heteroaryl, oxo, $-CN$, $-OR^{13c}$, $-SO_2R^{13c}$, $-SO_2NR^{13c}R^{13d}$, $-COR^{13c}$, $-CO_2R^{13c}$, $-CONR^{13c}R^{13d}$, $-NR^{13c}R^{13d}$, $-NR^{13c}COR^{13d}$, $-NR^{13c}CO_2R^{13d}$, or $-NR^{13c}SO_2R^{13d}$;

at each occurrence, R^{13a} , R^{13b} , R^{13c} and R^{13d} are each independently absent, hydrogen, $-C_1$ - C_8 alkyl, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, C_3 - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, C_6 - C_{12} aryl, or 5- to 12-membered heteroaryl;

L^4 , L^5 and L^6 are each independently absent, a single bond, $-O-$, $-NR^a$, $-(CR^aR^b)_{n8-}$, $-O(CR^aR^b)_{n8-}$, $-NR^a(CR^aR^b)_{n8-}$ or $-C(O)-$;

at each occurrence, X^1 , X^2 and X^7 are each independently $-CR^a$, or N ;

at each occurrence, X^3 , X^4 and X^8 are each independently $-NR^a$, $-O-$, $-S-$ or $-CR^aR^b$;

at each occurrence, X^5 and X^6 are each independently absent, a single bond, $-C(O)-$, $-NR^a$ or $-O-$;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, halogen, CN , $-C_1$ - C_8 alkyl, $-C_1$ - C_8 alkoxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, $-C_6$ - C_{12} aryl and 5- to 12-membered heteroaryl; wherein each of said $-C_1$ - C_8 alkyl, $-C_1$ - C_8 alkoxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, $-C_6$ - C_{12} aryl or 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from halogen, hydroxy, halogen, $-C_1$ - C_8 alkyl, $-C_1$ - C_8 alkoxy, $-C_2$ - C_8 alkenyl, $-C_2$ - C_8 alkynyl, $-C_3$ - C_8 cycloalkyl, 3- to 8-membered heterocyclyl, $-C_6$ - C_{12} aryl and 5- to 12-membered heteroaryl; or

m5, m6 and m7 are each independently 0, 1 or 2; provided that $m5+m6+m7 \geq 1$;

n1, n2, n3, n4 and n5 are each independently 0, 1, 2 or 3;

n6 is each independently 0, 1, 2, 3 or 4;

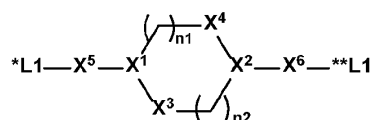
n7 and n8 are each independently 0, 1, 2 or 3;

s1 and s2 are each independently 0, 1, 2 or 3:

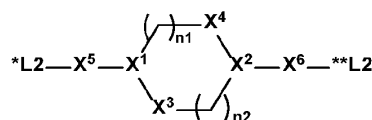
s5, s6 and s7 are each independently 0, 1, 2 or 3;

provided that:

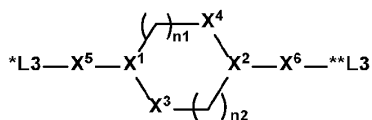
for any one of L¹, L² or L³, when X¹ is N, X⁵ is single bond, absent, or -C(O)-; and/or when X² is N, X⁶ is single bond, absent, or -C(O)-;



when L¹ is , when X¹ is N, then X⁵ is a single bond, absent, or -C(O)-, X³ is -CR^aR^b-; when X² is N, X⁶ is single bond, absent, or -C(O)-, and/or X⁴ is -CR^aR^b-;

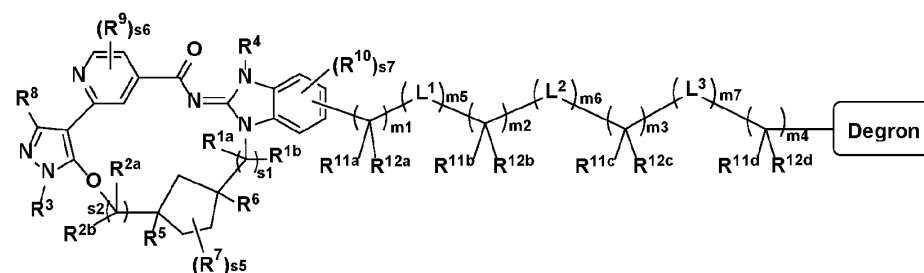


when L² is , when X¹ is N, then X⁵ is a single bond, absent, or -C(O)-, and/or X³ is -CR^aR^b-; when X² is N, then X⁶ is a single bond, absent, or -C(O)-, and/or X⁴ is -CR^aR^b-;



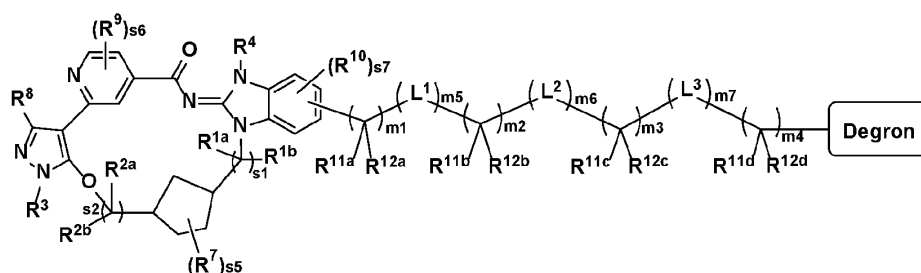
when L³ is , when X¹ is N, X⁵ is a single bond, absent, or -C(O)-, and/or X³ is -CR^aR^b-; when X² is N, X⁶ is a single bond, absent, or -C(O)-, and/or X⁴ is -CR^aR^b-.

2. The compound of claim 1, wherein the compound is selected from compounds of formula (IIa),



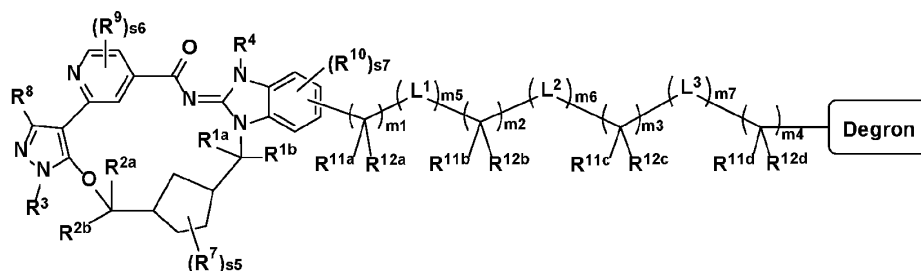
(IIa), or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

3. The compound of claim 1, wherein the compound is selected from compounds of formula (IIb):



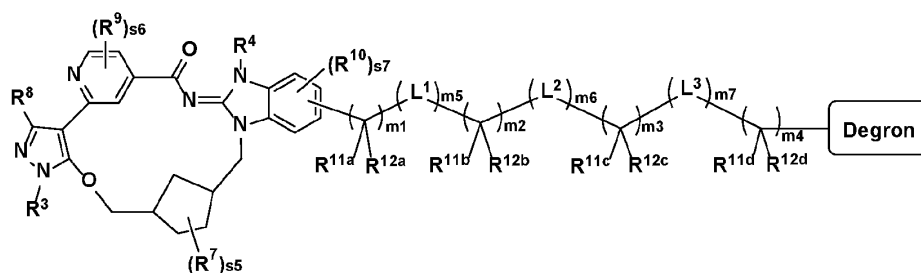
(IIb), or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

4. The compound of claim 1, wherein the compound is selected from compounds of formula (IIc):



(IIc), or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

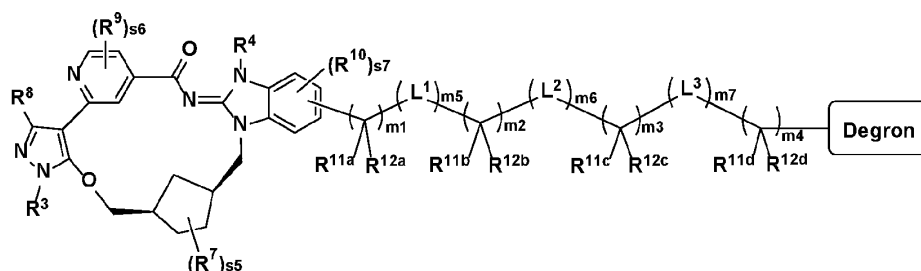
5. The compound of claim 1, wherein the compound is selected from compounds of formula (IId):



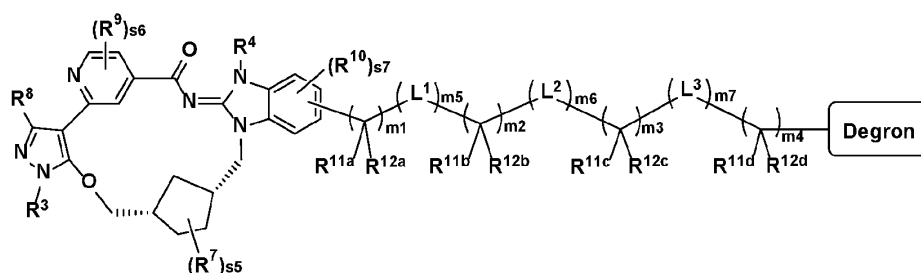
(IId),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, deuterated analog, or a prodrug thereof.

6. The compound of claim 1, wherein the compound is selected from compounds of formulae (IIe) and (IIf):



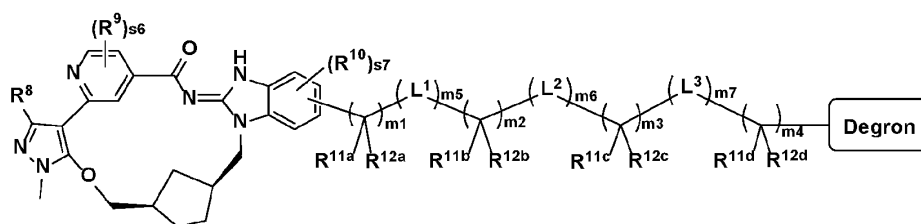
(IIe),



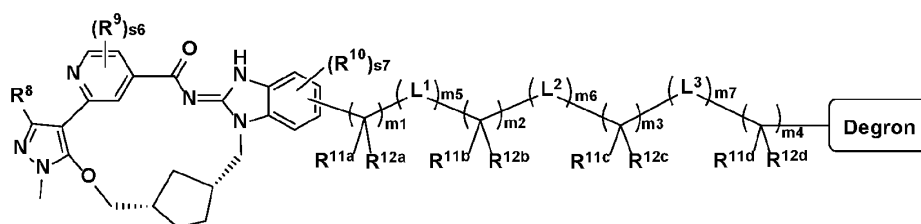
(IIf),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

7. The compound of claim 1, wherein the compound is selected from compounds of formulae (IIg) and (IIh):



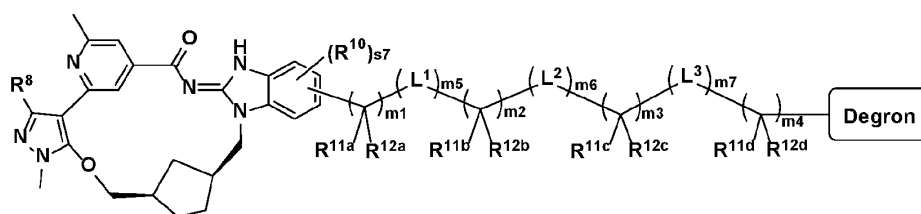
(IIg),



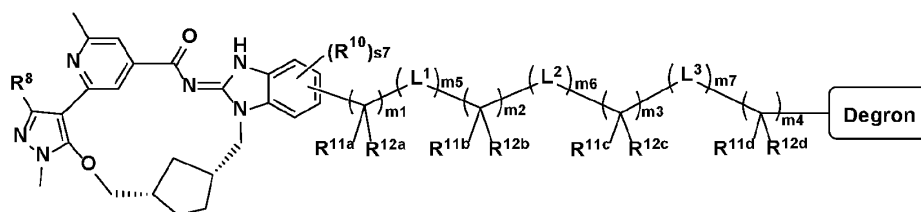
(IIh);

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer or deuterated analog thereof.

8. The compound of claim 1, wherein the compound is selected from compounds of formulae (IIIi) and (IIIj):

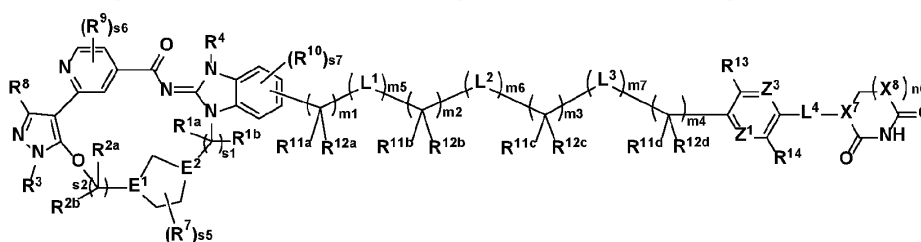


(IIIi)

 $(\Pi_j);$

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

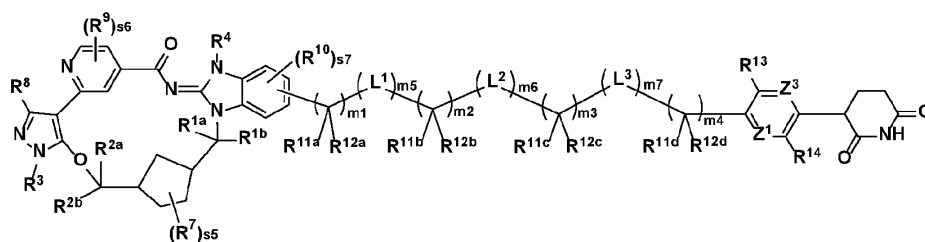
9. The compound of claim 1, wherein the compound is selected from compounds of formula (IIIa):



(IIIa),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

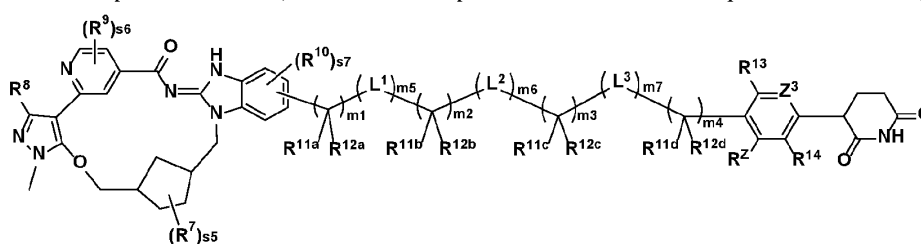
10. The compound of claim 1, wherein the compound is selected from compounds of formula (IIIb):



(IIIb),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

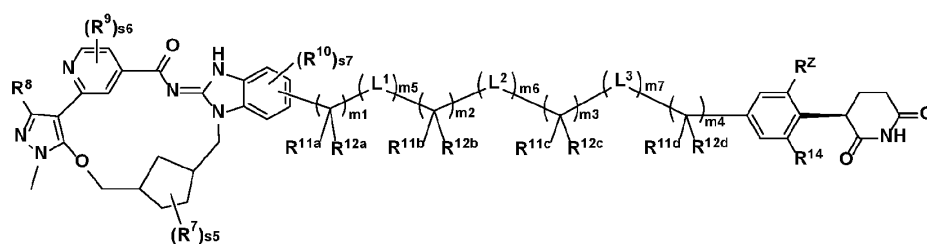
11. The compound of claim 1, wherein the compound is selected from compounds of formula (IIIc):



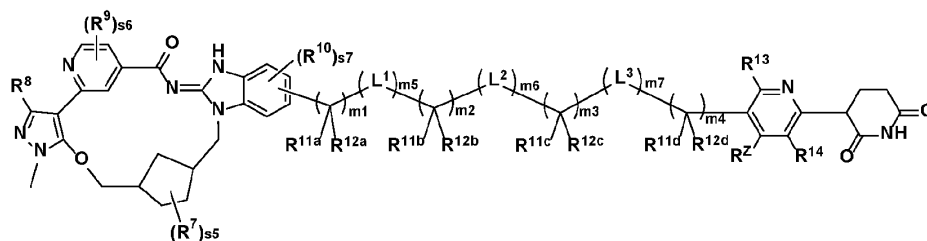
(IIIc),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

12. The compound of claim 1, wherein the compound is selected from compounds of formula (III_d) and (III_e):



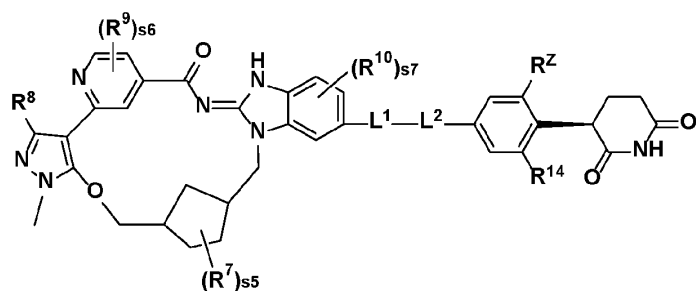
(IIIId)



(IIIe),

or an N-oxide, pharmaceutically acceptable salt, stereoisomer, tautomer, or deuterated analog thereof.

13. The compound of claim 1, wherein the compound is selected from compounds of formula (IIIIm):



(IIIIm);

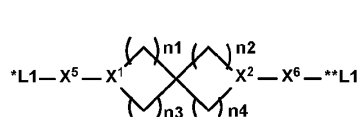
wherein

R⁷ is each independently absent, hydrogen, halogen or -C₁₋₃alkyl;

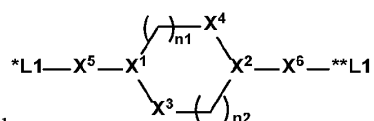
R⁸ and R⁹ are each independently selected from hydrogen, halogen, and -C₁₋₃alkyl;

R¹⁰ is each independently selected from hydrogen, halogen, or -C₁₋₃alkyl;

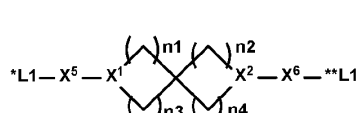
L¹ is selected from



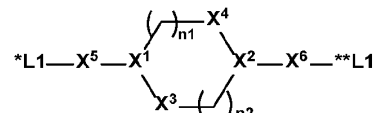
, and



;



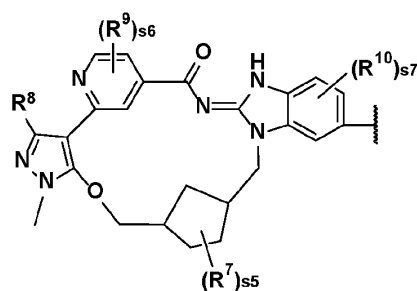
and



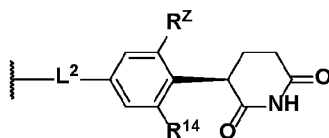
is

wherein each of said

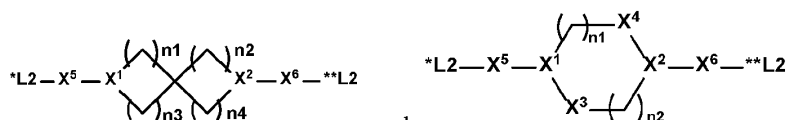
optionally substituted with at least one R^{L1c};



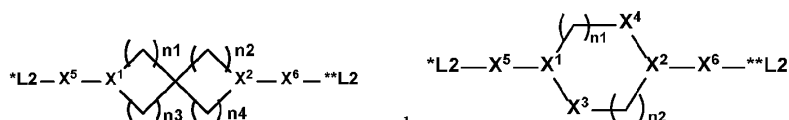
wherein $*L^1$ refers to the position attached to the moiety, and $**L^1$



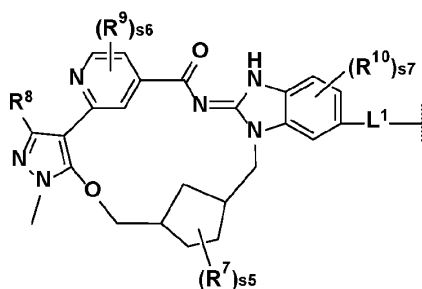
refers to the position attached to the moiety;



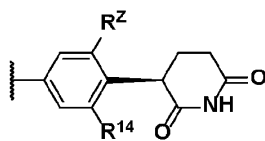
L^2 is selected from , and ; wherein



each of said and is optionally substituted with at least one R^{L2c} ;



wherein $*L^2$ refers to the position attached to the moiety, and $**L^2$



refers to the position attached to the moiety;

each of said R^{L1c} and R^{L2c} are independently absent, oxo (=O), halogen, hydroxy, $-C_1-C_3$ alkyl or $-C_1-C_3$ alkoxy;

each of said $-C_1-C_3$ alkyl and $-C_1-C_3$ alkoxy is optionally substituted with at least one R^{Lca} ;

R^{Lca} is each independently absent, halogen, hydroxy, or $-C_1-C_3$ alkoxy; or

two R^{L1c} together with the atoms to which they are attached, form a 3- to 5-membered ring, said ring comprising 0-1 heteroatoms independently selected from nitrogen and oxygen;

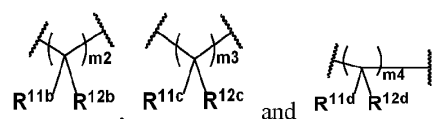
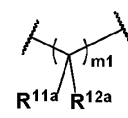
two R^{L2c} together with the atoms to which they are attached, form a 3- to 5-membered ring, said ring comprising 0-1 heteroatoms independently selected from nitrogen and oxygen;

R^z , at each occurrence, is independently absent, hydrogen, halogen, $-C_{1-3}$ alkyl or $-C_{1-3}$ alkoxy;
 R^{14} , at each occurrence, is independently absent, hydrogen, halogen, $-C_{1-3}$ alkyl or $-C_{1-3}$ alkoxy;
 at each occurrence, X^1 and X^2 are each independently $-CH$ or N ;
 at each occurrence, X^3 and X^4 are each independently $-NH-$ or $-CH_2-$;
 at each occurrence, X^5 and X^6 are each independently absent, a single bond, $-C(O)-$ or $-NR^a-$;
 at each occurrence, R^a is independently hydrogen or $-C_{1-3}$ alkyl;
 $n1, n2, n3$ and $n4$ are each independently 0, 1, or 2;
 $s5, s6$ and $s7$ are each independently 0, 1, or 2.

14. The compound of any one of claims 1-12, wherein $m1+m2+m3+m4 \leq 3$.

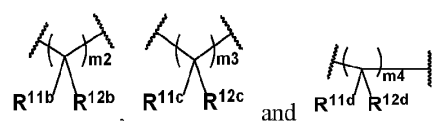
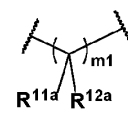
15. The compound of any one of claims 1-12, wherein $m1+m2+m3+m4 = 0, 1$ or 2 .

16. The compound of any one of claims 1-12, wherein the total number of $-CH_2-$ groups in the



moieties combined is no more than 4.

17. The compound of any one of claims 1-12, wherein the total number of $-CH_2-$ groups in the



moieties combined is no more than 3.

18. The compound of any one of claims 1-6 and 9-10, wherein R^3 and R^4 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; said methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, hydroxyl, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy.

19. The compound of any one of claims 1-6 and 9-10, wherein R^3 and R^4 are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

20. The compound of any one of the preceding claims, wherein R^3 is methyl, and R^4 is hydrogen.

21. The compound of any one of claims 1-4 and 9-10, wherein R^{1a} , R^{1b} , R^{2a} and R^{2b} are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or $-CN$; wherein each said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy,

pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or -CN.

22. The compound of any one of claims 1-4 and 9-10, wherein R^{1a} , R^{1b} , R^{2a} and R^{2b} are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CN$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$.

23. The compound of any one of claims 1-4 and 9-10, wherein R^{1a} , R^{1b} , R^{2a} and R^{2b} are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-CF_3$, $-CHF_2$, or $-CH_2OCH_3$.

24. The compound of any one of claims 1-4 and 9-10, wherein R^{1a} , R^{1b} , R^{2a} and R^{2b} are each independently hydrogen.

25. The compound of any one of claims 1-2 and 9, wherein R^5 and R^6 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CN$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$.

26. The compound of any one of claims 1-2 and 9, wherein R^5 and R^6 are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-CF_3$, $-CHF_2$, and $-CH_2OCH_3$.

27. The compound of any one of claims 1-6 and 9-13, wherein R^7 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CN$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, or $-CH_2CH_2OCH_2CH_3$.

28. The compound of any one of claims 1-6 and 9-13, wherein R^7 are each independently hydrogen, F, Cl, methyl, methoxy, cyclopropyl, $-CF_3$, $-CHF_2$, or $-CH_2OCH_3$.

29. The compound of any one of claims 1-6 and 9-13, wherein R^7 are each independently hydrogen.

30. The compound of any one of claims 1-7 and 9-13, wherein R^8 and R^9 are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; wherein said methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, hydroxy, F, Cl, Br, I, methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

31. The compound of any one of claims 1-7 and 9-13, wherein R^8 and R^9 are each independently hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-CF_3$, $-CHF_2$, $-CH_2OH$, or $-CH_2CH_2OH$.

32. The compound of any one of claims 1-7 and 9-13, wherein R^8 is hydrogen, methyl, $-F$, $-Cl$, $-CF_3$, $-CHF_2$, or $-CH_2OH$; and R^9 is F, methyl or $-CH_2OH$.

33. The compound of any one of claims 1-13, wherein R^{10} is each independently selected from hydrogen, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}alkenyl$, $-C_{2-8}alkynyl$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, $-NR^{10a}R^{10b}$, $-OR^{10a}$, $-SR^{10a}$, $-C(O)R^{10a}$, $-CO_2R^{10a}$, $-C(O)NR^{10a}R^{10b}$, $-NR^{10a}COR^{10b}$, $-NR^{10a}CO_2R^{10b}$, $-NR^{10a}SO_2R^{10b}$, and $-CN$; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl,

octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl or phenyl is optionally substituted with at least one R^{10c};

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, and phenyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, or phenyl is optionally substituted with at least one substituent R^{10d}, R^{10c} and R^{10d} are each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, oxo (=O), -NR^{10e}R^{10f}, -OR^{10e}, -SR^{10e}, -SO₂R^{10e}, -SO₂NR^{10e}R^{10f}, -C(O)R^{10e}, -CO₂R^{10e}, -C(O)NR^{10e}R^{10f}, -NR^{10e}COR^{10f}, -NR^{10e}CO₂R^{10f}, -NR^{10e}SO₂R^{10f}, and -CN; and

R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

34. The compound of any one of claims 1-13, wherein R¹⁰ is each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, -NR^{10a}R^{10b}, -OR^{10a}, -SR^{10a}, -C(O)R^{10a}, -CO₂R^{10a}, -C(O)NR^{10a}R^{10b}, -NR^{10a}COR^{10b}, -NR^{10a}CO₂R^{10b}, -NR^{10a}SO₂R^{10b}, and -CN; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl or phenyl is optionally substituted with at least one R^{10c};

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, and phenyl;

R^{10c} is each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, -C₂₋₈alkenyl, -C₂₋₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, 5- to 12-membered heteroaryl, oxo (=O), -NR^{10e}R^{10f}, -OR^{10e}, and -CN; and

R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

35. The compound of any one of claims 1-13, wherein R¹⁰ is each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3- to 8-membered heterocyclyl, -NR^{10a}R^{10b}, -OR^{10a}, -CO₂R^{10a}, and -C(O)NR^{10a}R^{10b}; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{10c};

R^{10a} and R^{10b} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 3-membered heterocyclyl, 4-membered heterocyclyl, 5-membered

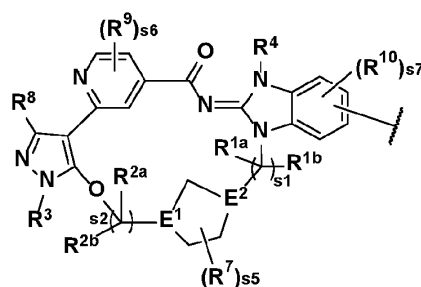
heterocyclyl, and 6-membered heterocyclyl;

R^{10c} is each independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, oxo (=O), $-NR^{10e}R^{10f}$, $-OR^{10e}$, and -CN; and

R^{10e} and R^{10f} are each independently selected from hydrogen, methyl, ethyl, propyl, cyclopropyl, cyclobutyl, and cyclopentyl.

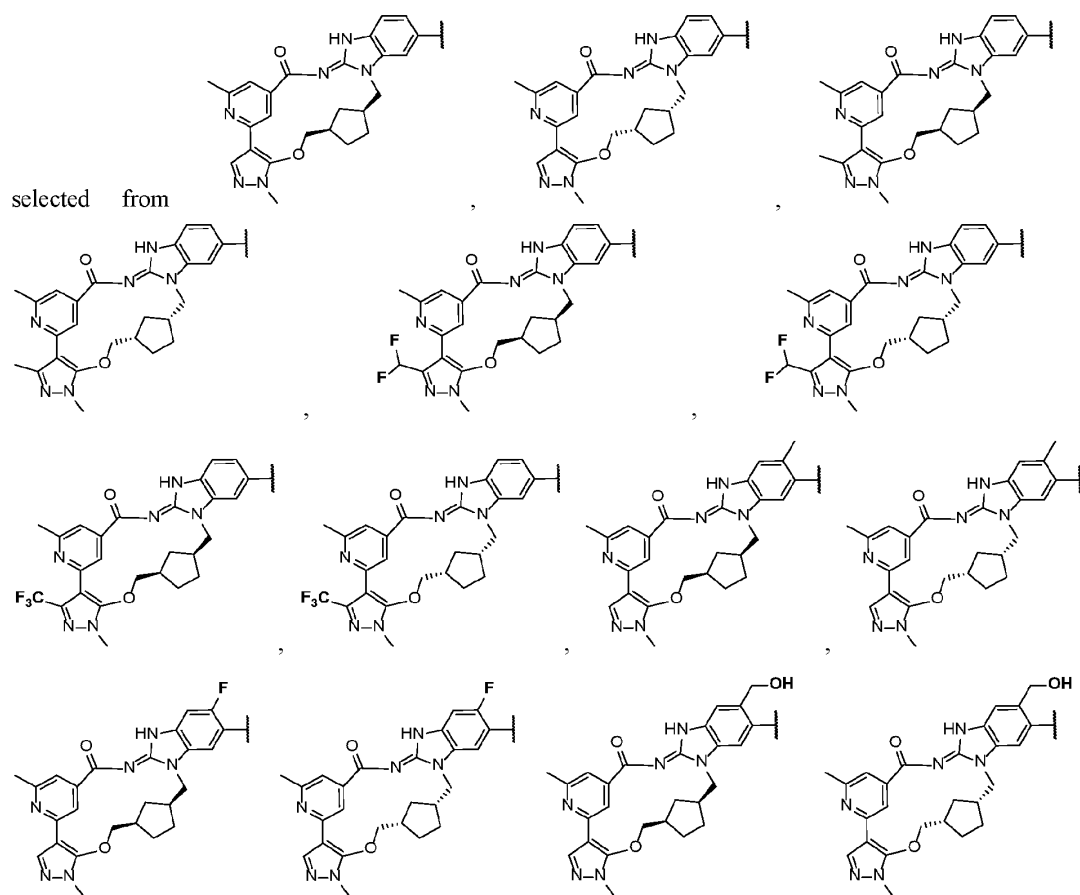
36. The compound of any one of claims 1-13, wherein R^{10} is each independently selected from H, F, Cl, Br, methyl, ethyl, propyl (n-propyl or iso-propyl), butyl(n-butyl, sec-butyl, iso-butyl or tert-butyl), cyclopropyl,

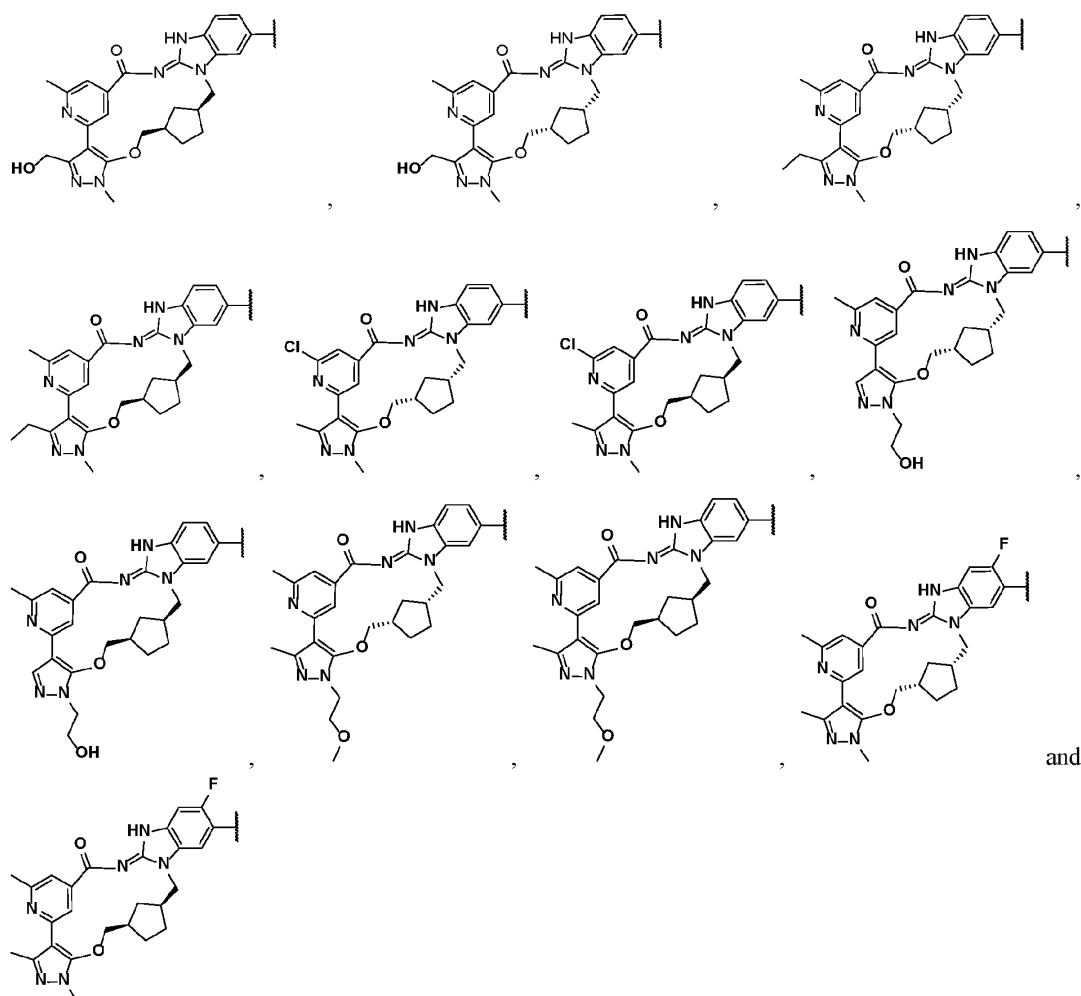
cyclobutyl, cyclopentyl, cyclohexyl, , , , -COOH, -CONH₂, -CH₂OCH₃ and -CH₂OH.



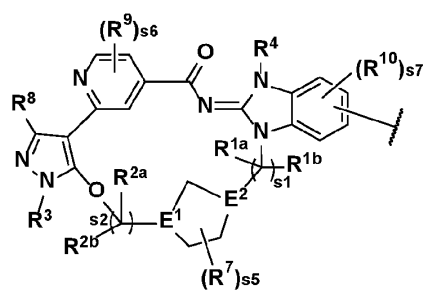
37. The compound of claim 1, wherein the

moiety is

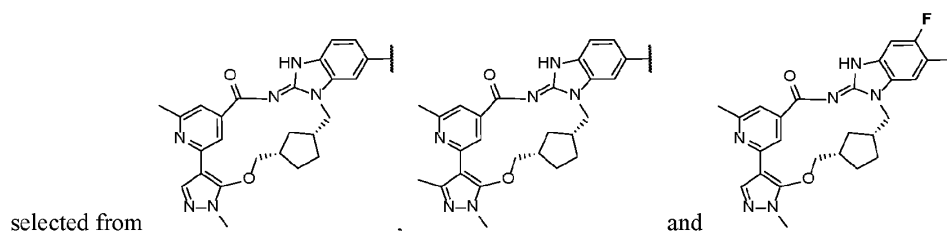




and



38. The compound of claim 1, wherein the moiety is



selected from

and

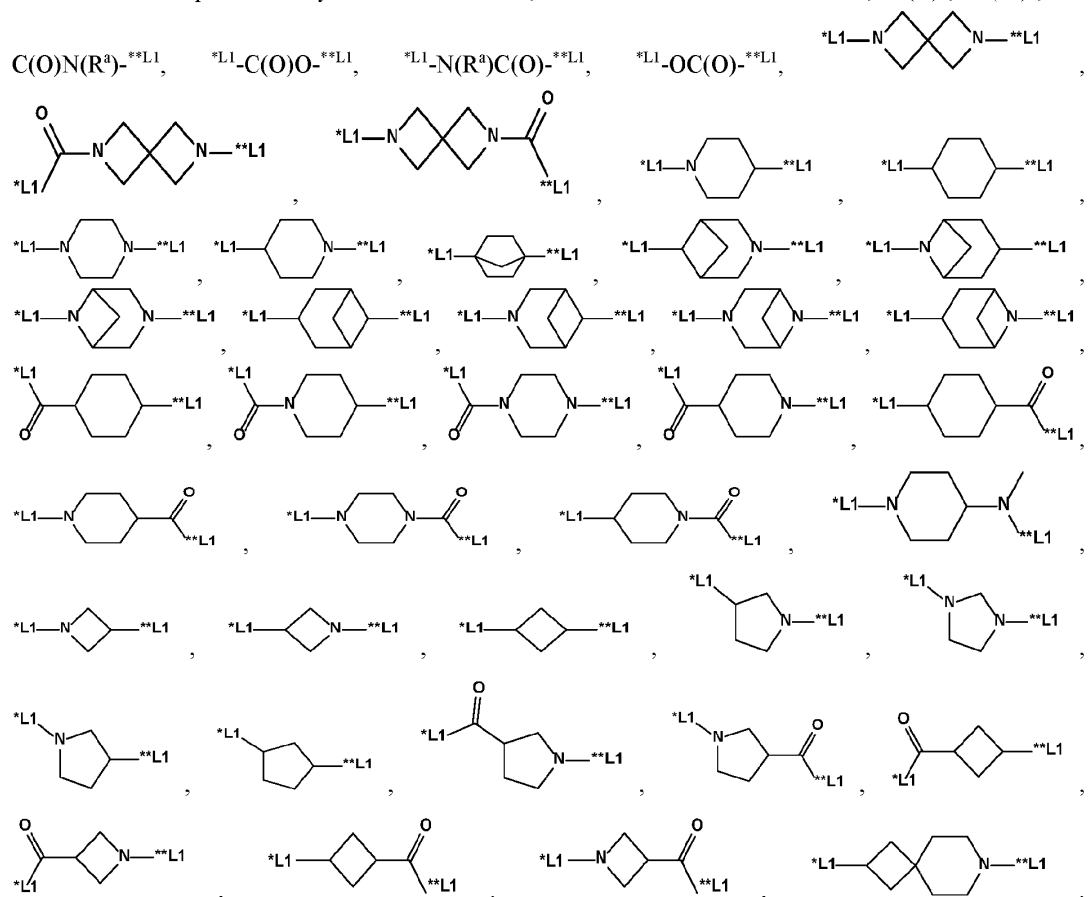
39. The compound of any one of claims 1-12, wherein R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are

each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl is optionally substituted with at least one substituent selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-C_{2-8}$ alkenyl, $-C_{2-8}$ alkynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy and $-CN$.

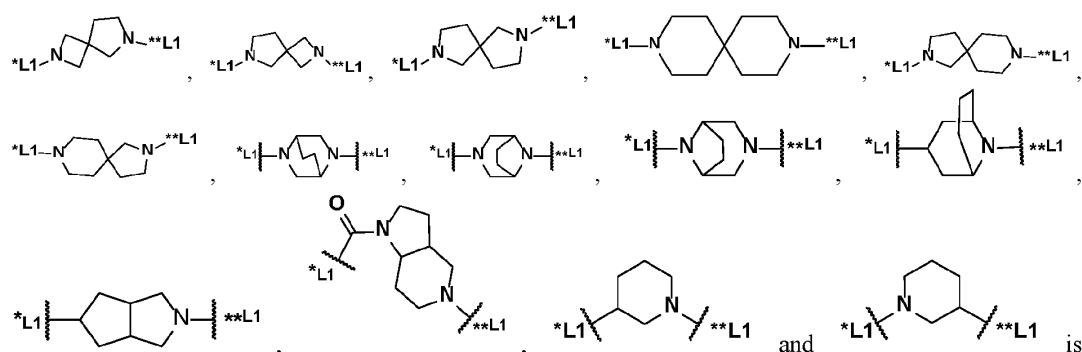
40. The compound of any one of claims 1-12, wherein R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; preferably, R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently oxo, hydrogen, F, Cl, Br, I, methyl, ethyl or propyl.

41. The compound of any one of the preceding claims, wherein R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , R^{12c} and R^{12d} are each independently hydrogen or methyl.

42. The compound of any one of claims 1-13, wherein L^1 is selected from $-O-$, $-C(O)-$, $-N(R^a)-$, $^{*}L1-$



wherein each of said



optionally substituted with at least one R^{L1c} ;

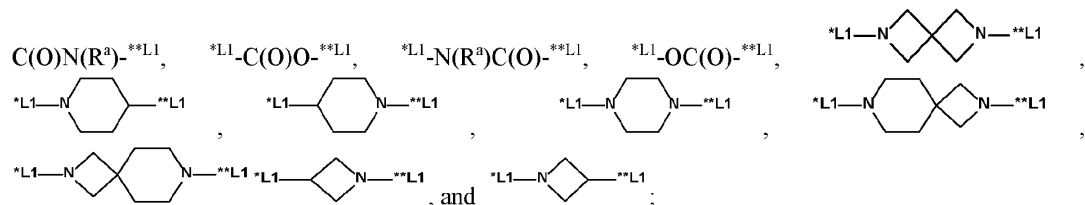
wherein each of said R^{L1c} is independently oxo ($=O$), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ;

R^{Lca} is independently oxo ($=O$), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl, or

two R^{L1c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; and

R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl is optionally substituted with at least one substituent selected from hydroxy, $-F$, $-Cl$, $-Br$, $-I$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

43. The compound of any one of claims 1-13, wherein L^1 is selected from $-O-$, $-C(O)-$, $-N(R^a)-$, $*L1-$



wherein each of said

, and is optionally substituted with at least one R^{L1c} ;

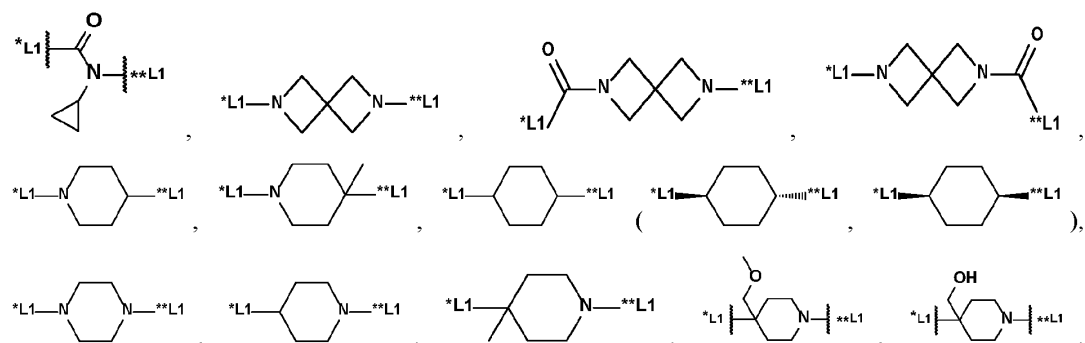
wherein each of said R^{L1c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ;

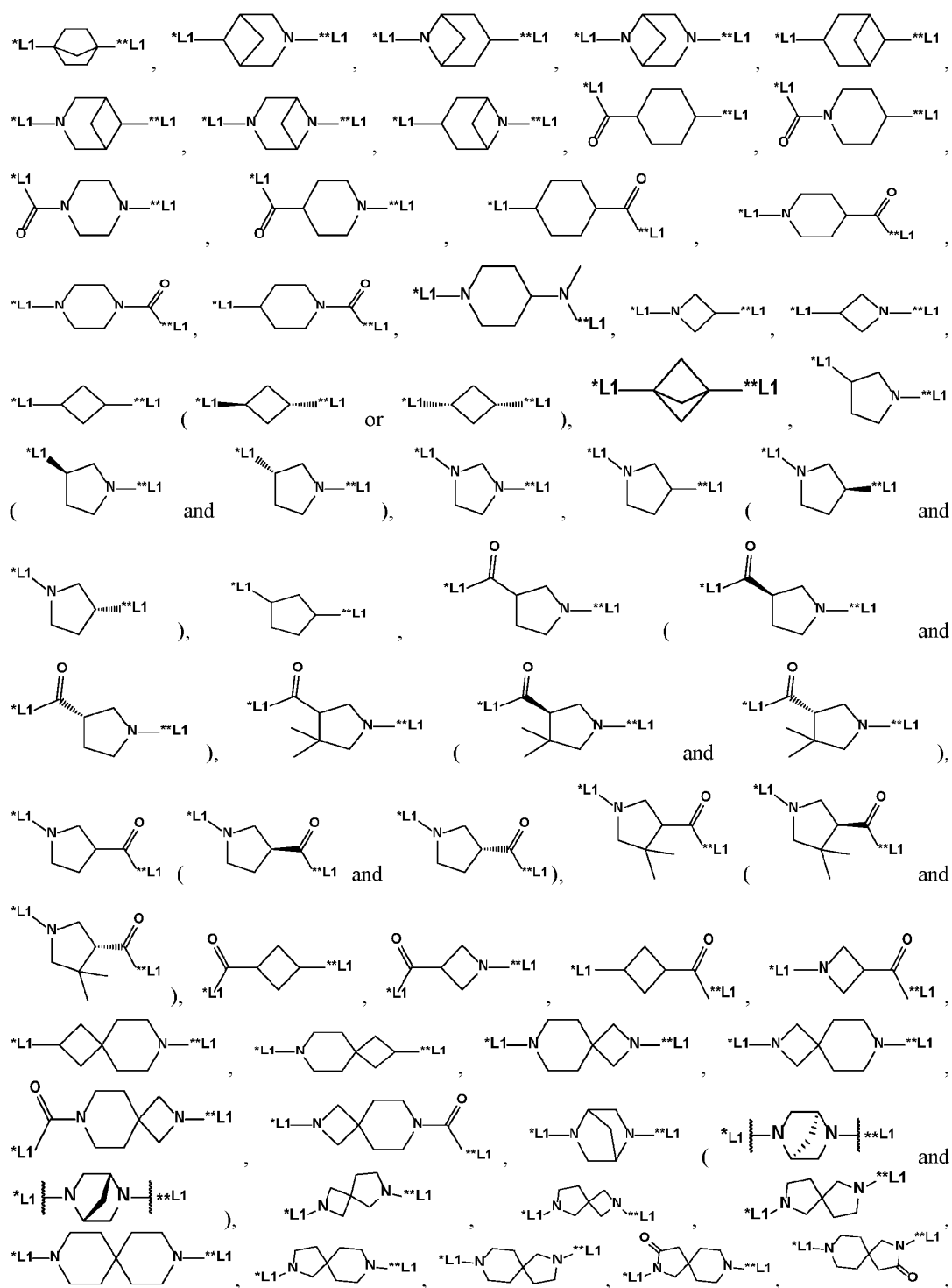
R^{Lca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl, or

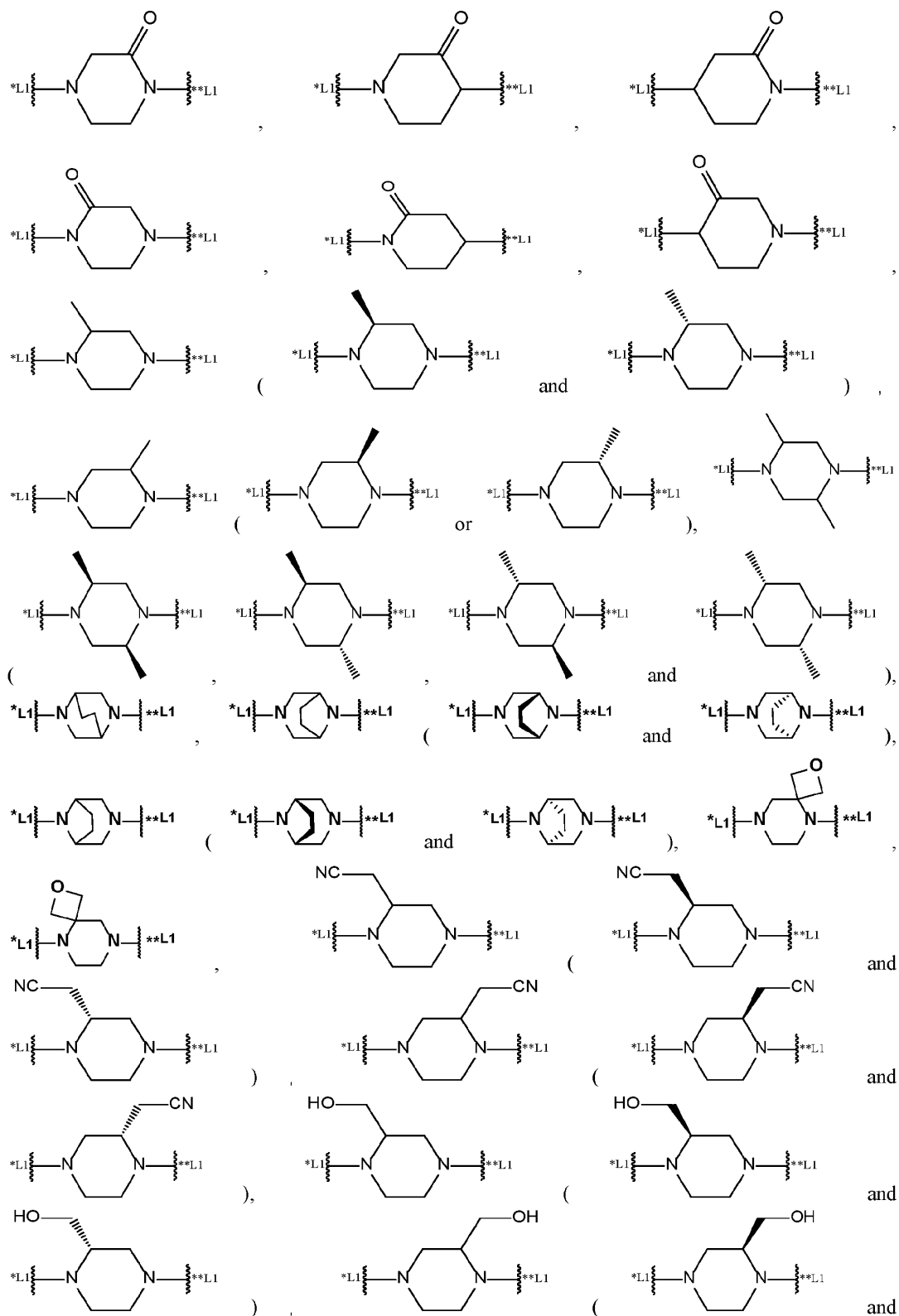
two R^{L1c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; and

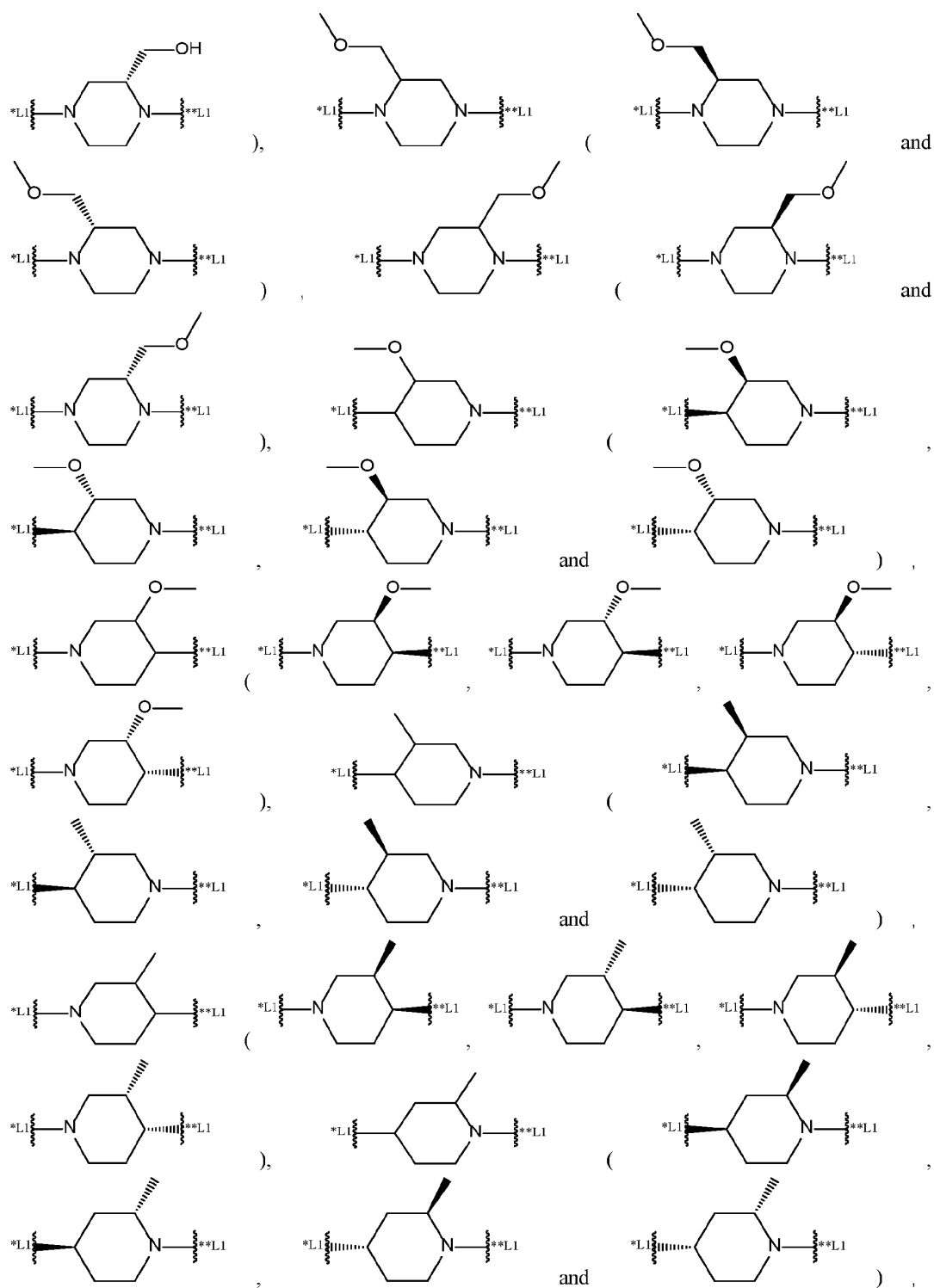
R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl is optionally substituted with at least one substituent selected from hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

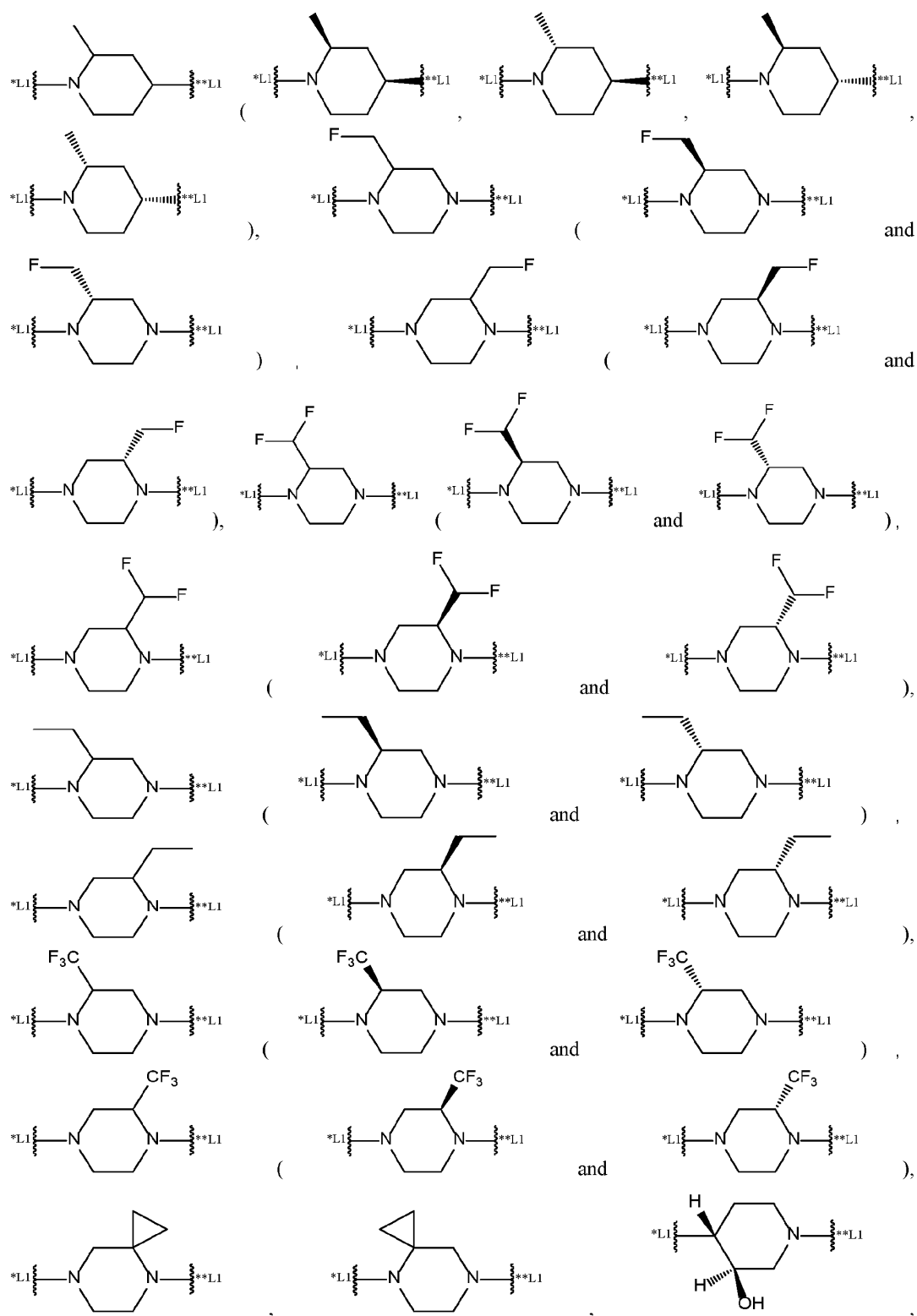
44. The compound of any one of claims 1-13, wherein L^1 is selected from -O-, -N(CH₃)-, -C(O)-, -NH-, $^{*}L^1$ -C(O)N(CH₃)- $^{**}L^1$, $^{*}L^1$ -C(O)NH- $^{**}L^1$, $^{*}L^1$ -C(O)O- $^{**}L^1$, $^{*}L^1$ -C(O)N(C₂H₅)- $^{**}L^1$, $^{*}L^1$ -C(O)N(C₃H₇)- $^{**}L^1$, $^{*}L^1$ -N(CH₃)C(O)- $^{**}L^1$, $^{*}L^1$ -NHC(O)- $^{**}L^1$, $^{*}L^1$ -OC(O)- $^{**}L^1$, $^{*}L^1$ -N(C₂H₅)C(O)- $^{**}L^1$, $^{*}L^1$ -N(C₃H₇)C(O)- $^{**}L^1$,

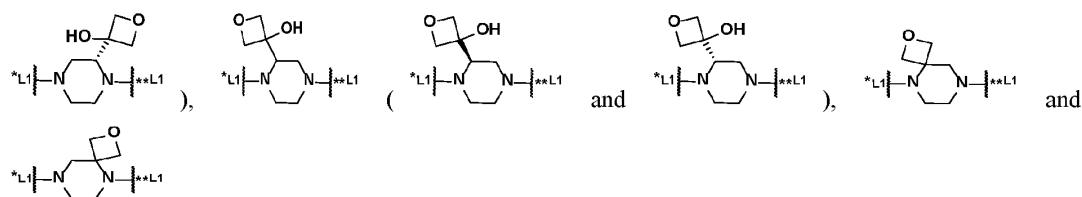




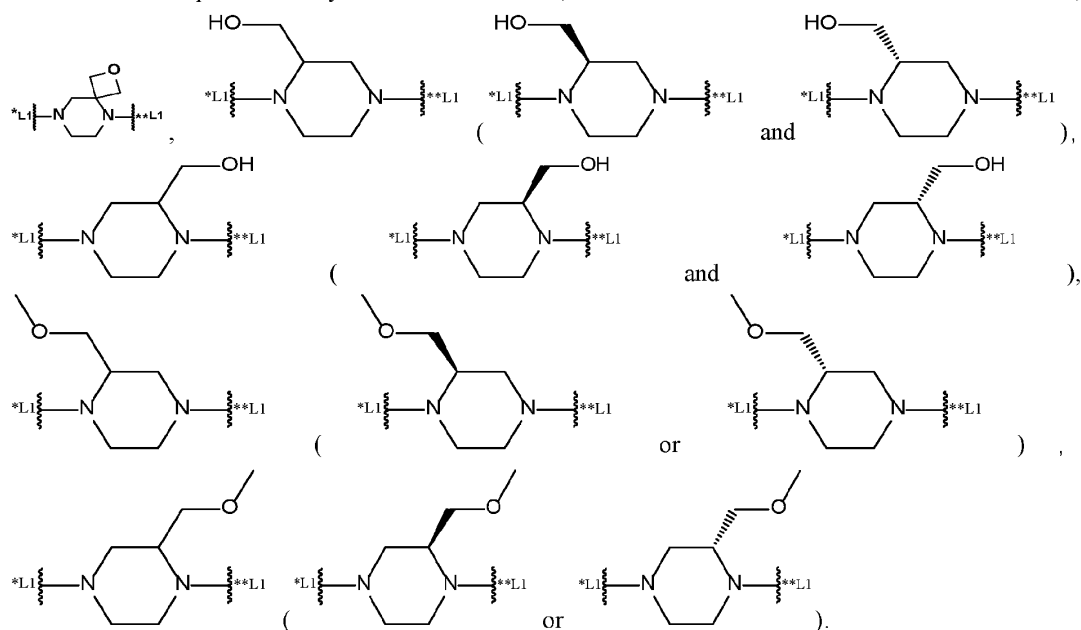




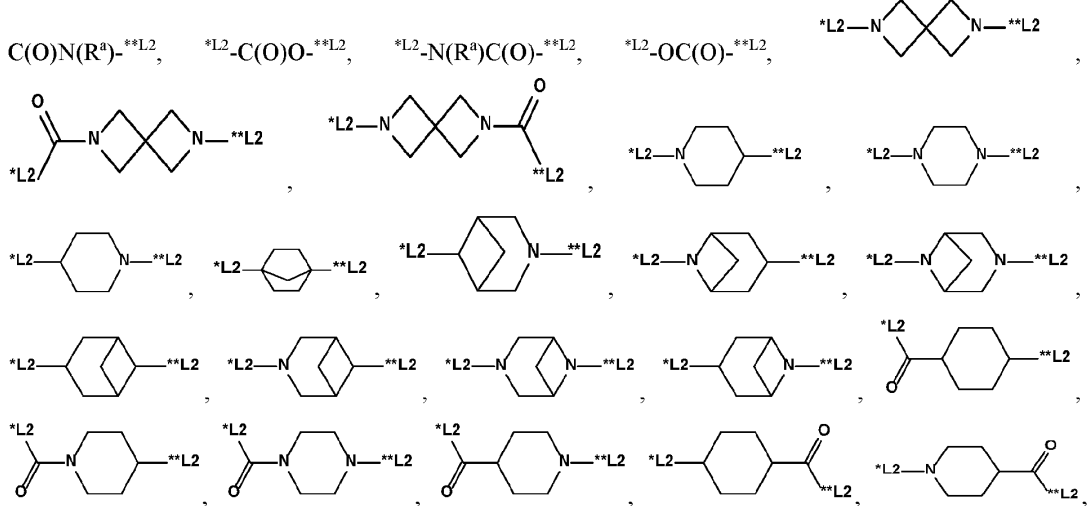


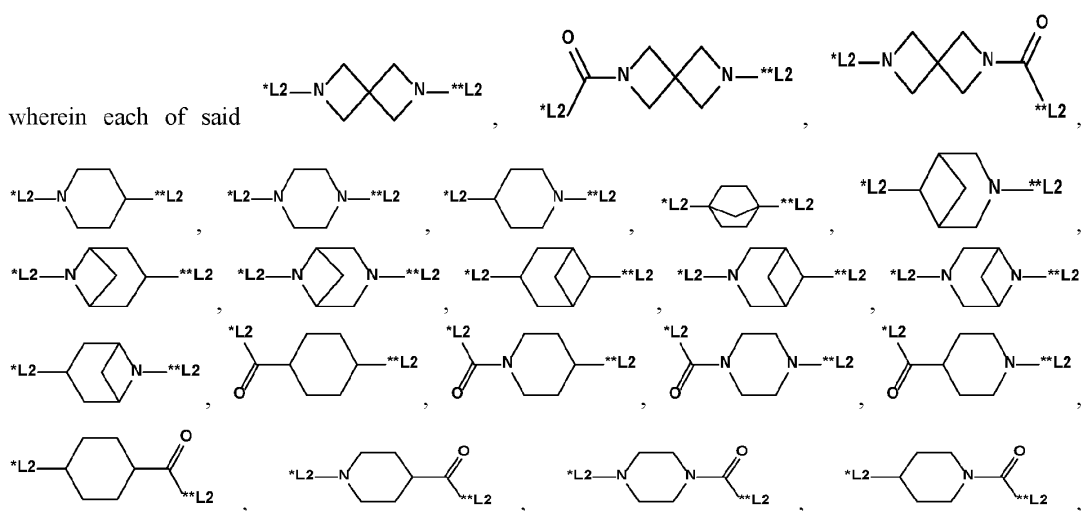
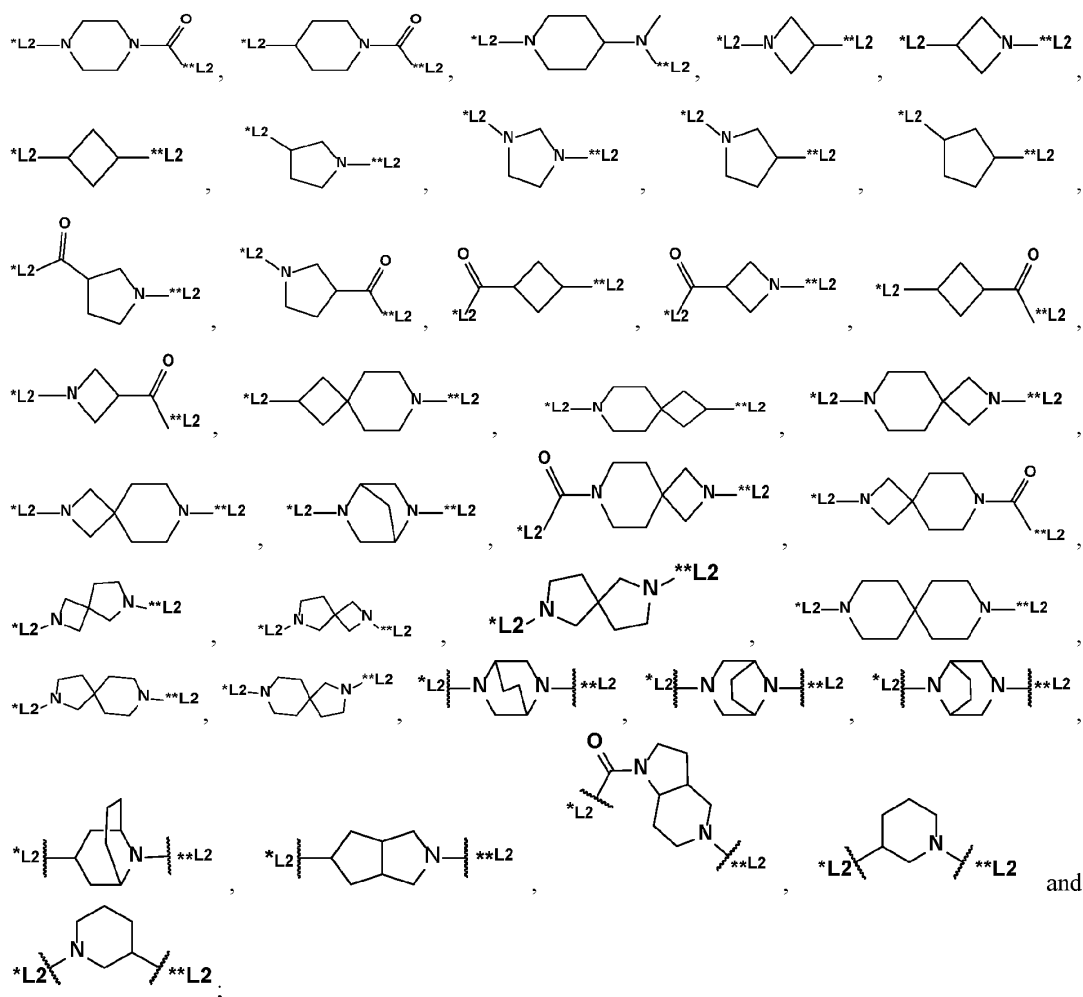


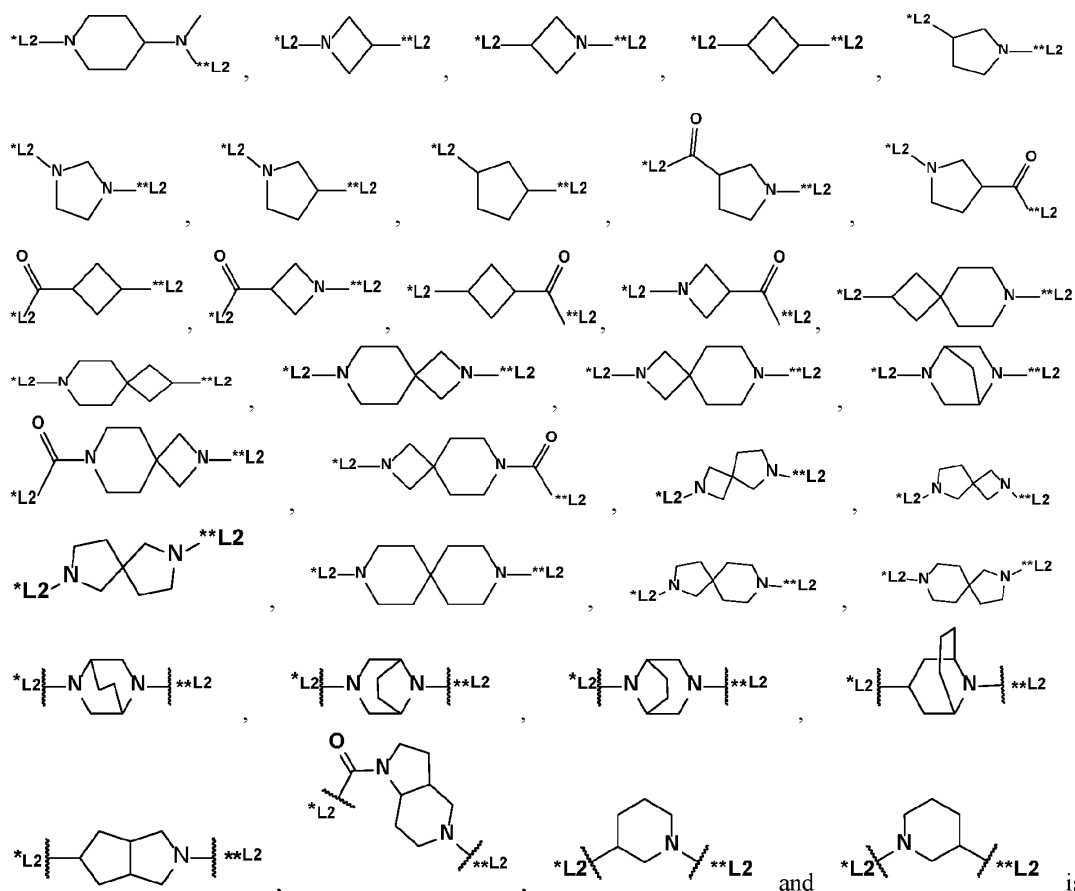
45. The compound of any one of claims 1-13, wherein L¹ is selected from ,



46. The compound of any one of claims 1-13, wherein L² is selected from -O-, -C(O)-, -N(R^a)-, *L².







optionally substituted with at least one R^{L2c} ;

each of said R^{L2c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca} ,

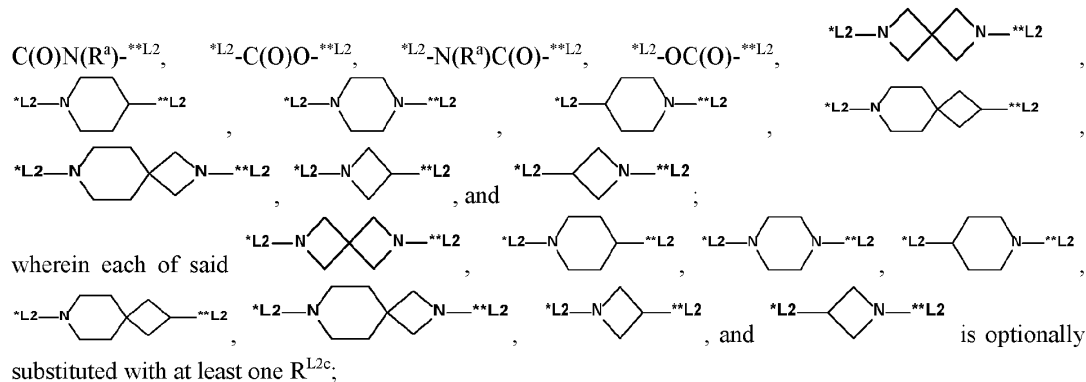
R^{Lca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; or

two R^{L2c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl;

R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, $-C_2-C_8$ alkenyl,

-C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent selected from hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

47. The compound of any one of claims 1-13, wherein L² is selected from -O-, -C(O)-, -N(R^a)-, *L²-

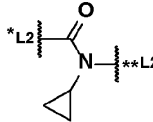
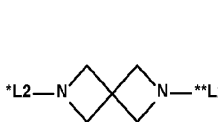
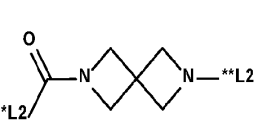
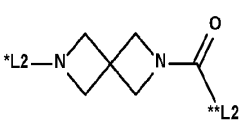


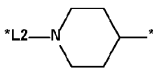
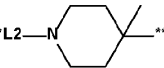
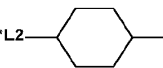
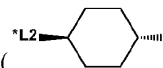
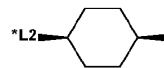
each of said R^{L2c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{Lca},

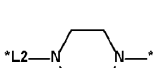
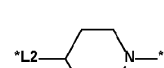
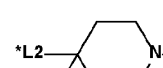
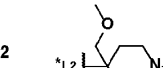
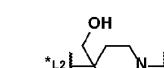
R^{Lca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; or

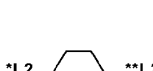
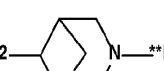
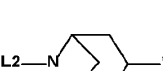
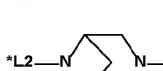
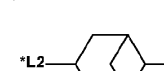
two R^{L2c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; wherein said ring is optionally substituted with at least one substituent F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl;

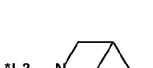
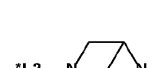
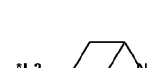
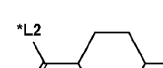
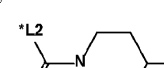
R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl, wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent selected from hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl,

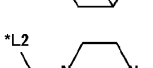
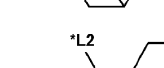
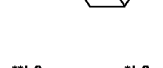
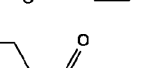
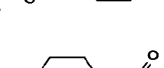





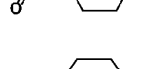
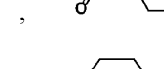






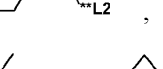
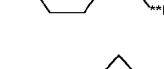






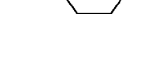
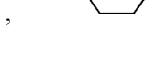






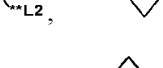
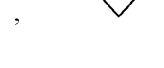






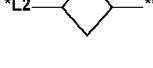
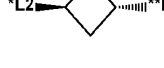
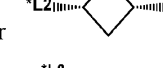
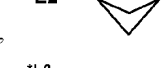
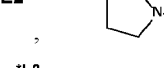






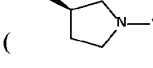
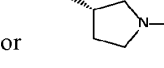
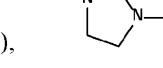
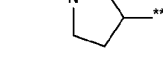
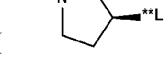



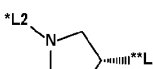
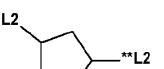
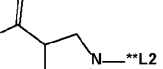
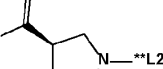
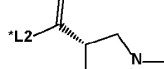



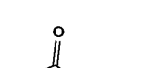



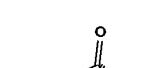
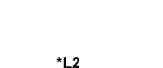



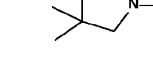
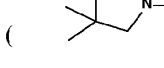
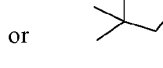
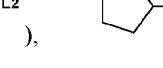
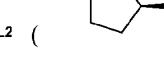






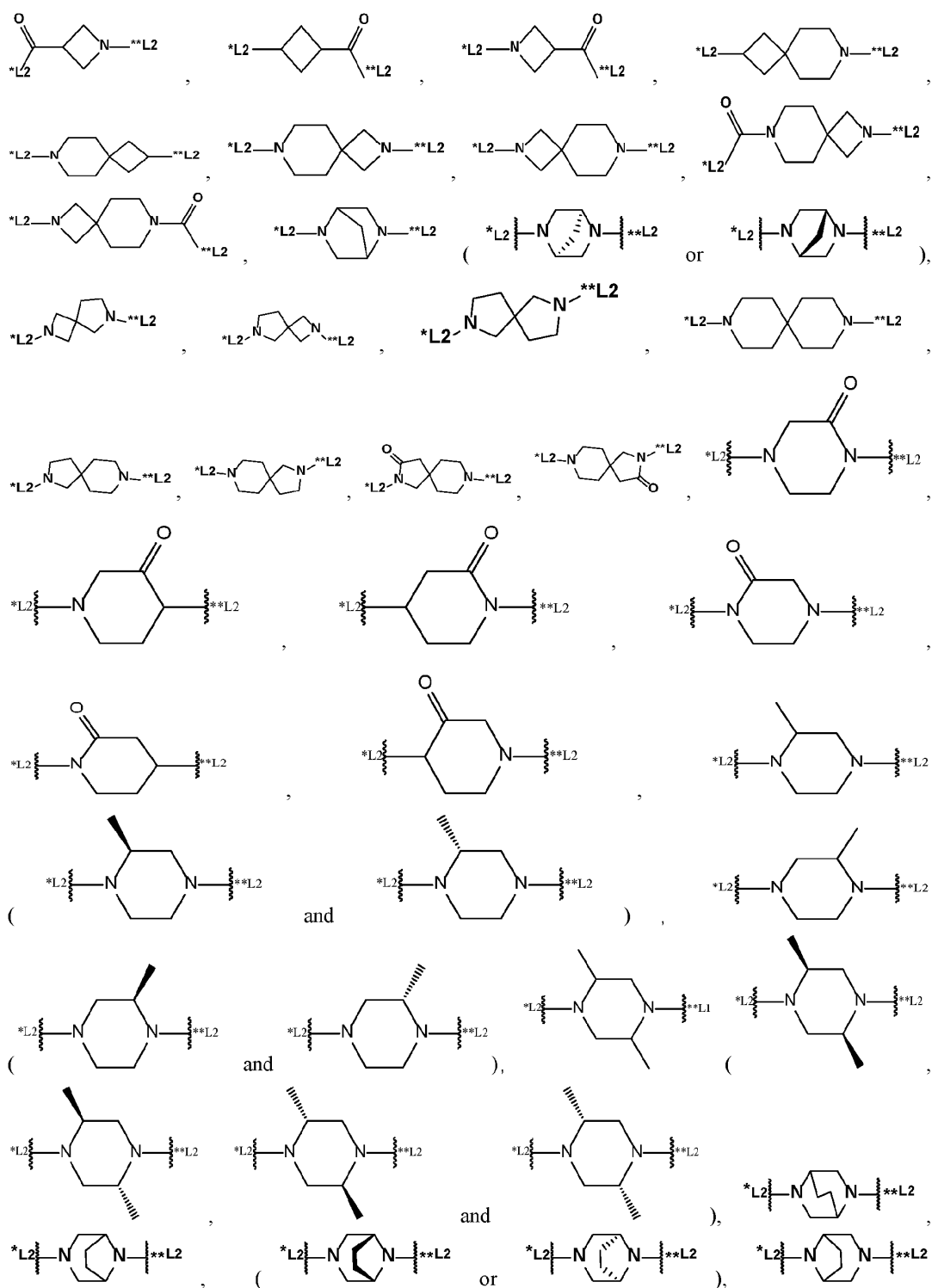






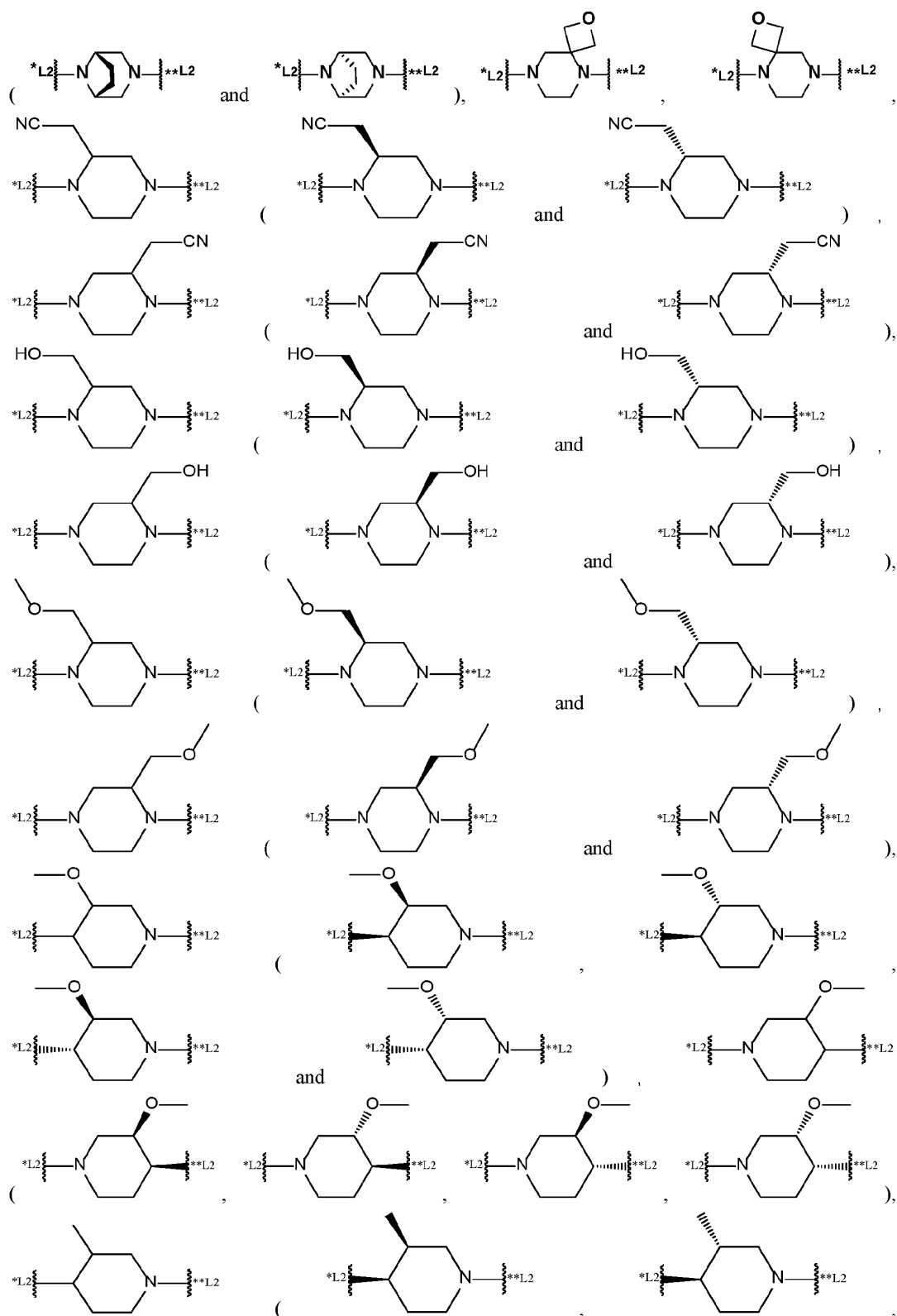






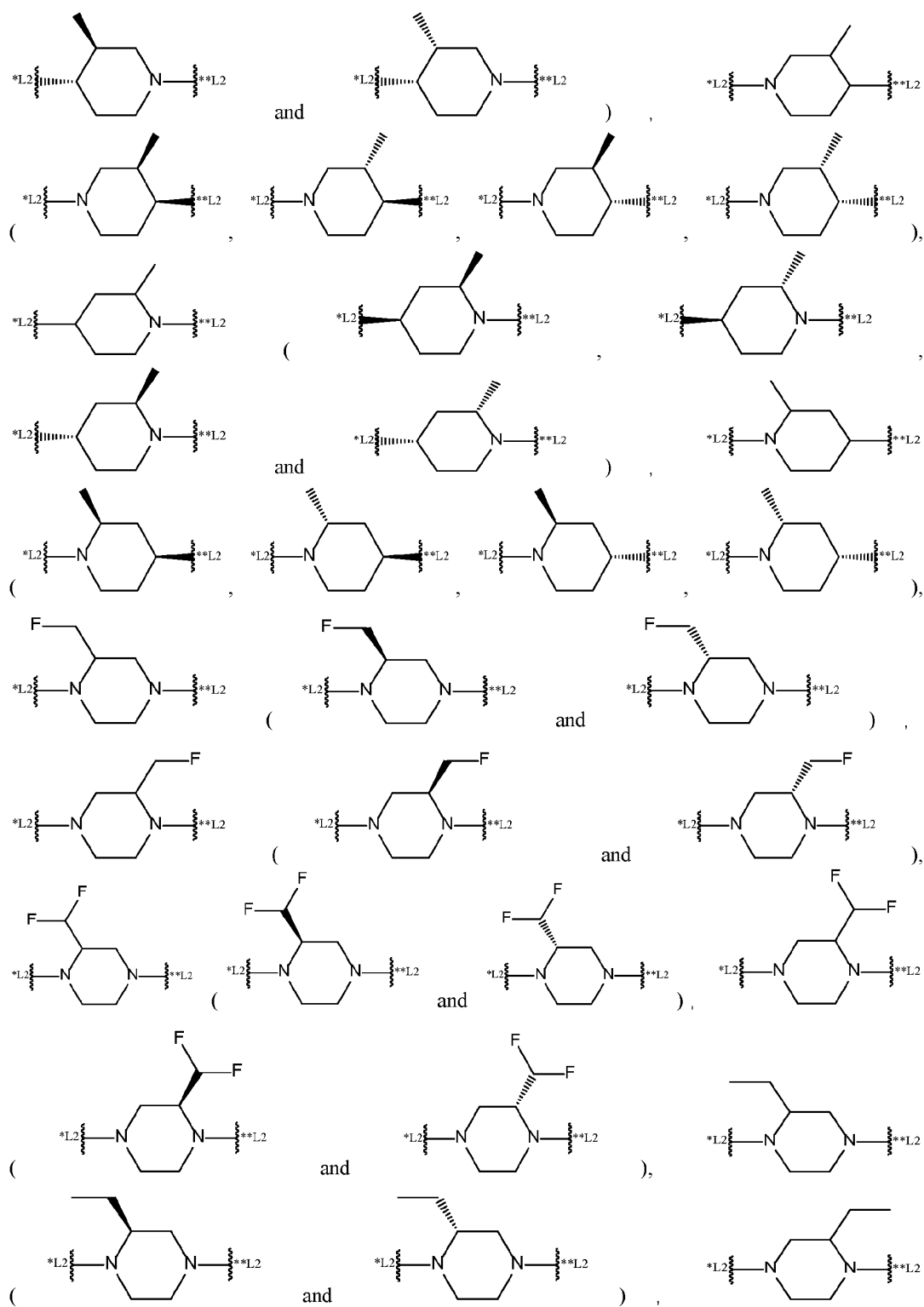


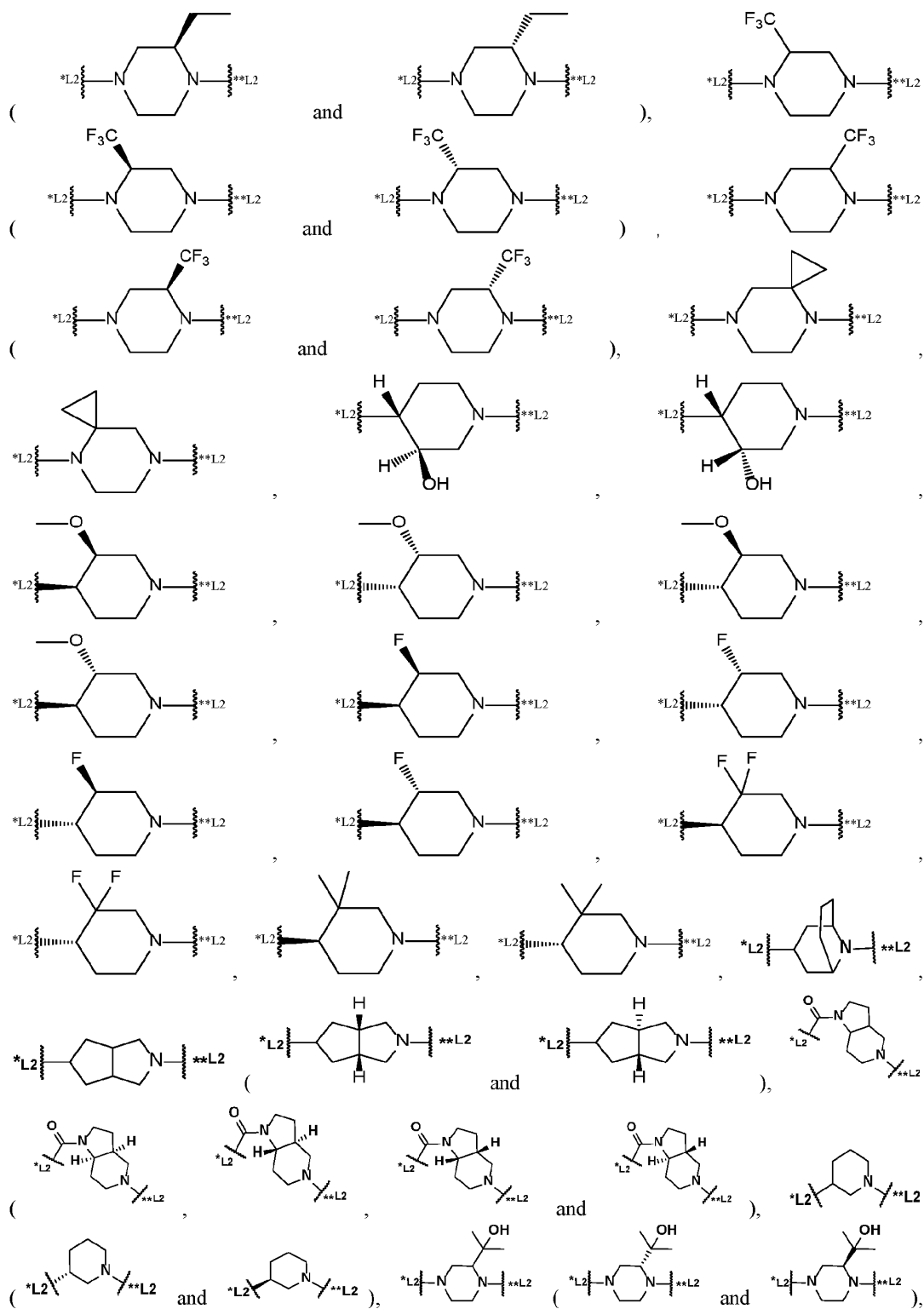



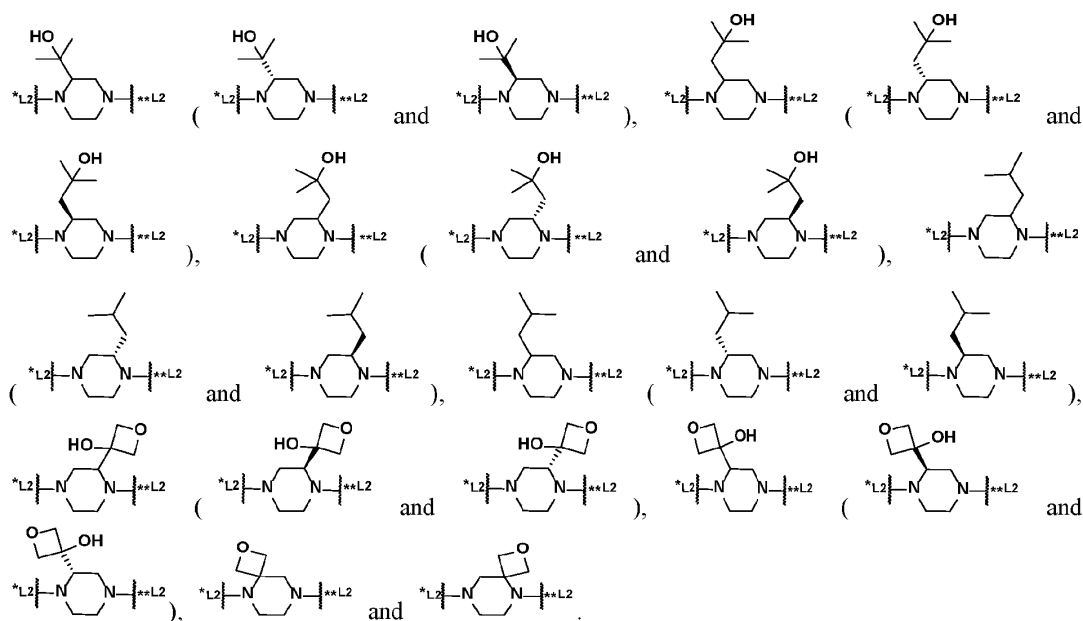









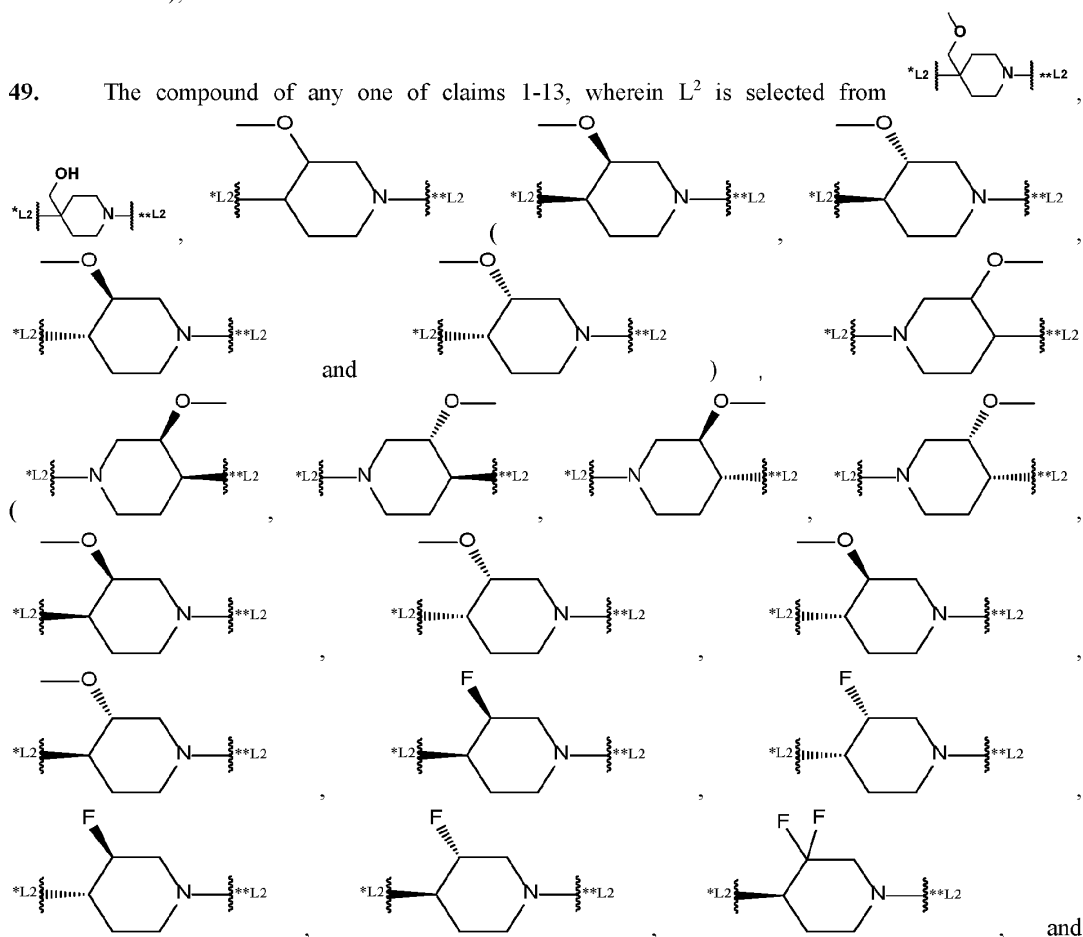


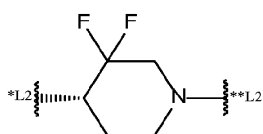




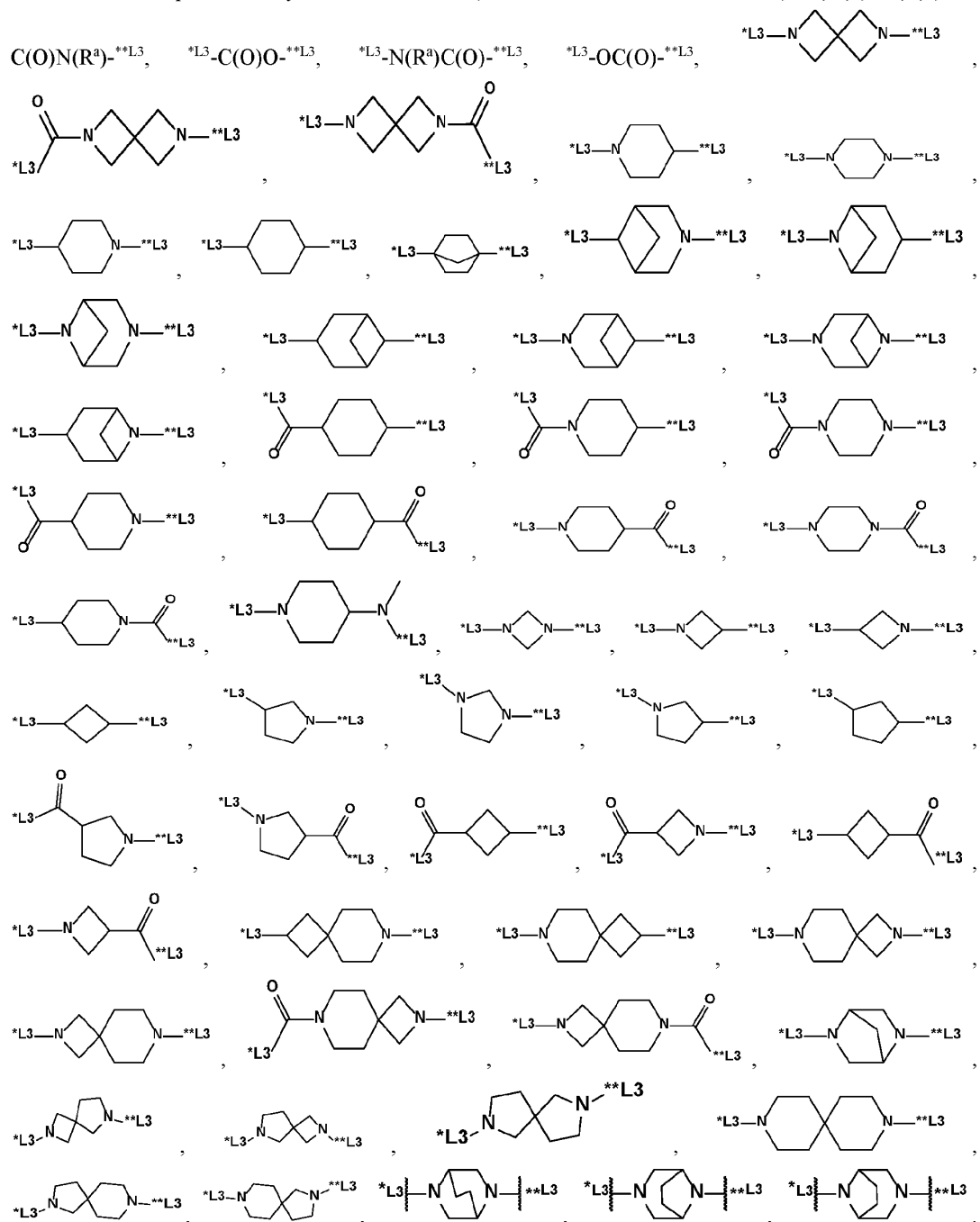


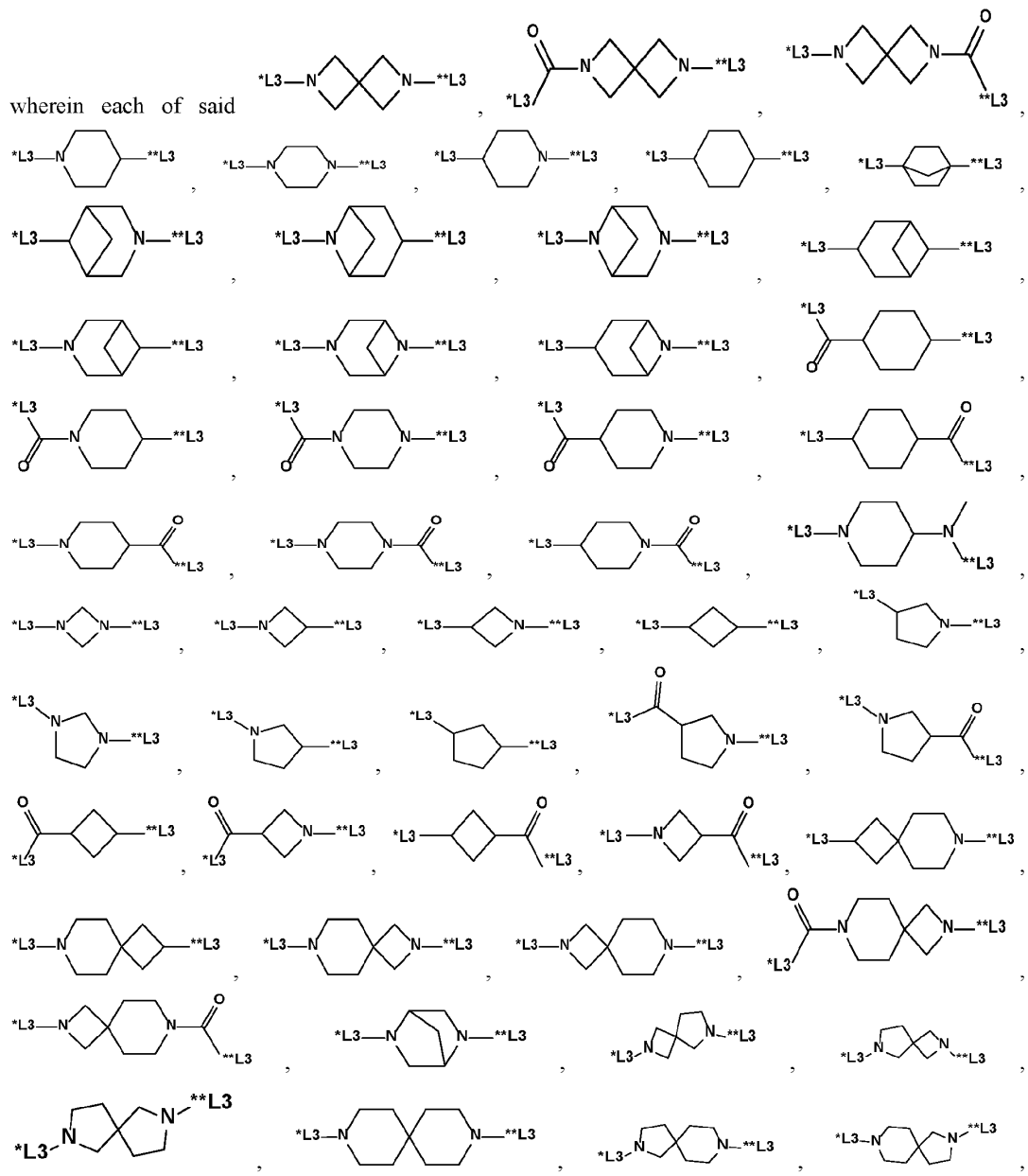
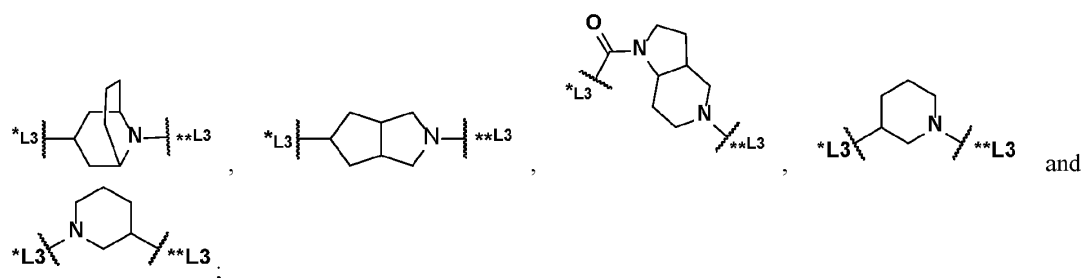
49. The compound of any one of claims 1-13, wherein L² is selected from

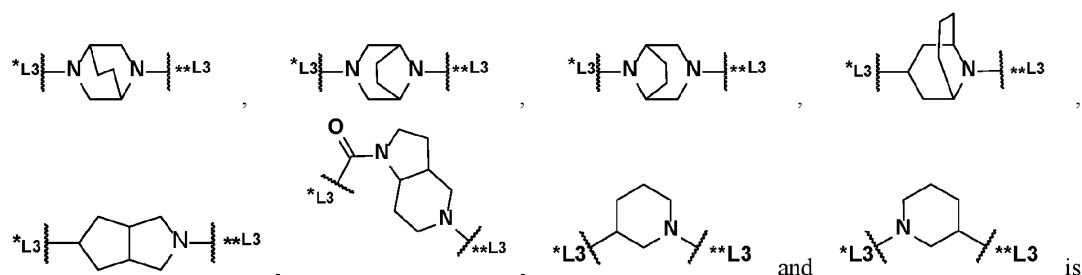




50. The compound of any one of claims 1-12, wherein L^3 is selected from -O-, -N(R^a)-, -C(O)-, *L³-





optionally substituted with at least one R^{L3c} ;

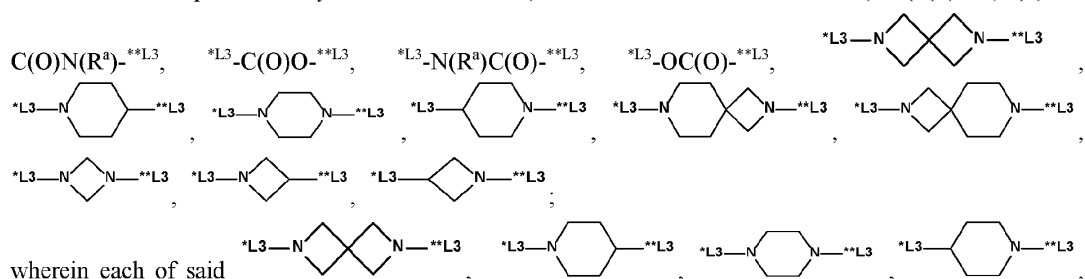
each of said R^{13c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{14a},

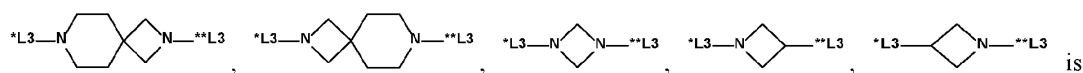
R^{1ca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; or

two R^{13c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent selected from F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl;

R^a is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent selected from halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

51. The compound of any one of claims 1-12, wherein L³ is selected from -O-, -C(O)-, -N(R^a)-, *L³-



optionally substituted with at least one R^{L3c} ;

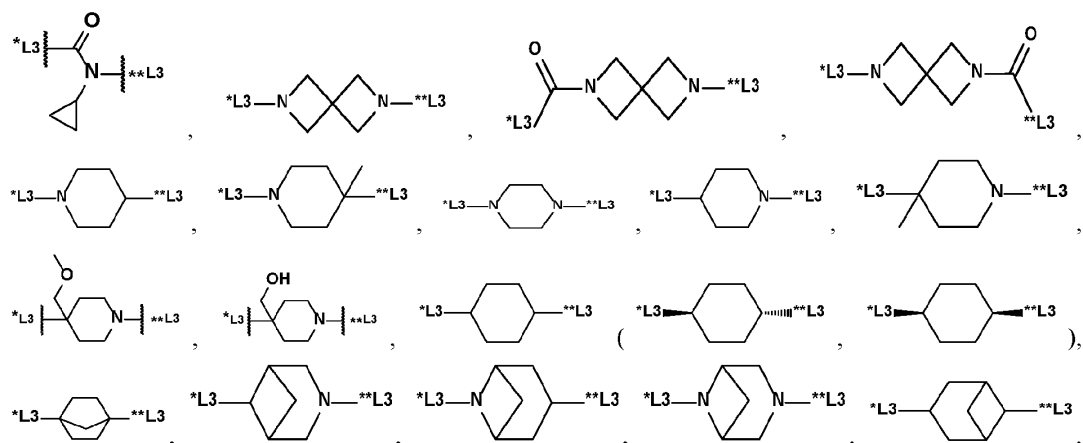
each of said R^{13c} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one R^{14a},

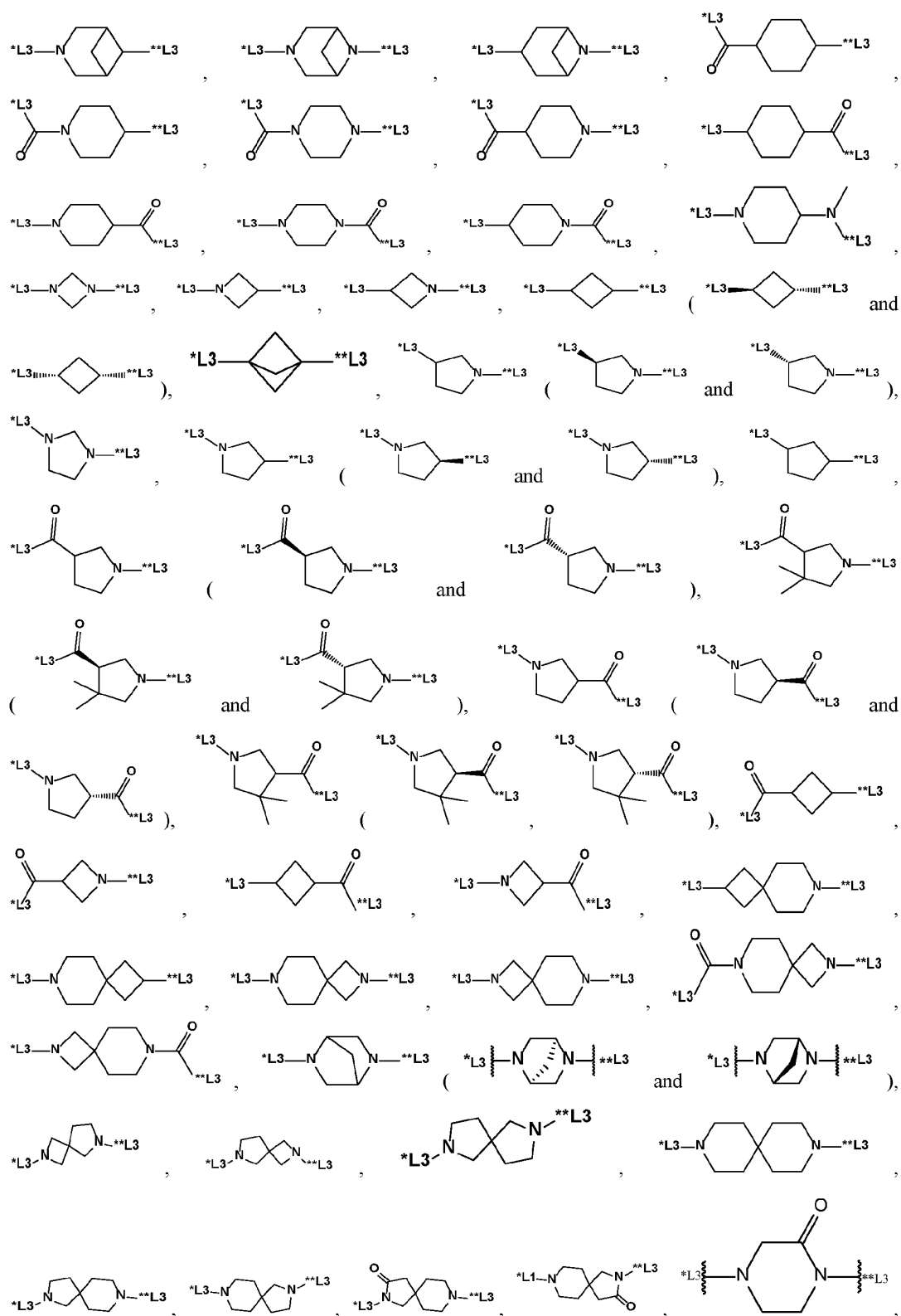
R^{1ca} is independently oxo (=O), F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroarvl; or

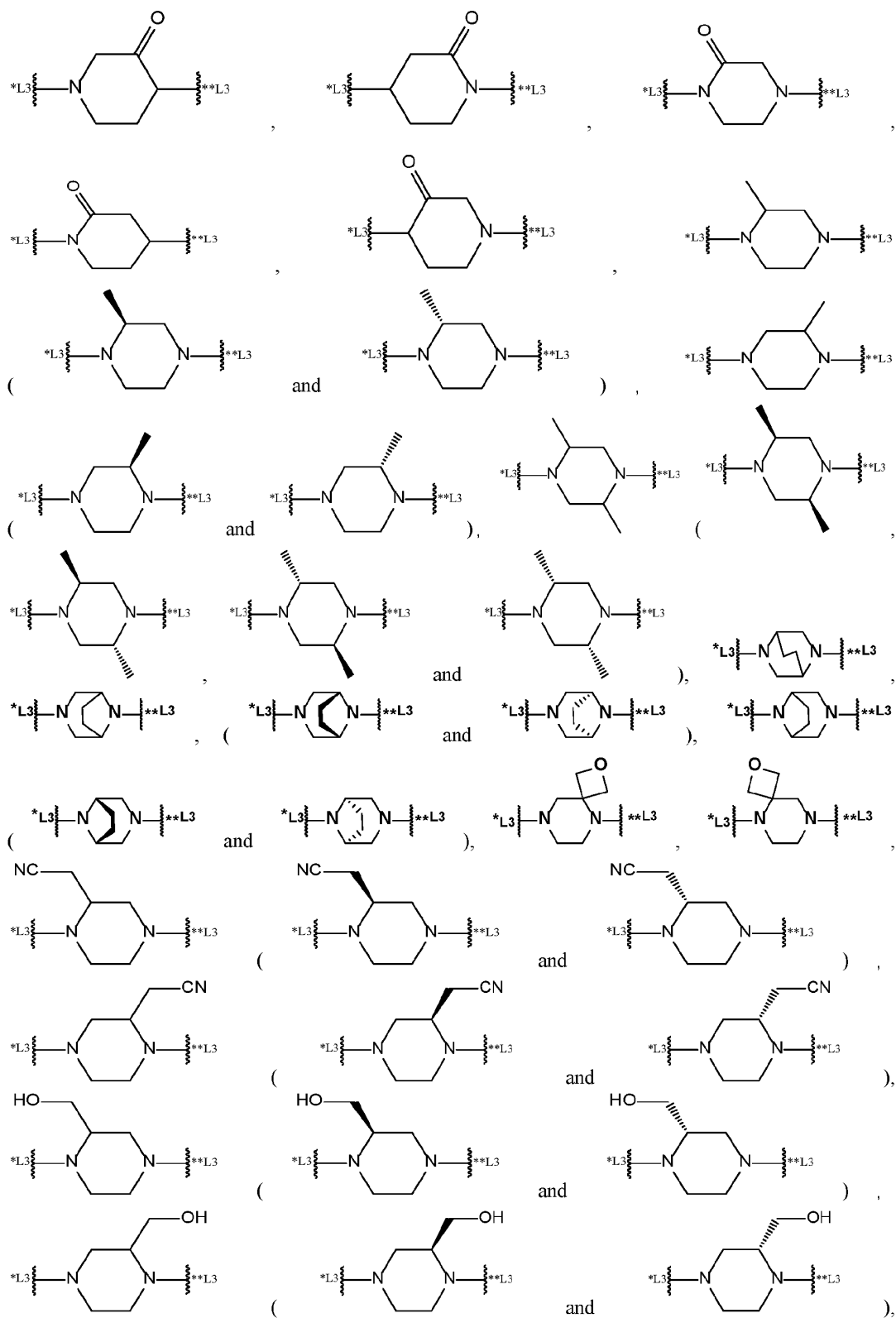
two R^{13c} together with the carbon atoms to which they are attached, form a 3-, 4-, 5-, 6-, 7- or 8-membered ring, said ring comprising 0, 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; wherein said ring is optionally substituted with at least one substituent selected from F, Cl, Br, I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl;

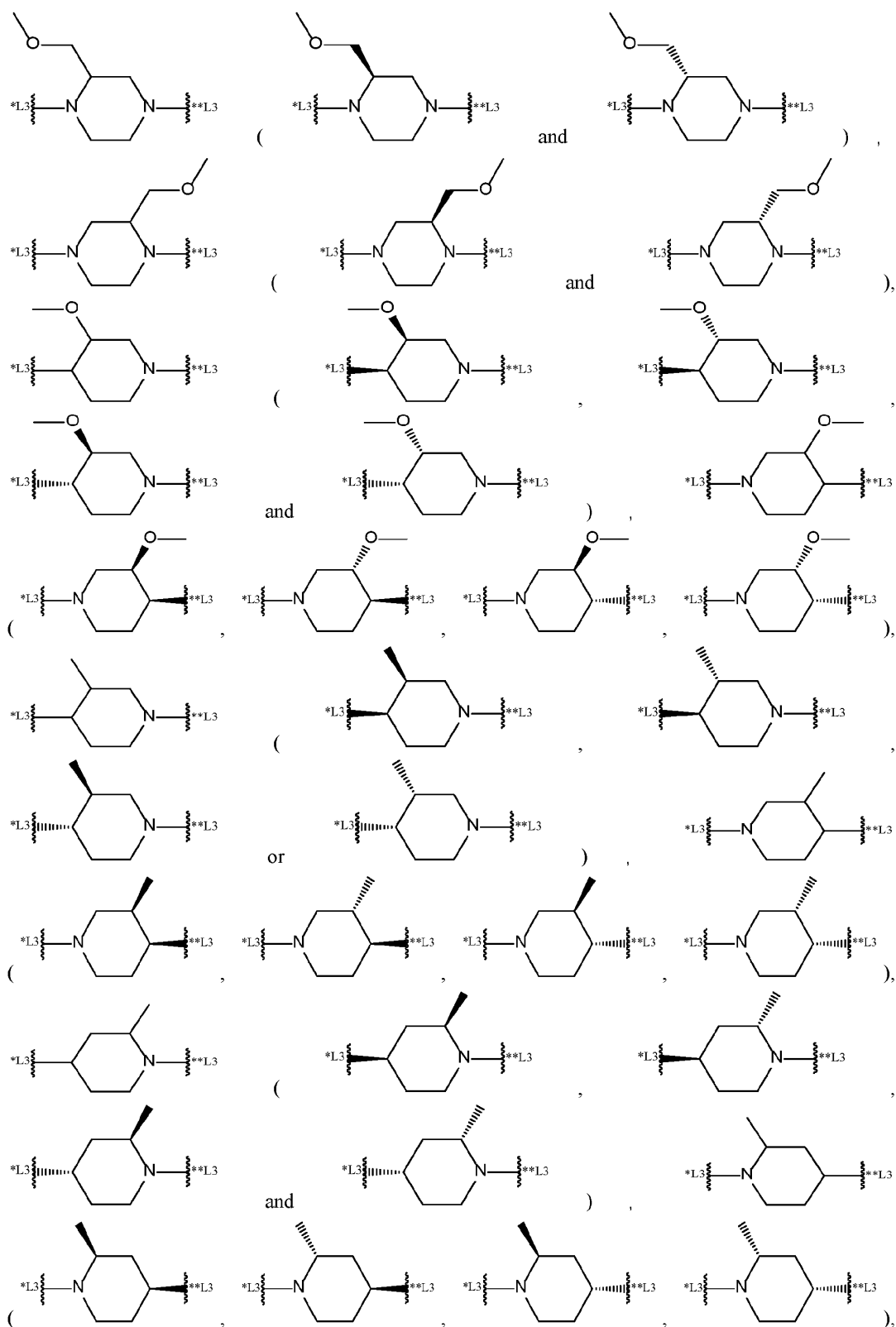
R³ is selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl is optionally substituted with at least one substituent selected from halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

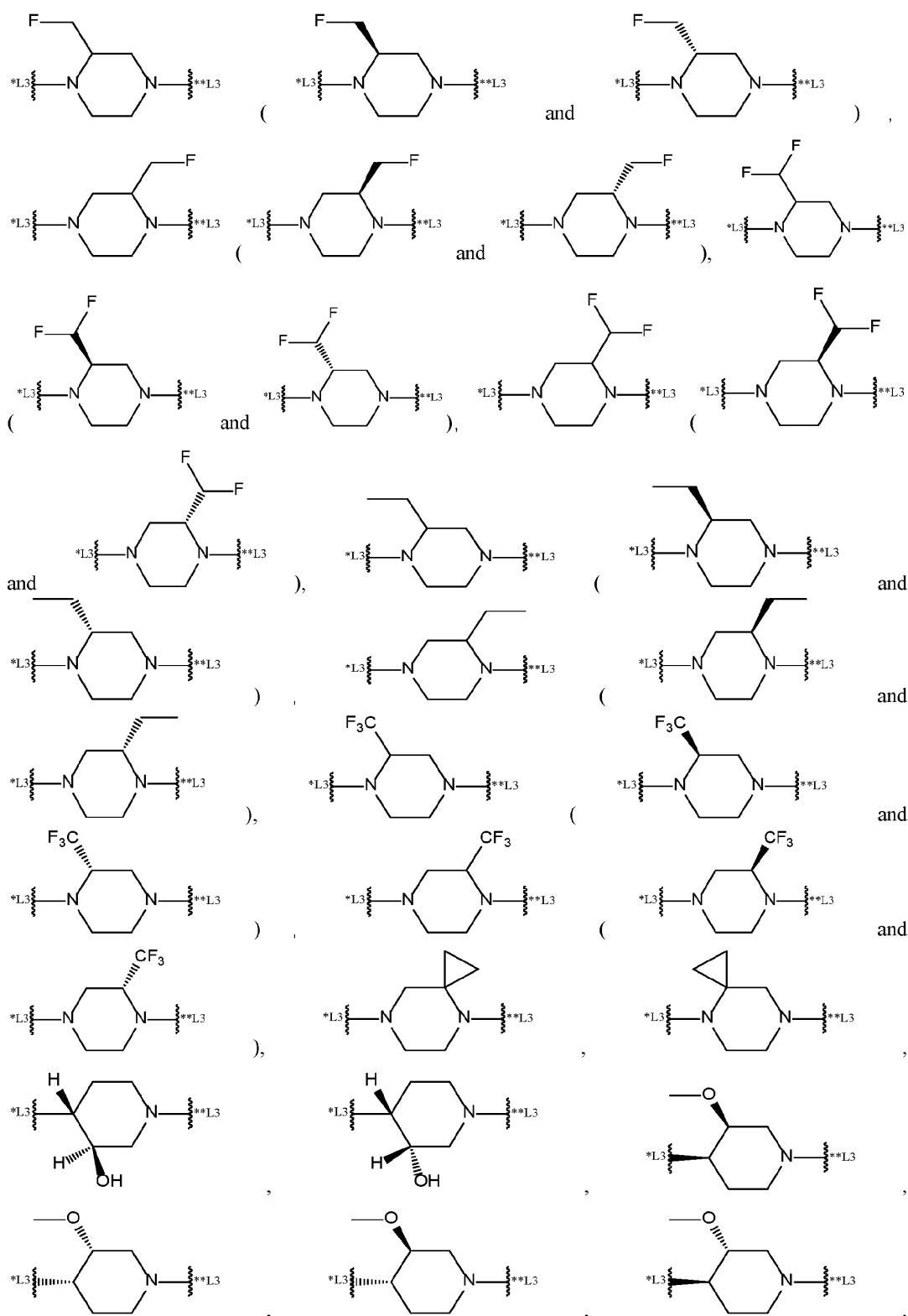
52. The compound of any one of claims 1-12, wherein L^3 is selected from -O-, -N(CH₃)-, -C(O)-, -NH-, ^{*L3}-C(O)N(CH₃)-^{**L3}, ^{*L3}-C(O)NH-^{**L3}, ^{*L3}-C(O)O-^{**L3}, ^{*L3}-C(O)N(C₂H₅)-^{**L3}, ^{*L3}-C(O)N(C₃H₇)-^{**L3}, ^{*L3}-N(CH₃)C(O)-^{**L3}, ^{*L3}-NHC(O)-^{**L3}, ^{*L3}-OC(O)-^{**L3}, ^{*L3}-N(C₂H₅)C(O)-^{**L3}, ^{*L3}-N(C₃H₇)C(O)-^{**L3}.

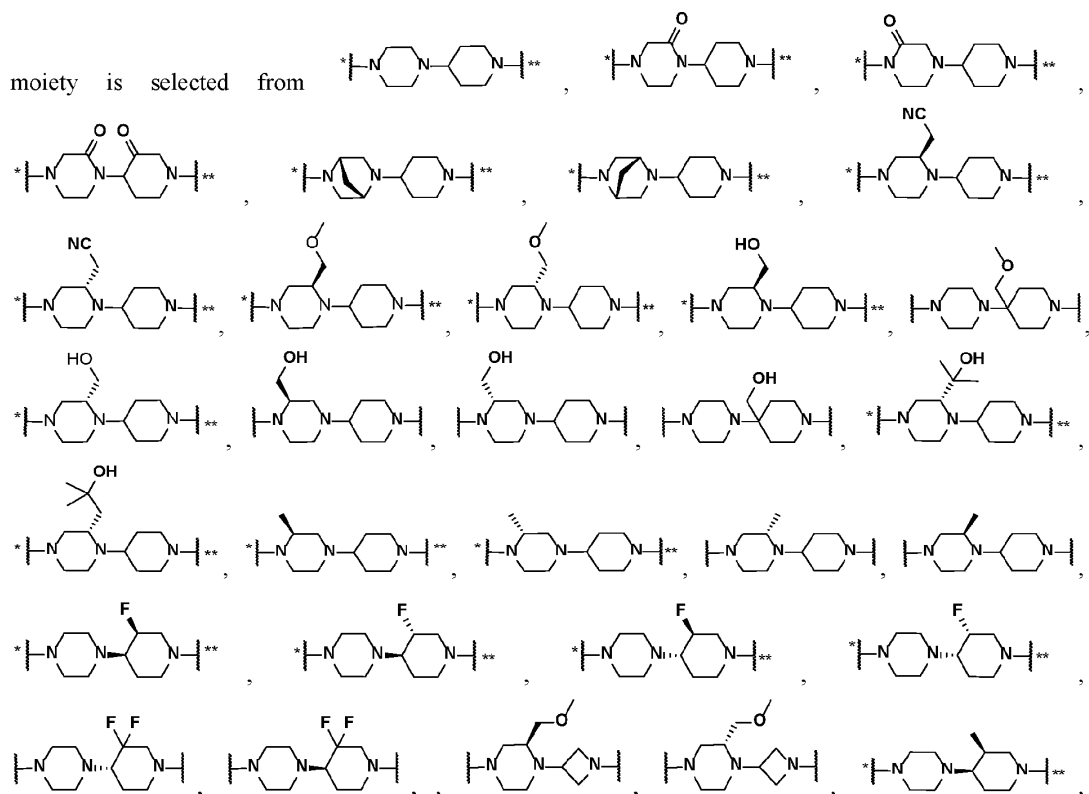
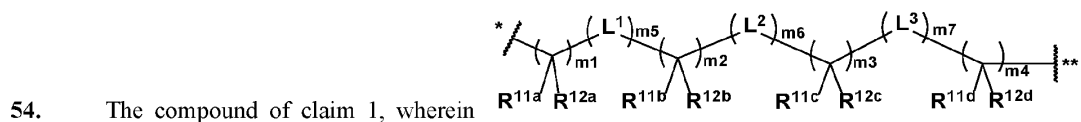
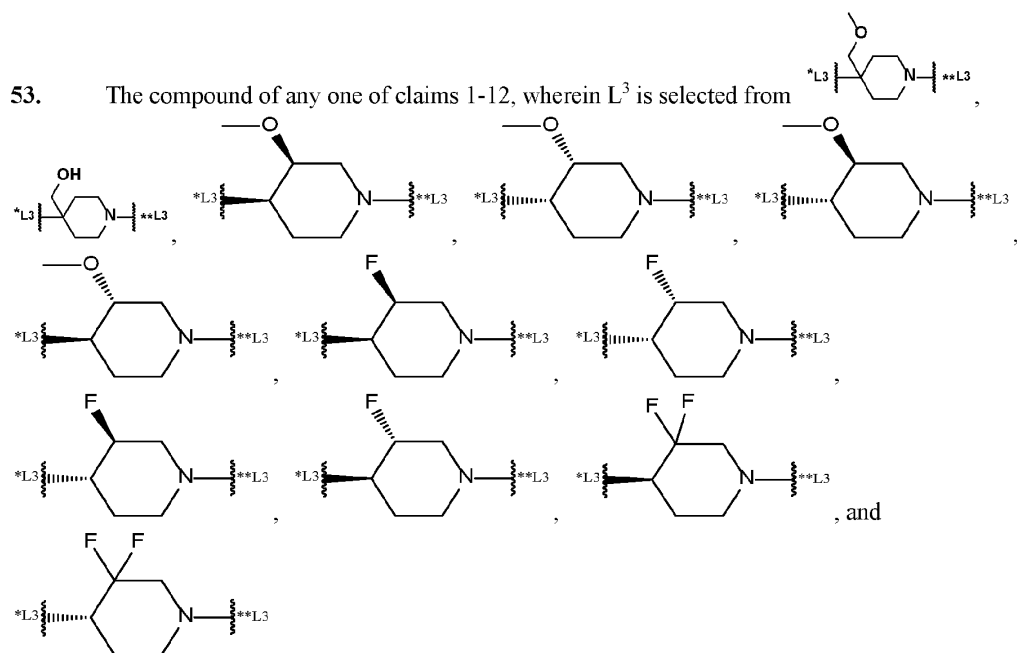


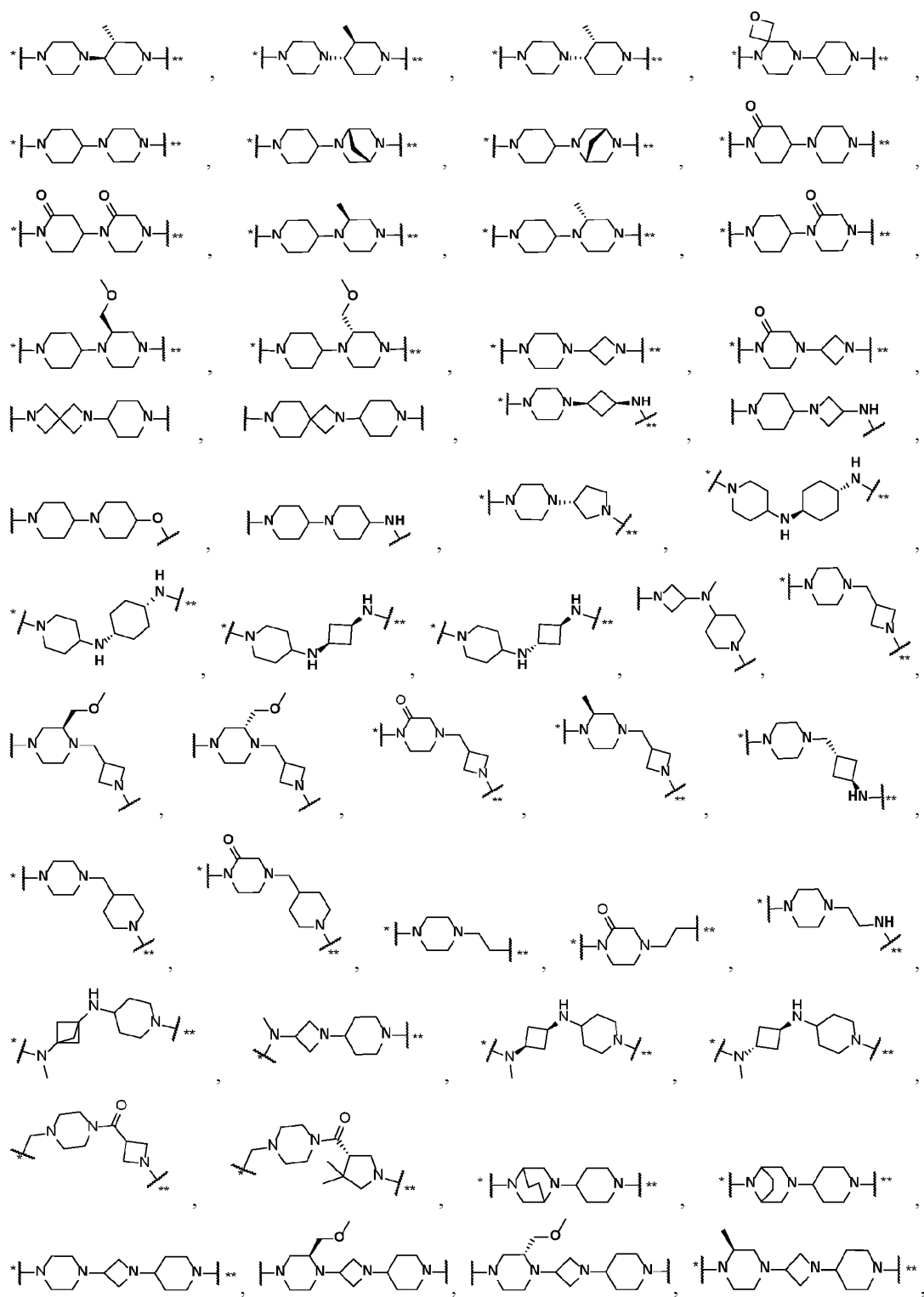


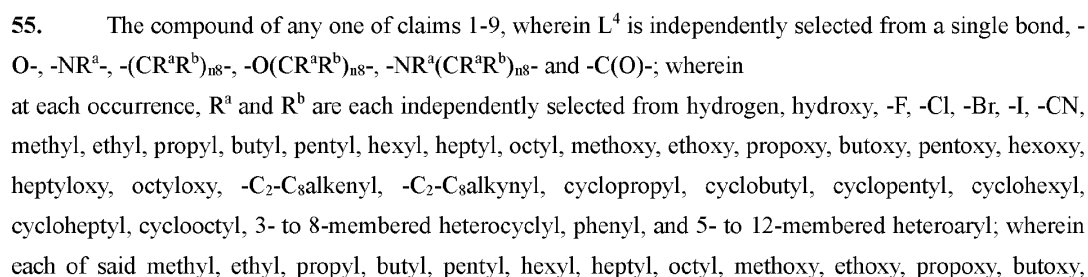












pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

56. The compound of any one of claims 1-9, wherein L⁴ is independently selected from a single bond.

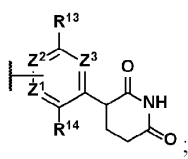
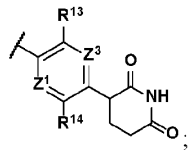
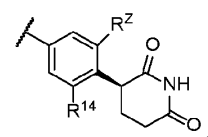
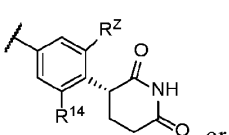
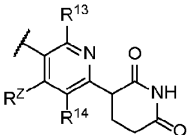
57. The compound of any one of claims 1-9, wherein X⁷ is independently selected from -CR^a, and N; R^a is independently selected from hydrogen, hydroxy, -F, -Cl, -Br, -I, -CN, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

58. The compound of any one of claims 1-9, wherein X⁷ is independently selected from -CH, -C(CH₃), or N; preferably X⁷ is independently selected from -CH.

59. The compound of any one of claims 1-9, wherein X⁸ is independently selected from -NR^a-, -O-, -S- and -CR^aR^b-;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, -F, -Cl, -Br, -I, -CN, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent selected from halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, -C₂-C₈alkenyl, -C₂-C₈alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl.

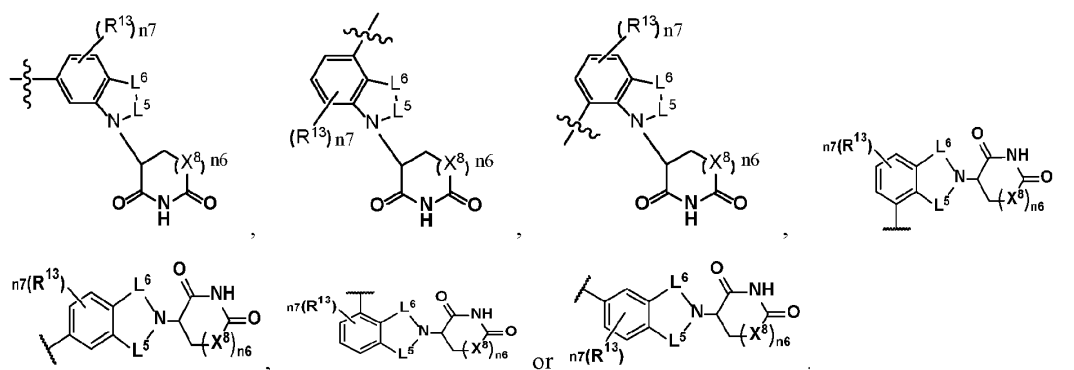
60. The compound of any one of claims 1-9, wherein X⁸ is independently selected from -NH- and -CH₂-; preferably X⁸ is independently selected from -CH₂-.

61. The compound of any one of claims 1-8, wherein  is selected from .
62. The compound of any one of claims 1-8, wherein  is selected from .
63. The compound of any one of claims 1-8, wherein  is selected from ,
-  or .
64. The compound of any one of claims 1-8, wherein at most one of Z^1 , Z^2 and Z^3 is N;
65. The compound of any one of claims 1-8, wherein Z^1 , Z^2 and Z^3 are each independently CR^z , or Z^1 is N, Z^2 and Z^3 are each independently CR^z .
66. The compound of any one of claims 1-8, wherein R^z , at each occurrence, is independently selected from hydrogen, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, $-NR^{Za}R^{Zb}$, $-OR^{Za}$, $-SR^{Za}$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, and CN; wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and 3- to 8-membered heterocyclyl is optionally substituted with at least one R^{Zc} ;
- R^{Za} and R^{Zb} are each independently selected from hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl; wherein each of said hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent R^{Zd} ;
- R^{Zc} and R^{Zd} are each independently -F, -Cl, -Br, -I, hydroxy, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 12-membered heteroaryl.
67. The compound of any one of claims 1-8, wherein R^z is selected from H, $-CH_3$, $-C_2H_5$, F, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OC_2H_5$, $-C_3H_7$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_3$, $-SCF_3$, $-CF_3$ and $-CH(OH)CH_3$.
68. The compound of any one of claims 1-8, wherein R^{13} and R^{14} are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy,

butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{C}_{2-8}\text{alkenyl}$, $-\text{C}_{2-8}\text{alkynyl}$, 3- to 8-membered heterocyclyl, $-\text{C}_6\text{-C}_{12}\text{aryl}$, 5- to 12-membered heteroaryl, $-\text{CN}$, $-\text{SO}_2\text{R}^{13a}$, $-\text{SO}_2\text{NR}^{13a}\text{R}^{13b}$, $-\text{COR}^{13a}$, $-\text{CO}_2\text{R}^{13a}$, $-\text{CONR}^{13a}\text{R}^{13b}$, $-\text{NR}^{13a}\text{R}^{13b}$, $-\text{NR}^{13a}\text{COR}^{13b}$, $-\text{NR}^{13a}\text{CO}_2\text{R}^{13b}$, and $-\text{NR}^{13a}\text{SO}_2\text{R}^{13b}$, wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{C}_{2-8}\text{alkenyl}$, $-\text{C}_{2-8}\text{alkynyl}$, 3- to 8-membered heterocyclyl, $-\text{C}_6\text{-C}_{12}\text{aryl}$, and 5- to 12-membered heteroaryl is optionally substituted with F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{C}_{2-8}\text{alkenyl}$, $-\text{C}_{2-8}\text{alkynyl}$, 3- to 8-membered heterocyclyl, $-\text{C}_6\text{-C}_{12}\text{aryl}$, 5- to 12-membered heteroaryl, oxo, $-\text{CN}$, $-\text{OR}^{13c}$, $-\text{SO}_2\text{R}^{13c}$, $-\text{SO}_2\text{NR}^{13c}\text{R}^{13d}$, $-\text{COR}^{13c}$, $-\text{CO}_2\text{R}^{13c}$, $-\text{CONR}^{13c}\text{R}^{13d}$, $-\text{NR}^{13c}\text{R}^{13d}$, $-\text{NR}^{13c}\text{COR}^{13d}$, $-\text{NR}^{13c}\text{CO}_2\text{R}^{13d}$, or $-\text{NR}^{13c}\text{SO}_2\text{R}^{13d}$, R^{13a} , R^{13b} , R^{13c} and R^{13d} are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{C}_{2-8}\text{alkenyl}$, $-\text{C}_{2-8}\text{alkynyl}$, 3- to 8-membered heterocyclyl, $-\text{C}_6\text{-C}_{12}\text{aryl}$, or 5- to 12-membered heteroaryl.

69. The compound of any one of claims 1-8, wherein R^{13} and R^{14} are each independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-\text{CN}$, $-\text{CHF}_2$, $-\text{CHF}_3$, $-\text{CF}_3$, $-\text{OCH}_2\text{F}$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_3$, $-\text{SCF}_3$, or phenyl.

70. The compound of any one of claims 1-8, wherein  is



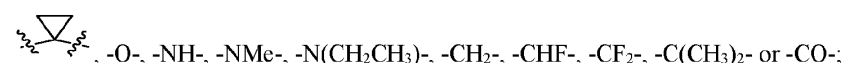
71. The compound of any one of claims 1-8, wherein L^5 and L^6 are each independently selected from a single bond, $-\text{O}-$, $-\text{NR}^a$, $-(\text{CR}^a\text{R}^b)_{n8}$, $-\text{O}(\text{CR}^a\text{R}^b)_{n8}$, $-\text{NR}^a(\text{CR}^a\text{R}^b)_{n8}$ and $-\text{C}(\text{O})-$;

X^8 is $-\text{CR}^a\text{R}^b-$;

at each occurrence, R^a and R^b are each independently selected from hydrogen, hydroxy, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-\text{C}_2\text{-C}_8\text{alkenyl}$, $-\text{C}_2\text{-C}_8\text{alkynyl}$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl, and 5- to 12-membered heteroaryl; wherein each of said methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl and 5- to 12-membered heteroaryl is optionally substituted with at least one substituent halogen, hydroxy, -F, -Cl, -Br, -I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 3- to 8-membered heterocyclyl, phenyl or 5- to 12-membered heteroaryl.

72. The compound of any one of claims 1-8, wherein L^5 and L^6 are each independently a single bond,



X^8 is CH₂; and

n_6 is 0 or 1.

73. The compound of any one of claims 1-8, wherein R^{13} is independently selected from hydrogen, F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, 5- to 12-membered heteroaryl, -CN, $-SO_2R^{13a}$, $-SO_2NR^{13a}R^{13b}$, $-COR^{13a}$, $-CO_2R^{13a}$, $-CONR^{13a}R^{13b}$, $-NR^{13a}R^{13b}$, $-NR^{13a}COR^{13b}$, $-NR^{13a}CO_2R^{13b}$, and $-NR^{13a}SO_2R^{13b}$, wherein each of methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, and 5- to 12-membered heteroaryl is optionally substituted with F, Cl, Br, I, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptyloxy, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, 5- to 12-membered heteroaryl, oxo, -CN, $-OR^{13c}$, $-SO_2R^{13c}$, $-SO_2NR^{13c}R^{13d}$, $-COR^{13c}$, $-CO_2R^{13c}$, $-CONR^{13c}R^{13d}$, $-NR^{13c}R^{13d}$, $-NR^{13c}COR^{13d}$, $-NR^{13c}CO_2R^{13d}$, or $-NR^{13c}SO_2R^{13d}$,

at each occurrence, R^{13a} , R^{13b} , R^{13c} and R^{13d} are each independently hydrogen, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, octyloxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, $-C_2-C_8$ alkenyl, $-C_2-C_8$ alkynyl, 3- to 8-membered heterocyclyl, $-C_6-C_{12}$ aryl, or 5- to 12-membered heteroaryl.

74. The compound of any one of claims 1-8, wherein R^{13} is independently selected from hydrogen, F, Cl, Br, I, CN, $-C_1-C_8$ alkyl, or $-C_1-C_8$ alkoxy.

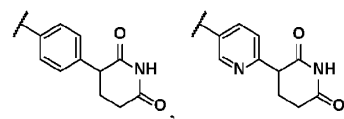
75. The compound of any one of claims 1-8, wherein R^{13} is independently selected from hydrogen, F, Cl, Br, I, CN, -Me, -Et, $-C_3H_7$, $-C_4H_9$, -OMe, -OEt, $-OC_3H_7$ or $-OC_4H_9$;

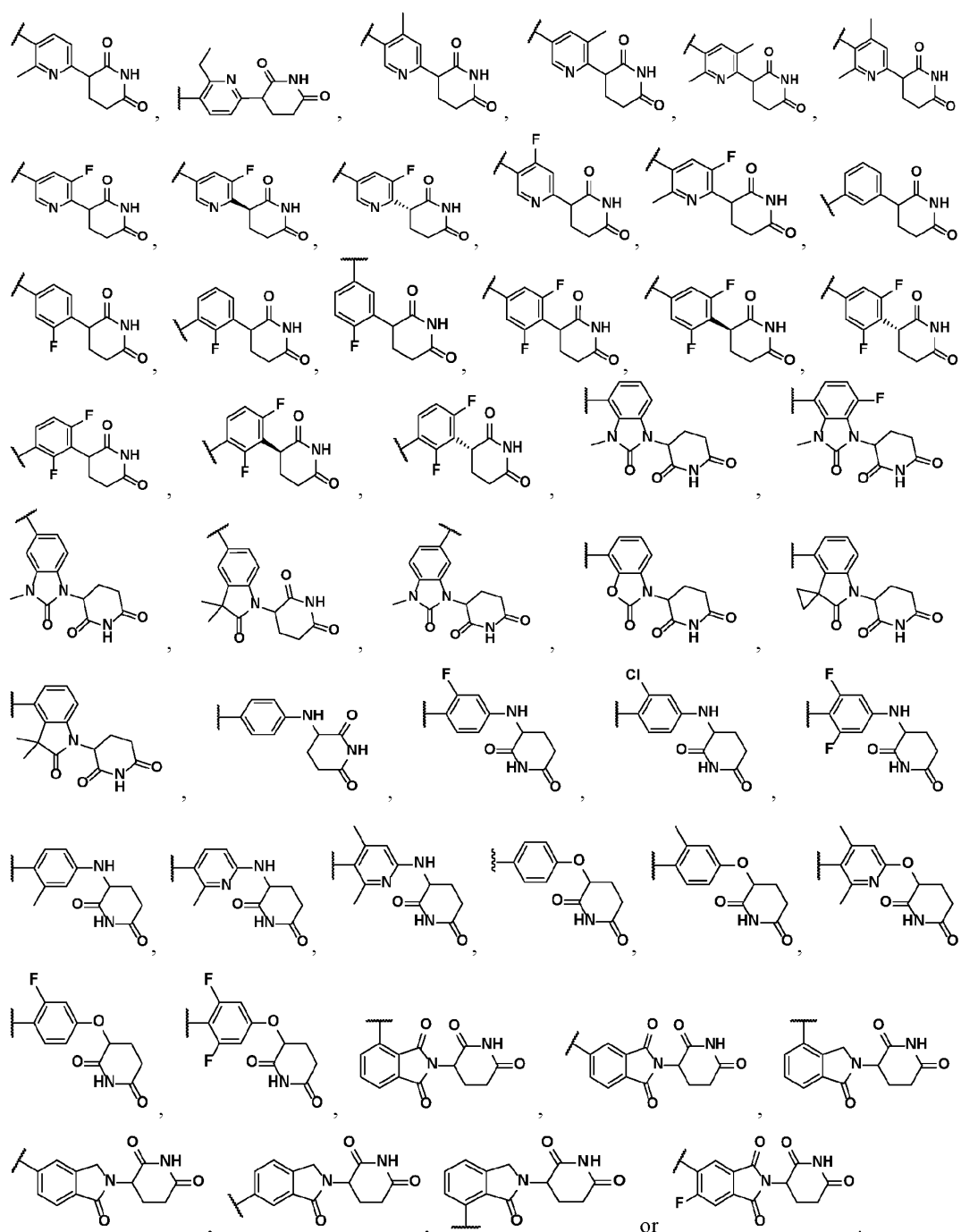
n_7 is 0, 1 or 2.

76. The compound of any one of claims 1-8, wherein

Degron

is





Compound 41, Compound 42, Compound 43, Compound 44, Compound 45, Compound 46, Compound 47, Compound 49, Compound 50, Compound 51, Compound 54, Compound 55, Compound 56, Compound 57, Compound 58, Compound 59, Compound 60, Compound 61, Compound 63, Compound 64, Compound 65, Compound 69, Compound 70, Compound 71, Compound 72, Compound 73, Compound 74, Compound 75, Compound 76, Compound 77, Compound 78, Compound 79, Compound 80, Compound 82, Compound 83, Compound 84, Compound 85, Compound 86, Compound 87, Compound 88, Compound 89, Compound 90, Compound 91, Compound 92, Compound 93, Compound 94, Compound 95, Compound 96, Compound 98, Compound 99, Compound 100, Compound 101, Compound 102, Compound 103, Compound 104, Compound 105, Compound 106, Compound 108, Compound 111, Compound 112, Compound 113, Compound 114, Compound 115, Compound 116, Compound 117, Compound 118, Compound 119, Compound 120, Compound 121, Compound 122, Compound 123, Compound 124, Compound 125, Compound 126, Compound 127, Compound 129, Compound 131, Compound 132, Compound 133, Compound 134, Compound 135, Compound 136, Compound 137, Compound 138, Compound 140, Compound 141, Compound 142, Compound 143, Compound 144, Compound 147, Compound 150, Compound 151, Compound 152, Compound 153, Compound 156, Compound 157, Compound 158, Compound 159, Compound 160, Compound 161, Compound 162, Compound 163, Compound 164, Compound 165, Compound 167, Compound 168, Compound 169, Compound 172, Compound 173, Compound 175, Compound 176, Compound 179, Compound 182, Compound 183, Compound 184, Compound 186, Compound 188, Compound 189, Compound 190, Compound 191, Compound 192, Compound 193, Compound 195, Compound 196, Compound 197, Compound 198, Compound 199, Compound 200, Compound 202, Compound 205, Compound 206, Compound 207, Compound 208, Compound 210, Compound 211, Compound 213 and Compound 214.

78. A pharmaceutical composition comprising a compound of any one of Claims 1-77 or a pharmaceutically acceptable salt, stereoisomer, tautomer, or a prodrug thereof, together with a pharmaceutically acceptable excipient.

79. A method of treating a disease that can be affected by EGFR modulation, comprises administering a subject in need thereof an effective amount of a compound of any one of Claims 1-77 or a pharmaceutically acceptable salt, stereoisomer, tautomer or prodrug thereof.

80. The method of Claim 79, wherein the disease is selected from cancer, preferably selected from pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, and non-small cell lung cancer.

81. Use of a compound of any one of Claims 1-77 or a pharmaceutically acceptable salt, stereoisomer, tautomer or prodrug thereof in the preparation of a medicament for treating a disease that can be affected by EGFR modulation.

82. The use of Claim 81, wherein the disease is cancer, preferably selected from pancreatic cancer, breast cancer, glioblastoma multiforme, head and neck cancer, and non-small cell lung cancer.