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(71) Applicant: **ACHILLION PHARMACEUTICALS, INC.** [US/US]; 300 George Street, New Haven, CT 065 11 (US).

(72) Inventors: **WILES, Jason, Allan;** 116 Blinnshed Road, Madison, CT 06443 (US). **PHADKE, Avinash, S.;** 5 1 Gilbert Lane, Branford, CT 06405 (US). **DESHPANDE, Milind;** 44 Field Brook Road, Madison, CT 06443 (US). **AGARWAL, Atul;** 75 Nicholas Court, Hamden, CT 0651 8 (US). **CHEN, Dawei;** 1117 Durham Road, Guilford, CT 06437 (US). **GADHACHANDA, Venkat, Rao;** 39 Ives Street, Unit 104, Hamden, CT 065 18 (US). **HASHIMOTO, Akihiro;** 47 Laurel Street, Branford, CT 06405 (US). **PAIS, Godwin;** 370 West Todd Street, Hamden, CT 065 18 (US). **WANG, Qiuping;** 79 Carriage Drive, Bethany, CT 06524 (US). **WANG, Xiangzhu;** 147 Foxbridge Village Road, Branford, CT 06405 (US). **GREENLEE, William;** c/o MedChem Discovery Consulting, LLC, 115 Herrick Avenue, Teaneck, NJ 07666 (US).

(74) Agents: **BELLOWS, Brent, R.** et al; Knowles Intellectual Property Strategies, LLC, 400 Perimeter Center Terrace NE, Suite 200, Atlanta, GA 30346 (US).

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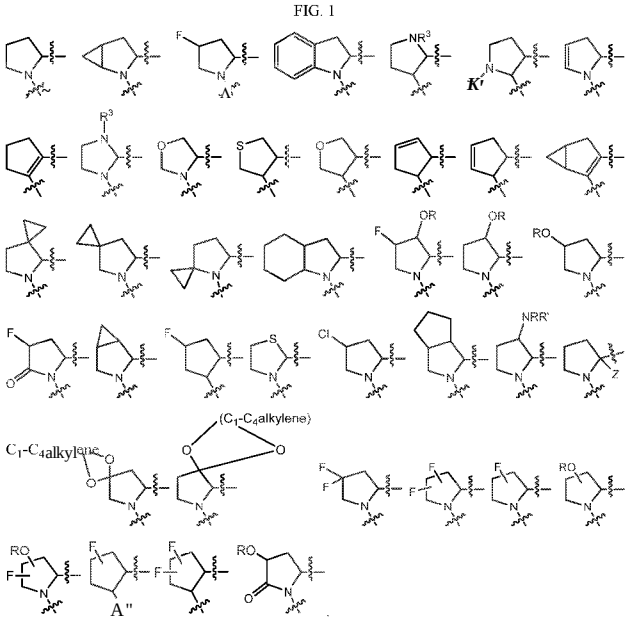
[Continued on nextpage]

(54) Title: ARYL, HETEROARYL, AND HETEROCYCLIC COMPOUNDS FOR TREATMENT OF IMMUNE AND INFLAMMATORY DISORDERS

FIG. 1



(57) Abstract: Compounds, methods of use, and processes for making inhibitors of complement Factor D are provided comprising Formula I, I" and Γ" or a pharmaceutically acceptable salt or composition thereof. The inhibitors described herein target Factor D and inhibit or regulate the complement cascade. The inhibitors of Factor D described herein reduces the excessive activation of complement.

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ARYL, HETEROARYL, AND HETEROCYCLIC COMPOUNDS FOR TREATMENT OF IMMUNE AND INFLAMMATORY DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional U.S. Application No. 62/210,116, filed August 26, 2015. The entirety of this application is hereby incorporated by reference for all purposes.

BACKGROUND

[0002] An immune disorder occurs when the immune system is not performing in a normal manner. Inflammation is a protective response that involves immune cells, the immune system generally, blood vessels, and molecular mediators. A wide variety of medical disorders are caused by detrimental immune or inflammatory responses, or the inability of a cell to respond to a normal immune or inflammatory process.

[0003] The complement system is a part of the innate immune system which does not adapt to changes over the course of the host's life, but is recruited and used by the adaptive immune system. For example, it assists, or complements, the ability of antibodies and phagocytic cells to clear pathogens. This sophisticated regulatory pathway allows rapid reaction to pathogenic organisms while protecting host cells from destruction. Over thirty proteins and protein fragments make up the complement system. These proteins act through opsonization (enhancing phaogytosis of antigens), chemotaxis (attracting macrophages and neutrophils), cell lysis (rupturing membranes of foreign cells) and agglutination (clustering and binding of pathogens together).

[0004] The complement system has three pathways: classical, alternative and lectin. Complement Factor D plays an early and central role in activation of the alternative pathway of the complement cascade. Activation of the alternative complement pathway is initiated by spontaneous hydrolysis of a thioester bond within C3 to produce **C3(H_20),** which associates with Factor B to form the C3(H_20)B complex. Complement Factor D acts to cleave Factor B within the C3(H_20)B complex to form Ba and Bb. The Bb fragment remains associated with **C3(H_20)** to form the alternative pathway C3 convertase C3(H_20)Bb. Additionally, C3b generated by any of the C3 convertases also associates with Factor B to form C3bB, which Factor D cleaves to generate the later stage alternative pathway C3 convertase C3bBb. This latter form of the alternative pathway C3 convertase may provide important downstream amplification within all three of the

defined complement pathways, leading ultimately to the recruitment and assembly of additional factors in the complement cascade pathway, including the cleavage of C5 to C5a and C5b. C5b acts in the assembly of factors C6, C7, C8, and C9 into the membrane attack complex, which can destroy pathogenic cells by lysing the cell.

[0005] The dysfunction of or excessive activation of complement has been linked to certain autoimmune, inflammatory, and neurodegenerative diseases, as well as ischemia-reperfusion injury and cancer. For example, activation of the alternative pathway of the complement cascade contributes to the production of C3a and C5a, both potent anaphylatoxins, which also have roles in a number of inflammatory disorders. Therefore, in some instances, it is desirable to decrease the response of the complement pathway, including the alternative complement pathway. Some examples of disorders mediated by the complement pathway include age-related macular degeneration (AMD), paroxysmal nocturnal hemoglobinuria (PNH), multiple sclerosis, and rheumatoid arthritis.

[0006] Age-related macular degeneration (AMD) is a leading cause of vision loss in industrialized countries. Based on a number of genetic studies, there is evidence of the link between the complement cascade and macular degeneration. Individuals with mutations in the gene encoding complement Factor H have a fivefold increased risk of macular degeneration and individuals with mutations in other complement factor genes also have an increased risk of AMD. Individuals with mutant Factor H also have increased levels of C-reactive protein, a marker of inflammation. Without adequate functioning Factor H, the alternative pathway of the complement cascade is overly activated leading to cellular damage. Inhibition of the alternative pathway is thus desired.

[0007] Paroxysmal nocturnal hemoglobinuria (PNH) is a non-malignant, hematological disorder characterized by the expansion of hematopoietic stem cells and progeny mature blood cells which are deficient in some surface proteins. PNH erythrocytes are not capable of modulating their surface complement activation, which leads to the typical hallmark of PNH - the chronic activation of complement mediated intravascular anemia. Currently, only one product, the anti-C5 monoclonal antibody eculizumab, has been approved in the U.S. for treatment of PNH. However, many of the patients treated with eculizumab remain anemic, and many patients continue to require blood transfusions. In addition, treatment with eculizumab requires life-long

intravenous injections. Thus, there is an unmet need to develop novel inhibitors of the complement pathway.

[0008] Other disorders that have been linked to the complement cascade include atypical hemolytic uremic syndrome (aHUS), hemolytic uremic syndrome (HUS), abdominal aortic aneurysm, hemodialysis complications, hemolytic anemia, or hemodialysis, neuromylitis (NMO), myasthenia gravis (MG), fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure, dermatomyocitis, and amyotrophic lateral sclerosis.

[0009] Factor D is an attractive target for inhibition or regulation of the complement cascade due to its early and essential role in the alternative complement pathway, and its potential role in signal amplification within the classical and lectin complement pathways. Inhibition of Factor D effectively interrupts the pathway and attenuates the formation of the membrane attack complex.

[0010] While initial attempts have been made to develop inhibitors of Factor D, there are currently no small molecule Factor D inhibitors in clinical trials. Examples of Factor D inhibitors or prolyl compounds are described in the following disclosures.

[001 1] Biocryst Pharmaceuticals US Pat. No. 6653340 titled "Compounds useful in the complement, coagulat and kallikrein pathways and method for their preparation" describes fused bicyclic ring compounds that are potent inhibitors of Factor D. Development of the Factor D inhibitor BCX1470 was discontinued due to lack of specificity and short half-life of the compound.

[0012] Novartis PCT patent publication WO2012/093101 titled "Indole compounds or analogues thereof useful for the treatment of age-related macular degeneration" describes certain Factor D inhibitors. Additional Factor D inhibitors are described in Novartis PCT patent publications WO20 14/002051, WO2014/002052, WO2014/002053, WO2014/002054, WO2014/002057, WO20 14/002058, WO2014/002059, WO2014/005150, and WO2014/009833.

[0013] Bristol-Myers Squibb PCT patent publication WO2004/045518 titled "Open chain prolyl urea-related modulators of androgen receptor function" describes open chain prolyl urea and thiourea related compounds for the treatment of androgen receptor-associated conditions, such as age-related diseases, for example, sarcopenia.

[0014] Japan Tobacco Inc. PCT patent publication WO 1999/048492 titled "Amide derivatives and nociceptin antagonists" describes compounds with a proline-like core and aromatic substituents connected to the proline core through amide linkages useful for the treatment of pain.

[0015] Ferring B.V. and Yamanouchi Pharmaceutical Co. 1TD. PCT patent publication WO 1993/020099 titled "CCK and/or gastrin receptor ligands" describes compounds with a proline-like core and heterocyclic substituents connected to the proline core through amide linkages for the treatment of, for example, gastric disorders or pain.

[0016] Alexion Pharmaceuticals PCT patent publication WO 1995/029697 titled "Methods and compositions for the treatment of glomerulonephritis and other inflammatory diseases" discloses antibodies directed to C5 of the complement pathway for the treatment of glomerulonephritis and inflammatory conditions involving pathologic activation of the complement system. Alexion Pharmaceutical's anti-C5 antibody eculizumab (Soliris®) is currently the only complement-specific antibody on the market, and is the first and only approved treatment for paroxysmal nocturnal hemoglobinuria (PNH).

[0017] On February 25, 2015, Achillion Pharmaceuticals filed PCT Patent Application No. PCT/US20 15/0 17523 and U.S. Patent Application No. 14/63 1,090 titled "Alkyne Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/U S20 15/0 17538 and U.S. Patent Application No. 14/63 1,233 titled "Amide Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017554 and U.S. Patent Application No. 14/631,312 titled "Amino Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017583 and U.S. Patent Application No. 14/631,440 titled "Carbamate, Ester, and Ketone Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US20 15/0 17593 and U.S. Patent Application No. 14/631,625 titled "Aryl, Heteroaryl, and Heterocyclic Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017597 and U.S. Patent Application No. 14/631,683 titled "Ether Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US20 15/0 17600 and U.S. Patent Application No. 14/631,785 titled "Phosphonate Compounds for Treatment of Complement Mediated Disorders"; and PCT Patent Application No. PCT/US20 15/0 17609 and U.S. Patent Application No. 14/631,828 titled "Compounds for Treatment of Complement Mediated Disorders" and U.S. Patent Application No. 14/630,959 titled "Factor D Inhibitors Useful for Treating Infectious Disorders."

[0018] Given the wide variety of medical disorders that are caused by detrimental immune or inflammatory responses, new uses and compounds are needed for medical treatment. In one

aspect, new uses and compounds are needed to mediate the complement pathway, and for example, which act as Factor D inhibitors for treatment of disorders in a host, including a human, associated with misregulation of the complement cascade, or with undesired result of the complement cascade performing its normal function.

SUMMARY

[0019] This invention includes an active compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt or composition thereof, wherein at least one of R^{12} or R^{13} on the A group is an aryl, heteroaryl or heterocycle substituent, for example R^{32}. In one embodiment, an active compound or its salt or composition, as described herein is used to treat a medical disorder which is an inflammatory or immune condition, a disorder mediated by the complement cascade (including a dysfunctional cascade), a disorder or abnormality of a cell that adversely affects the ability of the cell to engage in or respond to normal complement activity, or an undesired complement-mediated response to a medical treatment, such as surgery or other medical procedure or a pharmaceutical or biopharmaceutical drug administration, a blood transfusion, or other allogenic tissue or fluid administration.

[0020] These compounds can be used to treat such condition in a host in need thereof, typically a human. The active compound may act as an inhibitor of the complement factor D cascade. In one embodiment, a method for the treatment of such a disorder is provided that includes the administration of an effective amount of a compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below.

[0021] In one embodiment, the disorder is associated with the alternative complement cascade pathway. In yet another embodiment, the disorder is associated with the complement classical pathway. In a further embodiment, the disorder is associated with the complement lectin pathway. Alternatively, the active compound or its salt or prodrug may act through a different mechanism of action than the complement cascade, or in particular as a complement factor D inhibitor, to treat the disorder described herein.

[0022] In one embodiment, a method for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) is provided that includes the administration of an effective amount of a compound to a host of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt

thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of wet or dry age-related macular degeneration (AMD) in a host is provided that includes the administration of an effective amount of a compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of rheumatoid arthritis in a host is provided that includes the administration of an effective amount of a compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of multiple sclerosis in a host is provided that includes the administration of an effective amount of a compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0023] In other embodiments, an active compound or its salt or prodrug as described herein can be used to treat fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, and liver failure, dermatomyocitis, or amyotrophic lateral sclerosis.

[0024] The active compound or its pharmaceutically acceptable salt, prodrug or a pharmaceutical composition thereof as disclosed herein is also useful for administration in combination or alternation with a second pharmaceutical agent for use in ameliorating or reducing a side effect of the second pharmaceutical agent. For example, in one embodiment, the active compound may be used in combination with an adoptive cell transfer therapy to reduce an inflammatory response associated with such therapy, for example, a cytokine mediated response such as cytokine response syndrome. In one embodiment, the adoptive cell transfer therapy is a chimeric antigen receptor T-Cell (CAR T) or a dendritic cell used to treat a hematologic or solid tumor, for example, a B-cell related hematologic cancer. In one embodiment, the hematologic or solid tumor is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), pancreatic cancer, glioblastoma, or a cancer that expresses CD19. In one embodiment, the associated inflammatory response is a cytokine mediated response.

[0025] Another embodiment is provided that includes the administration of an effective amount of an active compound or a pharmaceutically acceptable salt thereof, optionally in a

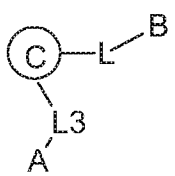
pharmaceutically acceptable carrier to a host to treat an ocular, pulmonary, gastrointestinal, or other disorder that can benefit from topical or local delivery.

[0026] Any of the compounds described herein (Formula I, Formula Γ or Formula I") can be administered to the eye in any desired form of administration, including via intravitreal, intrastromal, intracameral, sub-tenon, sub-retinal, retro-bulbar, peribulbar, suprachorodial, choroidal, subchoroidal, conjunctival, subconjunctival, episcleral, posterior juxtascleralscleral, circumcorneal, and tear duct injections, or through a mucus, mucin, or a mucosal barrier, in an immediate or controlled release fashion.

[0027] In other embodiments of the invention, an active compound provided herein can be used to treat or prevent a disorder in a host mediated by complement factor D, or by an excessive or detrimental amount of the complement-C3 amplification loop of the complement pathway. As examples, the invention includes methods to treat or prevent complement associated disorders that are induced by antibody-antigen interactions, a component of an immune or autoimmune disorder or by ischemic injury. The invention also provides methods to decrease inflammation or an immune response, including an autoimmune response, where mediated or affected by factor D.

[0028] In another embodiment, a method is provided for treating a host, typically a human, with a disorder mediated by the complement system, that includes administration of a prophylactic antibiotic or vaccine to reduce the possibility of a bacterial infection during the treatment using one of the compounds described herein. In certain embodiments, the host, typically a human, is given a prophylactic vaccine prior to, during or after treatment with one of the compounds described herein. In certain embodiments, the host, typically a human, is given a prophylactic antibiotic prior to, during or after treatment with one of the compounds described herein. In some embodiment, the infection is a meningococcal infection (e.g., septicemia and/or meningitis), an Aspergillus infection, or an infection due to an encapsulated organism, for example, Streptococcus pneumoniae or Haemophilus influenza type b (Hib), especially in children. In other embodiments, the vaccine or antibiotic is administered to the patient after contracting an infection due to, or concommitent with inhibition of the complement system.

[0029] The disclosure provides a compound of Formula I:



(I),

or a pharmaceutically acceptable composition, salt, isotopic analog, or prodrug thereof.

[0030] A is selected from Al, Al' and A2.

[0031] B is selected from Bl, Bl', B2, B3, and B4.

[0032] C is selected from CI, CI', C2, C3, and C4.

[0033] L is selected from LI, LI', L2, and L2'.

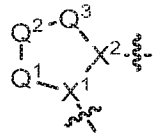
[0034] L3 is selected from L4 and L5.

[0035] At least one of A, B, C, L, or L3 is selected from A2, B3, C3, L2, L2', or L5.

[0036] Or at least one of A, B, C, L, or L3 is selected from A2, B3, C4, L2, L2', or L5

[0037] If C is CI, CI' or C2, then Formula I includes at least one of A2, B3, L2, L2' or L5.

[0038] If C is C3, then Formula I can be any of A, B, L or L3.

[0039] C1 is  .

[0040] Q^1 is N(R^1) or C^$R^{1'}$).

[0041] Q^2 is C($R^2R^{2'}$), C($R^2R^{2'}$)-C($R^2R^{2'}$), S, O, N(R^2) or C($R^2R^{2'}$)0.

[0042] Q^3 is N(R^3), S, or C($R^3R^{3'}$).

[0043] X^1 and X^2 are independently N, CH, or CZ, or X^1 and X^2 together are C=C.

[0044] Q^1, Q^2, Q^3, X^1, and X^2 are selected such that a stable compound results.

[0045] Z is F, CI, NH_2, CH_3, CH_2D, CHD_2, or CD_3.

[0046] R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently replaced at each occurrence, as appropriate, and only where a stable compound results, from hydrogen, halogen, hydroxyl, nitro, cyano, amino, Ci-C6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, Ci-C_6alkoxy, C_2-C_6alkynyl, C_2-Cealkanoyl, Ci-Cethioalkyl, hydroxyCi-Cealkyl, aminoCi-Cealkyl, -Co-C_4alkylNR^9R^{10}, -C(0)OR^9, -OC(0)R^9, -NR^9C(0)R^{10}, -C(0)NR^9R^{10}, -OC(0)NR^9R^{10}, -NR^9C(0)OR^{10}, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0047] R^9 and R^{10} are independently replaced at each occurrence from hydrogen, Ci-Cealkyl, (C_3-C7cycloalkyl)Co-C4alkyl, -Co-C4alkyl(C_3-C7cycloalkyl), and -0-Co-C_4alkyl(C_3-C7cycloalkyl).

[0048] In alternative embodiments, R^1 and $R^{1'}$ or R^3 and $R^{3'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing

1 or 2 heteroatoms independently replaced from N, O, or S; R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring; or R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered heterocyclic spiro ring; each of which spiro ring each of which ring may be unsubstituted or substituted with 1 or more substituents independently replaced from halogen (and in particular F), hydroxyl, cyano, -COOH, Ci-C4alkyl (including in particular methyl), C_2-C_4alkenyl, C2-C_4alkynyl, Ci-C_4alkoxy, C_2-C_4alkanoyl, hydroxyCi-C_4alkyl, (mono- and di-Ci-C_4alkylamino)Co-C_4alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), -0-Co-C_4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0049] In alternative embodiments, R^1 and R^2 may be taken together to form a 3-membered carbocyclic ring; R^1 and R^2 may be taken together to form a 4- to 6-membered carbocyclic or aryl ring or a 4- to 6-membered heterocyclic or heteroaryl ring containing 1 or 2 heteroatoms independently replaced from N, O, and S; or R^2 and R^3, if bound to adjacent carbon atoms, may be taken together to form a 3- to 6-membered carbocyclic or aryl ring or a 3- to 6-membered heterocyclic or heteroaryl ring; each of which ring may be unsubstituted or substituted with 1 or more substituents independently replaced from halogen (and in particular F), hydroxyl, cyano, -COOH, Ci-C_4alkyl (including in particular methyl), C_2-C_4alkenyl, C_2-C_4alkynyl, Ci-C_4alkoxy, C2-C_4alkanoyl, hydroxyCi-C_4alkyl, (mono- and di-Ci-C_4alkylamino)Co-C_4alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), -0-Co-C_4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0050] In alternative embodiments, R^1 and $R^{1'}$, R^2 and $R^{2'}$, or R^3 and $R^{3'}$ can be taken together to form a carbonyl group. In alternative embodiments, R^1 and R^2 or R^2 and R^3 can be taken together to form a carbon-carbon double bond.

[0051] Any of the structures illustrated herein, e.g., Al, Al', A2, Bl, Bl', B2, B3, B4, CI, CI', C2, C3, C4, LI, LI', L2, L2', L4 or L5 can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, of an R^{48} substituent.

[0052] Non-limiting examples of CI include the structures of Figure 1, wherein R and R' (see Figure 5) are independently replaced from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted or any other substituent group herein that provides the desired properties. In some embodiments, the ring includes one or more chiral carbon atoms. The invention includes embodiments in which the chiral carbon can be provided as an enantiomer, or mixtures of enantiomers, including a racemic mixture. Where the ring includes more than one stereocenter,

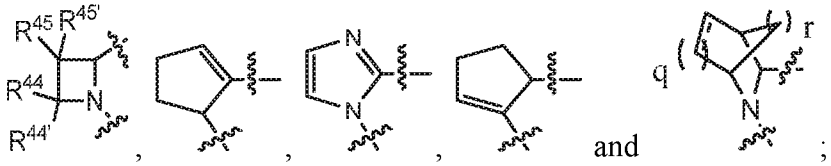
all of the enantiomers and diastereomers are included in the invention as individual species, unless stereochemistry is specified.

[0053] In one embodiment, CI is CI'.

[0054] Non-limiting examples of CI' include the structures of Figure 2.

[0055] In one embodiment, a methyl group in a structure illustrated in Figure 2 can be replaced with a different alkyl group, as defined herein. In another embodiment, the fluoro atoms in the structures illustrated in Fig. 2 can be replaced with any other halogen. As indicated above, any of the structures illustrated in Fig. 2 or otherwise can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, with an R^{48} substituent.

[0056] C2 is selected from:



wherein q is 0, 1, 2 or 3 and r is 1, 2 or 3.

[0057] R^{44}, $R^{44'}$, R^{45}, $R^{45'}$ are independently hydrogen, hydroxyl, amino, cyano, halogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; wherein each group can be optionally substituted, and such that a stable C2 results.

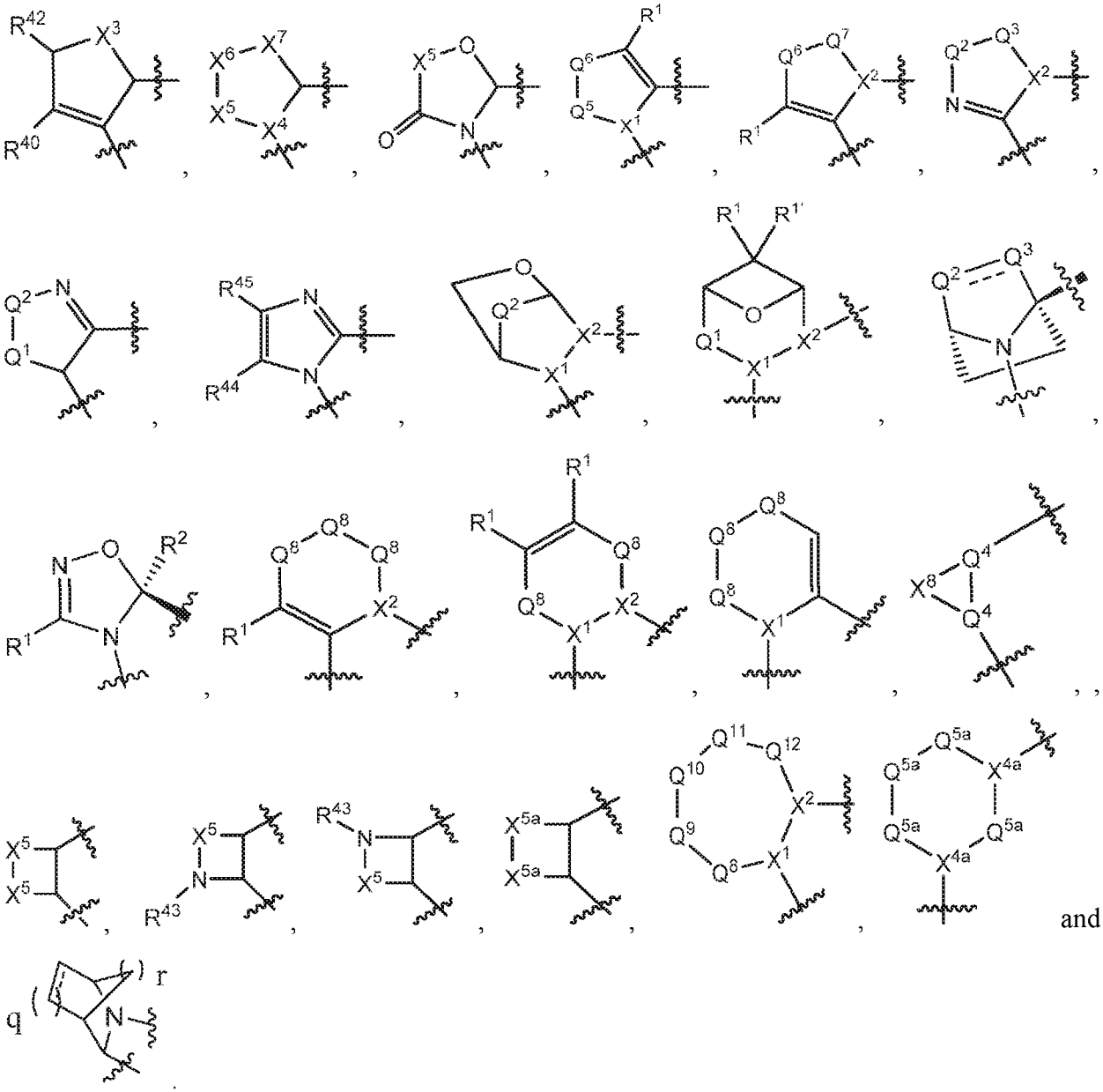
[0058] In one embodiment, R^{44} and $R^{44'}$, R^{45} and $R^{45'}$ or two R^{47} groups can be taken together to form a carbonyl group.

[0059] In an alternate embodiment, R^{44} and $R^{44'}$ or R^{45} and $R^{45'}$ or R^{46} and $R^{46'}$ can be taken together to form an optionally substituted 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently replaced from N, O, or S.

[0060] In one embodiment, R^{44} and R^{45} or $R^{44'}$ and $R^{45'}$ can be taken together to form a 4- to 6-membered carbocyclic or aryl ring or a 4- to 6-membered heterocyclic or heteroaryl ring; each of which ring may be unsubstituted or substituted with 1 or more substituents.

[0061] Non-limiting examples of C2 include the structures of Figure 3.

[0062] C3 is selected from:



and

.

[0063] X^3 is C^R $^{1'}$).

[0064] X^4 is N or CH.

[0065] X^{4a} is N, CH or CZ.

[0066] X^5 and X^6 are C^R $^{1'}$).

[0067] In alternative embodiments, X^4 and X^5 or X^5 and X^6 together are C=C.

[0068] X^7 is SO or SO_2.

[0069] X^8 is $C(R^1R^{1'})$ or $N(R^{43})$.

[0070] X^{5a} is C^R $^{1'}$) or O.

[0071] Q^4 is N or CH.

[0072] Q^5 is $N(R^{47})$ or $C(R^{46}R^{46'})$.

[0073] Q^{5a} is $C(R^{47}R^{47})$, $N(R^{47})$, O, S, SO, or $S0_2$.

[0074] Q^6 is $N(R^{47})$, $C(R^{46}R^{46'})$, S, or O.

[0075] Q^7 is $C(R^{46}R^{46'})$, S or $N(R^{47})$.

[0076] Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} are each independently $C(R^2R^{2'})$, S, SO, SO2, O, $N(R^2)$, $B(R^{50})$, $Si(R^{49})_2$, however if X^1 is N and X^2 is CH then L and B taken together cannot be anisole substituted in the 4 position.

[0077] In a typical embodiment, no more than one heteroatom is in a three or four membered C3 and no more than one, two or three heteroatoms can be in a five, six or seven membered C3. It is in general known by those of skill in the art which combinations of several heteroatoms will not form a stable ring system. For example, those of skill in the art would understand that the C3 ring system would not normally contain an -O-O-, -0-S-, -Si-Si-, -B-B-, -B-Si-, bond.

[0078] R^{40} is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted.

[0079] R^{42} is halo, hydroxy, Ci-Cealkoxy, Ci-Cehaloalkoxy, -SH, or -S(Ci-C_6alkyl).

[0080] R^{43} is hydrogen, acyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted.

[0081] R^{46} and $R^{46'}$ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted and at least one of R^{46} or $R^{46'}$ is not hydrogen.

[0082] R^{47} is hydrogen, acyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted.

[0083] R^{49} is halo, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted or two R^{49} groups can be taken together to form a double bond that can be optionally substituted.

[0084] R^{50} is hydroxy or Ci-Cealkyoxy.

[0085] In one embodiment, the bridged heterocyclic C3 compounds can be optionally substituted.

[0086] In one embodiment, X^1 and Q^8 or Q^8 and Q^9 or Q^9 and Q^{10} or Q^{10} and Q^{11} or Q^{11} and Q^{12} or Q^{12} and X^2 can form a carbon-carbon double bond.

[0087] In one embodiment, two Q^{5a} groups or a X^{4a} and a Q^{5a} group can form a carbon-carbon double bond.

[0088] All variables, including but not limited to X^1, X^2, X^3, X^4, X^5, X^{5a}, X^6, X^7, X^8, Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7, Q^8, Q^9, Q^{10}, Q^{11}, Q^{12}, R^1, R^{40}, R^{42}, R^{43}, R^{44}, $R^{44'}$, R^{45}, and $R^{45'}$ are independently replaced at each occurrence, as appropriate, and only where a stable compound results. For example, when C3 is a 7-membered ring and comprises silicon or boron, the ring will only comprise one $Si(R^{49})_2$ or $B(R^{50})$ moiety. In addition, 3, 4, 5, 6 and 7-membered rings will not comprise -O-O- or -O-S- bonds.

[0089] Non-limiting examples of C3 include the structures of Figure 4.

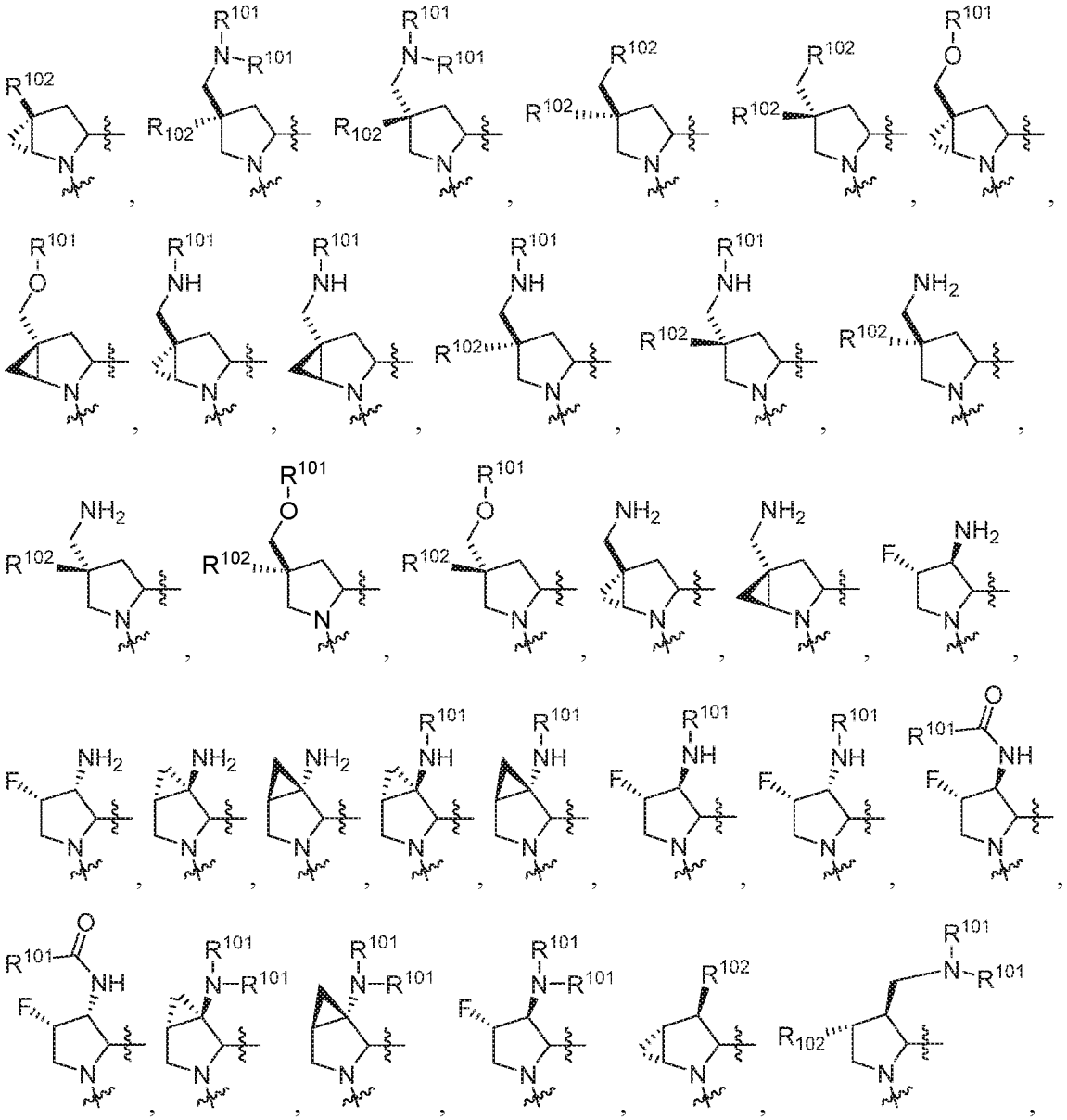
[0090] In one embodiment, the methyl groups in the structures illustrated in Fig. 4 can be replaced with a different alkyl group, as defined herein. In another embodiment, the fluoro atoms in the structures illustrated above can be replaced with another halo. In another embodiment, halo can be chloro. As indicated above, any of the structures in Fig. 4 or herein can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, with an R^{48} substituent.

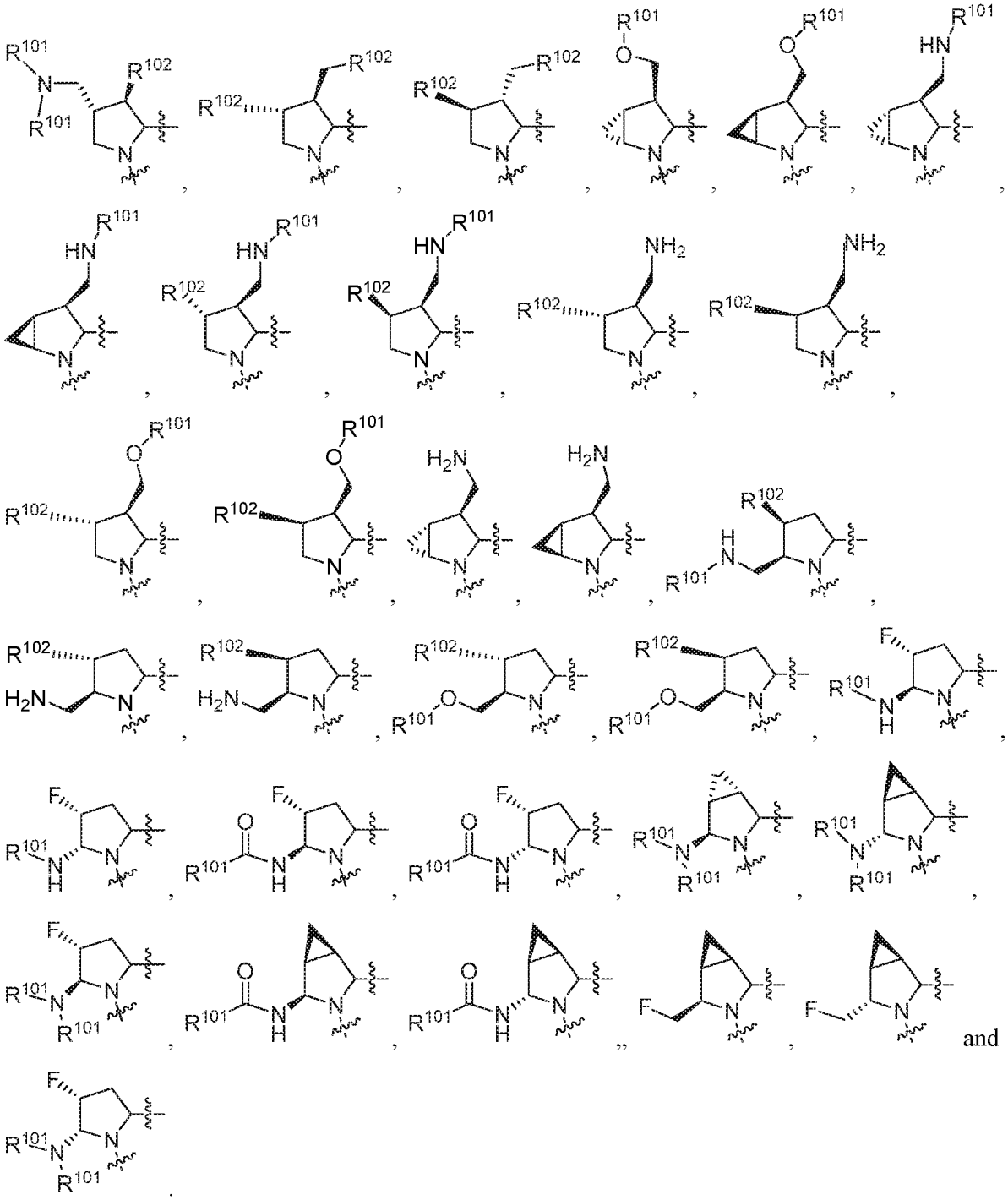
[0091] In an alternate embodiment, the central core moiety, C3, can comprise a small mimetic of a beta-turn such as a benzodiazepine, a Friedinger lactam, a 2-oxo-l,3-oxazolidine-4-caroxylate or a β-D-glucose scaffold. *See*, De Marco, R. et al., "In-peptide synthesis of di-oxazolidinone and dehydroamino acid-oxazolidinone motifs as β-turn inducers", J. Org. Biomol. Chem., 2013, 11, 4316-4326, Hirschmann, R.F. et al., The β-D-Glucose Scaffold as a β-Turn Mimetic, Accounts Chem. Res., 2009, 42, 1511-1520 and Smith, A.B, et al., Accounts of Chem. Res., 2011, 44,180-193. In another embodiment, the central core moiety, C, can comprise a reverse turn mimetic that can include, but is not limited to; a non-peptidic residue, a metal chelation based mimic, or a foldamer. *See*, Nair, R.V. et al., "Synthetic turn mimetics and hairpin nucleators: Quo Vadimus?", Chem. Comm., 2014, 50, 13874-13884. In some embodiments, the central core moiety, C, can comprise a conformationally constrained cyclic amino acid including but not limited to a (S)- or (R)-a-trifluoromethyl pyroglutamic acid derivative. *See*, Chaume, G. et al., "Concise access to enantiopure (S)- or (R)-a-trifluoromethyl pyroglutamic acids from ethyl

trifluoropyruvate-base chiral CF3-oxazolidines (Fox)", J. Fluor. Chem., 2008, 129, 1104-1 109 and Andre, C. et al., "(S)-ABOC: A Rigid Bicyclic β-Amino Acid as Turn Inducer", Org. Lett., 2012, 14, 960-963. In some embodiments, the central core moiety, C, can comprise a monomelic unit of a foldamer such as, but not limited to an oxazolidin-2-one. ***See,*** Tomasii, C , Angelicim G. and Castellucci, N., "Foldamers Based on Oxazolidin-2-ones", Eur. J. Org. Chem., 201 1, 3648-3669.

[0092] Examples of central core small mimetics of a beta-turn, beta turn inducers, reverse turn mimetics and foldamer monomers include, but are not limited to the structures of Figure 5.

[0093] C4 is selected from



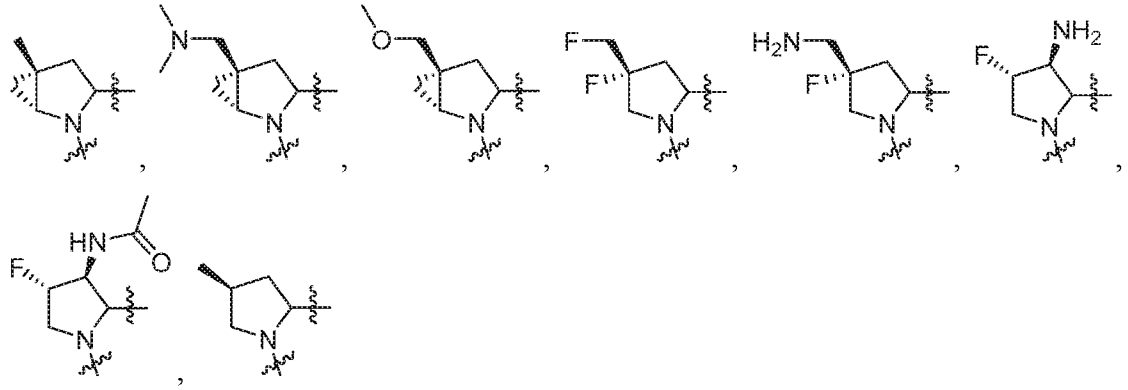


and

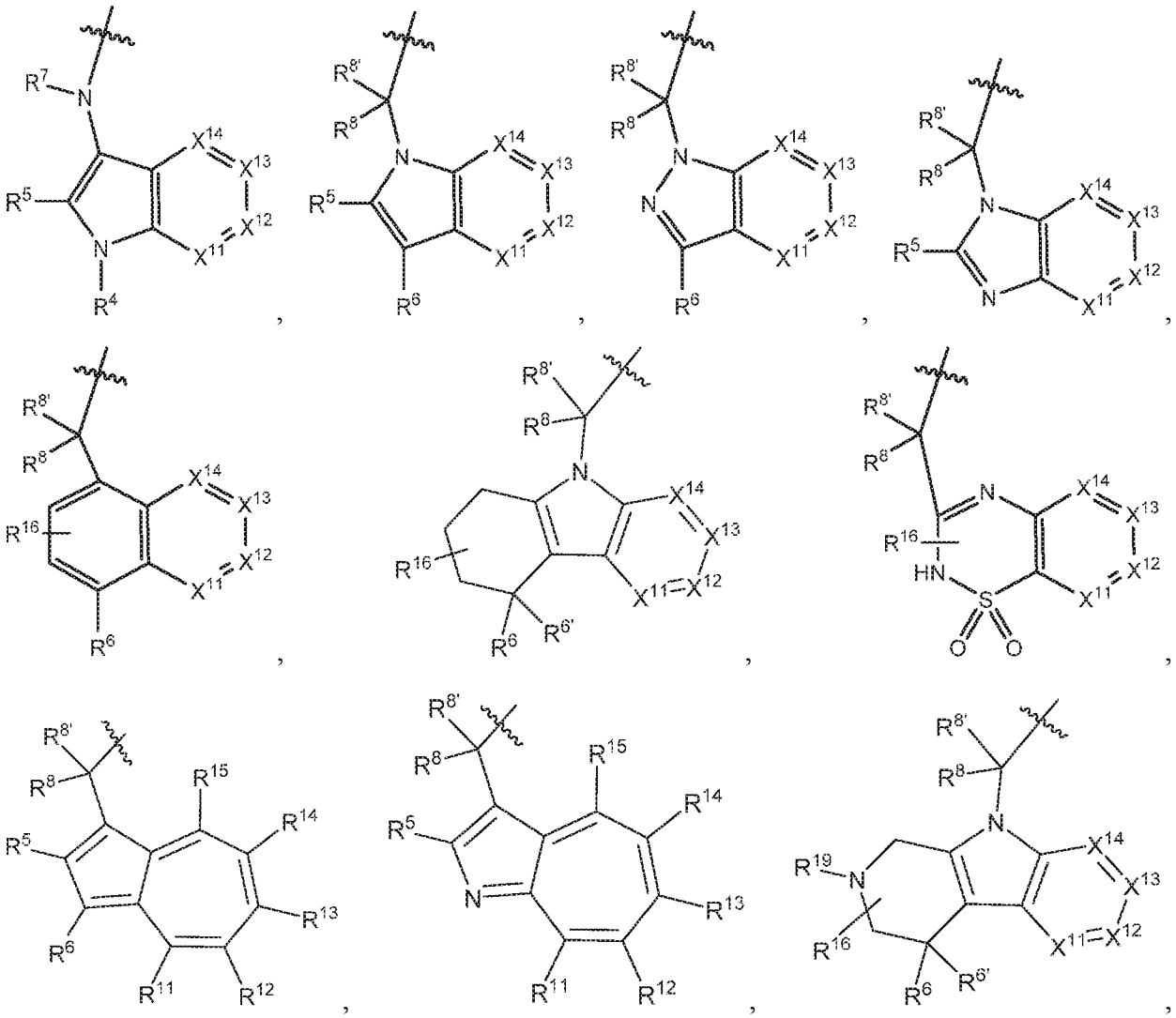
[0094] R^{101} is Ci-C_4 alkyl or C3-C7 cycloalkyl.

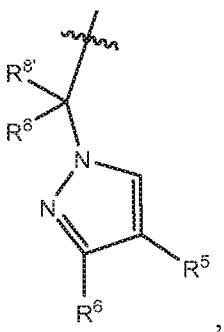
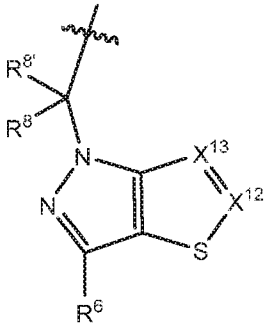
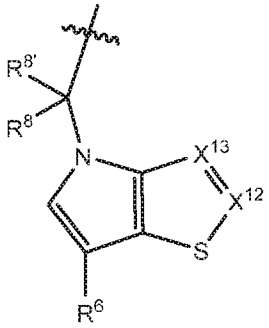
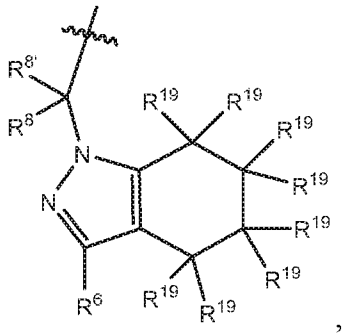
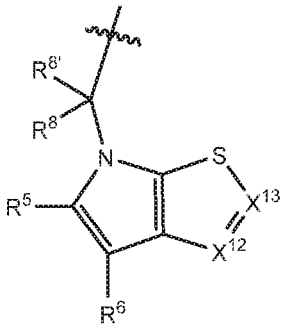
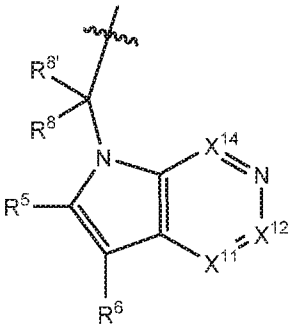
[0095] R^{102} is C1-C4 alkyl, fluorine, chlorine, or bromine.

[0096] Non-limiting examples of C4 include

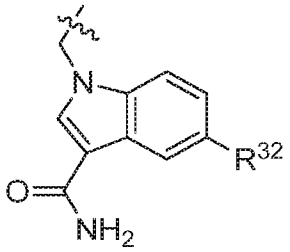
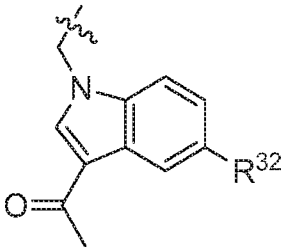
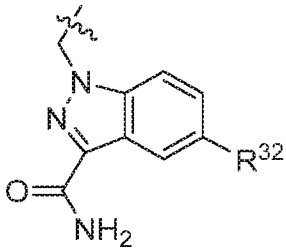


[0097] A1 is selected from:



[0098] Non-limiting examples of A1 include:

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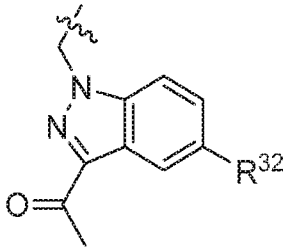
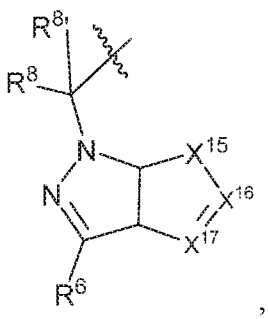


[0099] In one embodiment, A1 is A1'.

[0100] Non-limiting examples of A1' include the stmctures of Figure 6.

[0101] A2 is selected from: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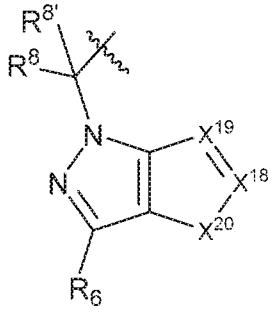
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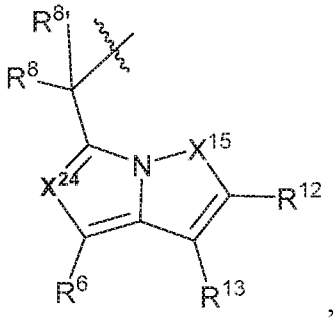
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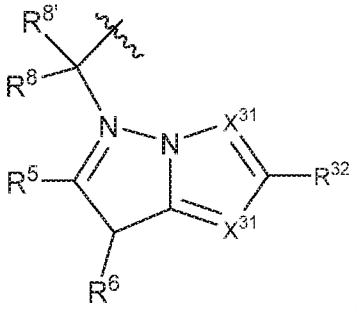
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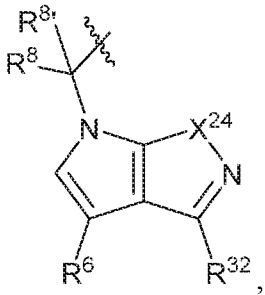
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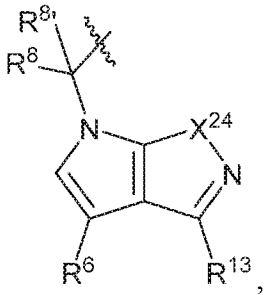
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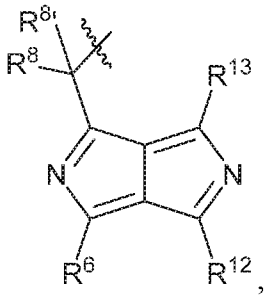
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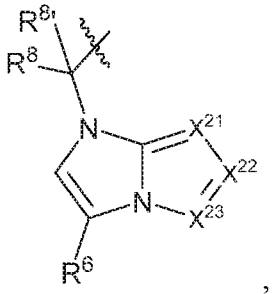
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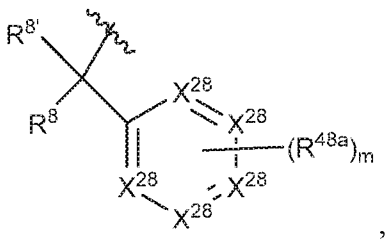
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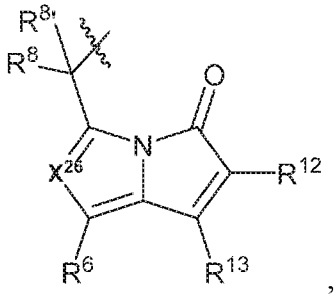
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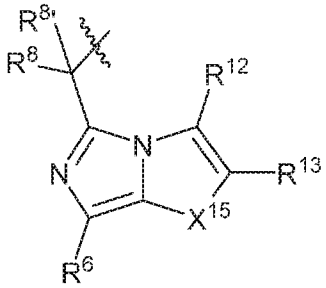
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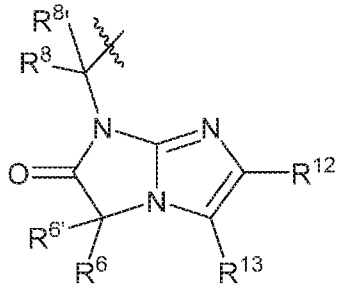
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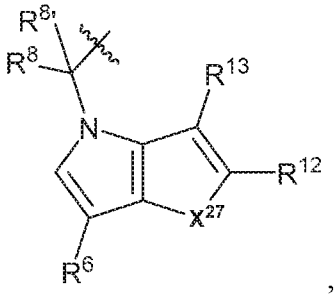
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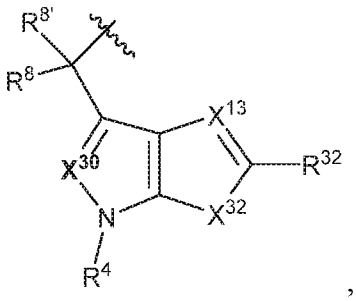
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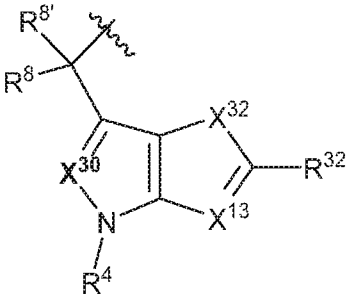
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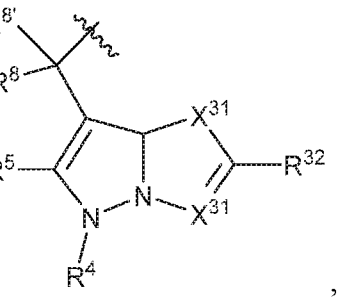
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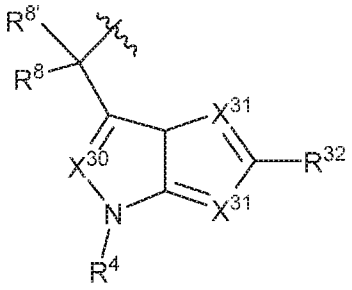
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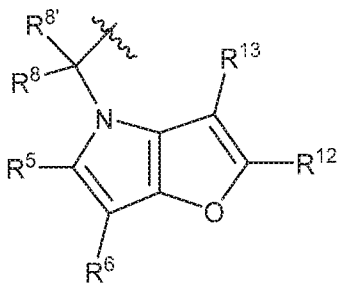
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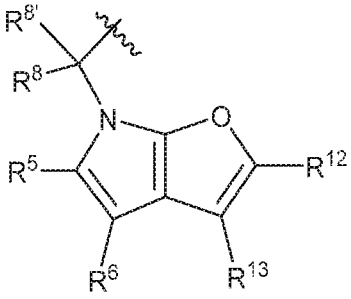
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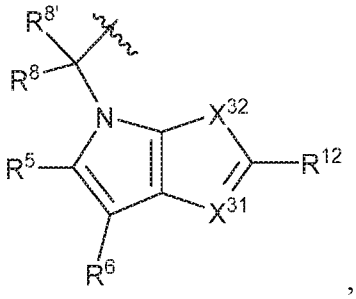
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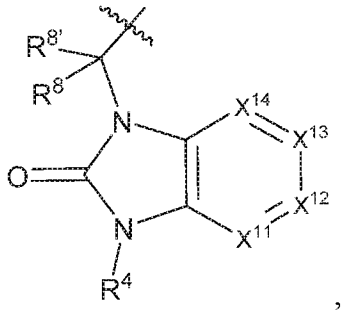
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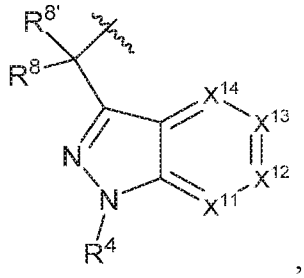
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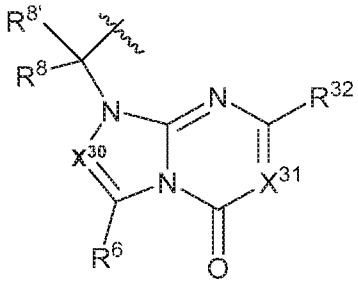
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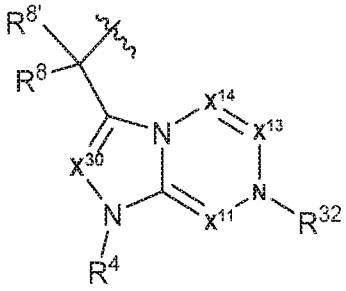
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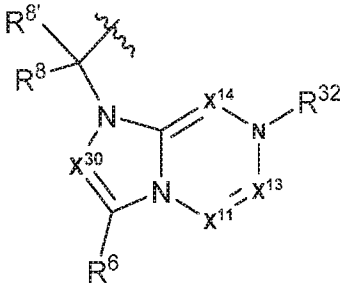
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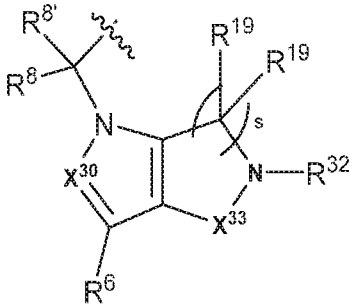
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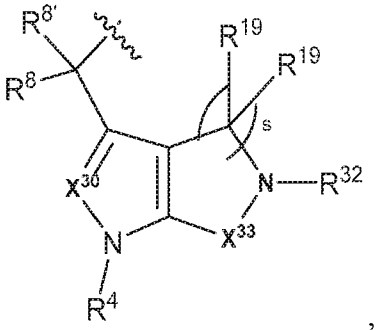
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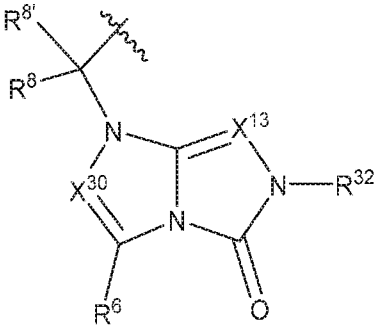
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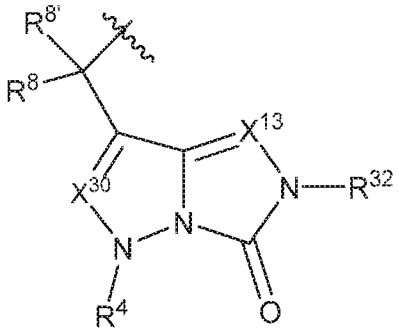
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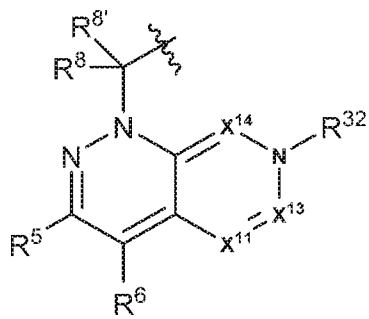
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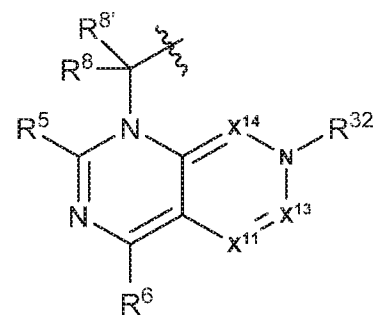
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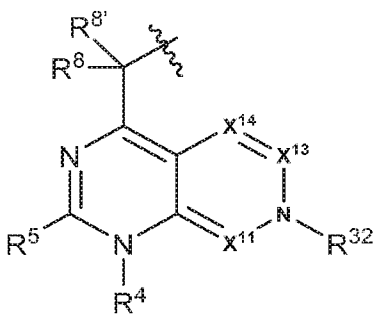
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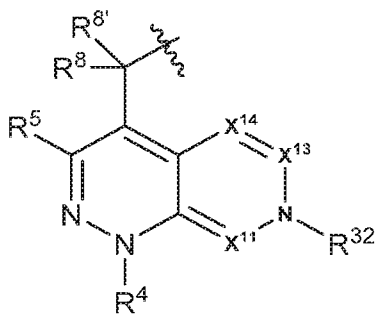
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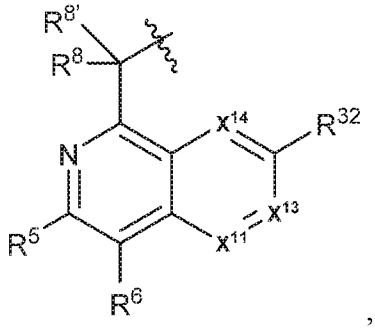
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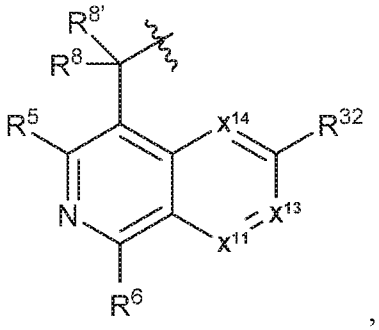
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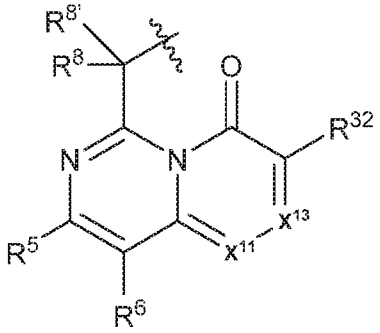
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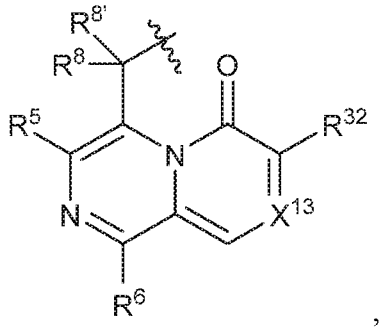
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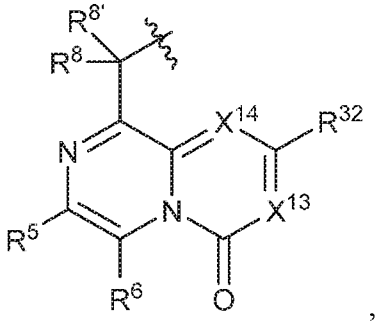
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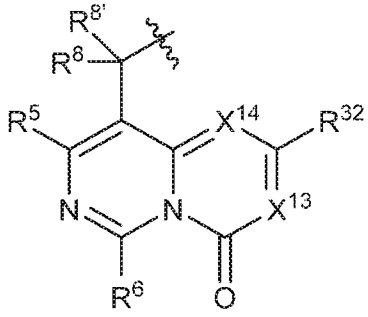
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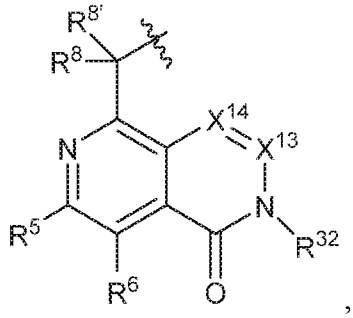
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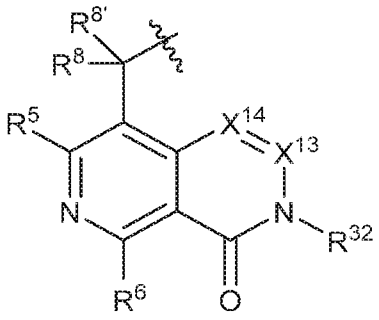
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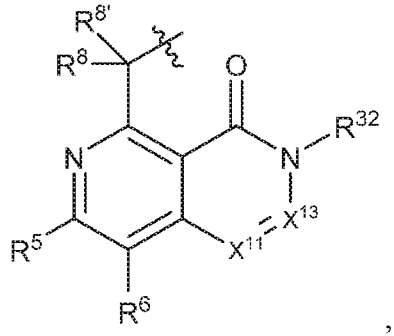
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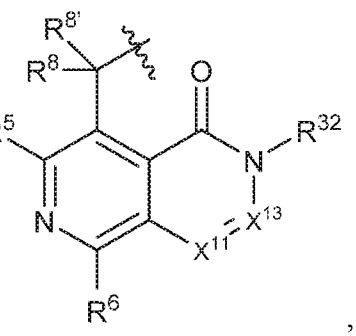
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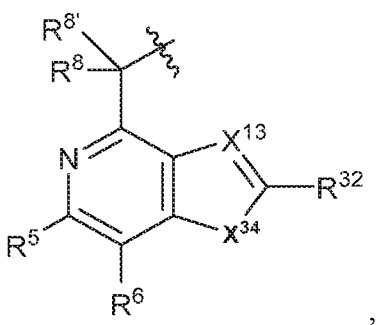
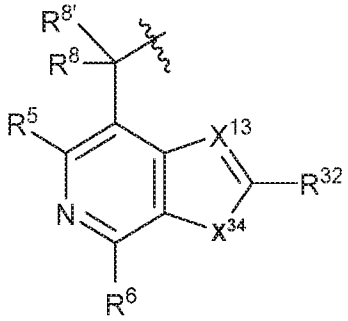
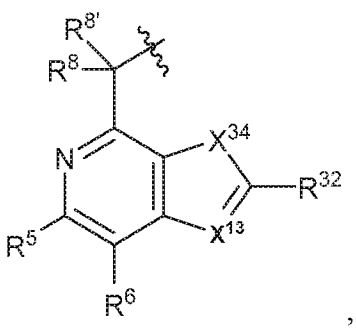
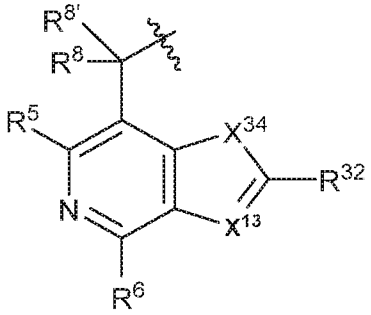
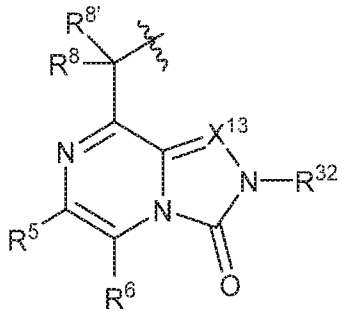
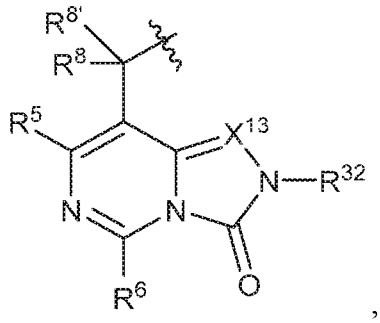
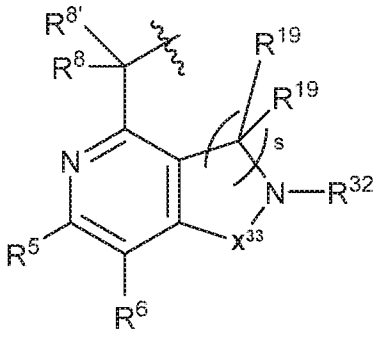
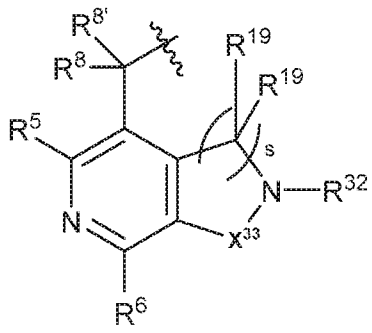
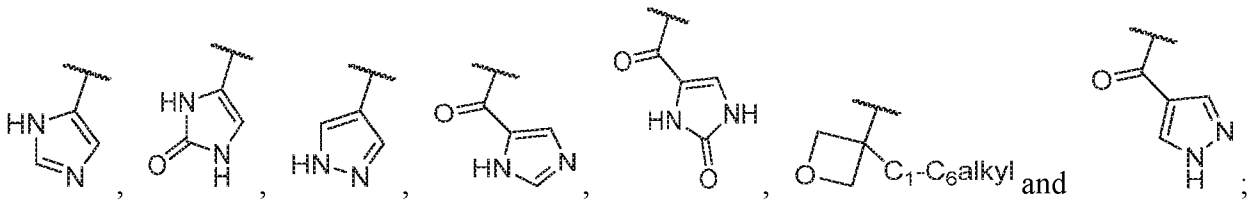








, and .

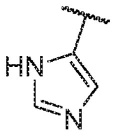
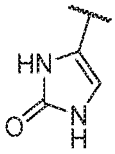
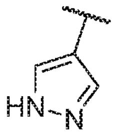
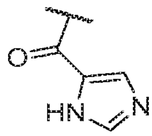
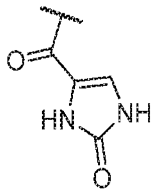
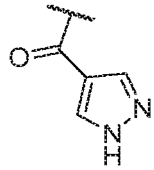
[0102] Non-limiting examples of A2 include the structures of Figure 7.

[0103] R^4, R^5, and R^6 are selected from hydrogen, -JCHO, -JC(0)NH_2, -JC_2-Cealkanoyl, -JC(0)NH(CH_3), -J-COOH, -JP(0)(OR^9)$_2$, -JOC(0)R^9, -JC(0)OR^9, -JC(0)N($CH_2CH_2R^9$)(R^{10}), -JNR^9C(0)R^{10}, -JS0$_2NH_2$, -JS(0)NH_2, -JC(CH_2)$_2$F, -JCH(CF_3)NH_2, -JC(0)Co-C$_2$alkyl(C_3-Cvcycloalkyl), -JNR^9(C_2-C_6alkanoyl), -JNR^9C(0)NR^9R^{10}, -JS0$_2$(Ci-C_6alkyl), -JS0$_2$(Ci-Cehaloalkyl), -JS0$_2$$NR^7R^7$, -JSO=NH(Ci-C$_6$alkyl), -J-nitro, -J-halogen, -J-hydroxyl, -J-phenyl, a 5- to 6-membered heteroaryl, -J-cyano, -J-cyanoimino, -J-amino, -J-imino, -Ci-C_6alkyl, -Co-C_4alkyl(C_3-C7heterocycloalkyl), -Co-C4alkyl(C_3-C7cycloalkyl),


and ;

each of which R^4, R^5 and R^6 other than hydrogen, nitro, halogen, cyano, cyanoimino, or -CHO, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, Ci-C2alkyl, Ci-C2alkoxy, -Co-C2alkyl(mono- and di-Ci-C4alkylamino), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0104] $R^{4'}$ is replaced from -JCHO, -JCONH2, JC_2-C_6alkanoyl, -JSO2NH2, -JC$(CH_2)_2$F, -JCH$(CF_3)NH_2$, Ci-Cealkyl, -Co-C4alkyl(C_3-C7cycloalkyl), -JC(0)Co-C_2alkyl(C_3-C7cycloalkyl), JNR^9(C2-C_6alkanoyl), $JNR^9C(0)NR\ ^9R^{10}$,

 ,  ,  ,  ,  , and  ;

each of which $R^{4'}$ other than -CHO, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, Ci-C2alkyl, Ci-C2alkoxy, -Co-C2alkyl(mono- and di-Ci-C4alkylamino), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0105] $R^{6'}$ is hydrogen, halogen, hydroxyl, Ci-C4alkyl, -Co-C4alkyl(C_3-C7cycloalkyl), or Ci-C4alkoxy; or R^6 and $R^{6'}$ may be taken together to form an oxo, vinyl, or imino group.

[0106] R^7 is hydrogen, Ci-Cealkyl, or -Co-C_4alkyl(C_3-C7cycloalkyl).

[0107] R^8 and $R^{8'}$ are independently replaced from hydrogen, halogen, hydroxyl, Ci-C_6alkyl, -Co-C4alkyl(C_3-C7cycloalkyl), Ci-C_6alkoxy, and (Ci-C4alkylamino)Co-C2alkyl; or R^8 and $R^{8'}$ are taken together to form an oxo group; or R^8 and $R^{8'}$ can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring.

[0108] R^{16} is absent or is independently selected from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, -Co-C4alkyl(mono- and di-Ci-C6alkylamino), -Co-C4alkyl(C_3-C7cycloalkyl), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0109] R^{19} is hydrogen, Ci-Cealkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -S0 $_2$Ci-C6alkyl, (mono- and di-Ci-C6alkylamino)Ci-C4alkyl, -Co-C4alkyl(C_3-C7cycloalkyl), -Co-C4alkyl(C_3-C7heterocycloalkyl), -Co-C4alkyl(aryl), Co-C4alkyl(heteroaryl), and wherein R^{19} other than hydrogen is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, amino, -COOH, and -C(0)OCi-C4alkyl.

[01 10] X^{11} is N or CR^{11}.

[01 11] X^{12} is N or CR^{12}.

[01 12] X^{13} is N or CR^{13}.

[01 13] X^{14} is N or CR^{14}.

[01 14] No more than 2 of X^{11}, X^{12}, X^{13}, and X^{14} are N.

[01 15] One of R^{12} and R^{13} is replaced from R^{31} and the other of R^{12} and R^{13} is replaced from R^{32}, however, each compound has at least one R^{32}. In an alternative embodiment, R^{12} and R^{13} are each independently selected from an R^{32} moiety.

[01 16] R^{31} is replaced from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, Ci-C_2haloalkyl, Ci-C_2haloalkoxy, Ci-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), C_2-C_6alkenyl, C_2-Cealkanoyl, Ci-Cealkoxy, C_2-C_6alkenyloxy, -C(0)OR^9, Ci-Cethioalkyl, -Co-C_4alkylNR^9R^{10}, -C(0)NR^9R^{10}, -S0 $_2R^9$, -S0 $_2NR^9R^{10}$, -OC(0)R^9, and -C(NR^9)NR^9R^{10}, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ Ci-C_2haloalkyl, and Ci-C_2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent replaced from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently replaced from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, Ci-C_6alkoxy, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, Ci-C_6alkylester, -Co-C4alkyl)(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[01 17] R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted. In certain illustrations, R^{32} is depicted as Z^{32}, which is intended to be the same moiety.

[01 18] R^{11}, R^{14}, and R^{15} are independently replaced at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -0(PO)(OR^9)$_2$, -(PO)(OR^9)$_2$, Ci-Cealkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C6alkenyl(aryl), C_2-C6alkenyl(cycloalkyl), C_2-C6alkenyl(heterocycle), C_2-C6alkenyl(heteroaryl), C_2-C_6alkynyl, C_2-C6alkynyl(aryl), C_2-C6alkynyl(cycloalkyl), C_2-C6alkynyl(heterocycle), C_2-C6alkynyl(heteroaryl), C_2-C_6alkanoyl, Ci-C_6alkoxy, Ci-C_6thioalkyl, -Co-C4alkyl(mono- and di-Ci-C6alkylamino), -Co-C4alkyl(C3-C7cycloalkyl), -Co-C4alkoxy(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[01 19] X^{15} is NH, O, or S.

[0120] X^{16} is CR^{12}.

[0121] X^{17} is N or CR^{13}.

[0122] X^{18} is CR^{12}.

[0123] X^{19} is N or CR^{13}.

[0124] X^{20} is NH or O.

[0125] X^{21} is N or CR^{14}.

[0126] X^{22} is N or CR^{13}.

[0127] X^{23} is CR^{12}.

[0128] X^{24} and X^{25} are each independently O or S.

[0129] X^{26} is N or CR^{41}.

[0130] X^{27} is CR^{12}, NH or O.

[0131] X^{28} is N or CH.

[0132] X^{30} is N or CR^{5}.

[0133] X^{31} is N, $C(R^{54})_2$ or CR^{54}.

[0134] X^{32} is NH, $C(R^{54})_2$ or CR^{54}.

[0135] X^{33} is -CO- or -SO- or -SO_2-.

[0136] X^{34} is CHR^{13}, NH, O, or S.

[0137] No more than 2 of X^{28} are N.

[0138] R^{41} is hydrogen, Ci-Cealkyl, or -(Co-C2alkyl)(C3-C_5cycloalkyl).

[0139] R^{48} is independently replaced from hydrogen, halogen, hydroxyl, nitro, cyano, amino, Ci-C_6alkyl, Ci-C_6haloalkyl, C2-C_6alkenyl, C2-C_6alkynyl, Ci-C_6thioalkyl, Ci-C_6alkoxy, -JC3-C_7cycloalkyl, -$B(OH)_2$, -JC(0)NR^9R^{23},-JOS0$_2$$OR^{21}$, -C(0)(CH$_2$)i-4S(0)$R^{21}$, -0(CH$_2$)i-$_4$S(0)$NR^{21}R^{22}$, -JOP(0)(OR^{21})(OR^{22}), -JP(0)(OR^{21})(OR^{22}), -JOP(0)(OR^{21})R^{22}, -JP(0)(OR^{21})R^{22}, -JOP(0)R$^{21}R^{22}$, -JP(0)R$^{21}R^{22}$, -JSP(0)(OR^{21})(OR^{22}), -JSP(0)(OR^{21})(R^{22}), -JSP(0)(R^{21})(R^{22}), -JNR^{9}P(0)(NHR^{21})(NHR^{22}), -JNR^{9}P(0)(OR^{21})(NHR^{22}), -JNR^{9}P(0)(OR^{21})(OR^{22}), -JC(S)R^{21}, -JNR^{21}S0$_2$$R^{22}$, -JNR^{9}S(O)$NR^{10}R^{22}$, -JNR^{9}SO2$NR^{10}R^{22}$, -JS0$_2$NR^{9}COR^{22}, -JS0$_2$NR^{9}CONR$^{21}R^{22}$, -JNR^{21}S0$_2$$R^{22}$, -JC(0)NR^{21}S0$_2$$R^{22}$, -JC(NH$_2$)=NR^{22}, -JCH(NH$_2$)NR^{9}S(0)$_2$$R^{22}$, -JOC(0)NR$^{21}R^{22}$, -JNR^{21}C(0)OR^{22}, -JNR^{21}OC(0)R^{22}, -(CH$_2$)i-$_4$C(0)NR$^{21}R^{22}$, -JC(0)NR$^{24}R^{25}$, -JNR^{9}C(0)R^{21}, -JC(0)R^{21}, -JNR^{9}C(O)$NR^{10}R^{22}$, -CCR^{21}, -(CH$_2$)i-$_4$OC(0)R^{21}, -JC(0)OR^{23}; each of which R^{48} may be unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)2, -Si(CH$_3$)3, -COOH, -CONH2, -P(0)(OH)2, Ci-Cealkyl, -Co-C_4alkyl(C3-C7cycloalkyl), Ci-

Cealkoxy, -Co-C4alkyl(mono- and di-Ci-C4alkylNR^{9}R^{10}), Ci-Cealkylester, Ci-C4alkylamino, Ci-C4hydroxylalkyl, Ci-C2haloalkyl, Ci-C2haloalkoxy, -OC(0)R ^{9}, -NR^{9}C(0)R ^{10}, -C(0)NR ^{9}R^{10}, -OC(0)NR ^{9}R^{10}, -NR^{9}C(0)OR ^{10}, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

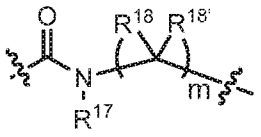
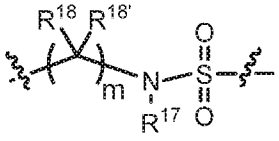
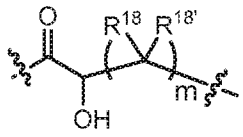
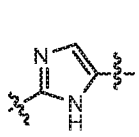
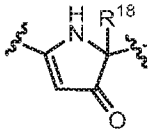
[0140] R^{48a} is R^{48}, S(0)=NHR ^{21}, SF$_5$, and JC(R^{9})=NR^{21} and SO2OR^{21}.

[0141] R^{54} is hydrogen, Ci-Cealkyl, C_2-C_6alkenyl, C2-C_6alkynyl, Ci-Cealkoxy, C2-C_6alkynyl, C2-C_6alkanoyl, Ci-C_6thioalkyl, hydroxyCi-Cealkyl, aminoCi-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), (phenyl)Co-C4alkyl-, (heterocycloalkyl)Co-C4alkyl and (heteroaryl)Co-C4alkyl- wherein the groups can be optionally substituted.

[0142] s is 1 or 2.

[0143] L is selected from LI, LI' and L2.

[0144] L I is a bond or is replaced from the formulas


, 
, 
, 
and 
.

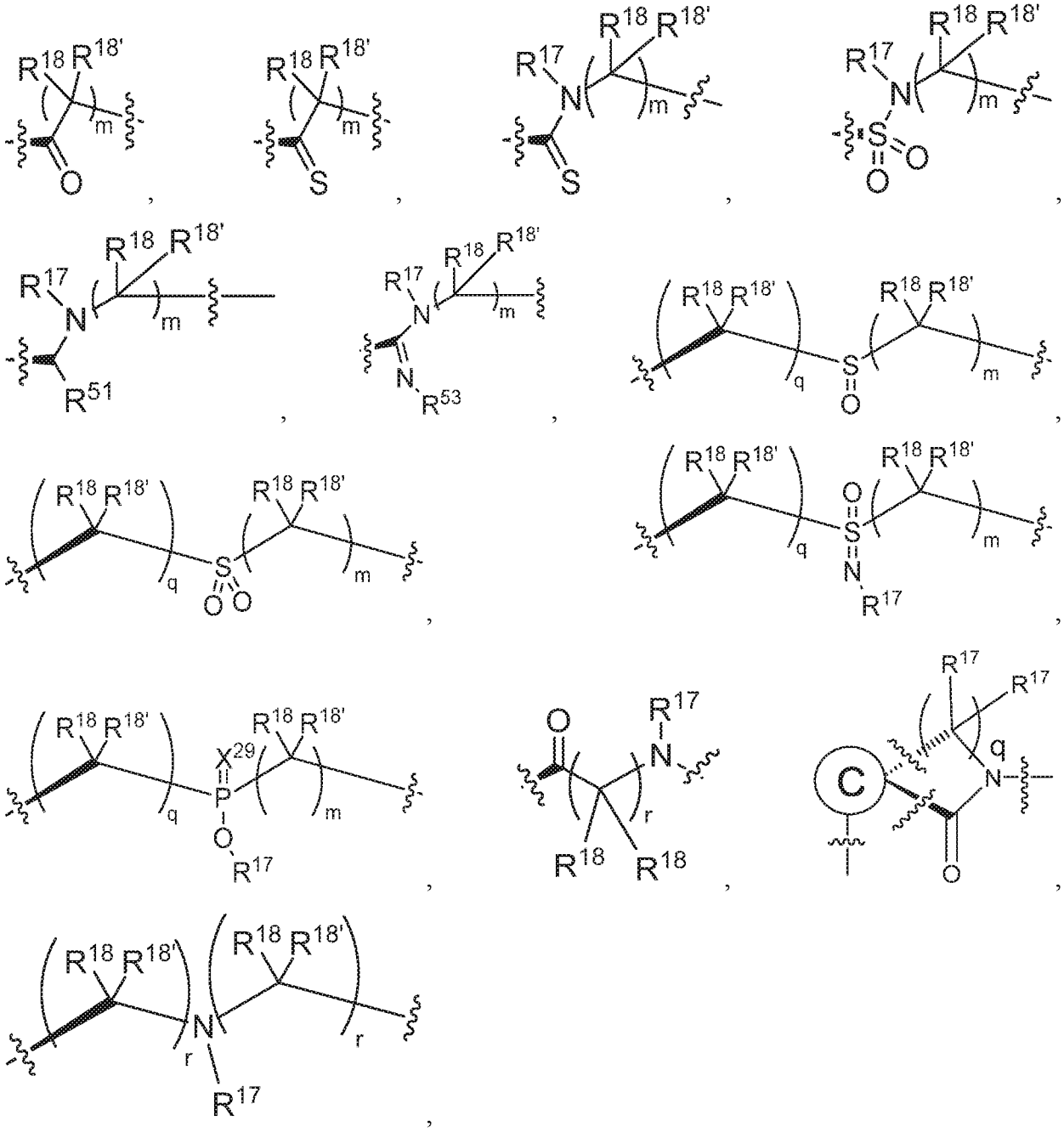
[0145] R^{17} is hydrogen, Ci-Cealkyl, or -Co-C_4alkyl(C3-C7cycloalkyl) and R^{18} and R$^{18'}$ are independently replaced from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3.

[0146] In one embodiment, L I is LI'.

[0147] Non-limiting examples of LI' include the structures of Figure 8.

[0148] In one embodiment, the methyl groups in the structures illustrated in Fig. 8 can be replaced with another alkyl group, as defined herein.

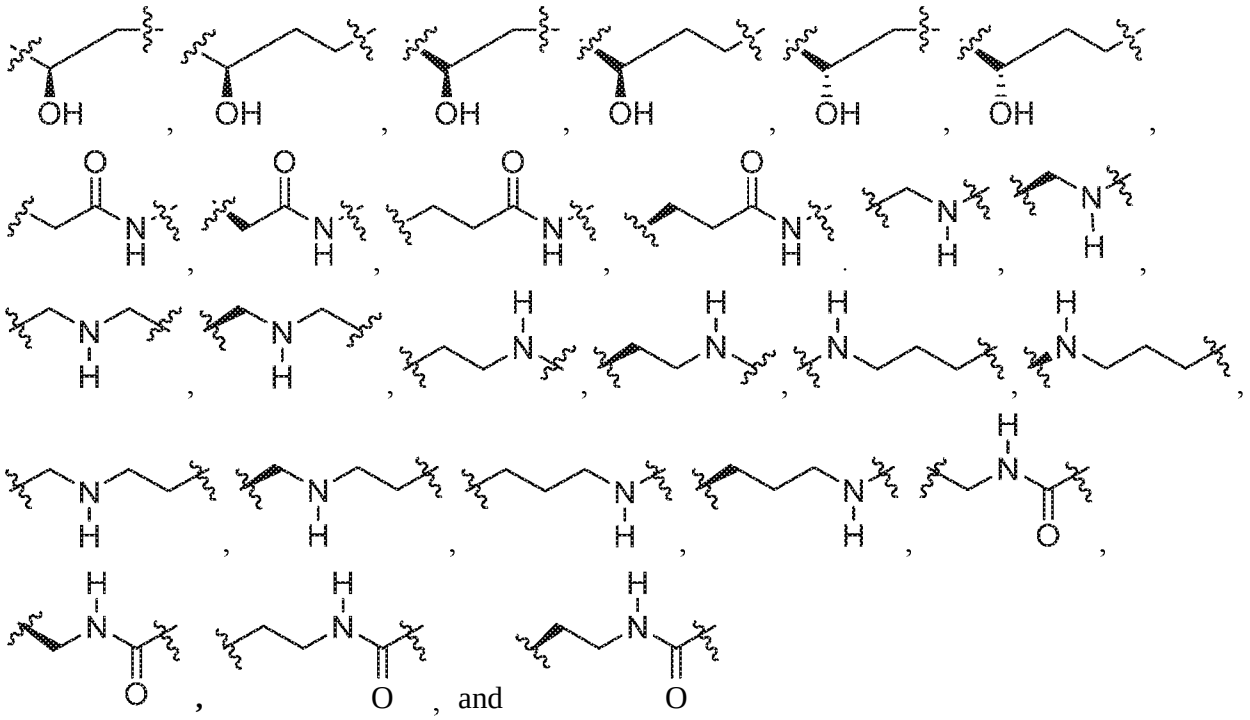
[0149] L2 is selected from:



Or an optionally substituted monocyclic or bicyclic carbocyclic; an optionally substituted monocyclic or bicyclic carbocyclic-oxy group; an optionally substituted monocyclic or bicyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring, an optionally substituted -(Co-C4alkyl)(aryl); an optionally substituted -(Co-C4alkyl)(5-membered heteroaryl) selected from pyrrole, furan, thiophene, pyrazole, oxazole, isoxazole, thiazole and isothiazole or a substituted imidazole; an optionally substituted -(Co-C4alkyl)(6-membered heteroaryl); an optionally substituted -(Co-C_4alkyl)(8-

membered heteroaryl); an optionally substituted -(Co-C4alkyl)(9-membered heteroaryl) selected from isoindole, indazole, purine, indolizine, benzothiophene, benzothiazole, benzoxazole, benzofuran, and furopyridine; and -(Co-C4alkyl)(10-membered heteroaryl); q is 1, 2 or 3.

[0150] L2' is selected from:



[0151] R^{51} is CH_3, CH_2F, CHF_2 or CF_3.

[0152] R^{53} is cyano, nitro, hydroxyl or Ci-C_6alkoxy.

[0153] X^{29} can be **O** or S.

[0154] In certain embodiment, L2 is a bond. In certain embodiments, if L2 is heterocyclic or heteroaryl, then B can be hydrogen.

[0155] Non-limiting examples of L2 include the structures of Figure 9.

[0156] In one embodiment, the methyl groups in the structures illustrated in Fig. 9 be replaced with another alkyl or acyl, as defined herein. In another embodiment, the carbocyclic, heterocyclic, aryl or heteroaryl rings can be optionally substituted. As indicated above, any of the structures illustrated above or below can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, of an R^{48} substituent.

[0157] L3 is selected from L4 or L5.

[0158] L4 is -C(0)-.

[0159] L5 is -C(S)-, -P(0)OH-, -S(O)-, -S(0)$_2$- or -C(R^{52})$_2$- wherein each R^{52} is independently selected from halo, hydrogen, or optionally substituted Cl-C6alkyl. In certain embodiments the two R^{52} groups can be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently replaced from N, O, or S.

[0160] Bl is a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C_2-C_6alkenyl; C_2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl), each of which Bl is unsubstituted or substituted with one or more substituents independently replaced from R^{33} and R^{34}, and 0 or 1 substituents replaced from R^{35} and R^{36}.

[0161] R^{33} is independently replaced from halogen, hydroxyl, -COOH, cyano, Ci-C_6alkyl, C_2-Cealkanoyl, Ci-Cealkoxy, -Co-C_4alkylNR^9R^{10}, -SOzR^9, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

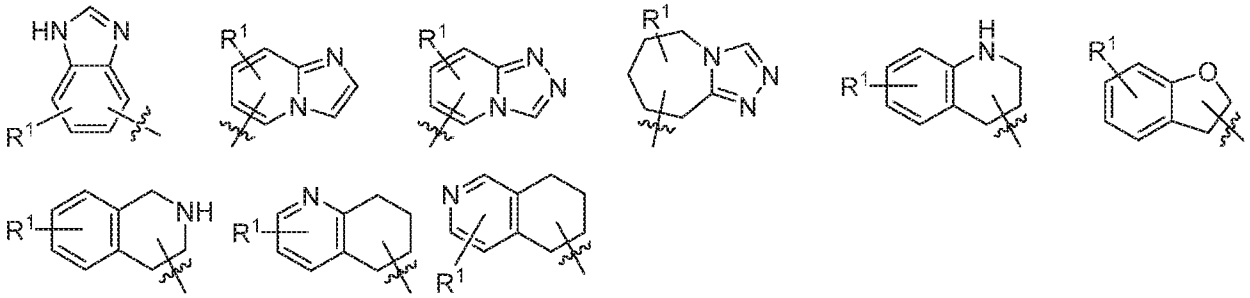
[0162] R^{34} is independently replaced from nitro, C_2-C_6alkenyl, C_2-C_6alkynyl, Ci-Cethioalkyl, -JC_3-C_7cycloalkyl, -B(OH)$_2$, -JC(0)NR^9R^{23},-JOS0$_2$$OR^{21}$, -C(0)(CH$_2$)i$_{-4}$S(0)$R^{21}$, -0(CH$_2$)i$_{-4}$S(0)$NR^{21}R^{22}$, -JOP(0)($OR^{21}$)($OR^{22}$), -JP(0)($OR^{21}$)($OR^{22}$), -JOP(0)($OR^{21}$)$R^{22}$, -JP(0)($OR^{21}$)$R^{22}$, -JOP(0)$R^{21}R^{22}$, -JP(0)$R^{21}R^{22}$, -JSP(0)($OR^{21}$)($OR^{22}$), -JSP(0)($OR^{21}$)($R^{22}$), -JSP(0)($R^{21}$)($R^{22}$), -J$NR^9$P(0)($NHR^{21}$)($NHR^{22}$), -J$NR^9$P(0)($OR^{21}$)($NHR^{22}$), -J$NR^9$P(0)($OR^{21}$)($OR^{22}$), -JC(S)$R^{21}$, -J$NR^{21}$S0$_2$$R^{22}$, -J$NR^9$S(O)$NR^{10}R^{22}$, -J$NR^9$$SO_2NR^{10}R^{22}$, -JS0$_2$$NR^9COR^{22}$, -JS0$_2$$NR^9CONR^{21}R^{22}$, -J$NR^{21}$S0$_2$$R^{22}$, -JC(0)$NR^{21}$S0$_2$$R^{22}$, -JC($NH_2$)=$NR^{22}$, -JCH($NH_2$)$NR^9$S(0)$_2$$R^{22}$, -JOC(0)$NR^{21}R^{22}$, -J$NR^{21}$C(0)$OR^{22}$, -J$NR^{21}$OC(0)$R^{22}$, -($CH_2$)i-$_4$C(0)$NR^{21}R^{22}$, -JC(0)$R^{24}R^{25}$, -J$NR^9$C(0)$R^{21}$, -JC(0)$R^{21}$, -J$NR^9$C(O)$NR^{10}R^{22}$, -C$CR^{21}$, -($CH_2$)i-40C(0)$R^{21}$, and -JC(0)$OR^{23}$; each of which R^{34} may be unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)$_2$, -Si(CH_3)$_3$, -COOH, -CONH_2, -P(0)(OH)$_2$, Ci-Cealkyl, -Co-C4alkyl(C_3-C7cycloalkyl), Ci-C_6alkoxy, -Co-C_2alkyl(mono- and di-Ci-C4alkylamino), Ci-C6alkylester, Ci-C4alkylamino, Ci-C4hydroxylalkyl, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0163] R^{35} is independently replaced from naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl containing 1 or 2 heteroatoms replaced from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R^{35} is unsubstituted or

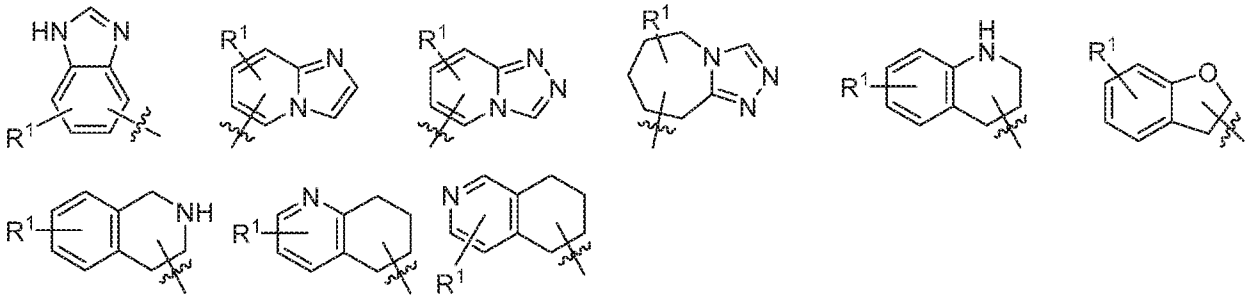
substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, Ci-C6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, Ci-Cealkylester, -Co-C_4alkyl(C3-C7cycloalkyl), -SO2R^9, Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0164] R^{36} is independently replaced from tetrazolyl, (phenyl)Co-C2alkyl, (phenyl)Ci-C2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently replaced from N, O, B, and S, each of which R^{36} is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, Ci-Cealkylester, -Co-C4alkyl(C3-C7cycloalkyl), -SO2R^9, -OSi$(CH_3)_2C(CH_3)_3$, -Si$(CH_3)_2C(CH_3)_3$, Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0165] In one additional alternative embodiment B is selected from:



[0166] In one additional alternative embodiment R^{36} is selected from:



[0167] In one embodiment R^1 is selected from F, CI, Br, and Ci-C_6alkyl.

[0168] In one embodiment R^1 is selected from hydroxyl and Ci-C_6alkoxy.

[0169] In one embodiment R^1 is selected from C2-C_6alkynyl, C2-C_6alkanoyl, and Ci-C_6thioalkyl.

[0170] In one embodiment R^1 is selected from aminoCi-Cealkyl and -Co-C4alkylNR^9R^{10}.

[0171] R^{21} and R^{22} are independently replaced at each occurrence from hydrogen, hydroxyl, cyano, amino, Ci-C6alkyl, Ci-C_6haloalkyl, Ci-C_6alkoxy, (C3-C7cycloalkyl)Co-C4alkyl, (phenyl)Co-C_4alkyl, -Ci-C4alkylOC(0)OCi-C_6alkyl, -Ci-C_4alkylOC(0)Ci-C6alkyl, -Ci-C4alkylC(0)OCi-C6alkyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and each R^{21} and R^{22} can be optionally substituted. In one embodiment, R^{21} and R^{22} can be taken together to form a carbocyclic or heterocyclic ring.

[0172] R^{23} is independently replaced at each occurrence from Ci-C_6alkyl, Ci-C_6haloalkyl, (aryl)Co-C4alkyl, (C3-C7cycloalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and each R^{23} can be optionally substituted.

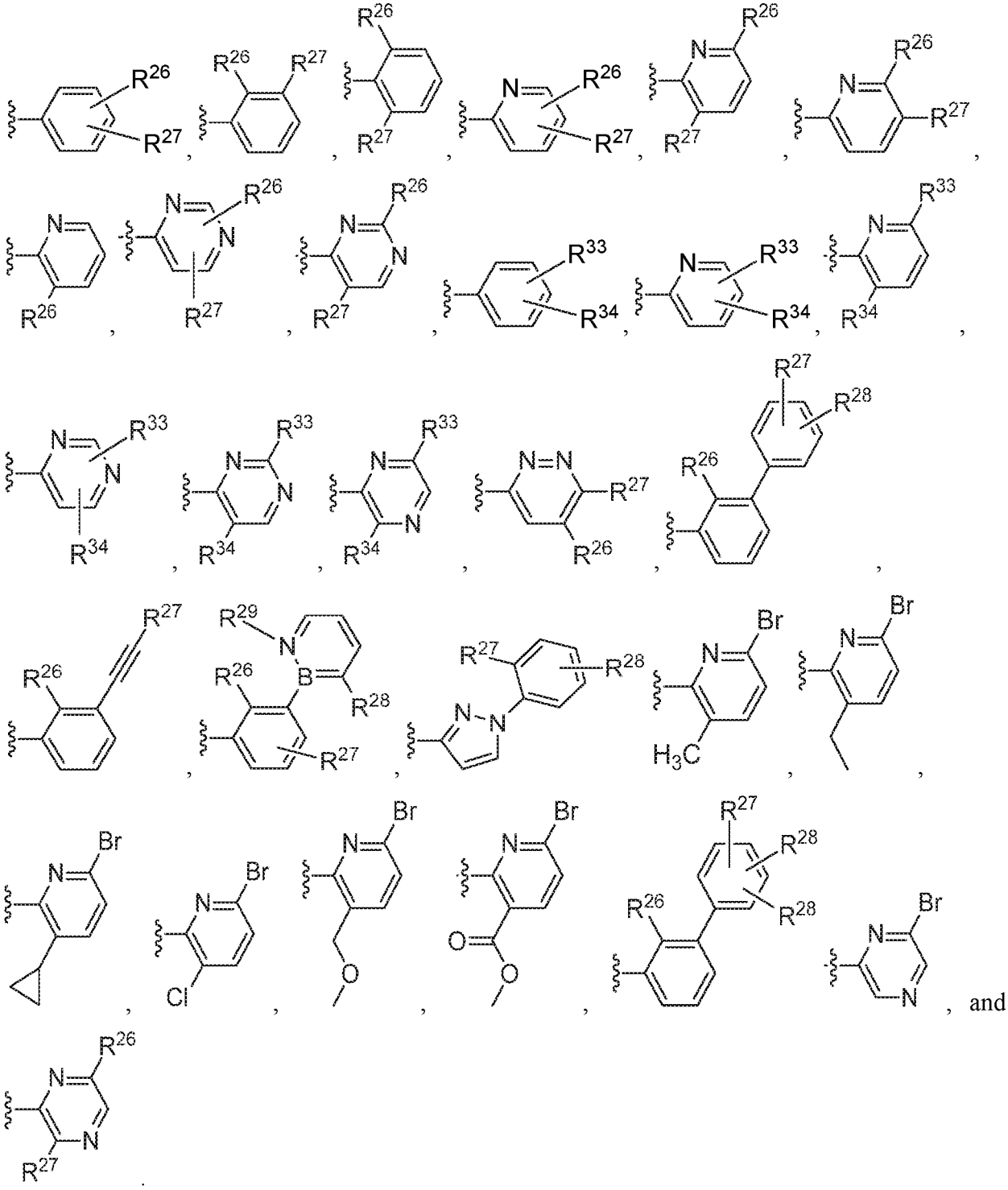
[0173] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyl group, or a 6- to 10- membered bicyclic heterocyclic group having fused, spiro, or bridged rings, and each R^{24} and R^{25} can be optionally substituted.

[0174] J is independently replaced at each occurrence from a covalent bond, Ci-C4alkylene, -OCi-C4alkylene, C2-C4alkenylene, and C2-C4alkynylene.

[0175] In one embodiment, B1 is selected from Figure 10, wherein R^{27} is hydrogen, methyl, or trifluoromethyl; R^{28} is hydrogen or halogen; and R^{29} is hydrogen, methyl, trifluoromethyl, or -Si$(CH_3)_2C(CH_3)_3$.

[0176] In one embodiment, B1 isB1'. Non-limiting examples of B1' include the structures of Figure 11 A-D.

[0177] Examples of B moieties include, but are not limited to



[0178] In one embodiment, B is B2 which is selected from the structures of Figure 12.

[0179] In one embodiment B3 is:

(I) a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1,

2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C2-C_6alkenyl; C2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl); each of which B3 is substituted with one or more of the following: S(0)=NHR 21, SF5, and JC(R^9)=NR21;

(II) a monocyclic, bicyclic, or tricyclic heterocyclic group that has at least one boron or silicon atom in the ring or a a monocyclic, bicyclic, or tricyclic heteroaryl group that has at least one boron in the ring;

(III) a 6-membered aryl group fused to a 5-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently replaced from N and S wherein one of the CH2 groups of the 5-membered cyclic group is optionally substituted by oxo (i.e., =0) excluding dihydrobenzofuran;

(IV) an 8-membered monocyclic or bicyclic heteroaryl, however; when A is A1 or A1'; C is Cl, CI' or C2; L is L I or LI' andL3 is L4 the following species are excluded: 6,7-dihydro-5H-pyrrolo[l,2-a]imidazole.

(V) a 9-membered monocyclic or bicyclic heteroaryl group, however; when A is A1 or Al'; C is Cl, CI' or C2; L is L I or LI' and L3 is L4 the following species are excluded: 6-chloro-lH-benzo[d]imidazole bonded at the 7 position, 6-fluoro-lH-benzo[d]imidazole bonded at the 7 position, 6-(methylthio)-lH-benzo[d]imidazole bonded at the 7 position, and 6-(methoxy)-lH-benzo[d]imidazole bonded at the 7 position, 7-chloro-imidazo[l,2-a]pyridine substituted at the eight position, 7-(methylthio)-imidazo[l,2-a]pyridine substituted at the eight position, 7-fluoro-imidazo[l,2-a]pyridine substituted at the eight position, 7-methoxyimidazo[l,2-a]pyridine substituted at the eight position, 4-fluoro-lH-indole substituted at the 4 position,[l,2,4]triazole[4,3-a]pyridine substituted at the 2 position, and [l,2,4]triazole[4,3-a]pyrimidine substituted at the 3 position;

(VI) a 10-membered aryl or heteroaryl group, however; when A is A1 or A1'; C is CI, CI' or C2; L is L I or LI' and L3 is L4 the following species are

excluded: an unsubstituted tetrahydroquinoline and 6,7,8,9-tetrahydro-5H-[l,2,4]triazolo[4,3-a]azepine substituted at the 3-position;

(VII) (optionally substituted alkyl)-(optionally substituted cycloalkyl), (optionally substituted alkenyl)-(optionally substituted cycloalkyl), or (optionally substituted alkynyl)-(optionally substituted cycloalkyl);

[0180] wherein B3 can be further substituted one or more times with the substituents independently selected from R^{35}, R^{36} and R^{48}.

[0181] Non-limiting examples of B3 include the structures of Figure 13.

[0182] In one embodiment, the methyl groups in the structures illustrated in Fig. 13 can be replaced by another alkyl group. In another embodiment, the B3 groups illustrated in Fig. 13 can be optionally substituted. As indicated above, any of the structures illustrated in Fig. 13 or otherwise herein can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, with an R^{48} substituent.

[0183] In an alternative embodiment, B3 can also be R^{21} when L2 is either an optionally substituted monocyclic or bicyclic carbocyclic; an optionally substituted monocyclic or bicyclic carbocyclic-oxy group; an optionally substituted monocyclic or bicyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring, an optionally substituted -(Co-C4alkyl)(aryl); an optionally substituted -(Co-C4alkyl)(5-membered heteroaryl) selected from pyrrole, furan, thiophene, pyrazole, oxazole, isoxazole, thiazole and isothiazole or a substituted imidazole; an optionally substituted -(Co-C4alkyl)(6-membered heteroaryl); an optionally substituted -(Co-C4alkyl)(8-membered heteroaryl); an optionally substituted -(Co-C4alkyl)(9-membered heteroaryl) selected from isoindole, indazole, purine, indolizine, benzothiophene, benzothiazole, benzoxazole, benzofuran, and furopyridine; or an optionally substituted -(Co-C4alkyl)(10-membered heteroaryl)

[0184] Non-limiting examples of L2-B3 where B3 is R^{21} include the structures of Figure 14.

[0185] B4 is one of the following defined embodiments and is subject to the restriction that either A is A2, or C is C3 (or C4), or L is L2, or L3 is L5:

(I) a 4-membered carbocyclic fused to a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S; wherein the 4-5 or 4-6 ring system can be optionally substituted;

(II) a 4-membered carbocyclic fused to a 6-membered aryl ring wherein the 4-6 ring system can be optionally substituted;

(III) a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C_2-C_6alkenyl; C_2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl); each of which B3 is substituted one or more times with $S(0)_2OR^{21}$;

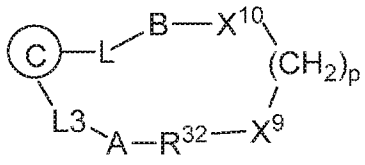
(IV) (cycloalkyl)-(optionally substituted aryl), (cycloalkyl)-(optionally substituted heteroaryl), (cycloalkyl)-(optionally substituted heterocyclic), (alkyl)-alkenyl), cycloalkyl-alkenyl;

(V) alkyl, (alkyl)-(alkenyl), alkyl(alkynyl), cycloalkyl-alkenyl each of which can be optionally substituted;

(VI) (optionally substituted alkyl)-(optionally substituted cycloalkyl), (alkenyl)-(optionally substituted cycloalkyl), (alkynyl)-(optinally substituted cycloalkyl), (optionally substituted cycloalkyl)-(optionally substituted cycloalkyl);

[0186] wherein B4 can be further substituted 1, 2, 3 or 4 times or more with the substituents independently selected from R^{33}, R^{34}, R^{35} R^{36} and R^{48}.

[0187] In an alternate embodiment, the R^{32} group can be bonded to B via a linking group to form a compound of Formula I':



Formula I';

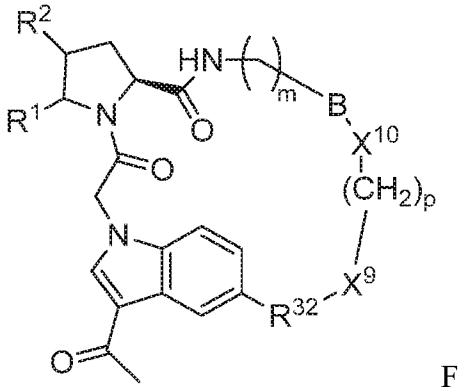
[0188] wherein;

[0189] X^9 and X^{10} are each independently CH_2, NR^9, O or S;

[0190] p is 2 to 10;

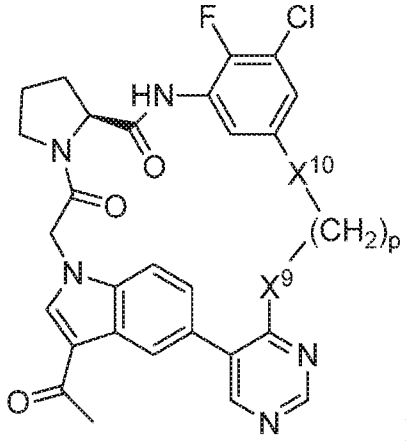
or a pharmaceutically acceptable composition, salt, isotopic analog, or prodrug thereof.

[0191] In one embodiment, the disclosure provides a compound of Formula IM.



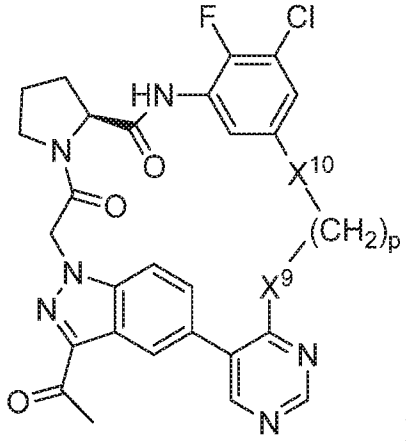
Formula IM.

[0192] In one embodiment, the disclosure provides a compound of Formula IN:



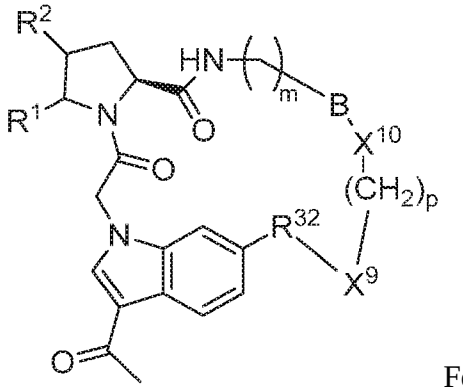
Formula IN.

[0193] In one embodiment, the disclosure provides a compound of Formula IO:



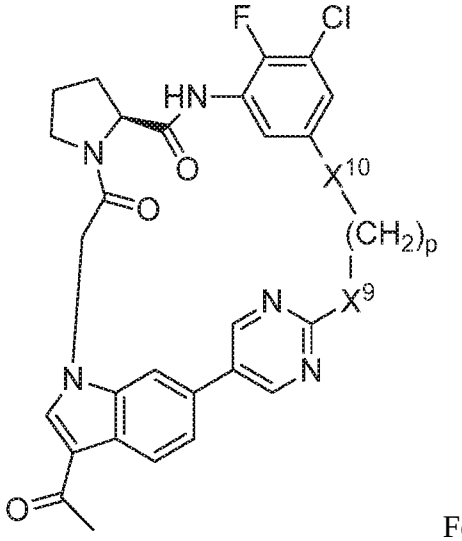
Formula IO.

[0194] In one embodiment, the disclosure provides a compound of Formula IP:



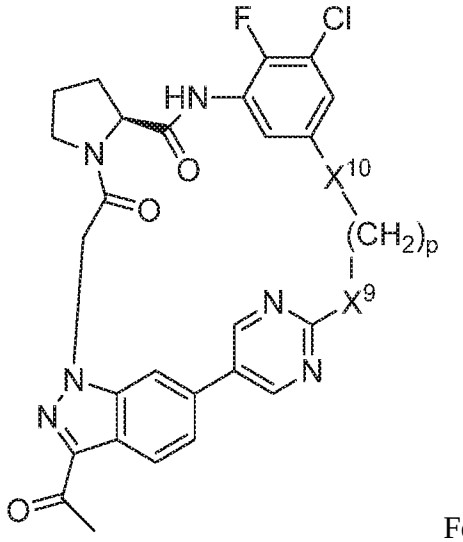
Formula IP.

[0195] In one embodiment, the disclosure provides a compound of Formula IQ:



Formula IQ.

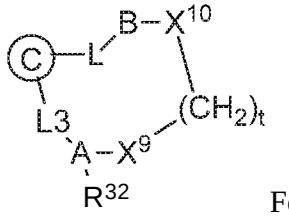
[0196] In one embodiment, the disclosure provides a compound of Formula IR:



Formula IR.

[0197] In an alternate embodiment, the X^9-(CH_2)p-X^{10} moiety can be saturated or partially unsaturated. In another embodiment, the X^9-$(CH2)_P$-X^{10} moiety can comprise one or more heteroatoms.

[0198] In an alternate embodiment, the A group can be bonded to B via a linking group to form a compound of Formula FA:



Formula I'A;

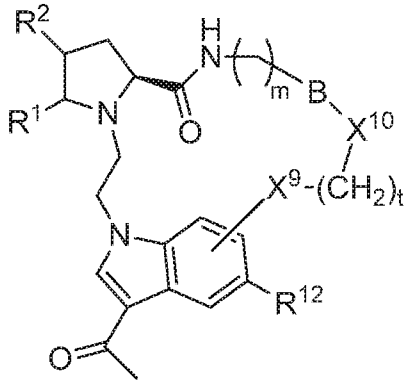
[0199] wherein;

[0200] X^9 and X^{10} are each independently CH_2, NR^9, O or S;

[0201] t is 1, 2, or 3;

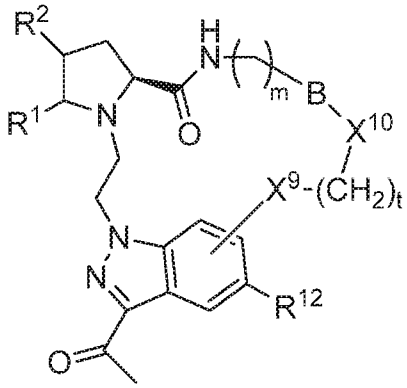
[0202] or a pharmaceutically acceptable composition, salt, isotopic analog, or prodrug thereof.

[0203] In one embodiment, the disclosure provides a compound of Formula IS:



Formula IS.

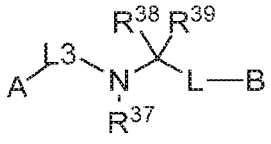
[0204] In one embodiment, the disclosure provides a compound of Formula IT:



Formula IT.

[0205] In an alternate embodiment, the X^9-(CH2)t-X^{10} moiety can be saturated or partially unsaturated. In another embodiment, the X^9-(CH2)t-X^{10} moiety can comprise one or more heteroatoms.

[0206] In an alternate embodiment, the disclosure provides compounds of Formula I"



(I"),

or a pharmaceutically acceptable composition, salt, isotopic analog, or prodrug thereof.

[0207] A is selected from Al, Al' and A2.

[0208] B is selected from Bl, Bl', B2, B3, and B4.

[0209] L is selected from LI, LI', L2 and L2'.

[0210] L3 is selected from L4 and L5.

[021 1] R^{37} is hydrogen, Ci-Cealkyl or -(Co-CialkylXCs-Cecylcoalkyl).

[0212] R^{38} and R^{39} are independently hydrogen (which as in any other location can be deuterium), Ci-C_6alkyl (including C1-C3 alkyl), Ci-C_6haloalkyl, Ci-C_6hydroxyalkyl, C2-C_6alkenyl, C2-C_6alkynyl, Ci-C_6alkoxy, (C3-C6cycloalkyl)Co-C4alkyl-, (aryl)Co-C2alkyl-, (heteroaiyl)Co-C2alkyl-, or a side chain of an amino acid (i.e., a moiety which is found on the carbon linking the amino group and the carboxyl group in an amino acid) or its isomer; each of which is optionally substituted. The R^{38} and R^{39} substituents independently include but are not limited to any corresponding R^{38} and R^{39} positions found in natural amino acids (or their D-counterpart) (i.e., the substituents on the carbon between the carbonyl and the amino group) and non-proteogenic amino acids, such as serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine (e.g., hydrogen), alanine, valine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, ornithine, glutamine, arginine, histidine, proline, hydroxyproline, selenomethionine, lanthionine, 2-aminoisobutyric acid or dehydroalanine (i.e., R^{38} or R^{39} is an exo-double bond), with optional protection of functional groups such as hydroxyl, amino, thiol, etc.

[0213] Pharmaceutical compositions comprising a compound or salt of Formula I, Formula Γ or Formula I" together with a pharmaceutically acceptable carrier are also disclosed.

[0214] The present invention thus includes at least the following features:

(a) a compound of Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt or prodrug thereof, for use in treating or preventing a disorder listed in the Detailed Description,

Part IV, including but not limited to the development of fatty liver and conditions stemming from fatty liver, such as nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, or liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy); paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, other ophthalmic diseases (e.g., geographic atrophy), a respiratory disease or a cardiovascular disease;

(b) a pharmaceutically acceptable composition of a compound of Formula I, Formula Γ or Formula I" or its pharmaceutically acceptable salt in a pharmaceutically acceptable carrier;

(c) a compound selected from Formula I, Formula Γ or Formula I" or a pharmaceutically acceptable salt or prodrug thereof, for use in treating or preventing a disorder mediated by the complement pathway, and for example, cascade Factor D;

(d) use of a compound of Formula I, Formula Γ or Formula I", as described herein, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, including but not limited to the development of fatty liver and conditions stemming from fatty liver, such as nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy); paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, other ophthalmic diseases (e.g., geographic atrophy), a respiratory disease or a cardiovascular disease;

(e) a process for manufacturing a medicament intended for the therapeutic use for treating or preventing a disorder listed in the Detailed Description, Part IV, or generally for treating or preventing disorders mediated by complement cascade Factor D, characterized in that a compound selected from Formula I, Formula Γ or Formula I" or an embodiment of the active compound is used in the manufacture;

(f) a compound selected from Formula I, Formula Γ or Formula I" or a salt thereof as described herein in substantially pure form (e.g., at least 90 or 95%):

(g) a compound of Formula I, Formula Γ or Formula I" as described herein, or a pharmaceutically acceptable salt or prodrug thereof, for use in treating a medical disorder which is an

inflammatory or immune condition, a disorder mediated by the complement cascade (including a dysfunctional cascade), a disorder or abnormality of a cell that adversely affects the ability of the cell to engage in or respond to normal complement activity, or an undesired complement-mediated response to a medical treatment, such as surgery or other medical procedure or a pharmaceutical or biopharmaceutical drug administration, a blood transfusion, or other allogenic tissue or fluid administration.

(h) For each of (a) through (g) above, and otherwise herein, each assembly of moieties in the Figures and each active compound made therefrom or its use is considered and deemed specifically and individually disclosed, as such depiction is for convenience of space only and not intended to describe a only a genus or even a subgenus for such indication.

BRIEF DESCRIPTION OF THE FIGURES

[0215] FIG. 1 provides non-limiting specific embodiments of the Central Core ring, wherein R, R', and R^3 are defined below.

[0216] FIGS. 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 21, 2J, 2K, 2L, and 2M, provide non-limiting embodiments of CI', wherein R^3 is as defined herein.

[0217] FIG. 3 provides non-limiting embodiments of C2.

[0218] FIGS. 4A, 4B, 4C, 4D, 4E, 4F, 4G, 4H, 41, 4J, 4K, 4L, 4M, and 4N, provide non-limiting embodiments of C3.

[0219] FIG. 5 provides non-limiting embodiments of central core small mimetics of a beta-turn, beta turn inducers, reverse turn mimetics and foldamer monomers.

[0220] FIG. 6 provides non-limiting embodiments of A1', wherein R^{32} is defined below.

[0221] FIGS. 7A, 7B, 7C, 7D, and 7E, provide non-limiting embodiments of A2, wherein R^{32} is defined below.

[0222] FIG. 8A, 8B, 8C, and 8D, provide non-limiting embodiments of LI'.

[0223] FIGS. 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, 91, and 9J, provide non-limiting embodiments of L2.

[0224] FIG. 10A, 10B, IOC, and 10D, provide non-limiting specific embodiments of B1 rings, wherein R^{27}, R^{28}, and R^{29} are defined below.

[0225] FIG. 11A, 1IB, 11C, 1ID, provide non-limiting specific embodiments of B1' rings, wherein halo is selected from F, CI, Br, or I.

[0226] FIG. 12 provides specific embodiments of B2 rings.

[0227] FIGS. 13A, 13B, 13C, 13D, 13E, 13F, 13G, 13H, 131, 13J, 13K, 13L, 13M, 13N, 130, 13P, 13Q, 13R, 13S, 13T, 13U, 13V, 13W, 13X, 13Y, and 13Z, provide specific embodiments of B3 moieties

[0228] FIG. 14 provides non-limiting embodiments of L2-B3 wherein B3 is R^{21}, and R^{21} is defined below.

[0229] FIGS. 15 provides non-limiting embodiments of R^{32}.

[0230] FIG. 16 provides non-limiting specific embodiments of $R^{32'}$.

[0231] FIGS. 17A, 17B, 17C, 17D, 17E, 17F, 17G 17H, 171, 17J, 17K, 17L, 17M, and 17N provide non-limiting examples of compounds included in the present invention, wherein $_{Z32}$ is the same as R^{32} as used herein.

DETAILED DESCRIPTION

I. TERMINOLOGY

[0232] Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0233] The compounds in any of the Formulas described herein include enantiomers, mixtures of enantiomers, diastereomers, tautomers, racemates and other isomers, such as rotamers, as if each is specifically described, unless otherwise indicated or otherwise unclear from the context.

[0234] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein

have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0235] The present invention includes compounds of Formula I, Formula Γ or Formula I" with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons.

[0236] Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}CI, ^{125}I respectively. In one embodiment, isotopically labelled compounds can be used in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0237] By way of general example and without limitation, isotopes of hydrogen, for example, deuterium (^{2}H) and tritium (^{3}H) may be used anywhere in described structures that achieves the desired result. Alternatively or in addition, isotopes of carbon, e.g., ^{13}C and ^{14}C, may be used. In one embodiment, the isotopic substitution is deuterium for hydrogen at one or more locations on the molecule to improve the performance of the drug, for example, the pharmacodynamics, pharmacokinetics, biodistribution, half-life, stability, AUC, Tmax, Cmax, etc. For example, the deuterium can be bound to carbon in a location of bond breakage during metabolism (an a-deuterium kinetic isotope effect) or next to or near the site of bond breakage (a β-deuterium kinetic isotope effect).

[0238] Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is 90, 95 or 99% or more enriched in an isotope at any location of interest. In one embodiments deuterium is 90, 95 or 99% enriched at a desired

location. Unless otherwise stated, the enrichment at any point is above natural abundance and enough to alter a detectable property of the drug in a human.

[0239] In one embodiment, the substitution of a hydrogen atom for a deuterium atom can be provided in any of Al, Al', A2, Bl, Bl', B2, B3, B4, CI, CI', C2, C3, C4, LI, LI', L2, L2', L4 or L5. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group selected from any of R, R', R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, R^5, R^6, $R^{6'}$, R^7, R^8, $R^{8'}$, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{19}, R^{21}, R^{22}, R^{23}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{71}, R^{101}, or R^{102}. For example, when any of R groups are, or contain for example through substitution, methyl, ethyl, or methoxy, the alkyl residue may be deuterated (in nonlimiting embodiments, CD3, CH2CD3, CD2CD3, CDH2, CD2H, CD3, CHDCH2D, CH2CD3, CHDCHD2, OCDH2, OCD2H, or OCD3 etc.). In certain other embodiments, an R group has a " ' " or an "a" designation, which in one embodiment can be deuterated. In certain other embodiments, when two substituents of the central core ring are combined to form a cyclopropyl ring, the unsubstituted methylene carbon may be deuterated.

[0240] The compound of the present invention may form a solvate with solvents (including water). Therefore, in one embodiment, the invention includes a solvated form of the active compound. The term "solvate" refers to a molecular complex of a compound of the present invention (including a salt thereof) with one or more solvent molecules. Nonlimiting examples of solvents are water, ethanol, dimethyl sulfoxide, acetone and other common organic solvents. The term "hydrate" refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D2O, d_6-acetone, d_6-DMSO. A solvate can be in a liquid or solid form.

[0241] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -(C=0)NH2 is attached through carbon of the keto (C=0) group.

[0242] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a moiety selected from the indicated group, provided that the designated atom's normal valence is not exceeded and the resulting compound is stable. For example, when the substituent is oxo (i.e., =0) then two hydrogens on the atom are replaced. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or

variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates.

[0243] A stable active compound refers to a compound that can be isolated and can be formulated into a dosage form with a shelf life of at least one month. A stable manufacturing intermediate or precursor to an active compound is stable if it does not degrade within the period needed for reaction or other use. A stable moiety or substituent group is one that does not degrade, react or fall apart within the period necessary for use. Nonlimiting examples of unstable moieties are those that combine heteroatoms in an unstable arrangement, as typically known and identifiable to those of skill in the art.

[0244] Any suitable group may be present on a "substituted" or "optionally substituted" position that forms a stable molecule and meets the desired purpose of the invention and includes, but is not limited to, e.g., halogen (which can independently be F, CI, Br or I); cyano; hydroxyl; nitro; azido; alkanoyl (such as a C2-C6 alkanoyl group); carboxamide; alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aiyloxy such as phenoxy; alkylthio including those having one or more thioether linkages; alkyl sulfinyl; alkylsulfonyl groups including those having one or more sulfonyl linkages; aminoalkyl groups including groups having one or more N atoms; aryl (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having for example, 1 to 3 separate or fused rings and from 6 to about 14 or 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy, for example, having 1 to 3 separate or fused rings with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen and amino. In certain embodiments "optionally substituted" includes one or more substituents independently replaced from halogen, hydroxyl, amino, cyano, -CHO, -COOH, -CONH2, Ci-Cealkyl, C2-Cealkenyl, C2-Cealkynyl, -Ci-Cealkoxy, C2-Cealkanoyl, Ci-Cealkylester, (mono- and di-Ci-C6alkylamino)Co-C2alkyl, Ci-C2haloalkyl, hydoxyCi-C_6alkyl, ester, carbamate, urea, sulfonamide,-Ci-C6alkyl(heterocyclo), Ci-C6alkyl(heteroaryl), -Ci-C_6alkyl(C3-

C7cycloalkyl), 0-Ci-C6alkyl(C3-C7cycloalkyl), $B(OH)_2$, phosphate, phosphonate and Ci-C_2haloalkoxy.

[0245] "Alkyl" is a branched or straight chain saturated aliphatic hydrocarbon group. In one embodiment, the alkyl contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the alkyl contains from 1 to about 8 carbon atoms. In certain embodiments, the alkyl is C1-C2, C1-C3, C1-C4, C1-C5 or Ci-C_6. The specified ranges as used herein indicate an alkyl group having each member of the range described as an independent species. For example, the term Ci-C_6 alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term Ci-C4alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. When Co-Cn alkyl is used herein in conjunction with another group, for example, (C3-C7cycloalkyl)Co-C4 alkyl, or -Co-C4alkyl(C3-C7cycloalkyl), the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond (Coalkyl), or attached by an alkyl chain in this case 1, 2, 3, or 4 carbon atoms. Alkyls can also be attached via other groups such as heteroatoms as in -0-Co-C4alkyl(C3-C7cycloalkyl). Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, *tert*-pentyl, neopentyl, n-hexyl, 2-methylpentane, 3-methylpentane, 2,2-dimethylbutane, 2,3-dimethylbutane, and hexyl. In one embodiment, the alkyl group is optionally substituted as described above. In one embodiment, trimethylsilyl can be used instead of t-butyl.

[0246] In one embodiment, when a term is used that includes "alk" it should be understood that "cycloalkyl" or "carbocyclic" can be considered part of the definition, unless unambiguously excluded by the context. For example and without limitation, the terms alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkenloxy, haloalkyl, aminoalkyl, alkylene, alkenylene, alkynylene, etc. can all be considered to include the cyclic forms of alkyl, unless unambiguously excluded by context.

[0247] "Alkenyl" is a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds that may occur at a stable point along the chain. Nonlimiting examples are C2-Csalkenyl, C_2-C7alkenyl, C2-C_6alkenyl, C2-Csalkenyl and C_2-C4alkenyl. The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkenyl

include, but are not limited to, ethenyl and propenyl. In one embodiment, the alkenyl group is optionally substituted as described above.

[0248] "Alkynyl" is a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain, for example, C2-C8alkynyl or C2-C_6alkynyl. The specified ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. In one embodiment, the alkynyl group is optionally substituted as described above.

[0249] "Alkylene" is a bivalent saturated hydrocarbon. Alkylenes, for example, can be a 1, 2, 3, 4, 5, 6, 7 to 8 carbon moiety, 1 to 6 carbon moiety, or an indicated number of carbon atoms, for example Ci-C2alkylene, Ci-C3alkylene, Ci-C4alkylene, Ci-Csalkylene, or Ci-C6alkylene.

[0250] "Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C2-C4alkenylene.

[0251] "Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C2-C4alkynylene.

[0252] "Alkoxy" is an alkyl group as defined above covalently bound through an oxygen bridge (-0-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly an "alkylthio" or a "thioalkyl" group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a sulfur bridge (-S-). In one embodiment, the alkoxy group is optionally substituted as described above.

[0253] "Alkenyloxy" is an alkenyl group as defined covalently bound to the group it substitutes by an oxygen bridge (-0-).

[0254] "Alkanoyl" is an alkyl group as defined above covalently bound through a carbonyl (C=0) bridge. The carbonyl carbon is included in the number of carbons, that is C2alkanoyl is a

CH3(C=0)- group. In one embodiment, the alkanoyl group is optionally substituted as described above.

[0255] "Alkylester" is an alkyl group as defined herein covalently bound through an ester linkage. The ester linkage may be in either orientation, e.g., a group of the formula -0(C=0)alkyl or a group of the formula -(C=0)Oalkyl.

[0256] "Amide" or "carboxamide" is -C(0)NR^{a}R^b wherein R^a and R^b are each independently selected from hydrogen, alkyl, for example, Ci-C$_6$alkyl, alkenyl, for example, C$_2$-C$_6$alkenyl, alkynyl, for example, C$_2$-C$_6$alkynyl, -Co-C4alkyl(C3-C7cycloalkyl), -Co-C4alkyl(C3-C7heterocycloalkyl), -Co-C4alkyl(aryl), and -Co-C4alkyl(heteroaryl); or together with the nitrogen to which they are bonded, R^a and R^b can form a C3-C7heterocyclic ring. In one embodiment, the R^a and R^b groups are each independently optionally substituted as described herein.

[0257] "Carbocyclic group", "carbocyclic ring", or "cycloalkyl" is a saturated or partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. A carbocyclic group typically contains 1 ring of 3 to 7 carbon atoms or 2 fused rings each containing 3 to 7 carbon atoms. Cycloalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents can have a cycloalkyl group, which is attached as a spiro group. Examples of carbocyclic rings include cyclohexenyl, cyclohexyl, cyclopentenyl, cyclopentyl, cyclobutenyl, cyclobutyl and cyclopropyl rings. In one embodiment, the carbocyclic ring is optionally substituted as described above. In one embodiment, the cycloalkyl is a partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. In another embodiment, the cycloalkyl is a saturated group containing all carbon ring atoms.

[0258] "Carbocyclic-oxy group" is a monocyclic carbocyclic ring or a mono- or bi-cyclic carbocyclic group as defined above attached to the group it substitutes via an oxygen, -0-, linker.

[0259] "Haloalkyl" indicates both branched and straight-chain alkyl groups substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, monofluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0260] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0261] "Hydroxyalkyl" is an alkyl group as previously described, substituted with at least one hydroxyl subsitutuent.

[0262] "Aminoalkyl" is an alkyl group as previously described, substituted with at least one amino subsitutuent.

[0263] "Halo" or "halogen" indicates independently, any of fluoro, chloro, bromo or iodo.

[0264] "Aryl" indicates an aromatic group containing only carbon in the aromatic ring or rings. In one embodiment, the aryl group contains 1 to 3 separate or fused rings and is 6 to about 14 or 18 ring atoms, without heteroatoms as ring members. When indicated, such aryl groups may be further substituted with carbon or non-carbon atoms or groups. Such substitution may include fusion to a 4 to 7 or a 5 to 7-membered saturated or partially unsaturated cyclic group that optionally contains 1, 2 or 3 heteroatoms independently replaced from N, O, B, P, Si and/or S, to form, for example, a 3,4-methylenedioxyphenyl group. Aryl groups include, for example, phenyl and naphthyl, including 1-naphthyl and 2-naphthyl. In one embodiment, aryl groups are pendant. An example of a pendant ring is a phenyl group substituted with a phenyl group. In one embodiment, the aryl group is optionally substituted as described above.

[0265] The term "heterocycle," or "heterocyclic ring" as used herein refers to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring without aromaticity) carbocyclic moiety of 3 to about 12, and more typically 3, 4, 5, 6, 7, 8 to 10 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus sulfur, silicon and boron, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described above. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, S, Si and B) or a bicycle having 6 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, S, Si and B), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur, boron or silicon. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, piperidonyl, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl,

azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, pyrazolidinylimidazolinyl, imidazolidinyl, 2-oxa-5-azabicyclo[2.2.2]octane, 3-oxa-8-azabicyclo[3.2.1]octane, 8-oxa-3-azabicyclo[3.2.1]octane, 6-oxa-3-azabicyclo[3.1.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl, quinolizinyl, N-pyridyl ureas, and pyrrolopyrimidine. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 1 or 2 ring carbon atoms are substituted with oxo (=0) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein, for example, 1, 2, or 3 substituents.

[0266] "Heterocyclicoxy group" is a monocyclic heterocyclic ring or a bicyclic heterocyclic group as described previously linked to the group it substitutes via an oxygen, -0-, linker.

[0267] "Heteroaryl" referes to a stable monocyclic aromatic ring which contains from 1 to 3, or in some embodiments from 1, 2 or 3 heteroatoms replaced from N, O, S, B or P with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5, 6, or 7 membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms replaced from N, O, S, B or P with remaining ring atoms being carbon. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Monocyclic heteroaryl groups typically have from 5, 6, or 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 8- to 10-membered heteroaryl groups, that is, groups containing 8 or 10 ring atoms in which one 5, 6, or 7 member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. In one embodiment, the total number of S and O atoms in the heteroaryl group is not more than 2. In another embodiment, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl,

thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, tetrahydrofuranyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein. "Heteroaryloxy" is a heteroaryl group as described bound to the group it substituted via an oxygen, -0-, linker.

[0268] "Heterocycloalkyl" is a saturated ring group. It may have, for example, 1, 2, 3, or 4 heteroatoms independently replaced from N, S, O, Si and B with remaining ring atoms being carbon. In a typical embodiment, nitrogen is the heteroatom. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

[0269] The term "mono- and/ or di-alkylamino" indicate a secondary or *ter*tiary alkylamino group, wherein the alkyl groups are independently replaced alkyl groups, as defined herein. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propyl-amino.

[0270] A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, implants, particles, spheres, creams, ointments, suppositories, inhalable forms, transdermal forms, buccal, sublingual, topical, gel, mucosal, and the like. A "dosage form" can also include an implant, for example an optical implant.

[0271] "Pharmaceutical compositions" are compositions comprising at least one active agent, and at least one other substance, such as a carrier. "Pharmaceutical combinations" are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat any disorder described herein.

[0272] A "pharmaceutically acceptable salt" is a derivative of the disclosed compound in which the parent compound is modified by making inorganic and organic, pharmaceutically acceptable, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional

chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are typical, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0273] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like, or using a different acid that produces the same counterion. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

[0274] The term "carrier" applied to pharmaceutical compositions/combinations of the invention refers to a diluent, excipient, or vehicle with which an active compound is provided.

[0275] A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition/combination that is generally safe, non-toxic and neither biologically nor otherwise inappropriate for administration to a host, typically a human. In one embodiment, an excipient is used that is acceptable for veterinary use.

[0276] A "patient" or "host" or "subject" is a human or non-human animal in need of treatment or prevention of any of the disorders as specifically described herein, including but not limited to by modulation of the complement Factor D pathway. Typically the host is a human. A "patient" or "host" or "subject" also refers to for example, a mammal, primate (e.g., human), cows, sheep, goat, horse, dog, cat, rabbit, rat, mice, fish, bird and the like.

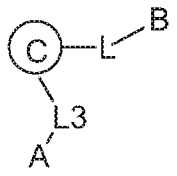
[0277] A "prodrug" as used herein, means a compound which when administered to a host *in vivo* is converted into a parent drug. As used herein, the term "parent drug" means any of the presently described chemical compounds described herein. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent. Prodrug strategies exist which provide choices in modulating the conditions for *in vivo* generation of the parent drug, all of which are deemed included herein. Nonlimiting examples of prodrug strategies include covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylation, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others.

[0278] "Providing a compound with at least one additional active agent," for example, in one embodiment can mean that the compound and the additional active agent(s) are provided simultaneously in a single dosage form, provided concomitantly in separate dosage forms, or provided in separate dosage forms for administration. In one embodiment, the compound administrations are separated by some amount of time that is within the time in which both the compound and the at least one additional active agent are within the blood stream of a patient. In certain embodiments the compound and the additional active agent need not be prescribed for a patient by the same medical care worker. In certain embodiments the additional active agent or agents need not require a prescription. Administration of the compound or the at least one additional active agent can occur via any appropriate route, for example, oral tablets, oral capsules, oral liquids, inhalation, injection, suppositories, parenteral, sublingual, buccal, intravenous, intraaortal, transdermal, polymeric controlled delivery, non-polymeric controlled delivery, nano or microparticles, liposomes, and/or topical contact. In one embodiment, the instructions for administration in a form of combination therapy is provided in the drug labeling.

[0279] A "therapeutically effective amount" of a pharmaceutical composition/combination of this invention means an amount effective, when administered to a host, to provide a therapeutic benefit such as an amelioration of symptoms or reduction or dimunition of the disease itself. In one embodiment, a therapeutically effective amount is an amount sufficient to prevent a significant increase or will significantly reduce the detectable level of complement Factor D in the patient's blood, serum, or tissues.

II. DETAILED DESCRIPTION OF THE ACTIVE COMPOUNDS

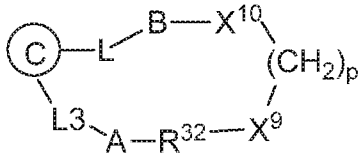
[0280] According to the present invention, a compound of Formula I is provided:



(I)

as well as the pharmaceutically acceptable salts and compositions thereof. Formula I can be considered to have a central core C, an L substituent, a B substituent, and an L3-A substituent. Formula I comprises at least one of the A2, B3, C3, L2, L2', or L5 (and in certain embodiments, C4) moieties described herein. The invention includes a compound of Formula I, or a pharmaceutically acceptable salt or composition thereof, wherein R^{12} or R^{13} on the A group is an aryl, heteroaryl or heterocycle, for example an R^{32}. In one embodiment, the compound is an inhibitor of complement factor D, and therefore can be used as an effective amount to treat a host in need of complement factor D modulation. In another embodiment, the compound acts through a mechanism other than inhibition of complement D to treat a disorder described herein in a host, typically a human.

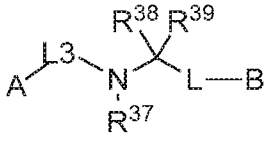
[0281] The present invention also includes a compound of Formula Γ:



(I')

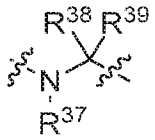
as well as the pharmaceutically acceptable salts and compositions thereof. Formula Γ has a central core C moiety, an A substituent, a L3 substituent, an L substituent, a B substituent and a -X^9-(CH2)p-X^{10} linker; wherein R^{12} or R^{13} on the A1 or A2 group is an an amide substituent, for example a divalent R^{32} moiety. In one embodiment, this compound is an inhibitor of complement factor D, and therefore can be used as an effective amount to treat a host in need of complement factor D modulation. Alternatively, the compound may act through a different mechanism of action to treat the disorders described herein.

[0282] In addition, the present invention provides a compound of Formula I":



(I")

as well as the pharmaceutically acceptable salts and compositions thereof. Formula I" has an

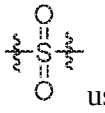


moiety, an A substituent, a L3 substituent, a L substituent and a B substituent. Compounds of Formula I", or a pharmaceutically acceptable salt or composition thereof, wherein R^{12} or R^{13} on the A1 or A2 group is an heteroaryl, aryl, or heterocycle substituent, for example an R^{32}. In one embodiment, this compound is an inhibitor of complement factor D, and therefore can be used as an effective amount to treat a host in need of complement factor D modulation. Alternatively, the compound may act through a different mechanism of action to treat the disorders described herein.

[0283] Non-limiting examples of compounds falling within Formula I and Formula Γ with variations in the variables e.g., A, B, R^R 3', and L, are described below.

[0284] Non-limiting examples of compounds falling within Formula I" with variations in the variables e.g., R^{37}, R^{38}, R^{39}, A, B, L and L3 are described below. The disclosure includes all combinations of these definitions as long as a stable compound results.

[0285] In certain embodiments, any of the active compounds can be provided in its N-oxide form to a patient in need thereof. In a different embodiment, an N-oxide of one of the active compounds or a precursor of the active compound is used in a manufacturing scheme. In yet another embodiment, the N-oxide is a metabolite of administration of one of the active compounds herein, and may have independent activity. The N-oxide can be formed by treating the compound of interest with an oxidizing agent, for example a suitable peroxyacid or peroxide, to generate an N-oxide compound. For example, a heteroaryl group, for example a pyridyl group, can be treated with an oxidizing agent such as sodium percarbonate in the presence of a rhenium-based catalyst under mild reaction conditions to generate an N-oxide compound. A person skilled in the art will understand that appropriate protecting groups may be necessary to carry out the chemistry. See, Jain, S.L. et al., "Rhenium-Catalyzed Highly Efficient Oxidations of Tertiary Nitrogen Compounds to N-Oxides Using Sodium Percarbonate as Oxygen Source, Syniett, 2261-2663, 2006.

[0286] In other embodiments, any of the active compounds with a sulfur can be provided in its sulfoxide or sulfone form to a patient in need thereof. In a different embodiment, a sulfoxide or sulfone of one of the active compounds or a precursor of the active compound is used in a manufacturing scheme. A sulfur atom in a selected compound as described herein can be oxidized to form a sulfoxide  or a sulfone  using known methods. For example, the compound l,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride (TAPC) is an efficient promoter for the oxidation of sulfides to sulfoxides. *See*, Bahrami, M. et a!., "TAPC-Promoted Oxidation of sulfides and Deoxygenation of Sulfoxides", J. Org. Chem., 75, 6208-6213 (2010). Oxidation of sulfides with 30% hydrogen peroxide catalyzed by tantalum carbide provides sulfoxides in high yields, see, Kirihara, A., et al., "Tantalum Carbide or Niobium Carbide Catalyzed Oxidation of Sulfides with Hydrogen Peroxide: Highly Efficient and Chemoselective Syntheses of Sulfoxides and Sulfones", Syniett, 1557-1561 (2010). Sulfides can be oxidized to sulfones using, for example, niobium carbide as the catalyst, see, Kirihara, A., et al., "Tantalum Cardide or Niobium Carbide Catalyzed Oxidation of Sulfides with Hydrogen Peroxide: Highly Efficient and Chemoselective Syntheses of Sulfoxides and Sulfones", Syniett, 1557-1 561 (2010). Urea-hydrogen peroxide adduct is a stable inexpensive and easily handled reagent for the oxidation of sulfides to sulfones, see Varnia, R.S. and Naicker, K.P., "The Urea-Hydrogen Peroxide Complex: Solid-State Oxidative Protocols for Hydroxy! ated Aldehydes and Ketones (Dakin Reaction), Nitriles, Sulfides, and Nitrogen Heterocycles", Org. Lett., 1, 189-191 (1999). One skilled in the art will appreciate that other heteroatonis, such as nitrogen, may need to be protected and then deprotected while carrying out the oxidation of a sulfur atom to produce the desired compound.

Formulas 2 through 654

[0287] In one aspect, the disclosure includes compounds and salts of Formulas 2 - 654 for any use and in any composition described in this application.

Table 1. Exemplary Compounds within the Present Invention.

Formula No.	Formula	Formula No.	Formula
2	A1L4C1L1B3	300	A1'L5C1'L1'B2
3	A1L4C1L1'B3	301	A1'L5C1'L1'B3
4	A1L4C1L2B1	302	A1'L5C1'L2B1
5	A1L4C1L2B1'	303	A1'L5C1'L2B1'
6	A1L4C1L2B2	304	A1'L5C1'L2B2
7	A1L4C1L2B3	305	A1'L5C1'L2B3
8	A1L4C1'L1B3	306	A1'L5C2L1B1
9	A1L4C1'L1'B3	307	A1'L5C2L1B1'
10	A1L4C1'L2B1	308	A1'L5C2L1B2
11	A1L4C1'L2B1'	309	A1'L5C2L1B3
12	A1L4C1'L2B2	310	A1'L5C2L1'B1
13	A1L4C1'L2B3	311	A1'L5C2L1'B1'
14	A1L4C2L1B3	312	A1'L5C2L1'B2
15	A1L4C2L1'B3	313	A1'L5C2L1'B3
16	A1L4C2L2B1	314	A1'L5C2L2B1
17	A1L4C2L2B1'	315	A1'L5C2L2B1'
18	A1L4C2L2B2	316	A1'L5C2L2B2
19	A1L4C2L2B3	317	A1'L5C2L2B3
20	A1L4C3L1B1	318	A1'L5C3L1B1
21	A1L4C3L1B1'	319	A1'L5C3L1B1'
22	A1L4C3L1B2	320	A1'L5C3L1B2
23	A1L4C3L1B3	321	A1'L5C3L1B3
24	A1L4C3L1'B1	322	A1'L5C3L1'B1
25	A1L4C3L1'B1'	323	A1'L5C3L1'B1'
26	A1L4C3L1'B2	324	A1'L5C3L1'B2
27	A1L4C3L1'B3	325	A1'L5C3L1'B3
28	A1L4C3L2B1	326	A1'L5C3L2B1
29	A1L4C3L2B1'	327	A1'L5C3L2B1'
30	A1L4C3L2B2	328	A1'L5C3L2B2
31	A1L4C3L2B3	329	A1'L5C3L2B3
32	A1L5C1L1B1	330	A2L4C1L1B1
33	A1L5C1L1B1'	331	A2L4C1L1B1'
34	A1L5C1L1B2	332	A2L4C1L1B2
35	A1L5C1L1B3	333	A2L4C1L1B3
36	A1L5C1L1'B1	334	A2L4C1L1'B1
37	A1L5C1L1'B1'	335	A2L4C1L1'B1'
38	A1L5C1L1'B2	336	A2L4C1L1'B2
39	A1L5C1L1'B3	337	A2L4C1L1'B3
40	A1L5C1L2B1	338	A2L4C1L2B1

Formula No.	Formula	Formula No.	Formula
41	A1L5C1L2B1'	339	A2L4C1L2B1'
42	A1L5C1L2B2	340	A2L4C1L2B2
43	A1L5C1L2B3	341	A2L4C1L2B3
44	A1L5C1'L1B1	342	A2L4C1'L1B1
45	A1L5C1'L1B1'	343	A2L4C1'L1B1'
46	A1L5C1'L1B2	344	A2L4C1'L1B2
47	A1L5C1'L1B3	345	A2L4C1'L1B3
48	A1L5C1'L1'B1	346	A2L4C1'L1'B1
49	A1L5C1'L1'B1'	347	A2L4C1'L1'B1'
50	A1L5C1'L1'B2	348	A2L4C1'L1'B2
51	A1L5C1'L1'B3	349	A2L4C1'L1'B3
52	A1L5C1'L2B1	350	A2L4C1'L2B1
53	A1L5C1'L2B1'	351	A2L4C1'L2B1'
54	A1L5C1'L2B2	352	A2L4C1'L2B2
55	A1L5C1'L2B3	353	A2L4C1'L2B3
56	A1L5C2L1B1	354	A2L4C2L1B1
57	A1L5C2L1B1'	355	A2L4C2L1B1'
58	A1L5C2L1B2	356	A2L4C2L1B2
59	A1L5C2L1B3	357	A2L4C2L1B3
60	A1L5C2L1'B1	358	A2L4C2L1'B1
61	A1L5C2L1'B1'	359	A2L4C2L1'B1'
62	A1L5C2L1'B2	360	A2L4C2L1'B2
63	A1L5C2L1'B3	361	A2L4C2L1'B3
64	A1L5C2L2B1	362	A2L4C2L2B1
65	A1L5C2L2B1'	363	A2L4C2L2B1'
66	A1L5C2L2B2	364	A2L4C2L2B2
67	A1L5C2L2B3	365	A2L4C2L2B3
68	A1L5C3L1B1	366	A2L4C3L1B1
69	A1L5C3L1B1'	367	A2L4C3L1B1'
70	A1L5C3L1B2	368	A2L4C3L1B2
71	A1L5C3L1B3	369	A2L4C3L1B3
72	A1L5C3L1'B1	370	A2L4C3L1'B1
73	A1L5C3L1'B1'	371	A2L4C3L1'B1'
74	A1L5C3L1'B2	372	A2L4C3L1'B2
75	A1L5C3L1'B3	373	A2L4C3L1'B3
76	A1L5C3L2B1	374	A2L4C3L2B1
77	A1L5C3L2B1'	375	A2L4C3L2B1'
78	A1L5C3L2B2	376	A2L4C3L2B2
79	A1L5C3L2B3	377	A2L4C3L2B3

Formula No.	Formula	Formula No.	Formula
80	A1'L4C1L1B3	378	A2L5C1L1B1
81	A1'L4C1L1'B3	379	A2L5C1L1B1'
82	A1'L4C1L2B1	380	A2L5C1L1B2
83	A1'L4C1L2B1'	381	A2L5C1L1B3
84	A1'L4C1L2B2	382	A2L5C1L1'B1
85	A1'L4C1L2B3	383	A2L5C1L1'B1'
86	A1'L4C1'L1B3	384	A2L5C1L1'B2
87	A1'L4C1'L1'B3	385	A2L5C1L1'B3
88	A1'L4C1'L2B1	386	A2L5C1L2B1
89	A1'L4C1'L2B1'	387	A2L5C1L2B1'
90	A1'L4C1'L2B2	388	A2L5C1L2B2
91	A1'L4C1'L2B3	389	A2L5C1L2B3
92	A1'L4C2L1B3	390	A2L5C1'L1B1
93	A1'L4C2L1'B3	391	A2L5C1'L1B1'
94	A1'L4C2L2B1	392	A2L5C1'L1B2
95	A1'L4C2L2B1'	393	A2L5C1'L1B3
96	A1'L4C2L2B2	394	A2L5C1'L1'B1
97	A1'L4C2L2B3	395	A2L5C1'L1'B1'
98	A1'L4C3L1B1	396	A2L5C1'L1'B2
99	A1'L4C3L1B1'	397	A2L5C1'L1'B3
100	A1'L4C3L1B2	398	A2L5C1'L2B1
101	A1'L4C3L1B3	399	A2L5C1'L2B1'
102	A1'L4C3L1'B1	400	A2L5C1'L2B2
103	A1'L4C3L1'B1'	401	A2L5C1'L2B3
104	A1'L4C3L1'B2	402	A2L5C2L1B1
105	A1'L4C3L1'B3	403	A2L5C2L1B1'
106	A1'L4C3L2B1	404	A2L5C2L1B2
107	A1'L4C3L2B1'	405	A2L5C2L1B3
108	A1'L4C3L2B2	406	A2L5C2L1'B1
109	A1'L4C3L2B3	407	A2L5C2L1'B1'
110	A1'L5C1L1B1	408	A2L5C2L1'B2
111	A1'L5C1L1B1'	409	A2L5C2L1'B3
112	A1'L5C1L1B2	410	A2L5C2L2B1
113	A1'L5C1L1B3	411	A2L5C2L2B1'
114	A1'L5C1L1'B1	412	A2L5C2L2B2
115	A1'L5C1L1'B1'	413	A2L5C2L2B3
116	A1'L5C1L1'B2	414	A2L5C3L1B1
117	A1'L5C1L1'B3	415	A2L5C3L1B1'
118	A1'L5C1L2B1	416	A2L5C3L1B2

Formula No.	Formula	Formula No.	Formula
119	A1'L5C1L2B1'	417	A2L5C3L1B3
120	A1'L5C1L2B2	418	A2L5C3L1'B1
121	A1'L5C1L2B3	419	A2L5C3L1'B1'
122	A1'L5C1'L1B1	420	A2L5C3L1'B2
123	A1'L5C1'L1B1'	421	A2L5C3L1'B3
124	A1'L5C1'L1B2	422	A2L5C3L2B1
125	A1'L5C1'L1B3	423	A2L5C3L2B1'
126	A1'L5C1'L1'B1	424	A2L5C3L2B2
127	A1'L5C1'L1'B1'	425	A2L5C3L2B3
128	A2L4C1L1B4	426	A1'L4C3L1B4
129	A2L4C1L1'B4	427	A1'L4C3L1'B4
130	A2L4C1L2B4	428	A1'L4C3L2B4
131	A2L4C1'L1B4	429	A1'L5C3L1B4
132	A2L4C1'L1'B4	430	A1'L5C3L1'B4
133	A2L4C1'L2B4	431	A1'L5C3L2B4
134	A2L4C2L1B4	432	A1L4C1L2B4
135	A2L4C2L1'B4	433	A1L4C1'L2B4
136	A2L4C2L2B4	434	A1L4C2L2B4
137	A2L4C3L1B4	435	A1L5C1L2B4
138	A2L4C3L1'B4	436	A1L5C1'L2B4
139	A2L4C3L2B4	437	A1L5C2L2B4
140	A2L5C1L1B4	438	A1'L4C1L2B4
141	A2L5C1L1'B4	439	A1'L4C1'L2B4
142	A2L5C1L2B4	440	A1'L4C2L2B4
143	A2L5C1'L1B4	441	A1'L5C1L2B4
144	A2L5C1'L1'B4	442	A1'L5C1'L2B4
145	A2L5C1'L2B4	443	A1'L5C2L2B4
146	A2L5C2L1B4	444	A1L5C1L1B4
147	A2L5C2L1'B4	445	A1L5C1L1'B4
148	A2L5C2L2B4	446	A1L5C1'L1B4
149	A2L5C3L1B4	447	A1L5C1'L1'B4
150	A2L5C3L1'B4	448	A1L5C2L1B4
151	A2L5C3L2B4	449	A1L5C2L1'B4
152	A1L4C3L1B4	450	A1'L5C1L1B4
153	A1L4C3L1'B4	451	A1'L5C1L1'B4
154	A1L4C3L2B4	452	A1'L5C1'L1B4
155	A1L5C3L1B4	453	A1'L5C1'L1'B4
156	A1L5C3L1'B4	454	A1'L5C2L1B4

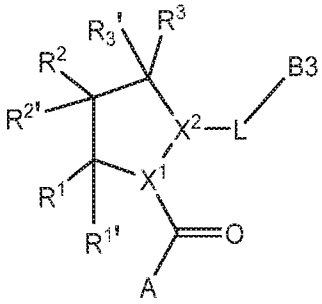
Formula No.	Formula	Formula No.	Formula
157	A1L5C3L2B4	455	A1'L5C2L1'B4
158	A1L4C4L2B1	456	A1'L5C4L2B1
159	A1L4C4L2B1'	457	A1'L5C4L2B1'
160	A1L4C4L2B2	458	A1'L5C4L2B2
161	A1L4C4L2B3	459	A1'L5C4L2B3
162	A1L5C4L2B1	460	A2L4C4L2B1
163	A1L5C4L2B1'	461	A2L4C4L2B1'
164	A1L5C4L2B2	462	A2L4C4L2B2
165	A1L5C4L2B3	463	A2L4C4L2B3
166	A1'L4C4L2B1	464	A2L5C4L2B1
167	A1'L4C4L2B1'	465	A2L5C4L2B1'
168	A1'L4C4L2B2	466	A2L5C4L2B2
169	A1'L4C4L2B3	467	A2L5C4L2B3
170	A2L4C4L2B4	468	A1'L4C4L2B4
171	A2L5C4L2B4	469	A1'L5C4L2B4
172	A1L4C4L2B4	470	A1'L5C4L2'B1
173	A1L5C4L2B4	471	A1'L5C4L2'B1'
174	A1L4C4L2'B1	472	A1'L5C4L2'B2
175	A1L4C4L2'B1'	473	A1'L5C4L2'B3
176	A1L4C4L2'B2	474	A2L4C4L2'B1
177	A1L4C4L2'B3	475	A2L4C4L2'B1'
178	A1L5C4L2'B1	476	A2L4C4L2'B2
179	A1L5C4L2'B1'	477	A2L4C4L2'B3
180	A1L5C4L2'B2	478	A2L5C4L2'B1
181	A1L5C4L2'B3	479	A2L5C4L2'B1'
182	A1'L4C4L2'B1	480	A2L5C4L2'B2
183	A1'L4C4L2'B1'	481	A2L5C4L2'B3
184	A1'L4C4L2'B2	482	A1'L4C4L2'B4
185	A1'L4C4L2'B3	483	A1'L5C4L2'B4
186	A2L4C4L2'B4	484	A1'L5C1'L2B1
187	A2L5C4L2'B4	485	A1'L5C1'L2B1'
188	A1L4C4L2'B4	486	A1'L5C1'L2B2
189	A1L5C4L2'B4	487	A1'L5C1'L2B3
190	A1L4C1L2B1	488	A1'L5C2L2B1
191	A1L4C1L2B1'	489	A1'L5C2L2B1'
192	A1L4C1L2B2	490	A1'L5C2L2B2
193	A1L4C1L2B3	491	A1'L5C2L2B3
194	A1L4C1'L2B1	492	A2L4C1L2B1

Formula No.	Formula	Formula No.	Formula
195	A1L4C1'L2B1'	493	A2L4C1L2B1'
196	A1L4C1'L2B2	494	A2L4C1L2B2
197	A1L4C1'L2B3	495	A2L4C1L2B3
198	A1L4C2L2B1	496	A2L4C1'L2B1
199	A1L4C2L2B1'	497	A2L4C1'L2B1'
200	A1L4C2L2B2	498	A2L4C1'L2B2
201	A1L4C2L2B3	499	A2L4C1'L2B3
202	A1L5C1L2B1	500	A2L4C2L2B1
203	A1L5C1L2B1'	501	A2L4C2L2B1'
204	A1L5C1L2B2	502	A2L4C2L2B2
205	A1L5C1L2B3	503	A2L4C2L2B3
206	A1L5C1'L2B1	504	A2L5C1L2B1
207	A1L5C1'L2B1'	505	A2L5C1L2B1'
208	A1L5C1'L2B2	506	A2L5C1L2B2
209	A1L5C1'L2B3	507	A2L5C1L2B3
210	A1L5C2L2B1	508	A2L5C1'L2B1
211	A1L5C2L2B1'	509	A2L5C1'L2B1'
212	A1L5C2L2B2	510	A2L5C1'L2B2
213	A1L5C2L2B3	511	A2L5C1'L2B3
214	A1'L4C1L2B1	512	A2L5C2L2B1
215	A1'L4C1L2B1'	513	A2L5C2L2B1'
216	A1'L4C1L2B2	514	A2L5C2L2B2
217	A1'L4C1L2B3	515	A2L5C2L2B3
218	A1'L4C1'L2B1	516	A1L4C1L2B4
219	A1'L4C1'L2B1'	517	A1L4C1'L2B4
220	A1'L4C1'L2B2	518	A1L4C2L2B4
221	A1'L4C1'L2B3	519	A1L5C1L2B4
222	A1'L4C2L2B1	520	A1L5C1'L2B4
223	A1'L4C2L2B1'	521	A1L5C2L2B4
224	A1'L4C2L2B2	522	A1'L4C1L2B4
225	A1'L4C2L2B3	523	A1'L4C1'L2B4
226	A1'L5C1L2B1	524	A1'L4C2L2B4
227	A1'L5C1L2B1'	525	A1'L5C1L2B4
228	A1'L5C1L2B2	526	A1'L5C1'L2B4
229	A1'L5C1L2B3	527	A1'L5C2L2B4
230	A2L4C1L2B4	528	A1'L5C1'L2'B1
231	A2L4C1'L2B4	529	A1'L5C1'L2'B1'
232	A2L4C2L2B4	530	A1'L5C1'L2'B2

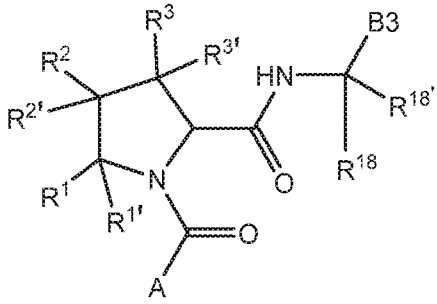
Formula No.	Formula	Formula No.	Formula
233	A2L5C1L2B4	531	A1'L5C1'L2'B3
234	A2L5C1'L2B4	532	A1'L5C2L2'B1
235	A2L5C2L2B4	533	A1'L5C2L2'B1'
236	A1L4C1L2'B1	534	A1'L5C2L2'B2
237	A1L4C1L2'B1'	535	A1'L5C2L2'B3
238	A1L4C1L2'B2	536	A2L4C1L2'B1
239	A1L4C1L2'B3	537	A2L4C1L2'B1'
240	A1L4C1'L2'B1	538	A2L4C1L2'B2
241	A1L4C1'L2'B1'	539	A2L4C1L2'B3
242	A1L4C1'L2'B2	540	A2L4C1'L2'B1
243	A1L4C1'L2'B3	541	A2L4C1'L2'B1'
244	A1L4C2L2'B1	542	A2L4C1'L2'B2
245	A1L4C2L2'B1'	543	A2L4C1'L2'B3
246	A1L4C2L2'B2	544	A2L4C2L2'B1
247	A1L4C2L2'B3	545	A2L4C2L2'B1'
248	A1L5C1L2'B1	546	A2L4C2L2'B2
249	A1L5C1L2'B1'	547	A2L4C2L2'B3
250	A1L5C1L2'B2	548	A2L5C1L2'B1
251	A1L5C1L2'B3	549	A2L5C1L2'B1'
252	A1L5C1'L2'B1	550	A2L5C1L2'B2
253	A1L5C1'L2'B1'	551	A2L5C1L2'B3
254	A1L5C1'L2'B2	552	A2L5C1'L2'B1
255	A1L5C1'L2'B3	553	A2L5C1'L2'B1'
256	A1L5C2L2'B1	554	A2L5C1'L2'B2
257	A1L5C2L2'B1'	555	A2L5C1'L2'B3
258	A1L5C2L2'B2	556	A2L5C2L2'B1
259	A1L5C2L2'B3	557	A2L5C2L2'B1'
260	A1'L4C1L2'B1	558	A2L5C2L2'B2
261	A1'L4C1L2'B1'	559	A2L5C2L2'B3
262	A1'L4C1L2'B2	560	A1L4C1L2'B4
263	A1'L4C1L2'B3	561	A1L4C1'L2'B4
264	A1'L4C1'L2'B1	562	A1L4C2L2'B4
265	A1'L4C1'L2'B1'	563	A1L5C1L2'B4
266	A1'L4C1'L2'B2	564	A1L5C1'L2'B4
267	A1'L4C1'L2'B3	565	A1L5C2L2'B4
268	A1'L4C2L2'B1	566	A1'L4C1L2'B4
269	A1'L4C2L2'B1'	567	A1'L4C1'L2'B4
270	A1'L4C2L2'B2	568	A1'L4C2L2'B4

Formula No.	Formula	Formula No.	Formula
271	A1'L4C2L2'B3	569	A1'L5C1L2'B4
272	A1'L5C1L2'B1	570	A1'L5C1'L2'B4
273	A1'L5C1L2'B1'	571	A1'L5C2L2'B4
274	A1'L5C1L2'B2	572	A2L4C4L1B4
275	A1'L5C1L2'B3	573	A2L4C4L1'B4
276	A2L4C1L2'B4	574	A2L5C4L1B4
277	A2L4C1'L2'B4	575	A2L5C4L1'B4
278	A2L4C2L2'B4	576	A1'L5C4L1B1
279	A2L5C1L2'B4	577	A1'L5C4L1B1'
280	A2L5C1'L2'B4	578	A1'L5C4L1B2
281	A2L5C2L2'B4	579	A1'L5C4L1B3
282	A2L4C4L1B1	580	A1'L5C4L1'B1
283	A2L4C4L1B1'	581	A1'L5C4L1'B1'
284	A2L4C4L1B2	582	A1'L5C4L1'B2
285	A2L4C4L1B3	583	A1'L5C4L1'B3
286	A2L4C4L1'B1	584	A1'L5C4L1B4
287	A2L4C4L1'B1'	585	A1'L5C4L1'B4
288	A2L4C4L1'B2	586	A1L5C4L1B1
289	A2L4C4L1'B3	587	A1L5C4L1B1'
290	A2L5C4L1B1	588	A1L5C4L1B2
291	A2L5C4L1B1'	589	A1L5C4L1B3
292	A2L5C4L1B2	590	A1L5C4L1'B1
293	A2L5C4L1B3	591	A1L5C4L1'B1'
294	A2L5C4L1'B1	592	A1L5C4L1'B2
295	A2L5C4L1'B1'	593	A1L5C4L1'B3
296	A2L5C4L1'B2	594	A1L5C4L1B4
297	A2L5C4L1'B3	595	A1L5C4L1'B4
298	A1'L4C4L1B3	596	A1L4C4L1B3
299	A1'L4C4L1'B3	597	A1L4C4L1'B3

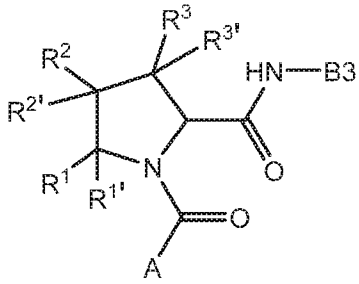
Table 2. Additional Exemplary Compounds within the Present Invention.



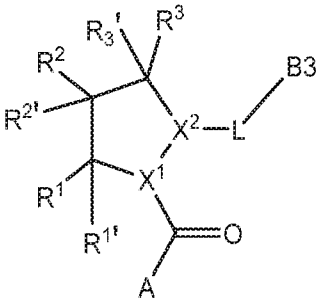
Formula 598



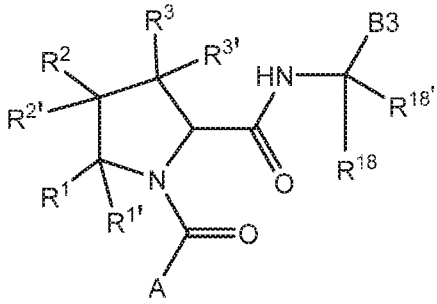
Formula 599



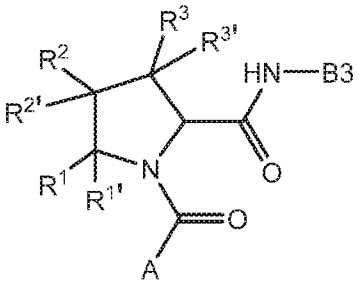
Formula 600



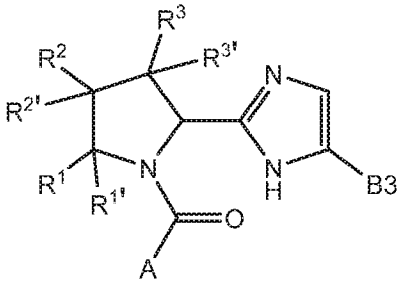
Formula 601



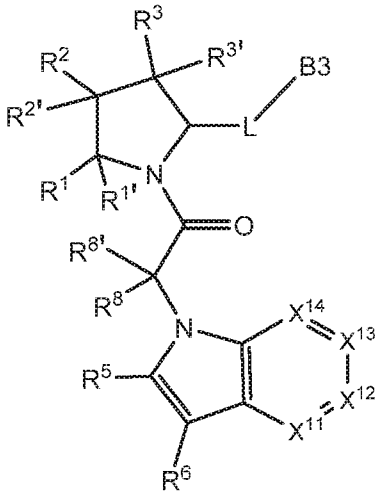
Formula 602



Formula 603



Formula 604



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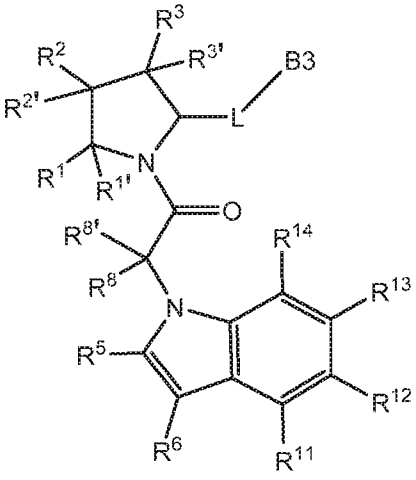

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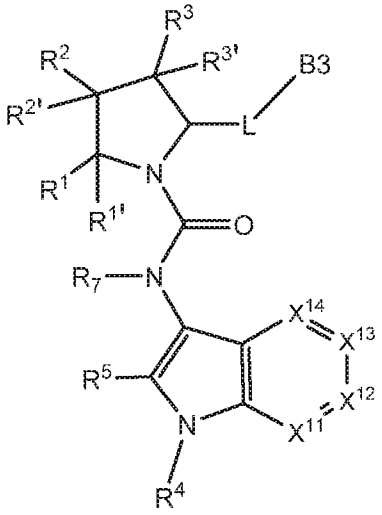
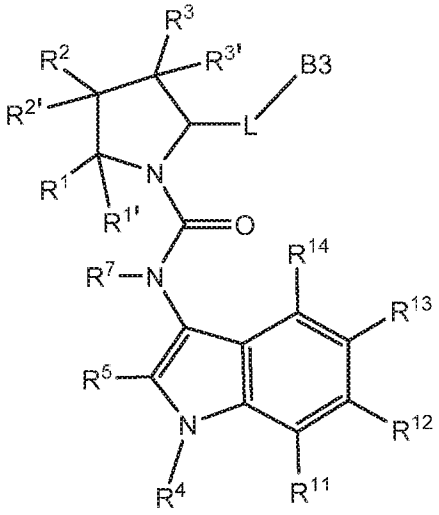
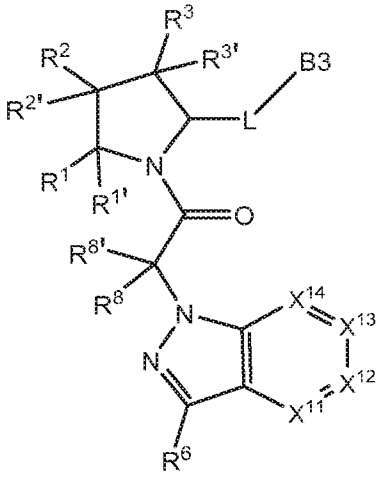


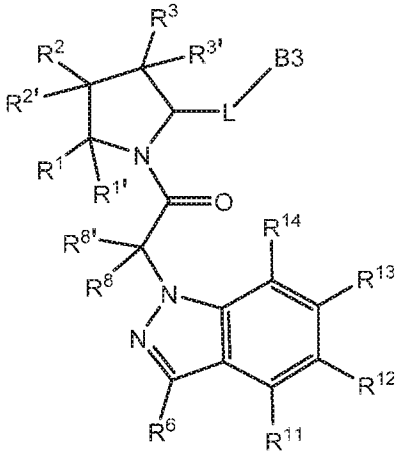
Formula 607



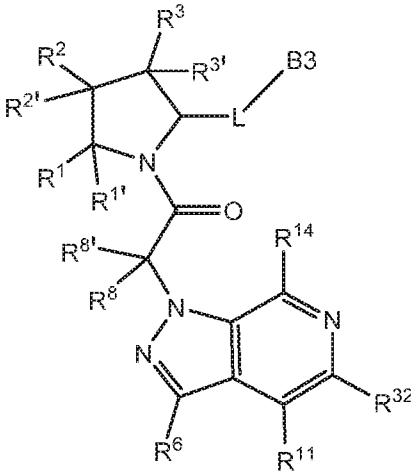
Formula 608



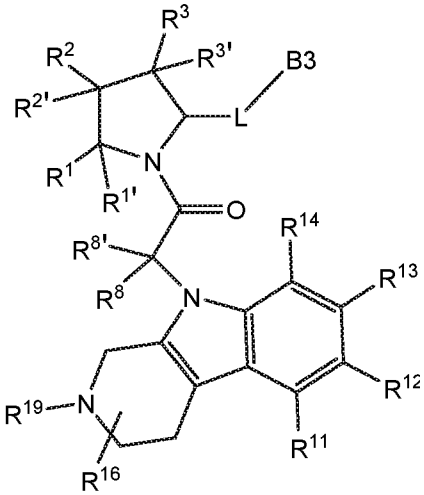
Formula 609



Formula 610



Formula 611



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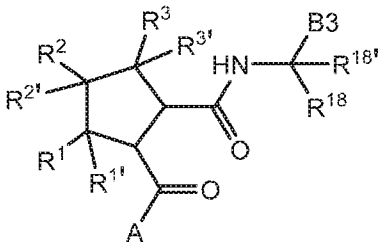
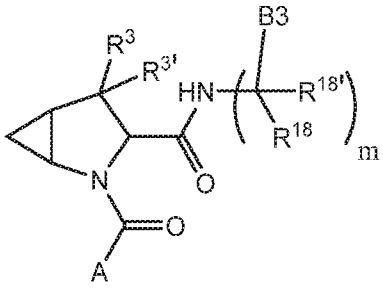
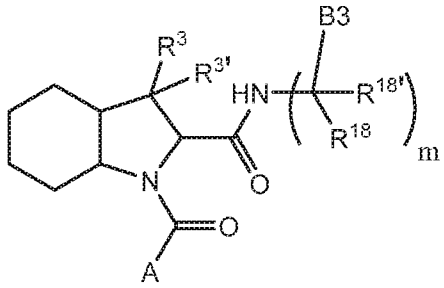


Formula 613



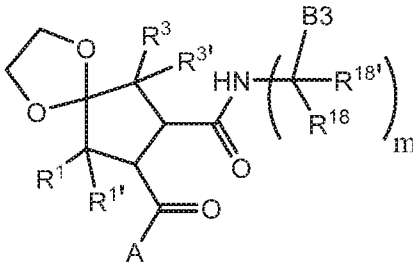
m is 0 or 1.

Formula 614



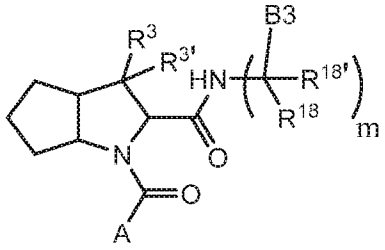
m is 0 or 1.

Formula 615



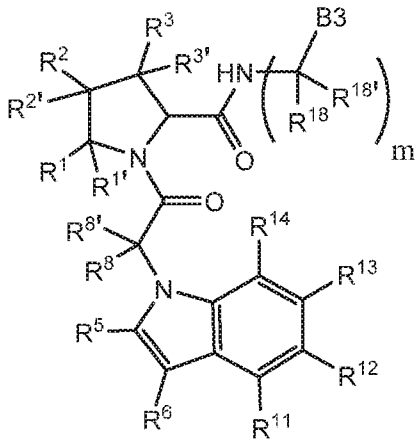
m is 0 or 1.

Formula 616



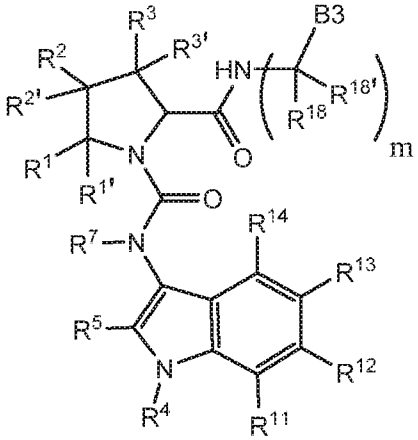
m is 0 or 1.

Formula 617



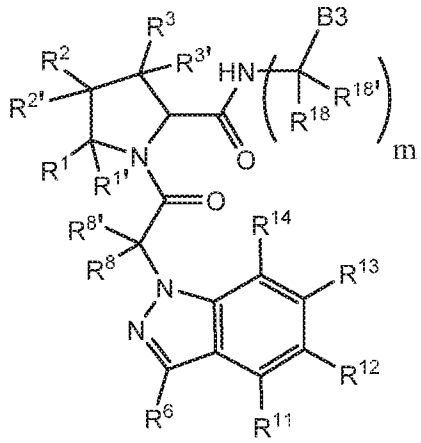
m is 0 or 1.

Formula 618



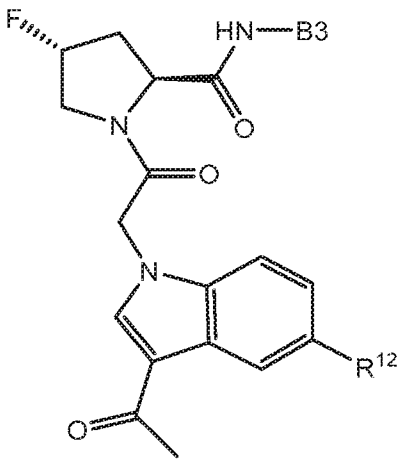
m is 0 or 1.

Formula 619

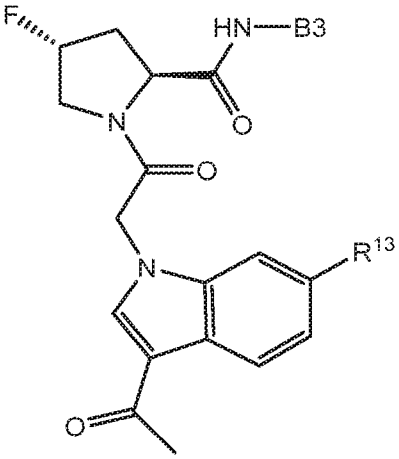


m is 0 or 1.

Formula 620



Formula 621



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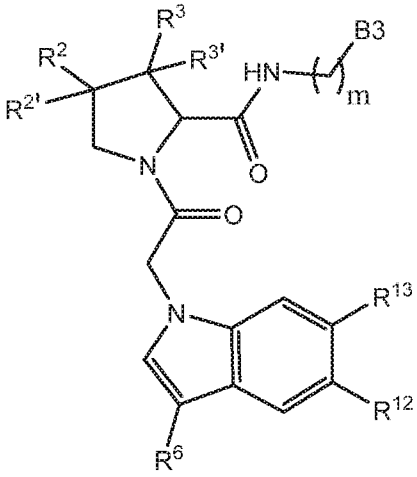
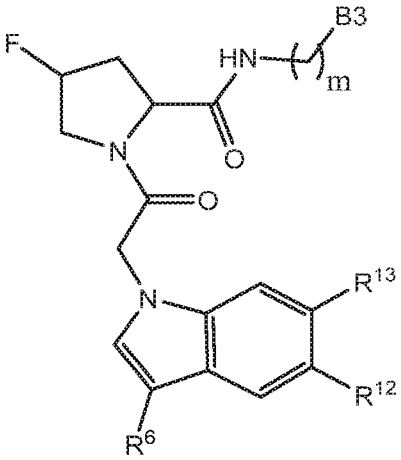


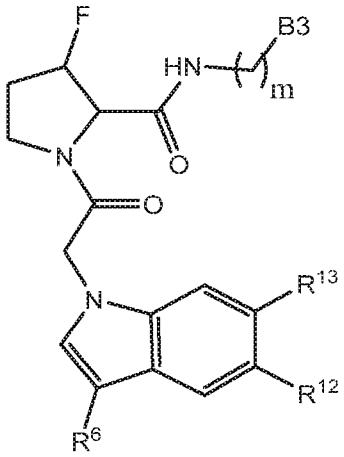
m is 0 or 1

Formula 623



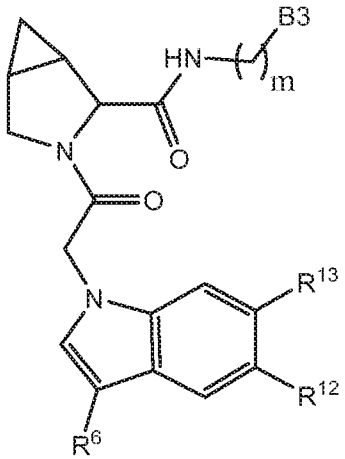
m is 0 or 1.

Formula 624



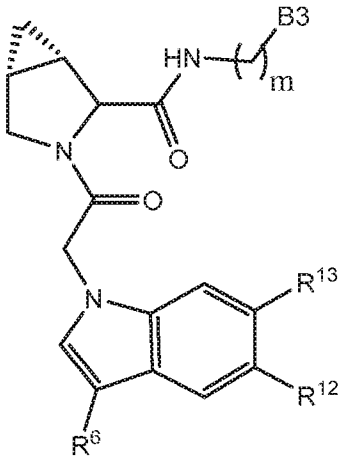
m is 0 or 1.

Formula 625



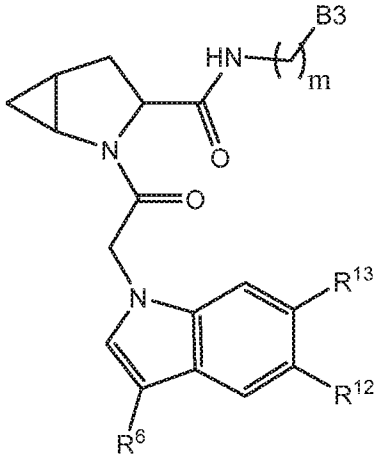
m is 0 or 1.

Formula 626



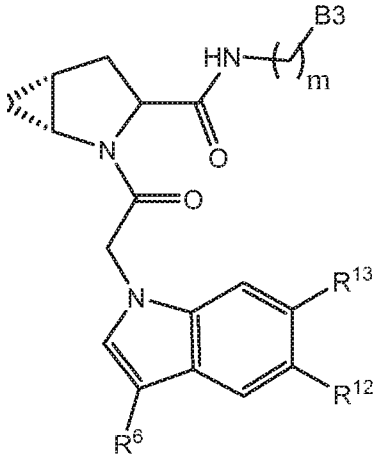
m is 0 or 1.

Formula 627



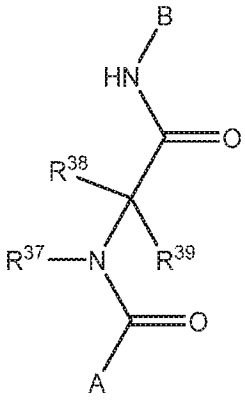
m is 0 or 1.

Formula 628

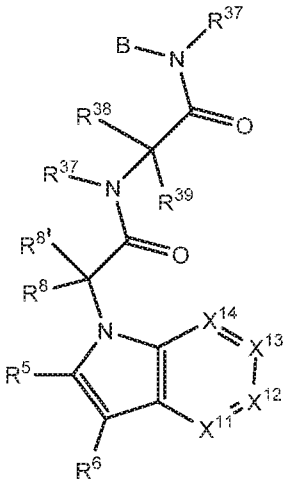


m is 0 or 1.

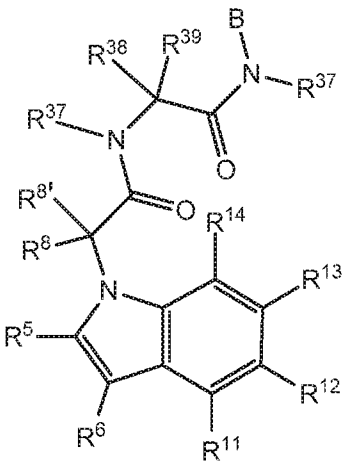
Formula 629



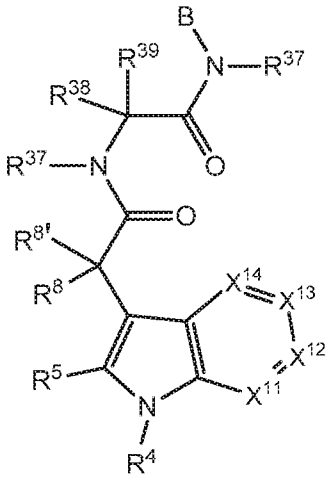
Formula 630,



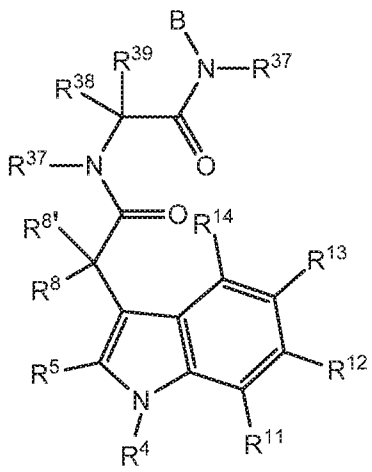
Formula 631,



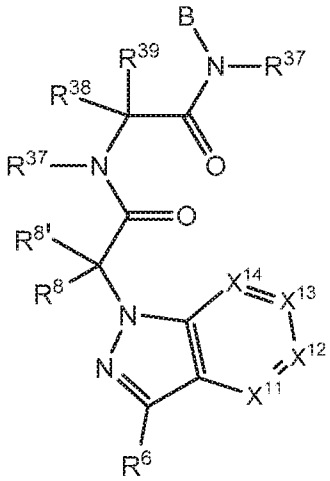
Formula 632



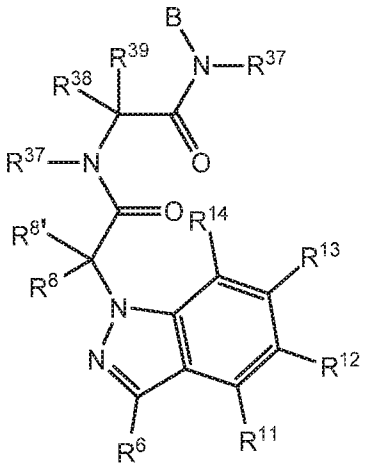
Formula 633 ,



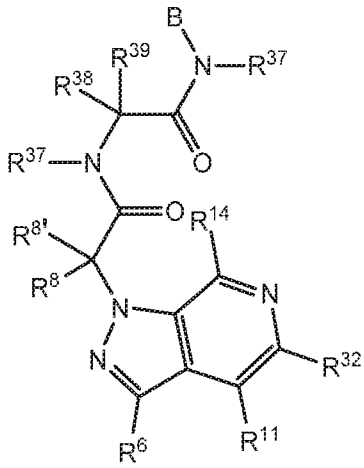
Formula 634 ,



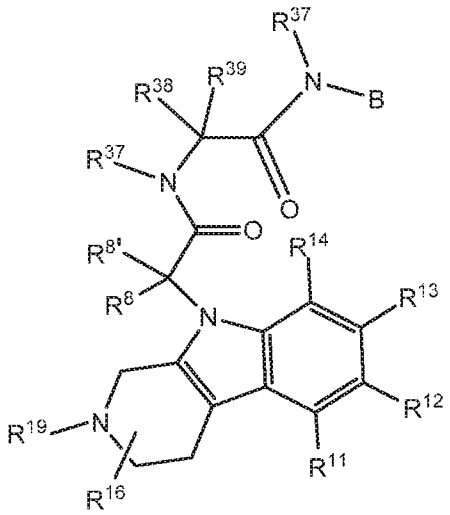
Formula 635 ,



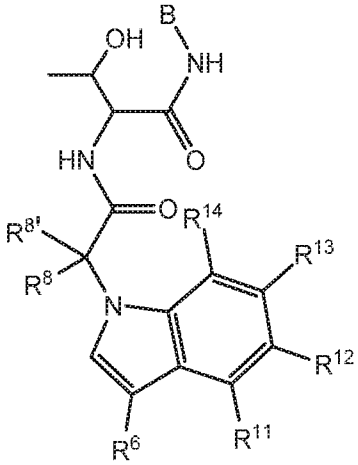
Formula 636 ,



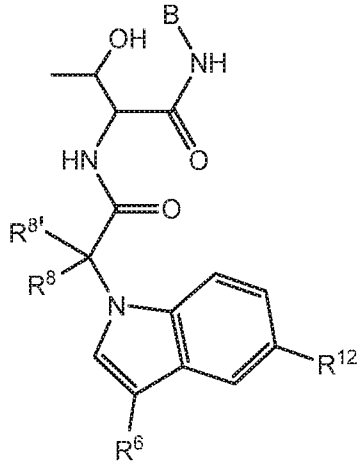
Formula 637 ,



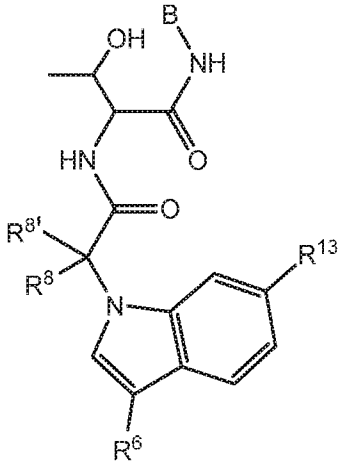
Formula 638 ,



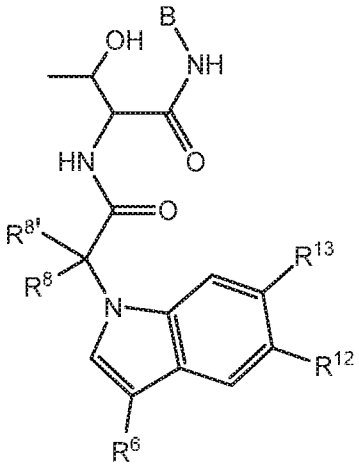
Formula 639 ,



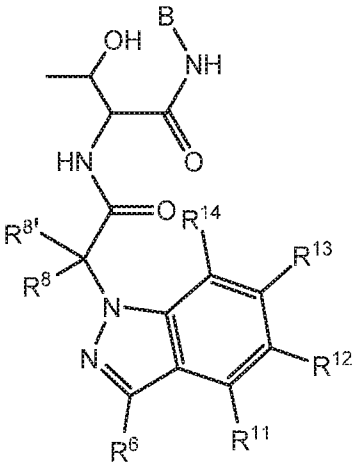
Formula 640 ,



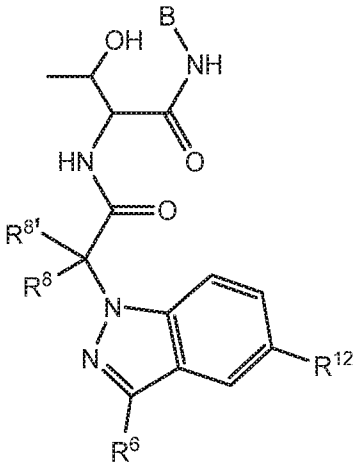
Formula 641 ,



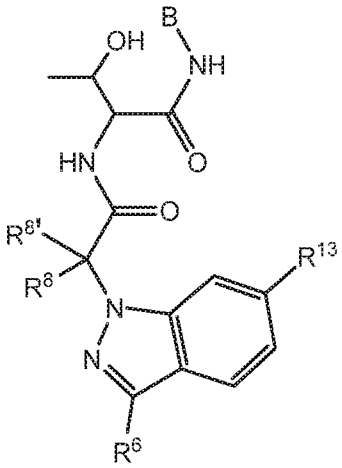
Formula 642 ,



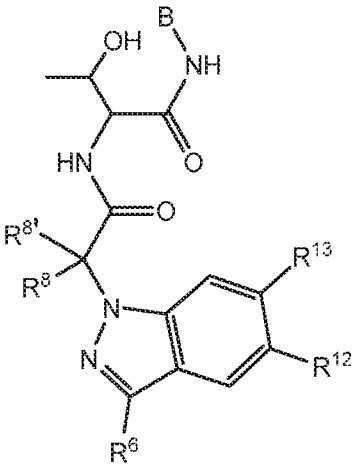
Formula 643 ,



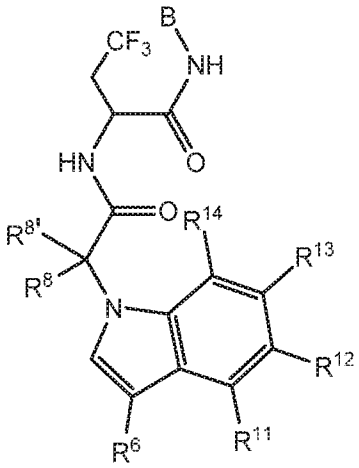
Formula 644 ,



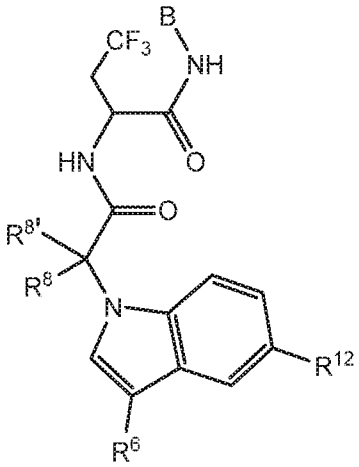
Formula 645 ,



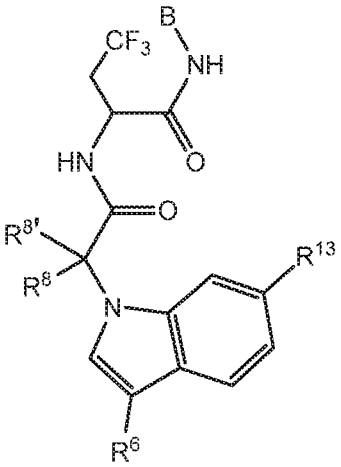
Formula 646 ,



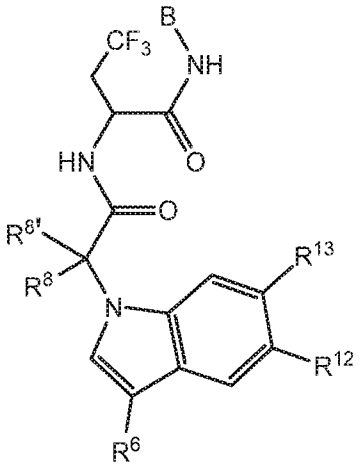
Formula 647 ,



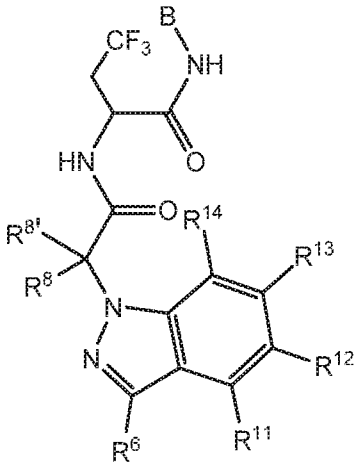
Formula 648 ,



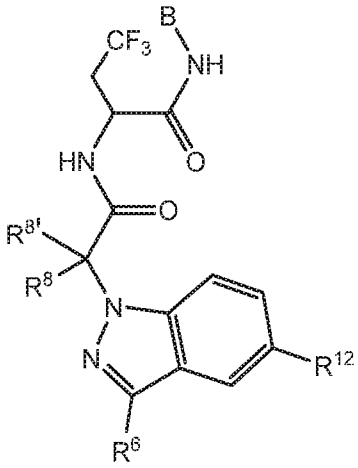
Formula 649 ,



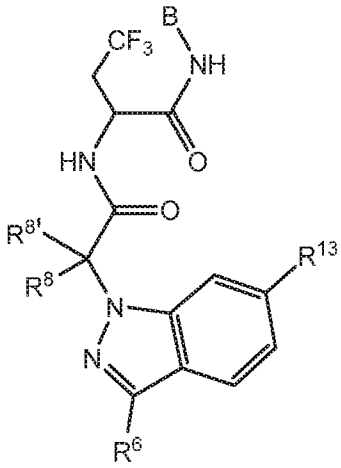
Formula 650 ,



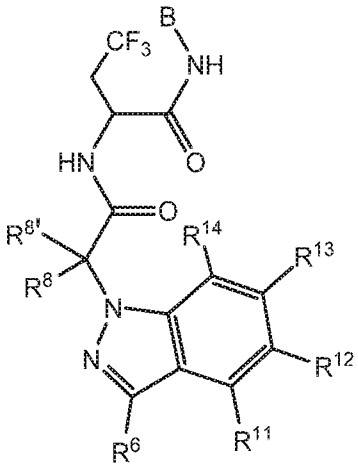
Formula 651 ,



Formula 652 ,



Formula 653 and



Formula 654 .

[0288] Additionally, the disclosure includes compounds and salts of Formula I, Formula Γ and Formula I" pharmaceutically acceptable compositions thereof, and any of their subformulae (2-654) in which at least one of the following conditions is met in the embodiments described below.

The R^{12} and R^{13} Aryl, Heteroaryl, and Heterocycle Substituents

[0289] The invention includes a compound of Formula I, Formula Γ or Formula I", a pharmaceutically acceptable salt or composition thereof, wherein at least one of R^{12} or R^{13} on the A1 or A2 group is an aryl, heteroaryl, or heterocycle for example, R^{32}.

[0290] One of R^{12} and R^{13} is selected from R^{31} and the other of R^{12} and R^{13} is replaced from R^{32}. In another embodiment, each of R^{12} and R^{13} can be independently selected from R^{32}.

[0291] R^{31} is selected from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, Ci-C2haloalkyl, Ci-C2haloalkoxy, Ci-C_6alkyl, -Co-C4alkyl(C3-C7cycloalkyl), C2-C_6alkenyl, C_2-Cealkanoyl, Ci-Cealkoxy, C2-C_6alkenyloxy, -C(0)OR^9, Ci-Cethioalkyl, -Co-C_4alkylNR^9R^{10}, -C(0)NR^9R^{10}, -SO2R^9, -S0 $_2NR^9R^{10}$, -OC(0)R^9, and -C(NR^9)NR^9R^{10}, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C2haloalkyl, and Ci-C2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -CONH 2 Ci-C2haloalkyl, and Ci-C2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent replaced from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently replaced from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, Ci-C_6alkylester, -Co-C4alkyl)(C3-C7cycloalkyl), Ci-C2haloalkyl, and Ci-C2haloalkoxy;

[0292] R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

[0293] Non-limiting examples of R^{32} include the moieties of Figure 15.

[0294] In one embodiment, R^{32} is $R^{32'}$.

[0295] $R^{32'}$ is selected from the structures of Figure 16.

Non-limiting R^{12}/R^{13} Embodiments

[0296] In one embodiment, R^{12} is R^{32}.

[0297] In one embodiment, R^{13} is R^{32}.

[0298] In one embodiment, R^{12} is R^{32}, which is aryl.

[0299] In one embodiment, R^{12} is optionally substituted aryl.

[0300] In one embodiment, R^{12} is an optionally substituted heteroaryl.

[0301] In one embodiment, R^{13} is an optionally substituted aryl.

[0302] In one embodiment, R^{13} is an optionally substituted heteroaryl.

[0303] In one embodiment, R^{13} is optionally substituted heteroaryl.

[0304] In one embodiment, R^{12} is R^{32}, which is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

[0305] In one embodiment, R^{12} is R^{32}, which is (4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, wherein the (4- to 7-membered heterocycloalkyl).

[0306] In one embodiment, R^{13} is R^{32}, which is aryl.

[0307] In one embodiment, the disclosure provides compounds of Formula I, wherein;

[0308] one of R^{12} and R^{13} is H and the other of R^{12} and R^{13} is R^{32},where

[0309] R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

[0310] In another embodiment, the disclosure provides compounds of Formula I and Formula I", wherein;

[03 11] R^{1}, $R^{1'}$, R^{2}, and $R^{3'}$ are all hydrogen;

[0312] R^{2} is fluoro and R^{3} is hydrogen, -Co-C_4alkyl(C3-C7cycloalkyl), or -O-Co-C_4alkyl(C3-C7cycloalkyl);

[0313] R^{5} is hydrogen, halogen, or Ci-C2alkyl;

[0314] R^{11}, R^{13}, R^{14}, and R^{15} if present, are independently replaced at each occurrence from hydrogen, halogen, hydroxyl, amino, Ci-C_4alkyl, Ci-C_4alkoxy, -Co-C2alkyl(mono- and di-Ci-C2alkylamino), trifluoromethyl, and trifluoromethoxy;

[0315] X^{12} is CR^{12}; and

[0316] R^{12} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

[0317] In one embodiment, the disclosure provides compounds of Formula I, wherein;

[0318] m is Oor 1;

[0319] R^{2} is halogen, $R^{2'}$ is hydrogen or halogen, and R^{3} is hydrogen, halogen, -Co-C_4alkyl(C3-C_7cycloalkyl), or -0-Co-C_4alkyl(C3-C7cycloalkyl);

[0320] R^{6} is -C(0)Ci-C_4alkyl, -C(0)NH_2, -C(0)CF_3, -C(0)(C3-C_7cycloalkyl), or -ethyl(cyanoimino);

[0321] one of R^{12} and R^{13} is selected from hydrogen, halogen, Ci-C_4alkyl, Ci-C_4alkoxy, trifluoromethyl, and trifluoromethoxy; the other of R^{12} and R^{13} is R^{32}, where

[0322] R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

[0323] In one embodiment, the disclosure provides compounds of Formula I and Formula I" wherein one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; and the other of R^{12} and R^{13} is R^{32}, where

[0324] R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring, which can be optionally substituted.

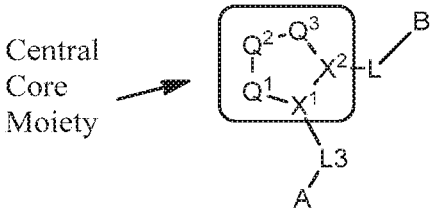
[0325] In one embodiment, R^{32} may be unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)2, -Si$(CH_3)_3$, -COOH, -CONH2, -P(**0**)(OH)2, Ci-Cealkyl, Ci-Cealkoxy, -Co-C_2alkyl(mono- and di-Ci-C4alkylamino), Ci-C6alkylester, Ci-C4alkylamino, Ci-C4hydroxylalkyl, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0326] In one embodiment, R^{31} is hydrogen and R^{32} is pyrimidinyl.

[0327] In another embodiment, R^{31} is hydrogen and R^{32} is pyrimidine substituted with a methyl group.

Central Core Moiety

[0328] The central core moiety, C, in Formula I is illustrated below:



[0329] C is CI, CI', C2, C3, or C4.

[0330] CI, CI', C2, C3 and C4 are described in the summary section.

Non-limiting Central Core Embodiments

[0331] In certain embodiments, R^1 and $R^{1'}$ or R^3 and $R^{3'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently replaced from N, O, or S; R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring; or R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered heterocyclic spiro ring; each of which ring may be unsubstituted or substituted with 1 or more substituents independently replaced from halogen (and in particular F), hydroxyl, cyano, -COOH, Ci-C4alkyl (including in particular methyl), C_2-C4alkenyl, C_2-C4alkynyl, Ci-

C4alkoxy, C_2-C4alkanoyl, hydroxyCi-C4alkyl, (mono- and di-Ci-C4alkylamino)Co-C4alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), -0-Co-C4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0332] In other embodiments, R^1 and R^2 may be taken together to form a 3-membered carbocyclic ring; R^1 and R^2 may be taken together to form a 4, 5 or 6-membered carbocyclic or an aryl ring or a 4, 5 to 6-membered heterocyclic or heteroaryl ring containing 1 or 2 heteroatoms independently replaced from N, O, and S; or R^2 and R^3, if bound to adjacent carbon atoms, may be taken together to form a 3- to 6-membered carbocyclic or aryl ring or a 3- to 6-membered heterocyclic or heteroaryl ring;

[0333] each of which ring may be unsubstituted or substituted with 1 or more substituents independently replaced from halogen (and in particular F), hydroxyl, cyano, -COOH, Ci-C4alkyl (including in particular methyl), C_2-C4alkenyl, C_2-C4alkynyl, Ci-C4alkoxy, C_2-C4alkanoyl, hydroxyCi-C4alkyl, (mono- and di-Ci-C4alkylamino)Co-C4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), -0-Co-C4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0334] In one embodiment, the central core moiety is proline.

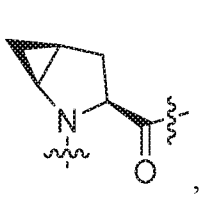
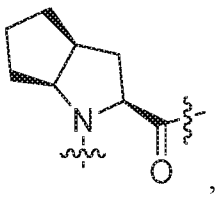
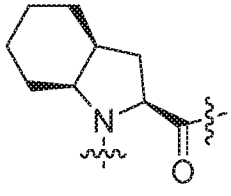
[0335] In one embodiment, the central core moiety is 4-fluoroproline.

[0336] In one embodiment, R^1, $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro.

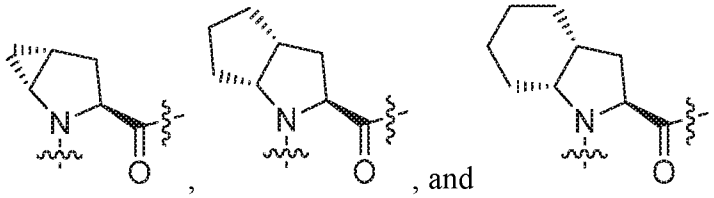
[0337] In one embodiment, R^1, $R^{1'}$, $R^{2'}$, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro and R^3 is -Co-C4alkyl(C3-C7cycloalkyl) or -0-Co-C4alkyl(C3-C7cycloalkyl).

[0338] In one embodiment, R^1 and R^2 are taken together to form a 3- to 6-membered cycloalkyl group, and $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, where present, are all hydrogen. In one embodiment, the bicycle is fused in a cis fashion. In one embodiment, the bicyclic ring is fused in a trans fashion.

[0339] In one embodiment, R^1 and R^2 are taken together to form a 3- to 6-membered cycloalkyl group that is cis with respect to the carboxyl group of L-proline as shown below:

[0340]  ,  , and  .

[0341] In one embodiment, R^1 and R^2 are taken together to form a 3- to 6-membered cycloalkyl group that is trans with respect to the carboxyl group of L-proline as shown below:

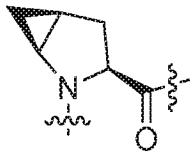
[0342] 

[0343] In one embodiment, R^1, $R^{1'}$, R^3, and $R^{3'}$, if present, are all hydrogen, and R^2 and $R^{2'}$ are taken together to form a 5- or 6-membered heterocycloalkyl group having 1 or 2 oxygen atoms.

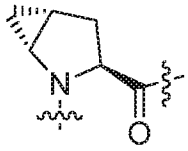
[0344] In one embodiment, R^1 is hydrogen and R^2 is fluoro.

[0345] In one embodiment, R^1 and R^2 are joined to form a 3 membered ring.

[0346] In one embodiment, R^1 and R^2 are taken together to form a 3-membered cycloalkyl group that is cis with respect to the carboxyl group of L-proline as shown below:

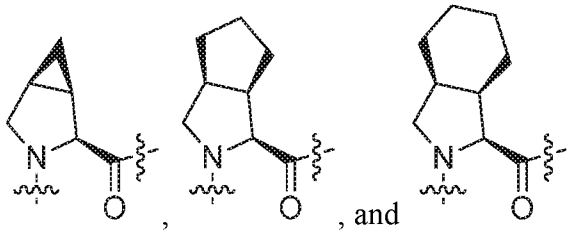
[0347] 

[0348] In one embodiment, R^1 and R^2 are taken together to form a 3-membered cycloalkyl group that is trans with respect to the carboxyl group of L-proline as shown below:

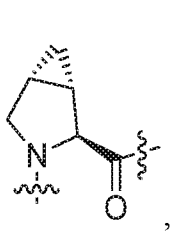
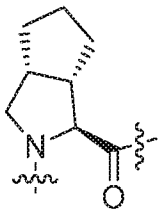
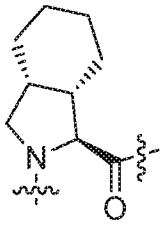
[0349] 

[0350] In one embodiment, R^2 and R^3 are taken together to form a 3- to 6-membered cycloalkyl group, and R^1, $R^{1'}$, $R^{2'}$ and $R^{3'}$, where present, are selected from hydrogen, C1-C3 alkyl or C1-C3 alkoxy.

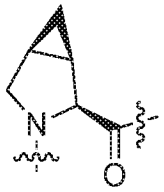
[0351] In one embodiment, R^2 and R^3 are taken together to form a 3- to 6-membered cycloalkyl group that is cis with respect to the carboxyl group of L-proline as shown below:

[0352] 

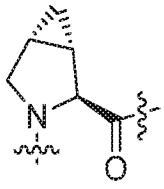
[0353] In one embodiment, R^2 and R^3 are taken together to form a 3- to 6-membered cycloalkyl group that is trans with respect to the carboxyl group of L-proline as shown below:

[0354]  ,  , and  .

[0355] In one embodiment, R^2 and R^3 are taken together to form a 3-membered cycloalkyl group that is cis with respect to the carboxyl group of L-proline as shown below:

[0356]  .

[0357] In one embodiment, R^2 and R^3 are taken together to form a 3-membered cycloalkyl group that is trans with respect to the carboxyl group of L-proline as shown below:

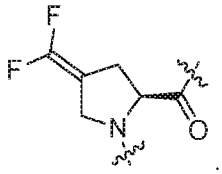
[0358]  .

[0359] In one embodiment, R^1, $R^{1'}$, R^3, and $R^{3'}$, if present, are all hydrogen, and R^2 and $R^{2'}$ are taken together to form a 5- or 6-membered heterocycloalkyl group having 1 or 2 oxygen atoms.

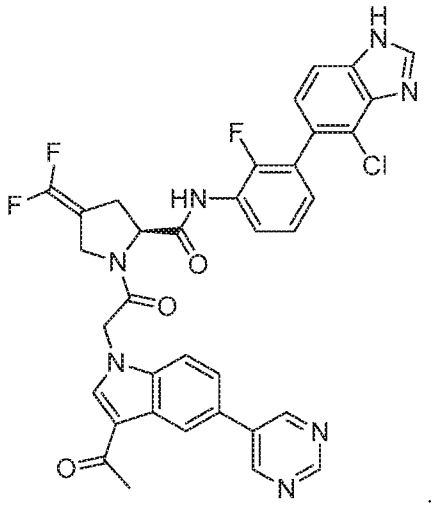
[0360] In one embodiment, R^1 is hydrogen and R^2 is fluoro.

[0361] In one embodiment, R^1 and R^2 are joined to form a 3 membered ring.

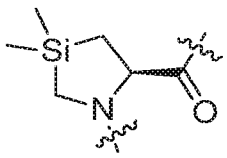
[0362] The disclosure includes compounds of Formula I in which the central pyrrolidine is vinyl substituted, for example:

 .

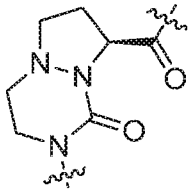
[0363] In one embodiment, the compound of Formula I has the structure:



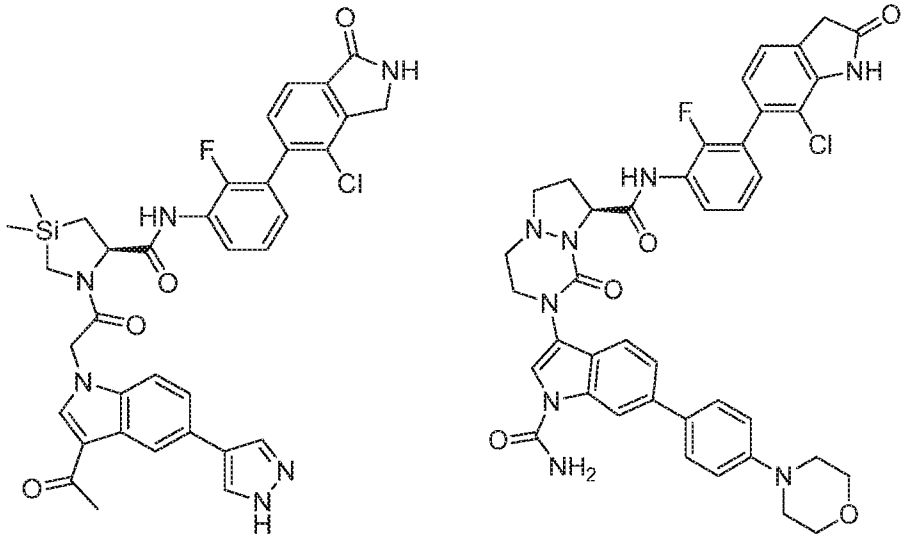
[0364] In one embodiment, the central pyrrolidine is modified by addition of a second heteroatom to a pyrrolidine ring, such as N, O, S, or Si, for example:



[0365] Another modification within the scope of the disclosure is joining a substituent on the central pyrrolidine ring to R^7 or R^8 to form a 5- to 6- membered heterocyclic ring, for example:

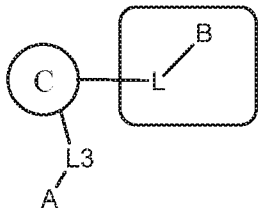


[0366] Example compounds having the modifications disclosed above include:



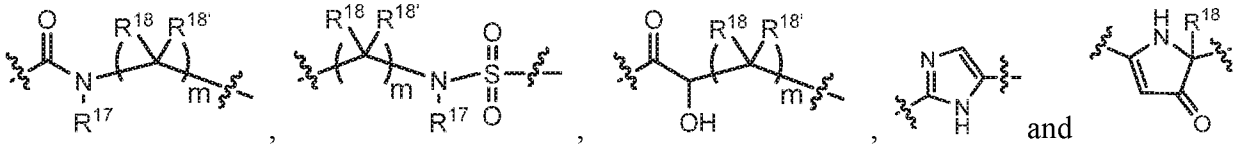
Central Core L-B Substituents

[0367] Illustrative core L substituents and B substituents in Formula I are described below:



[0368] L is selected from LI, LI', L2 and L2'.

[0369] L1 is a bond or is replaced from the formulas:

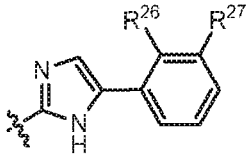
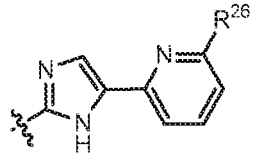


where R^{17} is hydrogen, Ci-C6alkyl, or -Co-C4alkyl(C3-C7cycloalkyl) and R^{18} and $R^{18'}$ are independently selected from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3.

[0370] L2 and L2' are described in the summary section.

[0371] B is selected from Bl, B1', B2, B3 and B4 which are described in the summary section.

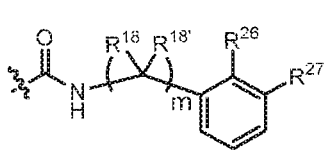
[0372] In one embodiment, –L1-B1- is


or

, where

R^{26} and R^{27} are independently replaced from hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-Cealkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, Ci-Cethioalkyl, -Co-C4alkyl(mono- and di-Ci-Cealkylamino), -Co-C4alkyl(C3-C_7cycloalkyl), -Co-C4alkoxy(C3-C7cycloalkyl), Ci-C2haloalkyl, Ci-C2haloalkoxy, and Ci-C2haloalkylthio.

Non-Limiting L-B Embodiments

[0373] In one embodiment, –L1-B1- is: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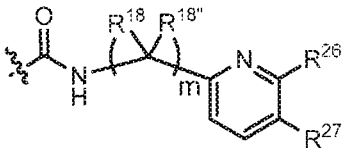
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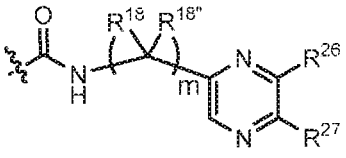
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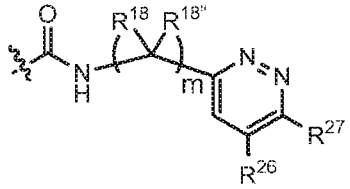
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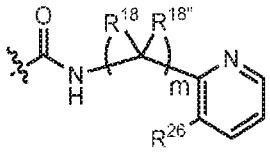
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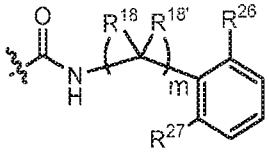
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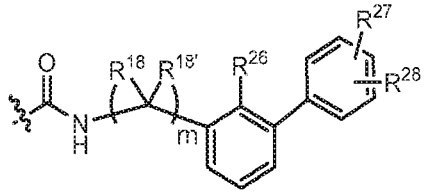
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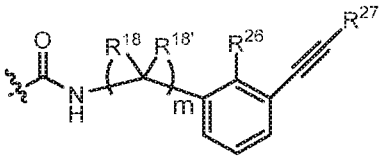
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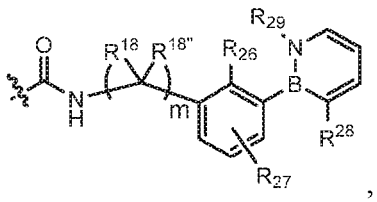
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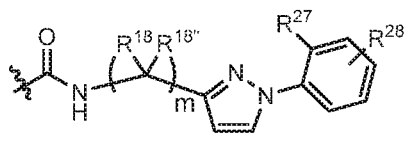
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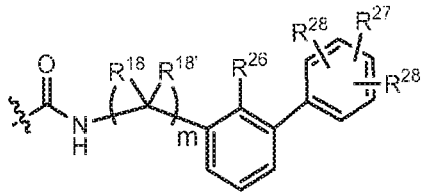

.

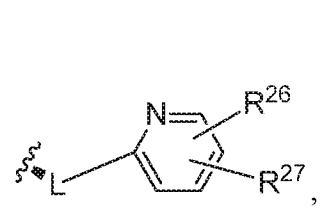
wherein

[0374] R^{18} and $R^{18'}$ are independently replaced from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0 or 1; and

[0375] R^{26}, R^{27}, and R^{28} are independently replaced from hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, Ci-C_6thioalkyl, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, (C3-C7cycloalkyl)Co-C4alkyl, (aryl)Co-C4alkyl-, (heteroaiyl)Co-C4alkyl-, and -Co-C4alkoxy(C3-C7cycloalkyl); each of which R^{26}, R^{27}, and R^{28} other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, amino, Ci-C2alkoxy, Ci-C2haloalkyl, (C3-C7cycloalkyl)Co-C4alkyl-, and Ci-C2haloalkoxy; and

[0376] R^{29} is hydrogen, Ci-C_2alkyl, CiC_2haloalkyl or -Si(CH3)2C(CH $_3$)3.

[0377] In one embodiment, -L-Bl- moiety is selected: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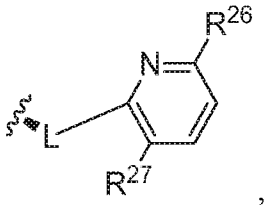
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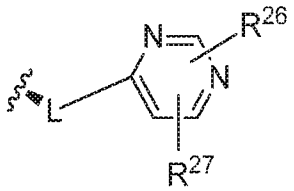
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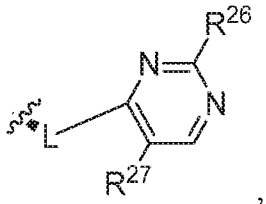
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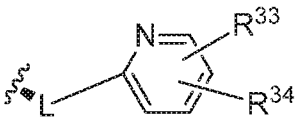
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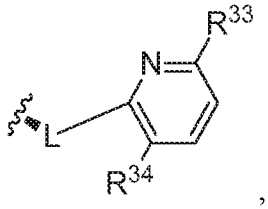
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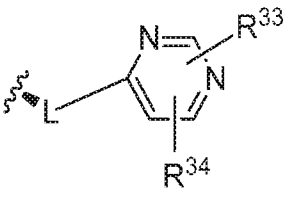
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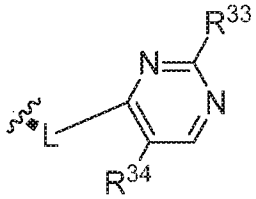
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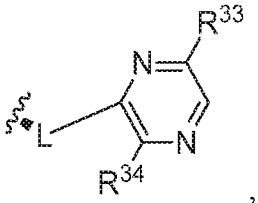
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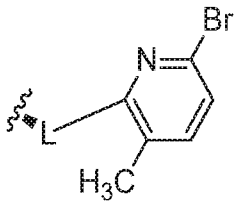
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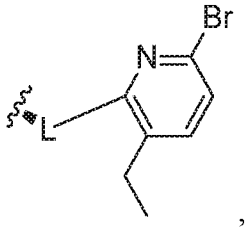
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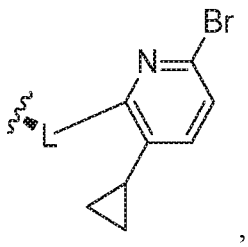
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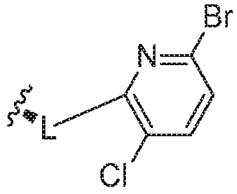
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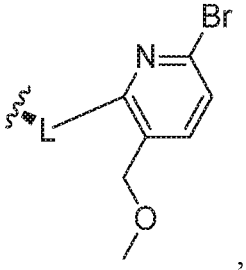
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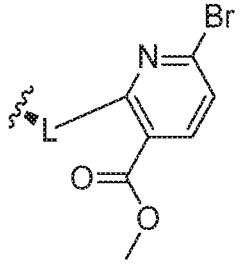
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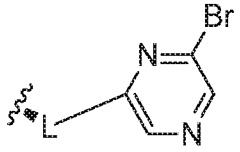
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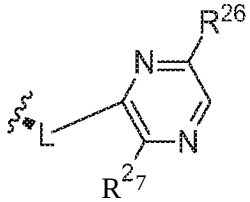
, and

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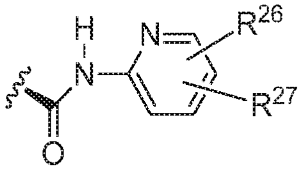
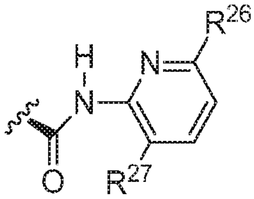
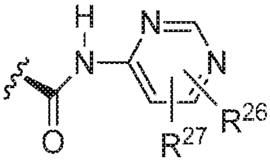
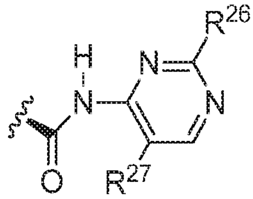
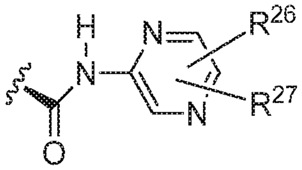
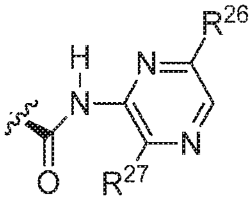
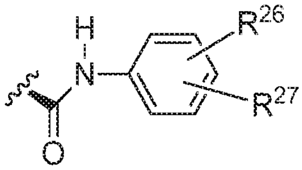
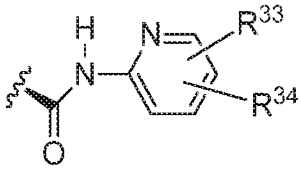
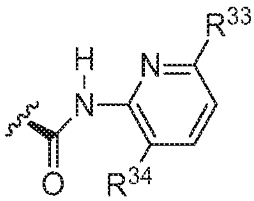
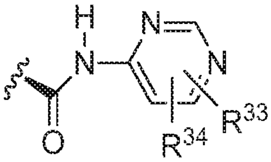
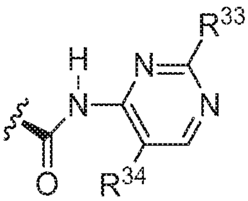
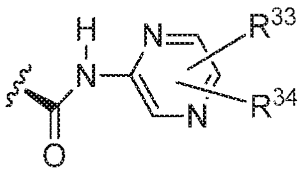
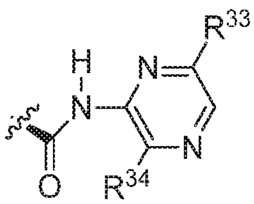
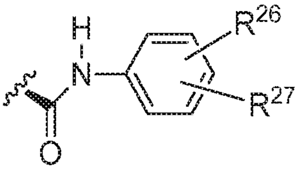
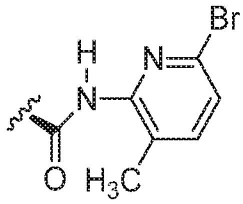
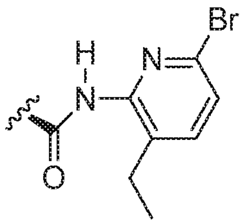
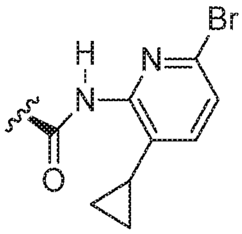
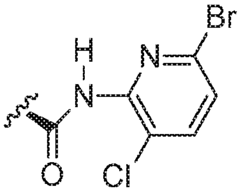
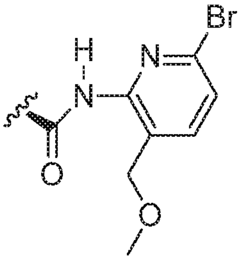
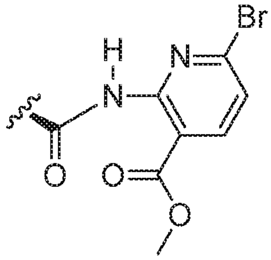
[0378] In one embodiment, –L1-B1- moiety is selected:

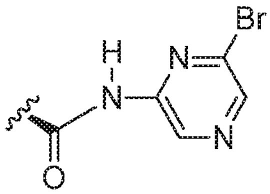
 ,  ,  ,  ,

 ,  ,  ,  ,

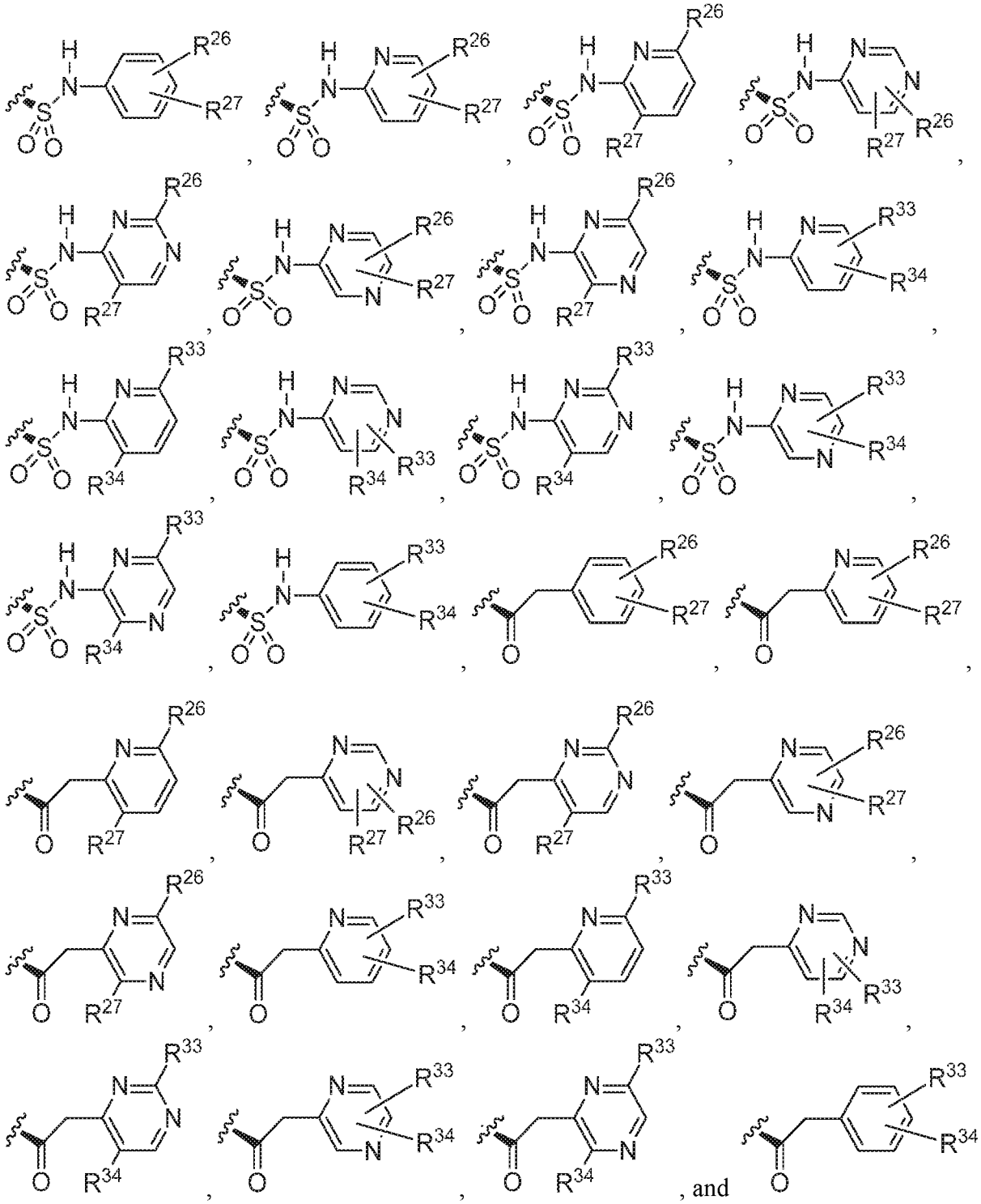
 ,   ,  ,

 ,  ,  ,  ,

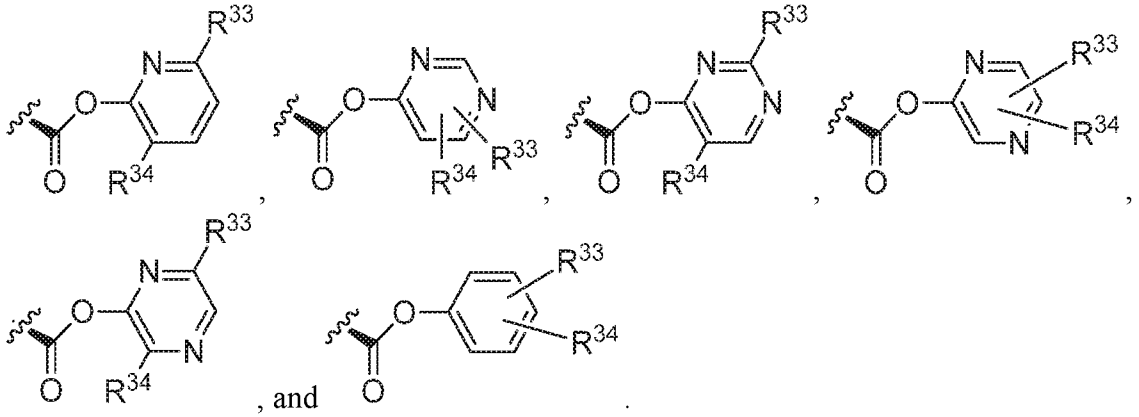
 ,  ,  ,  , and

 .

[0379] In one embodiment, -L2-B1- moiety is selected:



[0380] In one embodiment, **-L2'-B1-** moiety is selected:



[0381] In one embodiment, m is **0.**

[0382] In one embodiment, the disclosure further includes compounds and salts of Formula I in which **Bl** is **2**-fluoro-**3**-chlorophenyl. In another embodiment, another carbocyclic, aryl, heterocyclic, or heteroaryl group such as **2**-bromo-pyridin-**6**-yl, l-**(2,2,2**-trifluoroethyl**)-lH-**pyrazol-**3**-yl, **2,2**-dichlorocyclopropylmethyl, or **2**-fluoro-**3**-trimethylsilylphenyl is used.

[0383] In another embodiment, **Bl** is phenyl, pyridyl, or indanyl each of which is unsubstituted or substituted with one or more substituents independently replaced from hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, Ci-C_6thioalkyl, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, (C3-C7cycloalkyl)Co-C4alkyl, -Co-C4alkoxy(C3-C7cycloalkyl), (phenyl)Co-C2alkyl, (pyridyl)Co-C2alkyl; each of which substituents other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, amino, Ci-C2alkyl, Ci-C_2alkoxy, -OSi(CH$_3$)2C(CH3)3**,-Si** (CH3)2C(CH_3)3, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0384] In another embodiment, **Bl** is phenyl or pyridyl substituted with **1, 2,** or **3** substituents replaced from chloro, bromo, hydroxyl, -SCF3, Ci-C2alkyl, Ci-C2alkoxy, trifluoromethyl, phenyl and trifluoromethoxy each of which substituents other than chloro, bromo, hydroxyl, -SCF3, can be optionally substitued.

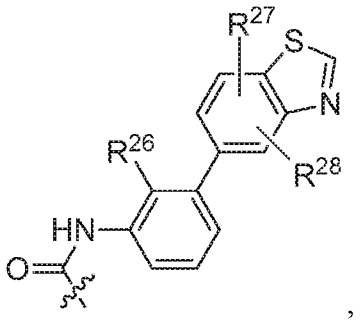
[0385] In certain embodiments, **Bl** is a **2**-fluoro-**3**-chlorophenyl or a **2**-fluoro-**3**-trifluoromethoxy phenyl group.

[0386] In one embodiment, **Bl** is pyridyl, optionally substituted with halogen, Ci-C2alkoxy, and trifluoromethyl.

[0387] In one embodiment, B1 is phenyl, substituted with 1, 2, or 3 substituents independently selected from halogen, Ci-C2alkyl, Ci-C2alkoxy, trifluorom ethyl, and optionally substituted phenyl.

[0388] In one embodiment, R^{23} is independently replaced at each occurrence from (C_3-C7cycloalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently replaced from N, O, and S.

[0389] In one embodiment, L1-B3 is: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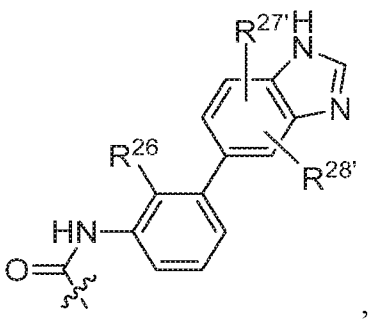
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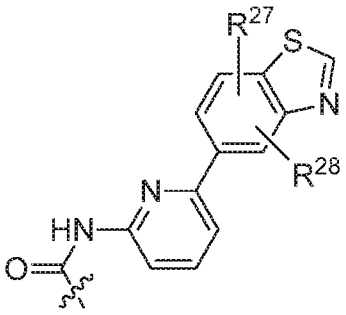
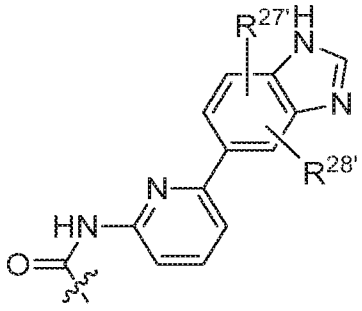
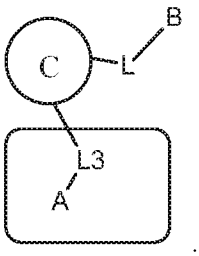

, or

.

[0390] $R^{27'}$, and $R^{28'}$ are independently replaced from hydrogen, fluoro, bromo, iodo, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, C2-C_6alkoxy, C2-C_6thioalkyl, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, (C_3-C7cycloalkyl)Co-C4alkyl, (aryl)Co-C4alkyl-, (heteroaryl)Co-C4alkyl-, and -Co-C4alkoxy(C_3-C7cycloalkyl); each of which $R^{27'}$, and $R^{28'}$ other than hydrogen, fluoro, bromo, iodo, hydroxyl, nitro, and cyano, is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, amino, Ci-C2alkoxy, Ci-C2haloalkyl, (C_3-C7cycloalkyl)Co-C4alkyl-, and Ci-C2haloalkoxy.

Central Core (L3)-A Substituent

[0391] The central core (L3)-A substituent in Formula I is illustrated below:



[0392] L3 is selected from L4 and L5;

[0393] L4 is -C(O)-.

[0394] L5 is described above in the summary section.

[0395] A is selected from Al, Al' and A2.

[0396] Al, A1' and A2 are described above in the summary section.

[0397] In one embodiment, R^5 and R^6 are independently replaced from -CHO, -C(0)NH_2, -C(0)NH(CH_3), C_2-Cealkanoyl, and hydrogen.

[0398] In one embodiment, each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and -COOH is unsubstituted or substituted with one or more substituents independently replaced from halogen, hydroxyl, amino, imino, cyano, cyanoimino, Ci-C_2alkyl, Ci-C4alkoxy, -Co-C_2alkyl(mono- and di-Ci-C4alkylamino), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0399] In one embodiment, R^8 and $R^{8'}$ are independently hydrogen or methyl.

[0400] In one embodiment, R^8 and $R^{8'}$ are hydrogen.

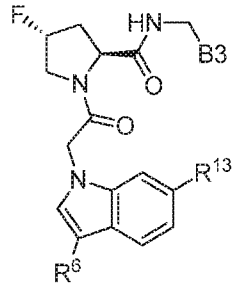
[0401] In one embodiment, R^7 is hydrogen or methyl.

[0402] In one embodiment, R^7 is hydrogen.

Embodiments of Formulas IA, IB, IC, and ID

[0403] To further illustrate the invention, various embodiments of Formula IA, IB, IC and ID are provided. These are presented by way of example to show some of the variations among presented compounds within the invention and can be applied to any of the Formulas herein, and are not intended to limit the invention.

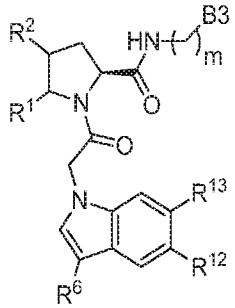
[0404] In one aspect, this disclosure includes compounds and salts of Formula IA:



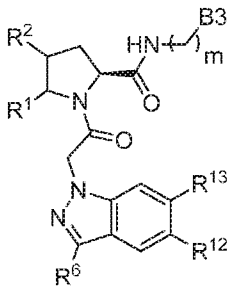
(IA) where

R^6, R^{13}, and B3 may carry any of the definitions set forth herein for this variable.

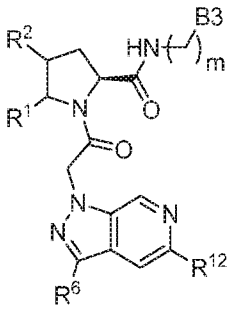
[0405] In another aspect, this disclosure includes compounds and salts of Formula IB, IC, and ID.



IB



IC



ID.

[0406] In Formulas IA, IB, IC, and ID, the variables may include any of the definitions set forth herein that results in a stable compound. In certain embodiments, the following conditions apply for Formula IB and IC.

[0407] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0408] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0409] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0410] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[041 1] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0412] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0413] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0414] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole

[0415] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0416] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0417] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SF_5.

[0418] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0419] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

[0420] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

[0421] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SF_5.

[0422] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

[0423] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0424] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0425] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0426] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is dihydroindole.

[0427] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0428] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0429] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0430] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is dihydroindole.

[0431] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0432] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0433] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SF_5.

[0434] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B3 is phenyl substituted with SFs.

[0435] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

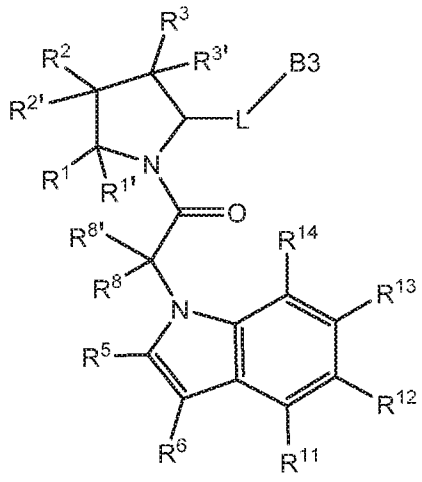
[0436] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

[0437] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SF_5.

[0438] In some embodiments, structures are provided including Formulas IB and IC, wherein m=l, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B3 is phenyl substituted with SFs.

Embodiments of Formula 606

[0439] To further illustrate the invention, various embodiments of Formula 606 are disclosed. In one aspect, the disclosure includes compounds and salts of Formula 606:



(Formula 606), wherein:

[0440] R^1, R^2, $R^{2'}$, and R^3 are independently replaced from hydrogen, halogen, Ci-C_4alkyl, Ci-C_4alkoxy, -Co-C_2alkylNR^9R^{10}, -Co-C_4alkyl(C3-C7cycloalkyl), -0-Co-C_4alkyl(C_3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

[0441] R^8 and $R^{8'}$ are independently replaced from hydrogen, halogen, and methyl;

[0442] R^5 is hydrogen, hydroxyl, cyano, -COOH, Ci-Cealkyl, Ci-Cealkoxy, C_2-Cealkanoyl -Co-C_4alkyl(C_3-C7cycloalkyl), -C(0)Co-C_4alkyl(C_3-C7cycloalkyl, Ci-C_2haloalkyl, or Ci-C_2haloalkoxy);

[0443] R^6 is -C(0)CH_3, -C(0)NH_2, -C(0)CF_3, -C(0)(cyclopropyl), or -ethyl(cyanoimino); and

[0444] R^{11} and R^{14} are independently replaced from hydrogen, halogen, hydroxyl, amino, nitro, cyano, Ci-C6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, Ci-C_6alkoxy, Ci-C_6thioalkyl, -Co-C_4alkyl(mono- and di-Ci-C6alkylamino), -Co-C_4alkyl(C_3-C7cycloalkyl), -OCo-C_4alkyl(C_3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy.

[0445] Prodrugs of Formula I, Formula Γ and Formula I" are also within the scope of the disclosure.

III. PHARMACEUTICAL PREPARATIONS

[0446] Active compounds described herein can be administered to a host in need thereof as the neat chemical, but are more typically administered as a pharmaceutical composition that

includes an effective amount for a host, typically a human, in need of such treatment of an active compound as described herein or its pharmaceutically acceptable salt. Thus, in one embodiment, the disclosure provides pharmaceutical compositions comprising an effective amount of compound or pharmaceutically acceptable salt together with at least one pharmaceutically acceptable carrier for any of the uses described herein. The pharmaceutical composition may contain a compound or salt as the only active agent, or, in an alternative embodiment, the compound and at least one additional active agent.

[0447] An effective amount of an active compound as described herein, or the active compound described herein in combination or alternation with, or preceded by, concomitant with or followed by another active agent, can be used in an amount sufficient to (a) inhibit the progression of a disorder mediated by the complement pathway, including an inflammatory, immune, including an autoimmune, disorder or complement Factor D related disorder; (b) cause a regression of an inflammatory, immune, including an autoimmune, disorder or complement Factor D related disorder; (c) cause a cure of an inflammatory, immune, including an autoimmune, disorder or complement Factor D related disorder; or inhibit or prevent the development of an inflammatory, immune, including an autoimmune, disorder or complement Factor D related disorder. Accordingly, an effective amount of an active compound or its salt or composition described herein will provide a sufficient amount of the active agent when administered to a patient to provide a clinical benefit.

[0448] The exact amount of the active compound or pharmaceutical composition described herein to be delivered to the host, typically a human, in need thereof, will be determined by the health care provider to achieve the desired clinical benefit.

[0449] In certain embodiments the pharmaceutical composition is in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of the active compound and optionally from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of an additional active agent in a unit dosage form. Examples are dosage forms with at least about 25, 50, 100, 200, 250, 300, 400, 500, 600, 700, 750, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, or 1700 mg of active compound, or its salt. In one embodiment, the dosage form has at least about 100 mg, 200 mg, 400 mg, 500 mg, 600 mg, lOOOmg, 1200 mg, or 1600 mg of active compound, or its salt. The

amount of active compound in the dosage form is calculated without reference to the salt. The dosage form can be administered, for example, once a day (q.d.), twice a day (b.i.d.), three times a day (t.i.d.), four times a day (q.i.d.), once every other day (Q2d), once every third day (Q3d), as needed, or any dosage schedule that provides treatment of a disorder described herein.

[0450] The pharmaceutical composition may for example include a molar ratio of the active compound and an additional active agent that achieves the desired result. For example, the pharmaceutical composition may contain a molar ratio of about 0.5:1, about 1:1, about 2:1, about 3:1 or from about 1.5:1 to about 4:1 of an additional active agent in combination with the active compound (additional active agent: active compound), or its salt, described herein. In one embodiment, the additional active agent is an anti-inflammatory or immunosuppressing agent.

[0451] Compounds disclosed herein or used as described herein may be administered orally, topically, parenterally, by inhalation or spray, sublingually, via implant, including ocular implant, transdermally, via buccal administration, rectally, as an ophthalmic solution, injection, including ocular injection, intravenous, intra-aortal, intracranial, subdermal, intraperitoneal, subcutaneous, transnasal, sublingual, intrathecal, or rectal or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers. For ocular delivery, the compound can be administered, as desired, for example, as a solution, suspension, or other formulation via intravitreal, intrastromal, intracameral, sub-tenon, sub-retinal, retro-bulbar, peribulbar, suprachorodial, subchorodial, chorodial, conjunctival, subconjunctival, episcleral, periocular, transscleral, retrobulbar, posterior juxtascleral, circumcorneal, or tear duct injections, or through a mucus, mucin, or a mucosal barrier, in an immediate or controlled release fashion or via an ocular device, injection, or topically administered formulation, for example a solution or suspension provided as an eye drop.

[0452] The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a gel cap, a pill, a microparticle, a nanoparticle, an injection or infusion solution, a capsule, a tablet, a syrup, a transdermal patch, a subcutaneous patch, a dry powder, an inhalation formulation, in a medical device, suppository, buccal, or sublingual formulation, parenteral formulation, or an ophthalmic solution or suspension. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

[0453] Pharmaceutical compositions, and methods of manufacturing such compositions, suitable for administration as contemplated herein are known in the art. Examples of known techniques include, for example, US Patent Nos. 4,983,593, 5,013,557, 5,456,923, 5,576,025, 5,723,269, 5,858,41 1, 6,254,889, 6,303,148, 6,395,302, 6,497,903, 7,060,296, 7,078,057, 7,404,828, 8,202,912, 8,257,741, 8,263,128, 8,337,899, 8,431,159, 9,028,870, 9,060,938, 9,21 1,261, 9,265,731, 9,358,478, and 9,387,252, incorporated by reference herein.

[0454] The pharmaceutical compositions contemplated here can optionally include a carrier. Carriers must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, fillers, flavorants, glidents, lubricants, pH modifiers, preservatives, stabilizers, surfactants, solubilizers, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin; talc, and vegetable oils. Examples of other matrix materials, fillers, or diluents include lactose, mannitol, xylitol, microcrystalline cellulose, calcium diphosphate, and starch. Examples of surface active agents include sodium lauryl sulfate and polysorbate 80. Examples of drug complexing agents or solubilizers include the polyethylene glycols, caffeine, xanthene, gentisic acid and cylodextrins. Examples of disintegrants include sodium starch gycolate, sodium alginate, carboxymethyl cellulose sodium, methyl cellulose, colloidal silicon dioxide, and croscarmellose sodium. Examples of binders include methyl cellulose, microcrystalline cellulose, starch, and gums such as guar gum, and tragacanth. Examples of lubricants include magnesium stearate and calcium stearate. Examples of pH modifiers include acids such as citric acid, acetic acid, ascorbic acid, lactic acid, aspartic acid, succinic acid, phosphoric acid, and the like; bases such as sodium acetate, potassium acetate, calcium oxide, magnesium oxide, trisodium phosphate, sodium hydroxide, calcium hydroxide, aluminum hydroxide, and the like, and buffers generally comprising mixtures of acids and the salts of said acids. Optional other active agents may be included in a

pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0455] In certain embodiments, the pharmaceutical composition for administration further includes a compound or salt of Formula I, Γ, or I" and optionally comprises one or more of a phosphoglyceride; phosphatidylcholine; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohol such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acid; fatty acid monoglyceride; fatty acid diglyceride; fatty acid amide; sorbitan trioleate (Span®85) glycocholate; sorbitan monolaurate (Span®20); polysorbate 20 (Tween®20); polysorbate 60 (Tween®60); polysorbate 65 (Tween®65); polysorbate 80 (Tween®80); polysorbate 85 (Tween®85); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidyl serine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebroside; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl sterate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipid; synthetic and/or natural detergent having high surfactant properties; deoxycholate; cyclodextrin; chaotropic salt; ion pairing agent; glucose, fructose, galactose, ribose, lactose, sucrose, maltose, trehalose, cellbiose, mannose, xylose, arabinose, glucoronic acid, galactoronic acid, mannuronic acid, glucosamine, galatosamine, and neuramic acid; pullulan, cellulose, microcrystalline cellulose, hydroxypropyl methylcellulose (FIPMC), hydroxycellulose (HC), methylcellulose (MC), dextran, cyclodextran, glycogen, hydroxy ethyl starch, carageenan, glycon, amylose, chitosan, N,O-carboxylmethylchitosan, algin and alginic acid, starch, chitin, inulin, konjac, glucommannan, pustulan, heparin, hyaluronic acid, curdlan, and xanthan, mannitol, sorbitol, xylitol, erythritol, maltitol, and lactitol, a pluronic polymer, polyethylene, polycarbonate (e.g. poly(l,3-dioxan-2one)), polyanhydride (e.g. poly(sebacic anhydride)), polypropylfumerate, polyamide (e.g. polycaprolactam), polyacetal, polyether, polyester (e.g., polylactide, polyglycolide, polylactide-co-glycolide, polycaprolactone, polyhydroxyacid (e.g. poly((P-hydroxyalkanoate))), poly(orthoester), polycyanoacrylate,

polyvinyl alcohol, polyurethane, polyphosphazene, polyacrylate, polymethacrylate, polyurea, polystyrene, and polyamine, polylysine, polylysine-PEG copolymer, and poly(ethyleneimine), poly(ethylene imine)-PEG copolymer, glycerol monocaprylocaprate, propylene glycol, Vitamin E TPGS (also known as d-a-Tocopheryl polyethylene glycol 1000 succinate), gelatin, titanium dioxide, polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC), block copolymers of ethylene oxide and propylene oxide (PEO/PPO), polyethyleneglycol (PEG), sodium carboxymethylcellulose (NaCMC), hydroxypropylmethyl cellulose acetate succinate (HPMCAS).

[0456] In some embodiments, the pharmaceutical preparation may include polymers for controlled delivery of the described compounds, including, but not limited to pluronic polymers, polyesters (e.g., polylactic acid, poly(lactic-co-glycolic acid), polycaprolactone, polyvalerolactone, poly(l,3-dioxan-2one)); polyanhydrides (e.g., poly(sebacic anhydride)); polyethers (e.g., polyethylene glycol); polyurethanes; polymethacrylates; polyacrylates; and polycyanoacrylates. In some embodiments, polymers may be modified with polyethylene glycol (PEG), with a carbohydrate, and/or with acyclic polyacetals derived from polysaccharides. See, e.g., Papisov, 2001, ACS Symposium Series, 786:301, incorporated by reference herein.

[0457] The compounds of the present invention can be formulated as particles. In one embodiment the particles are or include microparticles. In an alternative embodiment the particles are or include nanoparticles.

[0458] In an additional alternative embodiment, common techniques for preparing particles include, but are not limited to, solvent evaporation, solvent removal, spray drying, phase inversion, coacervation, and low temperature casting. Suitable methods of particle formulation are briefly described below. Pharmaceutically acceptable excipients, including pH modifying agents, disintegrants, preservatives, and antioxidants, can optionally be incorporated into the particles during particle formation.

[0459] In one embodiment, the particles are derived through a solvent evaporation method. In this method, a compound described herein (or polymer matrix and one or more compounds described herein) is dissolved in a volatile organic solvent, such as methylene chloride. The organic solution containing a compound described herein is then suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid nanoparticles or microparticles. The

resulting nanoparticles or microparticles are washed with water and dried overnight in a lyophilizer. Nanoparticles with different sizes and morphologies can be obtained by this method.

[0460] Pharmaceutical compositions which contain labile polymers, such as certain polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, methods which are performed in completely or substantially anhydrous organic solvents can be used to make the particles.

[0461] Solvent removal can also be used to prepare particles from a compound that is hydrolytically unstable. In this method, the compound (or polymer matrix and one or more compounds) is dispersed or dissolved in a volatile organic solvent such as methylene chloride. This mixture is then suspended by stirring in an organic oil (such as silicon oil) to form an emulsion. Solid particles form from the emulsion, which can subsequently be isolated from the supernatant. The external morphology of spheres produced with this technique is highly dependent on the identity of the drug.

[0462] In one embodiment an active compound as described herein is administered to a patient in need thereof as particles formed by solvent removal. In another embodiment the present invention provides particles formed by solvent removal comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by solvent removal comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by solvent removal comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by solvent removal can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by solvent removal are formulated into a tablet but the tablet is uncoated.

[0463] In one embodiment, the particles are derived by spray drying. In this method, a compound (or polymer matrix and one or more compounds) is dissolved in an organic solvent such as methylene chloride. The solution is pumped through a micronizing nozzle driven by a flow of compressed gas, and the resulting aerosol is suspended in a heated cyclone of air, allowing the solvent to evaporate from the micro droplets, forming particles. Microparticles and nanoparticles can be obtained using this method.

[0464] In one embodiment an active compound as described herein is administered to a patient in need thereof as a spray dried dispersion (SDD). In another embodiment the present invention provides a spray dried dispersion (SDD) comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the SDD comprises a compound of the present invention and an additional therapeutic agent. In a further embodiment the SDD comprises a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described spray dried dispersions can be coated to form a coated tablet. In an alternative embodiment the spray dried dispersion is formulated into a tablet but is uncoated.

[0465] Particles can be formed from the active compound as described herein using a phase inversion method. In this method, the compound (or polymer matrix and one or more active compounds) is dissolved in a suitable solvent, and the solution is poured into a strong non-solvent for the compound to spontaneously produce, under favorable conditions, microparticles or nanoparticles. The method can be used to produce nanoparticles in a wide range of sizes, including, for example, from nanoparticles to microparticles, typically possessing a narrow particle size distribution.

[0466] In one embodiment, an active compound as described herein is administered to a patient in need thereof as particles formed by phase inversion. In another embodiment the present invention provides particles formed by phase inversion comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by phase inversion comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by phase inversion comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by phase inversion can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by phase inversion are formulated into a tablet but the tablet is uncoated.

[0467] Techniques for particle formation using coacervation are known in the art, for example, as described in GB-B-929 406; GB-B-929 40 1; and U.S. Patent Nos. 3,266,987, 4,794,000, and 4,460,563. Coacervation involves the separation of a compound (or polymer matrix and one or more compounds) solution into two immiscible liquid phases. One phase is a dense

coacervate phase, which contains a high concentration of the compound, while the second phase contains a low concentration of the compound. Within the dense coacervate phase, the compound forms nanoscale or microscale droplets, which harden into particles. Coacervation may be induced by a temperature change, addition of a non-solvent or addition of a micro-salt (simple coacervation), or by the addition of another polymer thereby forming an interpolymer complex (complex coacervation).

[0468] In one embodiment an active compound as described herein is administered to a patient in need thereof as particles formed by coacervation. In another embodiment the present invention provides particles formed by coacervation comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by coacervation comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by coacervation comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by coacervation can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by coacervation are formulated into a tablet but the tablet is uncoated.

[0469] Methods for very low temperature casting of controlled release microspheres are described in U.S. Patent No. 5,019,400 to Gombotz *et al.* In this method, the compound is dissolved in a solvent. The mixture is then atomized into a vessel containing a liquid non-solvent at a temperature below the freezing point of the drug solution which freezes the compound droplets. As the droplets and non-solvent for the compound are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, hardening the microspheres.

[0470] In one embodiment, a compound of the present invention is administered to a patient in need thereof as particles formed by low temperature casting. In another embodiment the present invention provides particles formed by low temperature casting comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by low temperature casting comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by low temperature casting comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another

embodiment any of the described particles formed by low temperature casting can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by low temperature casting are formulated into a tablet but the tablet is uncoated.

[0471] In one aspect of the present invention, an effective amount of an active compound as described herein is incorporated into a nanoparticle, *e.g.* for convenience of delivery and/or extended release delivery. The use of materials in nanoscale provides one the ability to modify fundamental physical properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics, and/or immunogenicity. A number of nanoparticle-based therapeutic and diagnostic agents have been developed for the treatment of cancer, diabetes, pain, asthma, allergy, and infections. These nanoscale agents may provide more effective and/or more convenient routes of administration, lower therapeutic toxicity, extend the product life cycle, and ultimately reduce health-care costs. As therapeutic delivery systems, nanoparticles can allow targeted delivery and controlled release.

[0472] In addition, nanoparticle-based compound delivery can be used to release compounds at a sustained rate and thus lower the frequency of administration, deliver drugs in a targeted manner to minimize systemic side effects, or deliver two or more drugs simultaneously for combination therapy to generate a synergistic effect and suppress drug resistance. A number of nanotechnology-based therapeutic products have been approved for clinical use. Among these products, liposomal drugs and polymer-based conjugates account for a large proportion of the products. *See*, Zhang, L., et al., Nanoparticles in Medicine: Therapeutic Applications and Developments, Clin. Pharm. and Ther., 83(5):761-769, 2008.

[0473] Methods for producing nanoparticles are known in the art. For example, see Muller, R.H., et al., Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art, *Eur. H. Pharm. Biopharm.*, 50:161-177, 2000; US 8,691,750 to Consien et al.; WO 2012/145801 to Kanwar. US 8,580,31 1 to Armes, S. et al.; Petros, R.A. and DeSimone, J.M., Strategies in the design of nanoparticles for therapeutic applications, Nature Reviews/Drug Discovery, vol. 9:615-627, 2010; US 8,465,775; US 8,444,899; US 8,420,124; US 8,263,129; US 8,158,728; 8,268,446; Pellegrino et al., 2005, Small, 1:48; Murray et al., 2000, Ann. Rev. Mat. Sci., 30:545; and Trindade et al., 2001, Chem. Mat., 13:3843; all incorporated herein by reference. Additional methods have been described in the literature (see, e.g., Doubrow, Ed., "Microcapsules and Nanoparticles in Medicine and Pharmacy," CRC Press, Boca Raton, 1992; Mathiowitz et al.,

1987, J. Control. Release, 5:13; Mathiowitz etal., 1987, Reactive Polymers, 6:275; and Mathiowitz et al., 1988, J. Appl. Polymer Sci., 35:755; U.S. Pat. Nos. 5,578,325 and 6,007,845; P. Paolicelli et al., "Surface-modified PLGA-based Nanoparticles that can Efficiently Associate and Deliver Virus-like Particles" Nanomedicine. 5(6):843-853 (2010)), U.S. Pat. No. 5,543,158 to Gref et al., or WO publication WO2009/051837 by Von Andrian et al. Zauner et al., 1998, Adv. Drug Del. Rev., 30:97; and Kabanov et al., 1995, Bioconjugate Chem., 6:7;(PEI; Boussif et al., 1995, Proc. Natl. Acad. Sci., USA, 1995, 92:7297), and poly(amidoamine) dendnmers (Kukowska-Latallo et al., 1996, Proc. Natl. Acad. Sci., USA, 93:4897; Tang et al., 1996, Bioconjugate Chem., 7:703; and Haensler et al., 1993, Bioconjugate Chem., 4:372; Putnam et al., 1999, Macromolecules, 32:3658; Barrera et al., 1993, J. Am. Chem. Soc, 115:1 1010; Kwon et al., 1989, Macromolecules, 22:3250; Lim et al., 1999, J. Am. Chem. Soc, 121:5633; and Zhou et al., 1990, Macromolecules, 23:3399). Examples of these polyesters include poly(L-lactide-co-L-lysine) (Barrera et al., 1993, J. Am. Chem. Soc, 115:1 1010), poly(serine ester) (Zhou et al., 1990, Macromolecules, 23:3399), poly(4-hydroxy-L-proline ester) (Putnam et al., 1999, Macromolecules, 32:3658; and Lim et al., 1999, J. Am. Chem. Soc, 121:5633), and poly(4-hydroxy-L-proline ester) (Putnam et al., 1999, Macromolecules, 32:3658; and Lim et al., 1999, J. Am. Chem. Soc, 121:5633; U.S. Pat. No. 6,123,727; U.S. Pat. No. 5,804,178; U.S. Pat. No. 5,770,417; U.S. Pat. No. 5,736,372; U.S. Pat. No. 5,716,404; U.S. Pat. No. 6,095,148; U.S. Pat. No. 5,837,752; U.S. Pat. No. 5,902,599; U.S. Pat. No. 5,696,175; U.S. Pat. No. 5,514,378; U.S. Pat. No. 5,512,600; U.S. Pat. No. 5,399,665; U.S. Pat. No. 5,019,379; U.S. Pat. No. 5,010,167; U.S. Pat. No. 4,806,621; U.S. Pat. No. 4,638,045; and U.S. Pat. No. 4,946,929; Wang et al., 2001, J. Am. Chem. Soc, 123:9480; Lim et al., 2001, J. Am. Chem. Soc, 123:2460; Langer, 2000, Acc. Chem. Res., 33:94; Langer, 1999, J. Control. Release, 62:7; and Uhrich et al., 1999, Chem. Rev., 99:3181; Concise Encyclopedia of Polymer Science and Polymeric Amines and Ammonium Salts, Ed. by Goethals, Pergamon Press, 1980; Principles of Polymerization by Odian, John Wiley & Sons, Fourth Edition, 2004; Contemporary Polymer Chemistry by Allcock et al., Prentice-Hall, 1981; Deming et al., 1997, Nature, 390:386; and in U.S. Pat. Nos. 6,506,577, 6,632,922, 6,686,446, and 6,818,732; C. Astete et al., "Synthesis and characterization of PLGA nanoparticles" J. Biomater. Sci. Polymer Edn, Vol. 17, No. 3, pp. 247-289 (2006); K. Avgoustakis "Pegylated Poly(Lactide) and Poly(Lactide-Co-Glycolide) Nanoparticles: Preparation, Properties and Possible Applications in Drug Delivery" Current Drug Delivery 1:321-333 (2004); C. Reis et al., "Nanoencapsulation I. Methods for

preparation of drug-loaded polymeric nanoparticles" Nanomedicine 2:8-21 (2006); P. Paolicelli et al., "Surface-modified PLGA-based Nanoparticles that can Efficiently Associate and Deliver Virus-like Particles" Nanomedicine. 5(6):843-853 (2010); U.S. Pat. No. 6,632,671 to Unger Oct. 14, 2003, all incorporated herein by reference.

[0474] In one embodiment, the polymeric particle is between about 0.1 nm to about 10000 nm, between about 1 nm to about 1000 nm, between about 10 nm and 1000 nm, between about 1 and 100 nm, between about 1 and 10 nm, between about 1 and 50 nm, between about 100 nm and 800 nm, between about 400 nm and 600 nm, or about 500 nm. In one embodiment, the micro-particles are no more than about 0.1 nm, 0.5 nm, 1.0 nm, 5.0 nm, 10 nm, 25 nm, 50 nm, 75 nm, 100 nm, 150 nm, 200 nm, 250 nm, 300 nm, 400 nm, 450 nm, 500 nm, 550 nm, 600 nm, 650 nm, 700 nm, 750 nm, 800 nm, 850 nm, 900 nm, 950 nm, 1000 nm, 1250 nm, 1500 nm, 1750 nm, or 2000 nm. In some embodiments, a compound described herein may be covalently coupled to a polymer used in the nanoparticle, for example a polystyrene particle, PLGA particle, PLA particle, or other nanoparticle.

[0475] The pharmaceutical compositions can be formulated for oral administration. These compositions can contain any amount of active compound that achieves the desired result, for example between 0.1 and 99 weight % (wt.%) of the compound and usually at least about 5 wt.% of the compound. Some embodiments contain at least about 10%, 15%, 20%, 25 wt.% to about 50 wt. % or from about 5 wt.% to about 75 wt.% of the compound.

[0476] Pharmaceutical compositions suitable for rectal administration are typically presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[0477] Pharmaceutical compositions suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

[0478] Pharmaceutical compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Pharmaceutical compositions suitable for transdermal administration may also be delivered by iontophoresis *(see*, for example, *Pharmaceutical Research*

3 (6):3 18 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. In one embodiment, microneedle patches or devices are provided for delivery of drugs across or into biological tissue, particularly the skin. The microneedle patches or devices permit drug delivery at clinically relevant rates across or into skin or other tissue barriers, with minimal or no damage, pain, or irritation to the tissue.

[0479] Pharmaceutical compositions suitable for administration to the lungs can be delivered by a wide range of passive breath driven and active power driven single/-multiple dose dry powder inhalers (DPI). The devices most commonly used for respiratory delivery include nebulizers, metered-dose inhalers, and dry powder inhalers. Several types of nebulizers are available, including jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers. Selection of a suitable lung delivery device depends on parameters, such as nature of the drug and its formulation, the site of action, and pathophysiology of the lung.

[0480] Additional non-limiting examples of inhalation drug delivery devices and methods include, for example, US 7,383,837 titled "Inhalation device" (SmithKline Beecham Corporation); WO/2006/033584 titled "Powder inhaler" (Glaxo SmithKline Pharmaceuticals SA); WO/2005/044186 titled "Inhalable pharmaceutical formulations employing desiccating agents and methods of administering the same" (Glaxo Group Ltd and SmithKline Beecham Corporation); US9,095,670 titled "Inhalation device and method of dispensing medicament", US 8,205,61 1titled "Dry powder inhaler" (Astrazeneca AB); WO/2013/038170 titled "Inhaler" (Astrazeneca AB and Astrazeneca UK Ltd.); US/2014/0352690 titled "Inhalation Device with Feedback System", US 8,910,625 and US/2015/0165137 titled "Inhalation Device for Use in Aerosol Therapy" (Vectura GmbH); US 6,948,496 titled "Inhalers", US/2005/0152849 titled "Powders comprising anti-adherent materials for use in dry powder inhalers", US 6,582,678, US 8,137,657, US/2003/0202944, and US/2010/0330188 titled "Carrier particles for use in dry powder inhalers", US 6,221,338 titled "Method of producing particles for use in dry powder inhalers", US 6,989,155 titled "Powders", US/2007/0043030 titled "Pharmaceutical compositions for treating premature ejaculation by pulmonary inhalation", US 7,845,349 titled "Inhaler", US/2012/01 14709 and US 8,101,160 titled "Formulations for Use in Inhaler Devices", US/2013/0287854 titled "Compositions and Uses", US/2014/0037737 and US 8,580,306 titled "Particles for Use in a Pharmaceutical Composition", US/2015/0174343 titled "Mixing Channel for an Inhalation Device", US 7,744,855 and US/2010/0285142 titled "Method of making particles for use in a

pharmaceutical composition", US 7,541,022, US/2009/0269412, and US/2015/0050350 titled "Pharmaceutical formulations for dry powder inhalers" (Vectura Limited).

[0481] Many methods and devices for drug delivery to the eye are known in the art. Non-limiting examples are described in the following patents and patent applications (fully incorporated herein by reference). Examples are US 8,192,408 titled "Ocular trocar assembly" (Psivida Us, Inc.); US 7,585,517 titled "Transcleral delivery" (Macusight, Inc.); US 5,710,182 and US 5,795,913 titled "Ophthalmic composition" (Santen OY); US 8,663,639 titled "Formulations for treating ocular diseases and conditions", US 8,486,960 titled "Formulations and methods for vascular permeability-related diseases or conditions", US 8,367,097 and US 8,927,005 titled "Liquid formulations for treatment of diseases or conditions", US 7,455,855 titled "Delivering substance and drug delivery system using the same" (Santen Pharmaceutical Co., Ltd.); WO/201 1/050365 titled "Conformable Therapeutic Shield For Vision and Pain" and WO/2009/145842 titled "Therapeutic Device for Pain Management and Vision" (Forsight Labs, LLC); US 9,066,779 and US 8,623,395 titled "Implantable therapeutic device", WO/2014/160884 titled "Ophthalmic Implant for Delivering Therapeutic Substances", US 8,399,006, US 8,277,830, US 8,795,712, US 8,808,727, US 8,298,578, and WO/2010/088548 titled "Posterior segment drug delivery", WO/2014/152959 and US20140276482 titled "Systems for Sustained Intraocular Delivery of Low Solubility Compounds from a Port Delivery System Implant", US 8,905,963 and US 9,033,91 1 titled "Injector apparatus and method for drug delivery", WO/2015/057554 titled "Formulations and Methods for Increasing or Reducing Mucus", US 8,715,712 and US 8,939,948 titled "Ocular insert apparatus and methods", WO/2013/1 16061 titled "Insertion and Removal Methods and Apparatus for Therapeutic Devices", WO/2014/066775 titled "Ophthalmic System for Sustained Release of Drug to the Eye", WO/2015/085234 and WO/2012/019176 titled "Implantable Therapeutic Device", WO/2012/065006 titled "Methods and Apparatus to determine Porous Structures for Drug Delivery", WO/2010/141729 titled "Anterior Segment Drug Delivery", WO/201 1/050327 titled "Corneal Denervation for Treatment of Ocular Pain", WO/2013/022801 titled "Small Molecule Delivery with Implantable Therapeutic Device", WO/2012/019047 titled "Subconjunctival Implant for Posterior Segment Drug Delivery", WO/2012/068549 titled "Therapeutic Agent Formulations for Implanted Devices", WO/2012/019139 titled " Combined Delivery Methods and Apparatus", WO/2013/040426 titled "Ocular Insert Apparatus and

Methods", WO/2012/019136 titled "Injector Apparatus and Method for Drug Delivery", WO/2013/040247 titled "Fluid Exchange Apparatus and Methods" (ForSight Vision4, Inc.).

[0482] Additional non-limiting examples of how to deliver the active compounds are provided in WO/2015/085251 titled "Intracameral Implant for Treatment of an Ocular Condition" (Envisia Therapeutics, Inc.); WO/201 1/008737 titled "Engineered Aerosol Particles, and Associated Methods", WO/2013/0821 11 titled "Geometrically Engineered Particles and Methods for Modulating Macrophage or Immune Responses", WO/2009/132265 titled "Degradable compounds and methods of use thereof, particularly with particle replication in non-wetting templates", WO/2010/099321 titled "Interventional drug delivery system and associated methods", WO/2008/100304 titled "Polymer particle composite having high fidelity order, size, and shape particles", WO/2007/024323 titled "Nanoparticle fabrication methods, systems, and materials" (Liquidia Technologies, Inc. and the University of North Carolina at Chapel Hill); WO/2010/009087 titled "Iontophoretic Delivery of a Controlled-Release Formulation in the Eye", (Liquidia Technologies, Inc. and Eyegate Pharmaceuticals, Inc.) and WO/2009/132206 titled "Compositions and Methods for Intracellular Delivery and Release of Cargo", WO/2007/133808 titled "Nano-particles for cosmetic applications", WO/2007/056561 titled "Medical device, materials, and methods", WO/2010/065748 titled "Method for producing patterned materials", WO/2007/081876 titled "Nanostructured surfaces for biomedical/biomaterial applications and processes thereof (Liquidia Technologies, Inc.).

[0483] Additional non-limiting examples of methods and devices for drug delivery to the eye include, for example, WO201 1/106702 and US 8,889,193 titled "Sustained delivery of therapeutic agents to an eye compartment", WO2013/138343 and US 8,962,577 titled "Controlled release formulations for the delivery of HIF- 1 inhibitors", WO/20 13/1 38346 and US20 13/0272994 titled "Non-Linear Multiblock Copolymer-Drug Conjugates for the Delivery of Active Agents", WO2005/072710 and US 8,957,034 titled "Drug and Gene Carrier Particles that Rapidly Move Through Mucus Barriers", WO2008/030557, US20 10/02 15580, US20 13/0 164343 titled "Compositions and Methods for Enhancing Transport Through Mucous", WO2012/061703, US2012/0121718, and US2013/0236556 titled "Compositions and Methods Relating to Reduced Mucoadhesion", WO2012/039979 and US20 13/0 183244 titled "Rapid Diffusion of Large Polymeric Nanoparticles in the Mammalian Brain", WO2012/109363 and US2013/03233 13 titled "Mucus Penetrating Gene Carriers", WO 2013/090804 and US2014/0329913 titled "Nanoparticles

with enhanced mucosal penetration or decreased inflammation", WO2013/1 10028 titled "Nanoparticle formulations with enhanced mucosal penetration", WO20 13/1 66498 and US20 15/0086484 titled "Lipid-based drug carriers for rapid penetration through mucus linings" (The Johns Hopkins University); WO2013/166385 titled "Pharmaceutical Nanoparticles Showing Improved Mucosal Transport", US2013/0323179 titled "Nanocrystals, Compositions, And Methods that Aid Particle Transport in Mucus" (The Johns Hopkins University and Kala Pharmaceuticals, Inc.); WO/2015/066444 titled "Compositions and methods for ophthalmic and/or other applications", WO/2014/020210 and WO/2013/166408 titled "Pharmaceutical nanoparticles showing improved mucosal transport" (Kala Pharmaceuticals, Inc.); US 9,022,970 titled "Ophthalmic injection device including dosage control device", WO/201 1/153349 titled "Ophthalmic compositions comprising pbo-peo-pbo block copolymers", WO/201 1/140203 titled "Stabilized ophthalmic galactomannan formulations", WO/201 1/068955 titled "Ophthalmic emulsion" , WO/201 1/037908 titled "Injectable aqueous ophthalmic composition and method of use therefor", US2007/0149593 titled "Pharmaceutical Formulation for Delivery of Receptor Tyrosine Kinase Inhibiting (RTKi) Compounds to the Eye", US 8,632,809 titled "Water insoluble polymer matrix for drug delivery" (Alcon, Inc.).

[0484] Additional non-limiting examples of drug delivery devices and methods include, for example, US20090203709 titled "Pharmaceutical Dosage Form For Oral Administration Of Tyrosine Kinase Inhibitor" (Abbott Laboratories); US20050009910 titled "Delivery of an active drug to the posterior part of the eye via subconjunctival or periocular delivery of a prodrug", US 20130071349 titled "Biodegradable polymers for lowering intraocular pressure", US 8,481,069 titled "Tyrosine kinase microspheres", US 8,465,778 titled "Method of making tyrosine kinase microspheres", US 8,409,607 titled "Sustained release intraocular implants containing tyrosine kinase inhibitors and related methods", US 8,512,738 and US 2014/003 1408 titled "Biodegradable intravitreal tyrosine kinase implants", US 2014/0294986 titled "Microsphere Drug Delivery System for Sustained Intraocular Release", US 8,91 1,768 titled "Methods For Treating Retinopathy With Extended Therapeutic Effect" (Allergan, Inc.); US 6,495, 164 titled "Preparation of injectable suspensions having improved injectability" (Alkermes Controlled Therapeutics, Inc.); WO 2014/047439 titled "Biodegradable Microcapsules Containing Filling Material" (Akina, Inc.); WO 2010/132664 titled "Compositions And Methods For Drug Delivery" (Baxter International Inc. Baxter Healthcare SA); US20 120052041 titled "Polymeric nanoparticles with

enhanced drugloading and methods of use thereof (The Brigham and Women's Hospital, Inc.); US20140178475, US20140248358, and US20140249158 titled "Therapeutic Nanoparticles Comprising a Therapeutic Agent and Methods of Making and Using Same" (BIND Therapeutics, Inc.); US 5,869,103 titled "Polymer microparticles for drug delivery" (Danbiosyst UK Ltd.); US 8628801 titled "Pegylated Nanoparticles" (Universidad de Navarra); US20 14/0 107025 titled "Ocular drug delivery system" (Jade Therapeutics, LLC); US 6,287,588 titled "Agent delivering system comprised of microparticle and biodegradable gel with an improved releasing profile and methods of use thereof, US 6,589,549 titled "Bioactive agent delivering system comprised of microparticles within a biodegradable to improve release profiles" (Macromed, Inc.); US 6,007,845 and US 5,578,325 titled "Nanoparticles and microparticles of non-linear hydrophilichydrophobic multiblock copolymers" (Massachusetts Institute of Technology); US2004023461 1, US20080305172, US20120269894, and US20130122064 titled "Ophthalmic depot formulations for periocular or subconjunctival administration (Novartis Ag); US 6,413,539 titled "Block polymer" (Poly-Med, Inc.); US 20070071756 titled "Delivery of an agent to ameliorate inflammation" (Peyman); US 2008016641 1 titled "Injectable Depot Formulations And Methods For Providing Sustained Release Of Poorly Soluble Drugs Comprising Nanoparticles" (Pfizer, Inc.); US 6,706,289 titled "Methods and compositions for enhanced delivery of bioactive molecules" (PR Pharmaceuticals, Inc.); and US 8,663,674 titled "Microparticle containing matrices for drug delivery" (Surmodics).

IV. USES OF ACTIVE COMPOUNDS FOR TREATMENT OF SELECTED DISORDERS

[0485] In one aspect, an effective amount of an active compound or its salt or composition as described herein is used to treat a medical disorder which is an inflammatory or immune condition, a disorder mediated by the complement cascade (including a dysfunctional cascade) including a complement D-related disorder, a disorder or abnormality of a cell that adversely affects the ability of the cell to engage in or respond to normal complement activity, or an undesired complement-mediated response to a medical treatment, such as surgery or other medical procedure or a pharmaceutical or biopharmaceutical drug administration, a blood transfusion, or other allogenic tissue or fluid administration.

[0486] In one embodiment, the disorder is selected from fatty liver and conditions stemming from fatty liver, such as nonalcoholic steatohepatitis (NASH), liver inflammation,

cirrhosis and liver failure. In one embodiment of the present invention, a method is provided for treating fatty liver disease in a host by administering an effective amount of an active compound or its salt or composition as described herein.

[0487] In another embodiment, an active compound or its salt or composition as described herein is used to modulate an immune response prior to or during surgery or other medical procedure. One non-limiting example is use in connection with acute or chronic graft versus host disease, which is a common complication as a result of allogeneic tissue transplant, and can also occur as a result of a blood transfusion.

[0488] In one embodiment, the present invention provides a method of treating or preventing dermatomyositis by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein.

[0489] In one embodiment, the present invention provides a method of treating or preventing amyotrophic lateral sclerosis by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein.

[0490] In another embodiment, a method is provided for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceutical or biotherapeutic (e.g. CAR T-cell therapy or monoclonal antibody therapy) in a host by administering an effective amount of an active compound or its salt or composition as described herein. Various types of cytokine or inflammatory reactions may occur in response to a number of factors, such as the administrations of biotherapeutics. In one embodiment, the cytokine or inflammatory reaction is cytokine release syndrome. In one embodiment, the cytokine or inflammatory reaction is tumor lysis syndrome (which also leads to cytokine release). Symptoms of cytokine release syndrome range from fever, headache, and skin rashes to bronchospasm, hypotension and even cardiac arrest. Severe cytokine release syndrome is described as cytokine storm, and can be fatal.

[0491] Fatal cytokine storms have been observed in response to infusion with several monoclonal antibody therapeutics. See, Abramowicz D, et al. "Release of tumor necrosis factor, interleukin-2, and gamma-interferon in serum after injection of OKT3 monoclonal antibody in kidney transplant recipients" *Transplantation* (1989) 47(4):606-8; Chatenoud L, et al. "In vivo cell activation following OKT3 administration. Systemic cytokine release and modulation by corticosteroids" *Transplantation* (1990) 49(4):697-702; and Lim LC, Koh LP, and Tan P. "Fatal

cytokine release syndrome with chimeric anti-CD20 monoclonal antibody rituximab in a 71-year-old patient with chronic lymphocytic leukemia" *J. Clin Oncol.* (1999) 17(6): 1962-3.

[0492] Also contemplated herein, is the use of an active compound or its salt or composition as described herein to mediate an adverse immune response in patients receiving bi-specific T-cell engagers (BiTE). A bi-specific T-cell engager directs T-cells to target and bind with a specific antigen on the surface of a cancer cell. For example, Blinatumomab (Amgen), a BiTE has recently been approved as a second line therapy in Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukemia. Blinatumomab is given by continuous intravenous infusion in 4-week cycles. The use of BiTE agents has been associated with adverse immune responses, including cytokine release syndrome. The most significantly elevated cytokines in the CRS associated with ACT include IL-10, IL-6, and IFN-γ (Klinger et al., Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. Blood (2012) 119:6226-6233).

[0493] In another embodiment, the disorder is episcleritis, idiopathic episcleritis, anterior episcleritis, or posterior episcleritis. In one embodiment, the disorder is idiopathic anterior uveitis, HLA-B27 related uveitis, herpetic keratouveitis, Posner Schlossman syndrome, Fuch's heterochromic iridocyclitis, or cytomegalovirus anterior uveitis.

[0494] In yet another embodiment, the disorder is selected from:

(i) vitritis, sarcoidosis, syphilis, tuberculosis, or Lyme disease;

(ii) retinal vasculitis, Eales disease, tuberculosis, syphilis, or toxoplasmosis;

(iii) neuroretinitis, viral retinitis, or acute retinal necrosis;

(iv) varicella zoster virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, lichen planus, or Dengue-associated disease (e.g., hemorraghic Dengue Fever);

(v) Masquerade syndrome, contact dermatitis, trauma induced inflammation, UVB induced inflammation, eczema, granuloma annulare, or acne.

[0495] In an additional embodiment, the disorder is selected from:

(i) acute myocardial infarction, aneurysm, cardiopulmonary bypass, dilated cardiomyopathy, complement activation during cardiopulmonary bypass operations, coronary artery disease, restenosis following stent placement, or percutaneous transluminal coronary angioplasty (PTCA);

(ii) antibody-mediated transplant rejection, anaphylactic shock, anaphylaxis, allogenic transplant, humoral and vascular transplant rejection, graft dysfunction, graft-versus-host disease, Graves' disease, adverse drug reactions, or chronic graft vasculopathy;

(iii) allergic bronchopulmonary aspergillosis, allergic neuritis, drug allergy, radiation- induced lung injury, eosinophilic pneumonia, radiographic contrast media allergy, bronchiolitis obliterans, or interstitial pneumonia;

(iv) amyotrophic lateral sclerosis, parkinsonism-dementia complex, sporadic frontotemporal dementia, frontotemporal dementia with Parkinsonism linked to chromosome 17, frontotemporal lobar degeneration, tangle only dementia, cerebral amyloid angiopathy, cerebrovascular disorder, certain forms of frontotemporal dementia, chronic traumatic encephalopathy (CTE), PD with dementia (PDD), argyrophilic grain dementia, dementia pugilistica, dementia with Lewy Bodies (DLB), or multi-infarct dementia;

(v) Creutzfeldt-Jakob disease, Huntington's disease, multifocal motor neuropathy (MMN), prion protein cerebral amyloid angiopathy, polymyositis, postencephalitic parkinsonism, subacute sclerosing panencephalitis, non-Guamanian motor neuron disease with neurofibrillary tangles, neural regeneration, or diffuse neurofibrillary tangles with calcification.

[0496] In one embodiment, the disorder is selected from:

(i) atopic dermatitis, dermatitis, dermatomyositis, dermatomyositis bullous pemphigoid, scleroderma, sclerodermatomyositis, psoriatic arthritis, pemphigus vulgaris, Discoid lupus erythematosus, cutaneous lupus, chilblain lupus erythematosus, or lupus erythematosus-lichen planus overlap syndrome.;

(ii) cryoglobulinemic vasculitis, mesenteric/enteric vascular disorder, peripheral vascular disorder, antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), IL-2 induced vascular leakage syndrome, or immune complex vasculitis;

(iii) angioedema, low platelets (HELLP) syndrome, sickle cell disease, platelet refractoriness, red cell casts, or typical or infectious hemolytic uremic syndrome (tHUS);

(iv) hematuria, hemodialysis, hemolysis, hemorrhagic shock, immunothrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), idiopathic thrombocytopenic purpura (ITP), drug-induced thrombocytopenia, autoimmune hemolytic anemia (AIHA),

azotemia, blood vessel and/or lymph vessel inflammation, rotational atherectomy, or delayed hemolytic transfusion reaction;

(v) British type amyloid angiopathy, Buerger's disease, bullous pemphigoid, Clq nephropathy, cancer, or catastrophic antiphospholipid syndrome.

[0497] In another embodiment, the disorder is selected from:

(i) wet AMD, dry AMD, chorioretinal degeneration, choroidal neovascularization (CNV), choroiditis, loss of RPE function, loss of vision (including loss of visual acuity or visual field), loss of vision from AMD, retinal damage in response to light exposure, retinal degeneration, retinal detachment, retinal dysfunction, retinal neovascularization (RNV), retinopathy of prematurity, or RPE degeneration;

(ii) pseudophakic bullous keratopathy, symptomatic macular degeneration related disorder, optic nerve degeneration, photoreceptor degeneration, cone degeneration, loss of photoreceptor cells, pars planitis, scleritis, proliferative vitreoretinopathy, or formation of ocular drusen;

(iii) chronic urticaria, Churg-Strauss syndrome, cold agglutinin disease (CAD), corticobasal degeneration (CBD), cryoglobulinemia, cyclitis, damage of the Bruch's membrane, Degos disease, diabetic angiopathy, elevated liver enzymes, endotoxemia, epidermolysis bullosa, or epidermolysis bullosa acquisita;

(iv) essential mixed cryoglobulinemia, excessive blood urea nitrogen-BUN, focal segmental glomerulosclerosis, Gerstmann-Straussler-Scheinker disease, giant cell arteritis, gout, Hallervorden-Spatz disease, Hashimoto's thyroiditis, Henoch-Schonlein purpura nephritis, or abnormal urinary sediments;

(v) hepatitis, hepatitis A, hepatitis B, hepatitis C or human immunodeficiency virus (HIV),

(vi) a viral infection more generally, for example selected from Flaviviridae, Retroviruses, Coronaviridae, Poxviridae, Adenoviridae, Herpesviridae, Caliciviridae, Reoviridae, Picornaviridae, Togaviridae, Orthomyxoviridae, Rhabdoviridae, or Hepadnaviridae;

(vii) Neisseria meningitidis, shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS), Streptococcus, or poststreptococcal glomerulonephritis.

[0498] In a further embodiment, the disorder is selected from:

(viii) hyperlipidemia, hypertension, hypoalbuminemia, hypobolemic shock, hypocomplementemic urticarial vasculitis syndrome, hypophosphastasis, hypovolemic shock, idiopathic pneumonia syndrome, or idiopathic pulmonary fibrosis;

(ix) inclusion body myositis, intestinal ischemia, iridocyclitis, iritis, juvenile chronic arthritis, Kawasaki's disease (arteritis), or lipiduria;

(x) membranoproliferative glomerulonephritis (MPGN) I, microscopic polyangiitis, mixed cryoglobulinemia, molybdenum cofactor deficiency (MoCD) type A, pancreatitis, panniculitis, Pick's disease, polyarteritis nodosa (PAN), progressive subcortical gliosis, proteinuria, reduced glomerular filtration rate (GFR), or renovascular disorder;

(xi) multiple organ failure, multiple system atrophy (MSA), myotonic dystrophy, Niemann-Pick disease type C, chronic demyelinating diseases, or progressive supranuclear palsy;

(xii) spinal cord injury, spinal muscular atrophy, spondyloarthropathies, Reiter's syndrome, spontaneous fetal loss, recurrent fetal loss, pre-eclampsia, synucleinopathy, Takayasu's arteritis, post-partum thryoiditis, thyroiditis, Type I cryoglobulinemia, Type II mixed cryoglobulinemia, Type III mixed cryoglobulinemia, ulcerative colitis, uremia, urticaria, venous gas embolus (VGE), or Wegener's granulomatosis;

[0499] In one embodiment, an active compound or its salt or composition as described herein is useful for treating or preventing a disorder selected from autoimmune oophoritis, endometriosis, autoimmune orchitis, Ord's thyroiditis, autoimmune enteropathy, coeliac disease, Hashimoto's encephalopathy, antiphospholipid syndrome (APLS) (Hughes syndrome), aplastic anemia, autoimmune lymphoproliferative syndrome (Canale-Smith syndrome), autoimmune neutropenia, Evans syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adipose dolorosa (Dercum's disease), adult onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, eosinophilic fasciitis (Shulman's syndrome), Felty syndrome, IgG4-related disease, mixed connective tissue disease (MCTD), palindromic rheumatism (Hench-Rosenberg syndrome), Parry-Romberg syndrome, Parsonage-Turner syndrome, relapsing polychondritis (Meyenburg-Altherr-Uehlinger syndrome), retroperitonial fibrosis, rheumatic fever, Schnitzler syndrome, fibromyalgia, neuromyotonia (Isaac's disease), paraneoplastic degeneration, autoimmune inner ear disease, Meniere's disease, interstitial cystitis, autoimmune pancreatitis, zika virus-related disorders, chikungunya virus-related disorders, subacute bacterial endocarditis (SBE), IgA nephropathy, IgA vasculitis, polymyalgia rheumatic, rheumatoid

vasculitis, alopecia areata, autoimmune progesterone dermatitis, dermatitis herpetiformis, erythema nodosum, gestational pemphigoid, hidradenitis suppurativa, lichen sclerosus, linear IgA disease (LAD), morphea, myositis, pityriasis lichenoides et varioliformis acuta, vitiligo post-myocardial infarction syndrome (Dressier' s syndrome), post-pericardiotomy syndrome, autoimmune retinopathy, Cogan syndrome, Graves opthalmopathy, ligneous conjunctivitis, Mooren's ulcer, opsoclonus myoclonus syndrome, optic neuritis, retinocochleocerebral vasculopathy (Susac's syndrome), sympathetic opthalmia, Tolosa-Hunt syndrome, interstitial lung disease, anti synthetase syndrome, Addison's disease, autoimmune polyendocrine syndrome (APS) type I, autoimmune polyendocrine syndrome (APS) type II, autoimmune polyendocrine syndrome (APS) type III, disseminated sclerosis (multiple sclerosis, pattern II), rapidly progressing glomerulonephritis (RPGN), juvenile rheumatoid arthritis, enthesitis-related arthritis, reactive arthritis (Reiter's syndrome), autoimmune hepatitis or lupoid hepatitis, primary biliary cirrhosis (PBS), primary sclerosing cholangitis, microscopic colitis, latent lupus (undifferentiated connective tissue disease (UCTD)), acute disseminated encephalomyelitis (ADEM), acute motor axonal neuropathy, anti-n-methyl-D-aspartate receptor encephalitis, Balo concentric sclerosis (Schilders disease), Bickerstaffs encephalitis, chronic inflammatory demyelinating polyneuropathy, idiopathic inflammatory demyelinating disease, Lambert-Eaton mysathenic syndrome, Oshtoran syndrome, pediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS), progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, Sydenhem syndrome, transverse myelitis, lupus vasculitis, leukocytoclastic vasculitis, Microscopic Polyangiitis, polymyositis or ischemic-reperfusion injury of the eye.

[0500] In one embodiment, an active compound or its salt or composition as described herein is useful for treating or preventing a disorder that is mediated by the complement pathway, and in particular, a pathway that is modulated by complement Factor D. In another embodiment, the compound is effective to treat the disorder, albeit through a different mechanism.

[0501] In certain embodiments, the disorder is an inflammatory disorder, an immune disorder, an autoimmune disorder, or complement Factor D related disorders in a host. In one embodiment, the disorder is an ocular disorder or an eye disorder.

[0502] Examples of eye disorders that may be treated according to the compositions and methods disclosed herein include amoebic keratitis, fungal keratitis, bacterial keratitis, viral keratitis, onchorcercal keratitis, bacterial keratoconjunctivitis, viral keratoconjunctivitis, corneal

dystrophic diseases, Fuchs' endothelial dystrophy, Sjogren's syndrome, Stevens-Johnson syndrome, autoimmune dry eye diseases, environmental dry eye diseases, corneal neovascularization diseases, post-corneal transplant rejection prophylaxis and treatment, autoimmune uveitis, infectious uveitis, anterior uveitis, posterior uveitis (including toxoplasmosis), pan-uveitis, an inflammatory disease of the vitreous or retina, endophthalmitis prophylaxis and treatment, macular edema, macular degeneration, age related macular degeneration, proliferative and non-proliferative diabetic retinopathy, hypertensive retinopathy, an autoimmune disease of the retina, primary and metastatic intraocular melanoma, other intraocular metastatic tumors, open angle glaucoma, closed angle glaucoma, pigmentary glaucoma and combinations thereof.

[0503] In a further embodiment, the disorder is selected from age-related macular degeneration, glaucoma, diabetic retinopathy, neuromyelitis optica (NMO), vasculitis, hemodialysis, blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid, uveitis, adult macular degeneration, diabetic retinopa retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, postoperative inflammation, and retinal vein occlusion, or uveitis (including Behcet's disease and other sub-types of uveitis).

[0504] In some embodiments, complement mediated diseases include ophthalmic diseases (including early or neovascular age-related macular degeneration and geographic atrophy), autoimmune diseases (including arthritis, rheumatoid arthritis), respiratory diseases, cardiovascular diseases. In other embodiments, the compounds of the invention are suitable for use in the treatment of diseases and disorders associated with fatty acid metabolism, including obesity and other metabolic disorders.

[0505] Disorders that may be treated or prevented by an active compound or its salt or composition as described herein also include, but are not limited to:

(i) paroxysmal nocturnal hemoglobinuria (PNH), hereditary angioedema, capillary leak syndrome, atypical hemolytic uremic syndrome (aHUS), hemolytic uremic syndrome (HUS), abdominal aortic aneurysm, hemodialysis complications, hemolytic anemia, or hemodialysis;

(ii) myasthenia gravis, multiple sclerosis, C3 glomerulonephritis (C3GNs), MPGN II (dense deposit disease), neurological disorders, Guillain Barre Syndrome, diseases of the central nervous system and other neurodegenerative conditions, glomerulonephritis (including membrane proliferative glomerulonephritis), SLE nephritis, proliferative nephritis, liver fibrosis, tissue regeneration and neural regeneration, or Barraquer- Simons Syndrome;

(iii) inflammatory effects of sepsis, systemic inflammatory response syndrome (SIRS), disorders of inappropriate or undesirable complement activation, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, system lupus erythematosus (SLE), Crohn's disease, rheumatoid arthritis, inflammatory bowel disease, lupus nephritides, arthritis, immune complex disorders and autoimmune diseases, systemic lupus, or lupus erythematosus;

(iv) ischemia/ reperfusion injury (I/R injury), myocardial infarction, myocarditis, post-ischemic reperfusion conditions, balloon angioplasty, atherosclerosis, post-pump syndrome in cardiopulmonary bypass or renal bypass, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, antiphospholipid syndrome, autoimmune heart disease, ischemia-reperfusion injuries, obesity, or diabetes;

(v) Alzheimer's dementia, stroke, schizophrenia, traumatic brain injury, trauma, Parkinson's disease, epilepsy, transplant rejection, prevention of fetal loss, biomaterial reactions (e.g. in hemodialysis, inplants), hyperacute allograft rejection, xenograft rejection, transplantation, psoriasis, burn injury, thermal injury including burns or frostbite;

(vi) asthma, allergy, acute respiratory distress syndrome (ARDS), cystic fibrosis, adult respiratory distress syndrome, dyspnea, hemoptysis, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (e.g., silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, e.g., chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (e.g., burn, freeze), bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome (anti-glomerular basement membrane nephritis), pulmonary vasculitis, Pauci-immune vasculitis, or immune complex- associated inflammation.

In one embodiment, a method for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of age-related macular degeneration (AMD) in a host is provided that includes the administration of an effective amount an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of rheumatoid arthritis in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of multiple sclerosis in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of myasthenia gravis in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of atypical hemolytic uremic syndrome (aHUS) in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of C3 glomerulonephritis in host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of abdominal aortic aneurysm in host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In another embodiment, a method for the treatment of neuromyelitis optica (NMO) in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein.

[0506] In one embodiment, a method for the treatment of sickle cell in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of immunothrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), or idiopathic thrombocytopenic purpura (ITP) in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of ANCA-vasculitis in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of IgA nephropathy in a host is

provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of rapidly progressing glomerulonephritis (RPGN), in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of lupus nephritis, in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method for the treatment of hemorraghic dengue fever, in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein.

[0507] In some embodiments, the present invention provides methods of treating or preventing an inflammatory disorder or a complement related disease, by administering to a host in need thereof an effective amount of an active compound or its salt or composition as described herein. In some embodiments, the present invention provides methods of treating or preventing an inflammatory disorder more generally, an immune disorder, autoimmune disorder, or complement Factor D related disease in a host, by providing an effective amount of a compound or pharmaceutically acceptable salt of an active compound or its salt or composition as described herein to patient with a Factor D mediated inflammatory disorder. An active compound or its salt or composition as described herein as the only active agent or may be provided together with one or more additional active agents.

[0508] In one embodiment, a method for the treatment of a disorder associated with a dysfunction in the complement cascade in a host is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method of inhibiting activation of the alternative complement pathway in a subject is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein. In one embodiment, a method of modulating Factor D activity in a subject is provided that includes the administration of an effective amount of an active compound or its salt or composition as described herein.

[0509] In an additional alternative embodiment, an active compound or its salt or composition as described herein is used in the treatment of an autoimmune disorder.

[0510] The complement pathway enhances the ability of antibodies and phagocytic cells to clear microbes and damaged cells from the body. It is part of the innate immune system and in

healthy individuals is an essential process. Inhibiting the complement pathway will decrease the body's immune system response. Therefore, it is an object of the present invention to treat autoimmune disorders by administering an effective does of an active compound or its salt or composition as described herein to a subject in need thereof.

[051 1] In one embodiment the autoimmune disorder is caused by activity of the complement system. In one embodiment the autoimmune disorder is caused by activity of the alternative complement pathway. In one embodiment the autoimmune disorder is caused by activity of the classical complement pathway. In another embodiment the autoimmune disorder is caused by a mechanism of action that is not directly related to the complement system, such as the over-proliferation of T-lymphocytes or the over-production of cytokines.

[0512] Non-limiting examples of autoimmune disorders include: lupus, allograft rejection, autoimmune thyroid diseases (such as Graves' disease and Hashimoto's thyroiditis), autoimmune uveoretinitis, giant cell arteritis, inflammatory bowel diseases (including Crohn's disease, ulcerative colitis, regional enteritis, granulomatous enteritis, distal ileitis, regional ileitis, and terminal ileitis), diabetes, multiple sclerosis, pernicious anemia, psoriasis, rheumatoid arthritis, sarcoidosis, and scleroderma.

[0513] In one embodiment, an active compound or its salt or composition as described herein is used in the treatment of lupus. Non-limiting examples of lupus include lupus erythematosus, cutaneous lupus, discoid lupus erythematosus, chilblain lupus erythematosus, or lupus erythematosus-lichen planus overlap syndrome.

[0514] Lupus erythematosus is a general category of disease that includes both systemic and cutaneous disorders. The systemic form of the disease can have cutaneous as well as systemic manifestations. However, there are also forms of the disease that are only cutaneous without systemic involvement. For example, SLE is an inflammatory disorder of unknown etiology that occurs predominantly in women, and is characterized by articular symptoms, butterfly erythema, recurrent pleurisy, pericarditis, generalized adenopathy, splenomegaly, as well as CNS involvement and progressive renal failure. The sera of most patients (over 98%) contain antinuclear antibodies, including anti-DNA antibodies. High titers of anti-DNA antibodies are essentially specific for SLE. Conventional treatment for this disease has been the administration of corticosteroids or immunosuppressants.

[0515] There are three forms of cutaneous lupus: chronic cutaneous lupus (also known as discoid lupus erythematosus or DLE), subacute cutaneous lupus, and acute cutaneous lupus. DLE is a disfiguring chronic disorder primarily affecting the skin with sharply circumscribed macules and plaques that display erythema, follicular plugging, scales, telangiectasia and atrophy. The condition is often precipitated by sun exposure, and the early lesions are erythematous, round scaling papules that are 5 to 10 mm in diameter and display follicular plugging. DLE lesions appear most commonly on the cheeks, nose, scalp, and ears, but they may also be generalized over the upper portion of the trunk, extensor surfaces of the extremities, and on the mucous membranes of the mouth. If left untreated, the central lesion atrophies and leaves a scar. Unlike SLE, antibodies against double-stranded DNA (e.g., DNA-binding test) are almost invariably absent in DLE.

[0516] Multiple Sclerosis is an autoimmune demyelinating disorder that is believed to be T lymphocyte dependent. MS generally exhibits a relapsing-remitting course or a chronic progressive course. The etiology of MS is unknown, however, viral infections, genetic predisposition, environment, and autoimmunity all appear to contribute to the disorder. Lesions in MS patients contain infiltrates of predominantly T lymphocyte mediated microglial cells and infiltrating macrophages. CD4+ T lymphocytes are the predominant cell type present at these lesions. The hallmark of the MS lesion is plaque, an area of demyelination sharply demarcated from the usual white matter seen in MRI scans. Histological appearance of MS plaques varies with different stages of the disease. In active lesions, the blood-brain barrier is damaged, thereby permitting extravasation of serum proteins into extracellular spaces. Inflammatory cells can be seen in perivascular cuffs and throughout white matter. CD4+ T-cells, especially Thl, accumulate around postcapillary venules at the edge of the plaque and are also scattered in the white matter. In active lesions, up-regulation of adhesion molecules and markers of lymphocyte and monocyte activation, such as IL2-R and CD26 have also been observed. Demyelination in active lesions is not accompanied by destruction of oligodendrocytes. In contrast, during chronic phases of the disease, lesions are characterized by a loss of oligodendrocytes and hence, the presence of myelin oligodendrocyte glycoprotein (MOG) antibodies in the blood.

[05 17] Diabetes can refer to either type 1 or type 2 diabetes. In one embodiment an active compound or its salt or composition as described herein is provided at an effective dose to treat a

patient with type 1 diabetes. In one embodiment an active compound or its salt or composition as described herein is provided at an effective dose to treat a patient with type 2 diabetes.

[0518] Type 1 diabetes is an autoimmune disease. An autoimmune disease results when the body's system for fighting infection (the immune system) turns against a part of the body. The pancreas then produces little or no insulin.

V. COMBINATION THERAPY

[0519] In one embodiment an active compound or its salt or composition as described herein may be provided in combination or alternation with or preceded by, concomitant with or followed by, an effective amount of at least one additional therapeutic agent, for example, for treatment of a disorder listed herein. Non-limiting examples of second active agents for such combination therapy are provided below.

[0520] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination or alternation with at least one additional inhibitor of the complement system or a second active compound with a different biological mechanism of action. In the description below and herein generally, whenever any of the terms referring to an active compound or its salt or composition as described herein are used, it should be understood that pharmaceutically acceptable salts, prodrugs or compositions are considered included, unless otherwise stated or inconsistent with the text.

[0521] In non-limiting embodiments, an active compound or its salt or composition as described herein may be provided together with a protease inhibitor, a soluble complement regulator, a therapeutic antibody (monoclonal or polyclonal), complement component inhibitor, receptor agonist, or siRNA.

[0522] In other embodiments, an active compound described herein is administered in combination or alternation with an antibody against tumor necrosis factor (TNF), including but not limited to infliximab (Remicade), adalimumab, certolizumab, golimumab, or a receptor fusion protein such as etanercept (Embrel).

[0523] In another embodiment, an active compound as described herein can be administered in combination or alternation with an anti-CD20 antibody, including but not limited to rituximab (Rituxan), adalimumab (Humira), ofatumumab (Arzerra), tositumomab (Bexxar), obinutuzumab (Gazyva), or ibritumomab (Zevalin).

[0524] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with an anti-IL6 antibody, including but not limited to tocilizumab (Actemra) and siltuximab (Sylvant).

[0525] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with an IL17 inhibitor, including but not limited to secukibumab (Cosentyx).

[0526] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with a p40 (IL12/IL23) inhibitor, including but not limited to ustekinumab (Stelara).

[0527] In an alternative embodiment, an active compound as described herein can be administered in combination or alteration with an IL23 inhibitor, including but not limited to risankizumab.

[0528] In an alternative embodiment, an active compound as described herein can be administered in combination or alteration with an anti-interferon a antibody, for example but not limited to sifalimumab.

[0529] In an alternative embodiment, an active compound as described herein can be administered in combination or alteration with a kinase inhibitor, for example but not limited to a JAK1/JAK3 inhibitor, for example but not limited to tofacitinib (Xelianz). In an alternative embodiment, an active compound as described herein can be administered in combination or alteration with a JAK1/JAK2 inhibitor, for example but not limited to baracitibib.

[0530] In another embodiment, an active compound as described herein can be administered in combination or alternation with an immune checkpoint inhibitor. Non-limiting examples of checkpoint inhibitors are anti-PD-1 or anti-PDLl antibodies (for example, Nivolumab, Pembrolizumab, Pidilizumab and Atezolizumab) and anti-CTLA4 antibodies (Ipilimumab and Tremelimumab).

[053 1] Non-limiting examples of active agents that can be used in combination with active compounds described herein are:

[0532] Protease inhibitors: plasma-derived Cl-INH concentrates, for example Cetor® (Sanquin), Berinert-P® (CSL Behring, Lev Pharma), and Cinryze®; recombinant human Cl-inhibitors, for example Rhucin®; ritonavir (Norvir®, Abbvie, Inc.);

[0533] Soluble complement regulators: Soluble complement receptor 1 (TP10) (Avant Immunotherapeutics); sCRl-sLe ^{x}/TP-20 (Avant Immunotherapeutics); MLN-2222 /CAB-2 (Millenium Pharmaceuticals); Mirococept (Inflazyme Pharmaceuticals);

[0534] Therapeutic antibodies: Eculizumab/Soliris (Alexion Pharmaceuticals); Pexelizumab (Alexion Pharmaceuticals); Ofatumumab (Genmab A/S); TNX-234 (Tanox); TNX-558 (Tanox); TA106 (Taligen Therapeutics); Neutrazumab (G2 Therapies); Anti-properdin (Novelmed Therapeutics); HuMax-CD38 (Genmab A/S);

[0535] Complement component inhibitors: Compstatin/POT-4 (Potentia Pharmaceuticals); ARC 1905 (Archemix);

[0536] Receptor agonists: PMX-53 (Peptech Ltd.); JPE-137 (Jerini); JSM-7717 (Jerini);

[0537] Others: Recombinant human MBL (rhMBL; Enzon Pharmaceuticals);

[0538] Imides and glutarimide derivatives such as thalidomide, lenalidomide, pomalidomide;

[0539] Additional non-limiting examples that can be used in combination or alternation with an active compound or its salt or composition as described herein include the following.

Non-limiting examples of potential therapeutics for combination therapy			
Name	**Target**	**Company**	**Class of Molecule**
LFG316	C5	Novartis/Morphosys	Monoclonal antibody
4(1MEW)APL-1,APL-2	C3/C3b	Apella	Compstatin Family
4(1MeW)POT-4	C3/C3b	Potentia	Compstatin Family
Anti-C5 siRNA	C5	Alnylam	Si-RNA
Anti-FB siRNA	CFB	Alnylam	SiRNA
ARC1005	C5	Novo Nordisk	Aptamers
ATA	C5	N.A.	Chemical
Coversin	C5	Volution Immuno-Pharmaceuticals	Small animal protein
CP40/AMY-101,PEG-Cp40	C3/C3b	Amyndas	Compstatin Family
CRIg/CFH	CAP C3 convertase	NA	CFH-based protein
Cynryze	C1n/C1s	ViroPharma/Baxter	Human purified protein
FCFD4514S	CFD	Genentech/Roche	Monoclonal antibody
H17	C3 (C3b/iC3b)	EluSys Therapeutics	Monoclonal antibody
Mini-CFH	CAP C3 convertase	Amyndas	CFH-based protein

Mirococept (APT070)	CAP and CCP C3	NA	CR1-based protein
Mubodine	C5	Adienne	Monoclonal antibody
RA101348	C5	Rapharma	Small molecule
sCR1 (CDX-1135)	CAP and CP C3	Celldex	CR1-based protein
SOBI002	C5	Swedish Orphan Biovitrum	Affibody
SOMAmers	C5	SomaLogic	Aptamers
SOMAmers	CFB and CFD	SomaLogic	Aptamers (SELEX)
TA106	CFB	Alexion Pharmaceuticals	Monoclonal antibody
TNT003	C1s	True North	Monoclonal antibody
TT30 (CR2/CFH)	CAP C3 convertase	Alexion	CFH-based protein
TT32 (CR2/CR1)	CAP and CCP C3	Alexion Pharmaceuticals	CR1-based protein
Nafamostat (FUT-175, Futhan)	C1s, CFD, other proteases	Torri Pharmaceuticals	Small molecule
OMS721	MASP-2	Omeros	Monoclonal antibody
OMS906	MASP-2	Omeros	Monoclonal antibody
Bikaciomab, NM9308	CFB	Novelmed	Monoclonal antibody
NM9401	Properdin	Novelmed	Monoclonal antibody
CVF, HC-1496	C3	InCode	Recombinant peptide
ALXN1102/ALXN1103 (TT30)	C3-conv, C3b	Alexion Pharmaceuticals	Regulator
rFH	C3-conv, C3b	Optherion	Regulator
5C6, AMY-301	CFH	Amyndas	Regulator
Erdigna	C5	Adienne Pharma	Antibody
ARC1905	C5	Opthotech	Monoclonal Antibody
MEDI7814	C5/C5a	MedImmune	Monoclonal Antibody
NOX-D19	C5a	Noxxon	Aptamer (Spiegelmer)
IFX-1, CaCP29	C5a	InflaRx	Monoclonal Antibody
PMX53, PMX205	C5aR	Cephalon, Teva	Peptidomimetic
CCX168	C5aR	ChemoCentryx	Small molecule
ADC-1004	C5aR	Alligator Bioscience	Small molecule
Anti-C5aR-151, NN8209; Anti-C5aR-215, NN8210	C5aR	Novo Nordisk	Monoclonal Antibody
Imprime PGG	CR3	Biothera	Soluble beta-glucan

[0540] In one embodiment, an active compound or its salt or composition as described herein may be provided together with a compound that inhibits an enzyme that metabolizes an administered protease inhibitor. In one embodiment, a compound or salt may be provided together with ritonavir.

[0541] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with a complement C5 inhibitor or C5 convertase inhibitor. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with eculizumab, a monoclonal antibody directed to the complement factor C5 and manufactured and marketed by Alexion Pharmaceuticals under the tradename Soliris. Eculizumab has been approved by the U.S. FDA for the treatment of PNH and aHUS.

[0542] In one embodiment, an active compound or its salt or composition as described herein may be provided together with a compound that inhibits complement factor D. In one embodiment of the invention, an active compound or its salt or composition as described herein as described herein can be used in combination or alternation with a compound described in Biocryst Pharmaceuticals US Pat. No. 6,653,340 titled "Compounds useful in the complement, coagulate and kallikrein pathways and method for their preparation" describes fused bicyclic ring compounds that are potent inhibitors of Factor D; Novartis PCT patent publication WO2012/093101 titled "Indole compounds or analogues thereof useful for the treatment of age-related macular degeneration" describes certain Factor D inhibitors; Novartis PCT patent publications WO2014/002051, WO2014/002052, WO2014/002053, WO2014/002054, WO2014/002057, WO2014/002058, WO2014/002059, WO2014/005150, WO2014/009833, WO 2013/164802, WO 2015/009616, WO 2015/066241, Bristol-Myers Squibb PCT patent publication WO2004/045518 titled "Open chain prolyl urea-related modulators of androgen receptor function"; Japan Tobacco Inc. PCT patent publication WO1999/048492 titled "Amide derivatives and nociceptin antagonists"; Ferring B.V. and Yamanouchi Pharmaceutical Co. LTD. PCT patent publication WO1993/020099 titled "CCK and/or gastrin receptor ligands"; Alexion Pharmaceuticals PCT patent publication WO1995/029697 titled "Methods and compositions for the treatment of glomerulonephritis and other inflammatory diseases"; or Achillion Pharmaceuticals filed PCT Patent Application No. PCT/US2015/017523 and U.S. Patent Application No. 14/631,090 titled "Alkyne Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017538 and U.S. Patent Application No.

14/631,233 titled "Amide Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017554 and U.S. Patent Application No. 14/631,312 titled "Amino Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017583 and U.S. Patent Application No. 14/631,440 titled "Carbamate, Ester, and Ketone Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US20 15/0 17593 and U.S. Patent Application No. 14/631,625 titled "Aryl, Heteroaryl, and Heterocyclic Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US2015/017597 and U.S. Patent Application No. 14/631,683 titled "Ether Compounds for Treatment of Complement Mediated Disorders"; PCT Patent Application No. PCT/US20 15/0 17600 and U.S. Patent Application No. 14/631,785 titled "Phosphonate Compounds for Treatment of Complement Mediated Disorders"; and PCT Patent Application No. PCT/US20 15/0 17609 and U.S. Patent Application No. 14/631,828 titled "Compounds for Treatment of Complement Mediated Disorders."

[0543] In one embodiment, an active compound or its salt or composition as described herein is administered in combination with an anti-inflammatory drug, antimicrobial agent, anti-angiogenesis agent, immunosuppressant, antibody, steroid, ocular antihypertensive drug or combinations thereof. Examples of such agents include amikacin, anecortane acetate, anthracenedione, anthracycline, an azole, amphotericin B, bevacizumab, camptothecin, cefuroxime, chloramphenicol, chlorhexidine, chlorhexidine digluconate, clortrimazole, a clotrimazole cephalosporin, corticosteroids, dexamethasone, desamethazone, econazole, eftazidime, epipodophyllotoxin, fluconazole, flucytosine, fluoropyrimidines, fluoroquinolines, gatifloxacin, glycopeptides, imidazoles, itraconazole, ivermectin, ketoconazole, levofloxacin, macrolides, miconazole, miconazole nitrate, moxifloxacin, natamycin, neomycin, nystatin, ofloxacin, polyhexamethylene biguanide, prednisolone, prednisolone acetate, pegaptanib, platinum analogues, polymicin B, propamidine isethionate, pyrimidine nucleoside, ranibizumab, squalamine lactate, sulfonamides, triamcinolone, triamcinolone acetonide, triazoles, vancomycin, anti-vascular endothelial growth factor (VEGF) agents, VEGF antibodies, VEGF antibody fragments, vinca alkaloid, timolol, betaxolol, travoprost, latanoprost, bimatoprost, brimonidine, dorzolamide, acetazol amide, pilocarpine, ciprofloxacin, azithromycin, gentamycin, tobramycin, cefazolin, voriconazole, gancyclovir, cidofovir, foscarnet, diclofenac, nepafenac, ketorolac,

ibuprofen, indomethacin, fluoromethalone, rimexolone, anecortave, cyclosporine, methotrexate, tacrolimus and combinations thereof.

[0544] In one embodiment of the present invention, an active compound or its salt or composition as described herein can be administered in combination or alternation with at least one immunosuppressive agent. The immunosuppressive agent as non-limiting examples, may be a calcineurin inhibitor, e.g. a cyclosporin or an ascomycin, e.g. Cyclosporin A (NEORAL®), FK506 (tacrolimus), pimecrolimus, a mTOR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (RAPAMUNE®), Everolimus (Certican®), temsirolimus, zotarolimus, biolimus-7, biolimus-9, a rapalog, e.g.ridaforolimus, azathioprine, campath 1H, a SIP receptor modulator, e.g. fingolimod or an analogue thereof, an anti IL-8 antibody, mycophenolic acid or a salt thereof, e.g. sodium salt, or a prodrug thereof, e.g. Mycophenolate Mofetil (CELLCEPT®), OKT3 (ORTHOCLONE OKT3®), Prednisone, ATGAM®, THYMOGLOBULIN®, Brequinar Sodium, OKT4, T10B9.A-3A, 33B3. 1, 15-deoxyspergualin, tresperimus, Leflunomide ARAVA®, CTLAI-Ig, anti-CD25, anti-IL2R, Basiliximab (SIMULECT®), Daclizumab (ZENAPAX®), mizorbine, methotrexate, dexamethasone, ISAtx-247, SDZ ASM 981 (pimecrolimus, Elidel®), CTLA41g (Abatacept), belatacept, LFA31g, etanercept (sold as Enbrel® by Immunex), adalimumab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, gavilimomab, antithymocyte immunoglobulin, siplizumab, Alefacept efalizumab, pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, tocilizumab (Actemra), siltuximab (Sylvant), secukibumab (Cosentyx), ustekinumab (Stelara), risankizumab, sifalimumab, aspirin and ibuprofen.

[0545] Examples of anti-inflammatory agents include methotrexate, dexamethasone, dexamethasone alcohol, dexamethasone sodium phosphate, fluromethalone acetate, fluromethalone alcohol, lotoprendol etabonate, medrysone, prednisolone acetate, prednisolone sodium phosphate, difluprednate, rimexolone, hydrocortisone, hydrocortisone acetate, lodoxamide tromethamine, aspirin, ibuprofen, suprofen, piroxicam, meloxicam, flubiprofen, naproxan, ketoprofen, tenoxicam, diclofenac sodium, ketotifen fumarate, diclofenac sodium, nepafenac, bromfenac, flurbiprofen sodium, suprofen, celecoxib, naproxen, rofecoxib, glucocorticoids, diclofenac, and any combination thereof. In one embodiment, an active compound or its salt or composition as described herein is combined with one or more non-steroidal anti-inflammatory drugs (NSAIDs) selected from naproxen sodium (Anaprox), celecoxib (Celebrex), sulindac

(Clinoril), oxaprozin (Daypro), salsalate (Disalcid), diflunisal (Dolobid), piroxicam (Feldene), indomethacin (Indocin), etodolac (Lodine), meloxicam (Mobic), naproxen (Naprosyn), nabumetone (Relafen), ketorolac tromethamine (Toradol), naproxen/esomeprazole (Vimovo), and diclofenac (Voltaren), and combinations thereof.

[0546] In one embodiment, an active compound or its salt or composition as described herein is administered in combination or alteration with an omega-3 fatty acid or a peroxisome proliferator-activated receptor (PPARs) agonist. Omega-3 fatty acids are known to reduce serum triglycerides by inhibiting DGAT and by stimulating peroxisomal and mitochondrial beta oxidation. Two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been found to have high affinity for both PPAR-alpha and PPAR-gamma. Marine oils, e.g., fish oils, are a good source of EPA and DHA, which have been found to regulate lipid metabolism. Omega-3 fatty acids have been found to have beneficial effects on the risk factors for cardiovascular diseases, especially mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. Omega-3 fatty acids lower serum triglycerides, increase serum HDL- cholesterol, lower systolic and diastolic blood pressure and the pulse rate, and lower the activity of the blood coagulation factor Vll-phospholipid complex. Further, omega-3 fatty acids seem to be well tolerated, without giving rise to any severe side effects. One such form of omega-3 fatty acid is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA and is sold under the trademark Omacor®. Such a form of omega-3 fatty acid is described, for example, in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594, the disclosures of which are incorporated herein by reference.

[0547] Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily ligand-activated transcription factors that are related to retinoid, steroid and thyroid hormone receptors. There are three distinct PPAR subtypes that are the products of different genes and are commonly designated PPAR-alpha, PPAR-beta/delta (or merely, delta) and PPAR-gamma. General classes of pharmacological agents that stimulate peroxisomal activity are known as PPAR agonists, e.g., PPAR-alpha agonists, PPAR-gamma agonists and PPAR-delta agonists. Some pharmacological agents are combinations of PPAR agonists, such as alpha/gamma agonists, etc., and some other pharmacological agents have dual agonist/antagonist activity. Fibrates such as fenofibrate, bezafibrate, clofibrate and gemfibrozil, are PPAR-alpha agonists and are used in patients to decrease lipoproteins rich in triglycerides, to

increase HDL and to decrease atherogenic-dense LDL. Fibrates are typically orally administered to such patients. Fenofibrate or 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, has been known for many years as a medicinally active principle because of its efficacy in lowering blood triglyceride and cholesterol levels.

[0548] In one embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination with an anti-VEGF agent. Non-limiting examples of anti-VEGF agents include, but are not limited to, aflibercept (Eylea®; Regeneron Pharmaceuticals); ranibizumab (Lucentis®: Genentech and Novartis); and pegaptanib (Macugen®; OSI Pharmaceuticals and Pfizer); Bevacizumab (Avastin; Genentech/Roche); anecortane acetate, squalamine lactate, and corticosteroids, including, but not limited to, triamcinolone acetonide.

[0549] In one embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein with an additional inhibitor of the complement system or another active compound with a different biological mechanism of action. In another embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination or alternation with eculizumab. In another embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination or alternation with CP40. In one embodiment, the additional agent is PEGylated-CP40. CP40 is a peptide inhibitor that shows a strong binding affinity for C3b and inhibits hemolysis of paroxysmal nocturnal hemoglobinuria (PNH) erythrocytes.

[0550] In one embodiment, the present invention provides a method of treating or preventing rheumatoid arthritis by administering to a subject in need thereof an effective amount of a composition comprising an active compound or its salt or composition as described herein in combination or alternation with an additional inhibitor of the complement system, or an active agent that functions through a different mechanism of action. In another embodiment, the present

invention provides a method of treating or preventing rheumatoid arthritis by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination or alternation with methotrexate. In certain embodiments, an active compound or its salt or composition as described herein is administered in combination or alternation with at least one additional therapeutic agent selected from: salicylates including aspirin (Anacin, Ascriptin, Bayer Aspirin, Ecotrin) and salsalate (Mono-Gesic, Salgesic); nonsteroidal anti-inflammatory drugs (NSAIDs); nonselective inhibitors of the cyclo-oxygenase (COX-1 and COX-2) enzymes, including diclofenac (Cataflam, Voltaren), ibuprofen (Advil, Motrin), ketoprofen (Orudis), naproxen (Aleve, Naprosyn), piroxicam (Feldene), etodolac (Lodine), indomethacin, oxaprozin (Daypro), nabumetone (Relafen), and meloxicam (Mobic); selective cyclo-oxygenase-2 (COX-2) inhibitors including Celecoxib (Celebrex); disease-modifying antirheumatic drugs (DMARDs), including azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold salts (Ridaura, Solganal, Aurolate, Myochrysine), hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate (Rheumatrex), penicillamine (Cuprimine), and sulfasalazine (Azulfidine); biologic drugs including abatacept (Orencia), etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), and anakinra (Kineret); corticosteroids including betamethasone (Celestone Soluspan), cortisone (Cortone), dexamethasone (Decadron), methylprednisolone (SoluMedrol, DepoMedrol), prednisolone (Delta-Cortef), prednisone (Deltasone, Orasone), and triamcinolone (Aristocort); gold salts, including Auranofin (Ridaura); Aurothioglucose (Solganal); Aurolate; Myochrysine; or any combination thereof.

[0551] In one embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination or alternation with an additional inhibitor of the complement system, or an active agent that functions through a different mechanism of action. In another embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a subject in need thereof an effective amount of an active compound or its salt or composition as described herein in combination or alternation with a corticosteroid. Examples of corticosteroids include, but are not limited to, prednisone, dexamethasone, solumedrol, and methylprednisolone. In one embodiment, an active compound or its salt or composition as described herein is combined with at least one

anti-multiple sclerosis drug, for example, selected from: Aubagio (teriflunomide), Avonex (interferon beta-1a), Betaseron (interferon beta-1b), Copaxone (glatiramer acetate), Extavia (interferon beta-1b), Gilenya (fingolimod), Lemtrada (alemtuzumab), Novantrone (mitoxantrone), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a), Tecfidera (dimethyl fumarate), Tysabri (natalizumab), Solu-Medrol (methylprednisolone), High-dose oral Deltasone (prednisone), H.P. Acthar Gel (ACTH), or a combination thereof.

[0552] In one embodiment, an active compound or its salt or composition as described herein is useful in a combination with another pharmaceutical agent to ameliorate or reduce a side effect of the agent. For example, in one embodiment, an active compound or its salt or composition as described herein may be used in combination with adoptive cell transfer therapies to reduce an associated inflammatory response associated with such therapies, for example, a cytokine mediated response such as cytokine release syndrome. In one embodiment, the adoptive cell transfer therapy includes the use of a chimeric antigen receptor T-Cell (CAR T). In one embodiment, the adoptive cell transfer therapy includes the use of a chimeric antigen receptor T-Cell (CAR T) or a dendritic cell to treat a hematologic or solid tumor, for example, a B-cell related hematologic cancer. In one embodiment, the hematologic or solid tumor is acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), pancreatic cancer, glioblastoma, or a cancer that expresses CD19.

[0553] In an additional alternative embodiment, an active compound or its salt or composition as described herein may be provided in combination with eculizumab for the treatment of PNH, aHUSs, STEC-HUS, ANCA-vasculitis, AMD, CAD, chronic hemolysis, neuromyelitis optica, or transplantation rejection. In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with compstatin or a compstatin derivative for the treatment of PNH, aHUSs, STEC-HUS, ANCA-vasculitis, AMD, CAD, chronic hemolysis, neuromyelitis optica, or transplantation rejection.

[0554] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with rituxan for the treatment of a complement mediated disorder. In one embodiment, the complement mediated disorder is, for example, rheumatoid arthritis, Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis), and Microscopic Polyangiitis (MPA). In one embodiment, the disorder is Lupus.

[0555] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with cyclophosphamide for the treatment of a complement mediated disorder. In one embodiment, the disorder is an autoimmune disease. In one embodiment, the complement mediated disorder is, for example, rheumatoid arthritis, Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis), and Microscopic Polyangiitis (MPA). In one embodiment, the disorder is Lupus.

[0556] In one embodiment, an active compound or its salt or composition as described herein is dosed in combination with a conventional DLE treatment for the treatment of lupus to a subject in need thereof.

[0557] Examples of conventional DLE treatments include topical corticosteroid ointments or creams, such as triamcinolone acetonide, fluocinolone, flurandrenolide, betamethasone valerate, or betamethasone dipropionate. Resistant plaques can be injected with an intradermal corticosteroid. Other potential DLE treatments include calcineurin inhibitors such as pimecrolimus cream or tacrolimus ointment. Particularly resistant cases can be treated with systemic antimalarial drugs, such as hydroxychloroquine (PLAQUENIL).

[0558] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with methotrexate for the treatment of Lupus.

[0559] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with azathioprine for the treatment of Lupus.

[0560] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with a non-steroidal anti-inflammatory drug for the treatment of Lupus.

[0561] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with a corticosteroid for the treatment of Lupus.

[0562] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with a belimumab (Benlysta) for the treatment of Lupus.

[0563] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with hydroxychloroquine (Plaquenil) for the treatment of Lupus.

[0564] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with sifalimumab for the treatment of Lupus.

[0565] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with OMS721 (Omeros) for the treatment of a complement mediated disorder. In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with OMS906 (Omeros) for the treatment of a complement mediated disorder. In one embodiment, the complement mediated disorder is, for example, thrombotic thrombocytopenic purpura (TTP) or aHUS.

[0566] In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with an anti-inflammatory agent, immunosuppressive agent, or anti-cytokine agent for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics (e.g. adoptive T-cell therapy (ACT) such as CAR T-cell therapy, or monoclonal antibody therapy). In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with a corticosteroid, for example prednisone, dexamethasone, solumedrol, and methylprednisolone, and/or anti-cytokine compounds targeting, e.g., IL-4, IL-10, IL-1 1, IL-13 and TGFp. In one embodiment, an active compound or its salt or composition as described herein may be provided in combination with an anti-cytokine inhibitor including, but are not limited to, adalimumab, infliximab, etanercept, protopic, efalizumab, alefacept, anakinra, siltuximab, secukibumab, ustekinumab, golimumab, and tocilizumab, or a combination thereof. Additional anti-inflammatory agents that can be used in combination with an active compound or its salt or composition as described herein include, but are not limited to, non-steroidal anti-inflammatory drug(s) (NSAIDs); cytokine suppressive anti-inflammatory drug(s) (CSAIDs); CDP-571/BAY-10-3356 (humanized anti-TNFa antibody; Celltech/Bayer); cA2/infliximab (chimeric anti-TNFa antibody; Centocor); 75 kdTNFR-IgG/etanercept (75 kD TNF receptor-IgG fusion protein; Immunex); 55 kdTNF-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IDEC-CE9.1/SB 210396 (non-depleting primatized anti-CD4 antibody; IDEC/SmithKline); DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins; Seragen); Anti-Tac (humanized anti-IL-2Ra; Protein Design Labs/Roche); IL-4 (anti-inflammatory cytokine; DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10, anti-inflammatory cytokine; DNAX/Schering); IL-4; IL-10 and/or IL-4 agonists (e.g., agonist antibodies); IL-IRA (IL-1 receptor antagonist; Synergen/Amgen); anakinra (Kineret®/Amgen); TNF-bp/s-TNF (soluble TNF binding protein); R973401 (phosphodiesterase Type IV inhibitor); MK-966 (COX-2 Inhibitor); Iloprost, leflunomide (anti-

inflammatory and cytokine inhibiton); tranexamic acid (inhibitor of plasminogen activation); T-614 (cytokine inhibitor); prostaglandin El; Tenidap (non-steroidal anti-inflammatory drug); Naproxen (non-steroidal anti-inflammatory drug); Meloxicam (non-steroidal anti-inflammatory drug); Ibuprofen (non-steroidal anti-inflammatory drug); Piroxicam (non-steroidal anti-inflammatory drug); Diclofenac (non-steroidal anti-inflammatory drug); Indomethacin (non-steroidal anti-inflammatory drug); Sulfasalazine; Azathioprine; ICE inhibitor (inhibitor of the enzyme interleukin- ï β converting enzyme); zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck); TNF-convertase inhibitors; anti-IL-12 antibodies; anti-IL-18 antibodies; interleukin-1 1; interleukin-13; interleukin-17 inhibitors; gold; penicillamine; chloroquine; chlorambucil; hydroxychloroquine; cyclosporine; cyclophosphamide; anti-thymocyte globulin; anti-CD4 antibodies; CD5-toxins; orally-administered peptides and collagen; lobenzarit disodium; Cytokine Regulating Agents (CRAB) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligo-deoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP 10; T Cell Sciences, Inc.); prednisone; orgotein; glycosaminoglycan polysulphate; minocycline; anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids); auranofin; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; azaribine; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-chlorodeoxyadenosine).

[0567] In a specific embodiment, an active compound or its salt or composition as described herein may be provided in combination with a corticosteroid for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with etarnercept for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with tocilizumab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with etarnercept and tocilizumab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics. In another embodiment, an active compound

or its salt or composition as described herein may be provided in combination with infliximab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with golimumab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of pharmaceuticals or biotherapeutics.

VI. COMBINATIONS FOR PROPHYLACTIC OR CONCOMMITANT ANTI¬ BACTERIAL THERAPY

[0568] In one aspect of the present invention, a method is provided for treating a host in need thereof that comprises administering an effective amount of a prophylactic anti-bacterial vaccine prior to administration of an active compound or its salt or composition for any of the disorders described herein. In another aspect of the present invention, a method is provided for treating a host in need thereof that comprises administering an effective amount of a prophylactic anti-bacterial drug, such as a pharmaceutical drug, prior to administration of an active compound or its salt or composition for any of the disorders described herein. In one aspect of the present invention, a method is provided for treating a host in need thereof that comprises administering an effective amount of an anti-bacterial vaccine after administration of an active compound or its salt or composition for any of the disorders described herein. In another aspect of the present invention, a method is provided for treating a host in need thereof that comprises administering an effective amount of an anti-bacterial drug, such as a pharmaceutical drug, after administration of an active compound or its salt or composition for any of the disorders described herein. In one embodiment, the disorder is PNH or aHUS. In one embodiment, the host has received an organ or other tissue or biological fluid transplant. In one embodiment, the host is also administered eculizumab.

[0569] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a host concomitantly to a subject following the prophylactic administration of a vaccine against a bacterial infection. In one embodiment, the complement mediated disorder is PNH or aHUS. In one embodiment, the subject has received an organ or other tissue or biological fluid transplant. In one embodiment, the subject is also administered eculizumab.

[0570] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a subject concomitantly with the prophylactic administration of a vaccine against a bacterial infection. In one embodiment, the complement mediated disorder is PNH or aHUS. In one embodiment, the subject has received an organ or other tissue or biological fluid transplant. In one embodiment, the subject is also administered eculizumab.

[0571] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a subject and, during the administration period of the compound or salt, a vaccine against a bacterial infection is administered to the subject. In one embodiment, the complement mediated disorder is PNH or aHUS. In one embodiment, the subject has received an organ or other tissue or biological fluid transplant. In one embodiment, the subject is also administered eculizumab.

[0572] In one aspect of the present invention, the subject is administered an active compound or its salt or composition as described herein in combination with an antibiotic compound for the duration of factor D inhibitor administration. In one embodiment, the complement mediated disorder is PNH or aHUS. In one embodiment, the subject has received an organ or other tissue or biological fluid transplant. In one embodiment, the subject is also administered eculizumab.

[0573] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a subject following the prophylactic administration of a vaccine against a bacterial infection, and in combination with an antibiotic compound for the duration of factor D inhibitor administration. In one embodiment, the complement mediated disorder is PNH or aHUS. In one embodiment, the subject has received an organ or other tissue or biological fluid transplant. In one embodiment, the subject is also administered eculizumab.

[0574] In one embodiment, the subject, prior to receiving an active compound or its salt or composition as described herein, is vaccinated against abacterial infection caused by the bacterium Neisseria meningitidis. In one embodiment, the subject is vaccinated against a bacterial infection caused by the bacterium Haemophilus influenzae. In one embodiment, the Haemophilus influenzae is Haemophilus influenzae serotype B (Hib). In one embodiment, the subject is vaccinated against a bacterial infection caused by Streptococcus pneumoniae. In one embodiment, the subject is vaccinated against a bacterial infection caused by the bacterium Nisseria meningitidis, Haemophilus influenzae, or Streptococcus pneumoniae, or a combination of one or

more of Nisseria meningitidis, Haemophilus influenzae, or Streptococcus pneumoniae. In one embodiment, the subject is vaccinated against a bacterial infection caused by the bacterium Nisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae.

[0575] In other embodiments, the subject is vaccinated against a bacterial infection caused by a bacterium selected from a Gram-negative bacterium. In one embodiment, the subject is vaccinated against a bacterial infection caused by a bacterium selected from a Gram-positive bacterium. In one embodiment, the subject is vaccinated against a bacterial infection caused by the bacterium Nisseria meningitidis, Haemophilus influenzae, or Streptococcus pneunemoniae, or a combination of one or more of Nisseria meningitidis, Haemophilus influenzae, or Streptococcus pneumoniae, and one or more of, but not limited to, Bacillus anthracis, Bordetella pertussis, Clostridium tetani, Corynebacterium diphtheria, Coxiella burnetii, Mycobacterium tuberculosis, Salmonella typhi, Vibrio cholerae, Anaplasma phagocytophilum, Ehrlichia ewingii, Ehrlichia chaffeensis, Ehrlichia canis, Neorickettsia sennetsu, Mycobacterium leprae, Borrelia burgdorferi, Borrelia mayonii, Borrelia afzelii, Borrelia garinii, Mycobacterium bovis, Staphylococcus aureus, Streptococcus pyogenes, Treponema pallidum, Francisella tularensis, Yersinia pestis,

[0576] In one embodiment, the subject is vaccinated with one or more vaccines selected from, but not limited to, typhoid vaccine, live (Vivotif Berna Vaccine, PaxVax), typhoid Vi polysaccharide vaccine (Typhim Vi, Sanofi), pneumococcal 23-polyvalent vaccine, PCV13 (Pneumovax 23, Merck), pneumococcal 7-valent vaccine, PCV7 (Prevnar, Pfizer), pneumococcal 13-valent vaccine, PCV13 (Prevnar 13, Pfizer), haemophilus b conjugate (prp-t) vaccine (ActHIB, Sanofi; Hibrix, GSK), haemophilus b conjugate (hboc) vaccine (HibTITER, Neuron Biotech), haemophilus b conjugate (prp-omp) vaccine (PedvaxHIB, Merck), haemophilus b conjugate (prp-t) vaccine/meningococcal conjugate vaccine (MenHibrix, GSK), haemophilus b conjugate (prp-t) vaccine/meningococcal conjugate vaccine/Hepatitis B vaccine (Comvax, Merck), meningococcal polysaccharide vaccine (Menomune A / C / Y / W-135, Sanofi), meningococcal conjugate vaccine/diphtheria CRM197 conjugate (Menveo, GSK; Menactra, Sanofi), meningococcal group B vaccine (Bexsero, GSK; Trumenba, Pfizer), anthrax vaccine adsorbed (Biothrax, Emergent Biosolutions), tetanus toxoid (Te Anatoxal Berna, Hendricks Regional Health), Bacillus Calmette and Guerin, live, intravesical (TheraCys, Sanofi; Tice BCG, Organon), cholera vaccine, live, oral (Vachora, Sanofi; Dukoral, SBL Vaccines; ShanChol, Shantha Biotec; Micromedex, Truven Health), tetanus toxoids and diphtheria absorbed (Tdap; Decavac, Sanofi; Tenivac, Sanofi; td,

Massachusetts Biological Labs), diphtheria and tetanus toxois and pertussis (DTap; Daptacel, Sanofi; Infanrix, GSK; Tripedia, Sanofi), diphtheria and tetanus toxois and pertussis/polio (Kinrix, GSK; Quadracel, Sanofi), diphtheria and tetanus toxois and pertussis tetanus/hepatitis B/polio (Pediarix, GSK), diphtheria and tetanus toxois and pertussis/ polio, haemophilus influenza tybe b (Pentacel, Sanofi), and/or diphtheria, and pertussis (Tdap; Boostrix, GSK; Adacel, Sanofi), or a combination thereof.

[0577] As described above, a subject receiving a compound of the present invention to treat a disorder is prophylactically administered an antibiotic compound in addition to a factor D inhibitor described herein. In one embodiment, the subject is administered an antibiotic compound for the duration of administration of the active compound to reduce the development of a bacterial infection. Antibiotic compounds for concomitant administration with a factor D inhibitor described herein can be any antibiotic useful in preventing or reducing the effect of a bacterial infection. Antibiotics are well known in the art and include, but are not limited to, amikacin (Amikin), gentamicin (Garamycin), kanamycin (Kantrex), neomycin (Neo-Fradin), netilmicin (Netromycin), tobramycin (Nebcin), paromomycin (Humatin), streptomycin, spectinomycin (Trobicin), geldanamycin, herbimycin, rifaximin (Xifaxan), loracarbef (Lorabid), ertapenem (Invanz), doripenem (Doribax), imipenem/cilastatin (Primaxin), meropenem (Merrem), cefadroxil (Duricef), cefazolin (Ancef), cefalotin/cefalothin (Keflin), cephalexin (Keflex), cefaclor (Distaclor), cefamandole (Mandol), cefoxitin (Mefoxin), cefprozil (Cefzil), cefuroxime (Ceftin, Zinnat), cefixime (Cefspan), cefdinir (Omnicef, Cefdiel), cefditoren (Spectracef, Meiact), cefoperazone (Cefobid), cefotaxime (Claforan), cefpodoxime (Vantin) ceftazidime (Fortaz), ceftibuten (Cedax), ceftizoxime (Cefizox), ceftriaxone (Rocephin), cefepime (Maxipime), ceftaroline fosamil (Teflaro), ceftobiprole (Zeftera), teicoplanin (Targocid), vancomycin (Vancocin), telavancin (Vibativ), dalbavancin (Dalvance), oritavancin (Orbactiv), clindamycin (Cleocin), lincomycin (Lincocin), daptomycin (Cubicin), azithromycin (Zithromax, Sumamed, Xithrone), clarithromycin (Biaxin), dirithromycin (Dynabac), erythromycin (Erythocin, Erythroped), roxithromycin, troleandomycin (Tao), telithromycin (Ketek), spiramycin (Rovamycine), aztreonam (Azactam), furazolidone (Furoxone), nitrofurantoin (Macrodantin, Macrobid), linezolid (Zyvox), posizolid, radezolid, torezolid, amoxicillin (Novamox, Amoxil), ampicillin (Principen),azlocillin, carbenicillin (Geocillin), cloxacillin (Tegopen), dicloxacillin (Dynapen), flucloxacillin (Floxapen), mezlocillin (Mezlin), methicillin (Staphcillin), nafcillin

(Unipen),oxacillin (Prostaphlin), penicillin G (Pentids),penicillin V (Veetids (Pen-Vee-K), piperacillin (Pipracil), penicillin G (Pfizerpen), temocillin (Negaban),ticarcillin (Ticar), amoxicillin/clavulanate (Augmentin), ampicillin/sulbactam (Unasyn), piperacillin/tazobactam (Zosyn), ticarcillin/clavulanate (Timentin),bacitracin, colistin (Coly-Mycin-S), polymyxin B, ciprofloxacin (Cipro, Ciproxin, Ciprobay), enoxacin (Penetrex), gatifloxacin (Tequin), gemifloxacin (Factive), levofloxacin (Levaquin), lomefloxacin (Maxaquin), moxifloxacin (Avelox), nalidixic acid (NegGram), norfloxacin (Noroxin), ofloxacin (Floxin, Ocuflox), trovafloxacin (Trovan), grepafloxacin (Raxar), sparfloxacin (Zagam), temafloxacin (Omniflox), mafenide (Sulfamylon), sulfacetamide (Sulamyd, Bleph-10), sulfadiazine (Micro-Sulfon), silver sulfadiazine (Silvadene), sulfadimethoxine (Di-Methox, Albon), sulfamethizole (Thiosulfil Forte), sulfamethoxazole (Gantanol), sulfanilamide, sulfasalazine (Azulfidine), sulfisoxazole (Gantrisin), trimethoprim-sulfamethoxazole (Co-trimoxazole) (TMP-SMX) (Bactrim, Septra), sulfonamidochrysoidine (Prontosil), demeclocycline (Declomycin), doxycycline (Vibramycin), minocycline (Minocin), oxytetracycline (Terramycin), tetracycline (Sumycin, Achromycin V, Steclin), clofazimine (Lamprene), dapsone (Avlosulfon), capreomycin (Capastat), cycloserine (Seromycin), ethambutol (Myambutol), ethionamide (Trecator), isoniazid (I.N.H.), pyrazinamide (Aldinamide), rifampicin (Rifadin, Rimactane), rifabutin (Mycobutin), rifapentine (Priftin), streptomycin, arsphenamine (Salvarsan), chloramphenicol (Chloromycetin), fosfomycin (Monurol, Monuril), fusidic acid (Fucidin), metronidazole (Flagyl), mupirocin (Bactroban), platensimycin, quinupristin/dalfopristin (Synercid), thiamphenicol, tigecycline (Tigacyl), tinidazole (Tindamax Fasigyn), trimethoprim (Proloprim, Trimpex), and/or teixobactin, or a combination thereof.

[0578] In one embodiment, the subject is administered a prophylactic antibiotic selected from cephalosporin, for example, ceftriaxone or cefotaxime, ampicillin-sulbactam, Penicillin G, ampicillin, chloramphenicol, fluoroquinolone, aztreonam, levofloxacin, moxifloxacin, gemifloxacin, vancomycin, clindamycin, cefazolin, azithromycin, meropenem, ceftaroline, tigecycline, clarithromycin, moxifloxacin, trimethoprim/sulfamethoxazole, cefuroxime, axetil, ciprofloxacin, rifampin, minocycline, spiramycin, and cefixime, or a combination of two or more thereof.

VII. PROCESS OF PREPARATION OF COMPOUNDS OF FORMULA I, FORMULA I' AND FORMULA I"

ABBREVIATIONS

ACN	Acetonitrile
Ac	Acetyl
Ac_20	Acetic anhydride
AcOEt, EtOAc	ethyl acetate
AcOH	Acetic acid
B0C2O	di-*tert*-butyl dicarbonate
Bu	Butyl
CAN	Ceric ammonium nitrate
CBz	Carboxybenzyl
CDI	Carbonyldiimidazole
CH3OH, MeOH	Methanol
CsF	Cesium fluoride
Cul	Cuprous iodide
DCM, CH2CI2	Dichloromethane
DIEA, DIPEA	N,N-diisopropylethylamine
DMA	N,N-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphoryl azide
EDCI	l-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	Ethyl
Et_3N, TEA	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
JJ_{ATU}	l-[Bis(dimethylamino)methylene]-lH-l,2,3-triazolo[4,5-b]pyridinium3-oxide hexafluorophosphate
HC1	Hydrochloric acid
HOBT	Hydroxybenzotriazole
iBu, /-Bu, isoBu	Isobutyl
iPr, /-Pr, isoPr	Isopropyl
^{i}PnNEt	N,N-diisopropylethylamine
K2CO3	Potassium carbonate
K_2CO_3	Potassium carbonate

LiOH	Lithium hydroxide
Me	Methyl
Mel	Methyl iodide
Ms	Mesyl
MsCl	Mesylchloride
MTBE	Methyl ¾utylether
Na_2S04	Sodium sulfate
NaCl	Sodium chloride
NaH	Sodium hydride
NaHCCb	Sodium bicarbonate
NBS	N-bromo succinimide
NCS	N-chloro succinimide
NEt3	Trimethylamine
NMP	N-Methyl-2-pyrrolidone
PCC	Pyridinium chlorochromate
Pd (OAc)2	Palladium acetate
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino) ferrocene]dichloropalladium(II)
$Pd(PPh3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(PPh_{3)4}$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on carbon
Pd_2 (dba) 3	Tris(dibenzylideneacetone)dipalladium(0)
PMB	4-Methoxybenzyl ether
PPh_3	Triphenylphosphine
Pr	Propyl
Py, py	Pyridine
RT	Room temperature
TBAF	Tetra-n-butylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
tBu, *t*-Bu	*ter t*butyl
tBuOK	Potassium ter*t*-butoxide
TEA	Trimethylamine
Tf_20	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilane
TMSBr	Bromotrimethylsilane
tR	Retention time
Troc	2,2,2-Trichlorethoxycarbonyl chloride

$Zn(CN)_2$ Zinc cyanide

GENERAL METHODS

[0579] All nonaqueous reactions were performed under an atmosphere of dry argon or nitrogen gas using anhydrous solvents. The progress of reactions and the purity of target compounds were determined using one of the two liquid chromatography (LC) methods listed below. The structure of starting materials, intermediates, and final products was confirmed by standard analytical techniques, including NMR spectroscopy and mass spectrometry.

LC Method A

Instrument: Waters Acquity Ultra Performance LC

Column: ACQUITY UPLC BEH C18 2.1 x 50 mm, 1.7 μιη

Column Temperature: 40 °C

Mobile Phase: Solvent A: H_20 + 0.05% FA; Solvent B: CH3CN + 0.05% FA

Flow Rate: 0.8 mL/min

Gradient: 0.24 min @ 15% B, 3.26 min gradient (15-85% B), then 0.5 min @ 85% B.

Detection: UV (PDA), ELS, and MS (SQ in EI mode)

LC Method B

Instrument: Shimadzu LC-2010A HT

Column: Athena, C18-WP, 50 × 4.6 mm, 5 μιη

Column Temperature: 40 °C

Mobile Phase: Solvent A: **H2O/CH3OH /FA** = 90/10/0.1; Solvent B: **H2O/CH3OH /FA** = 10/90/0.1

Flow Rate: 3 mL/min

Gradient: 0.4 min @ 30% B, 3.4 min gradient (30-100% B), then 0.8 min @ 100% B

Detection: UV (220/254 nm)

LC Method C

Instrument: Agilent 1100 / 1200 series LC system with DAD detector

Column: Atlantis dC18 (250 x 4.6) mm, 5 μιη

Column Temperature: Ambient

Mobile Phase A: 0.1% TFA in water, Mobile Phase B: Acetonitrile

Flow Rate: l.O mL/min

Gradient:

Time (min)	0.0	15	20	23	30
% B	10	100	100	10	10

Detection: (210-400 nm)

LC Method D

Instrument: Shimadzu LC 20AD system with PDA detector

Column: Phenomenex Gemini NX C18 (150 x 4.6) mm, 5 μιη

Column Temperature: Ambient

Mobile Phase A: lOmM NH4OAC in water, Mobile Phase B: Acetonitrile

Flow Rate: l.O mL/min

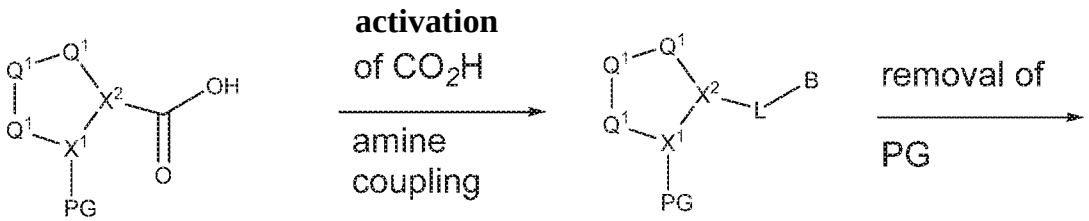
Gradient:

Time (min)	0.0	15	20	23	30
% B	10	100	100	10	10

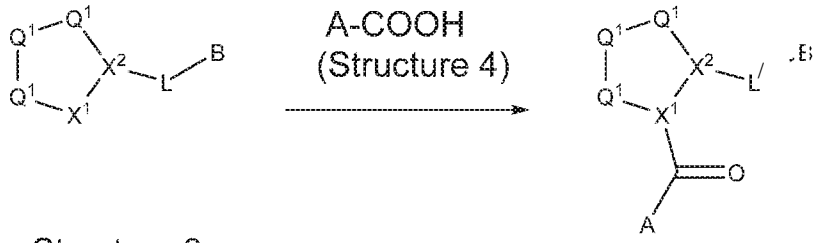
Detection: (210-400 nm)

EXAMPLE 1. GENERAL ROUTE OF SYNTHESIS

[0580] A compound of the present invention can be prepared, for example, from a central core. In one embodiment, for example, the central core Structure 1 is an N-protected aminoacid where X^1 is nitrogen and PG = protecting group. In one embodiment, the central core is coupled to an amine to generate an amide of Structure 2 (wherein L-B includes a C(0)N moiety). Structure 2 can then be deprotected to generate Structure 3. Structure 3 is coupled to Structure 4 (A-COOH) to generate a second amide bond, forming a compound within Formula I. The chemistry is illustrated in Route 1.



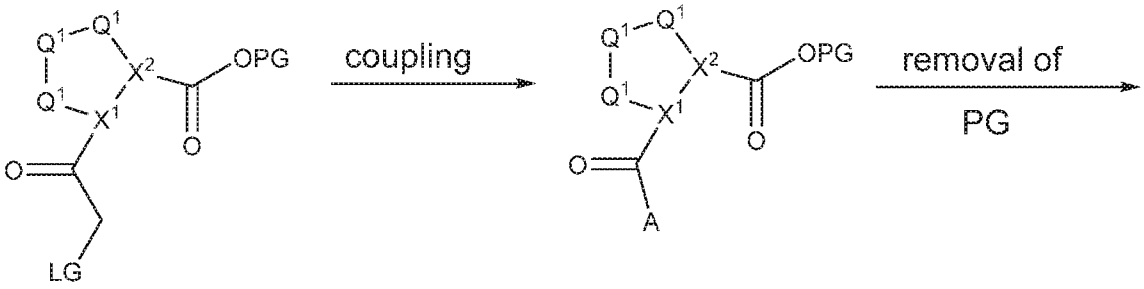
Structure 1 **Structure 2**



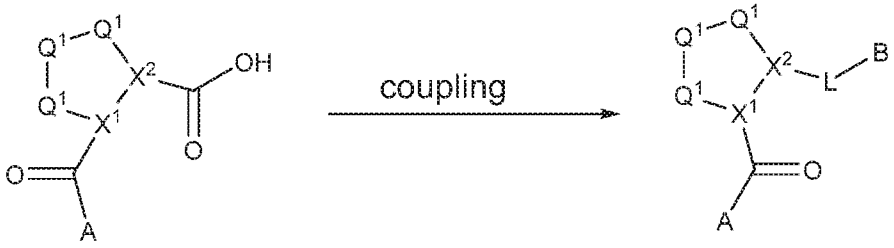
Structure 3 **Formula I**

Route 1

[0581] In an alternative embodiment, central core Structure 5 is reacted with a heterocyclic or heteroaryl compound to generate a compound of Structure 6. In one embodiment, Structure 6 is deprotected to generate a carboxylic acid, Structure 7. In one embodiment, Structure 7 is coupled to an amine to generate a compound of Formula I. This chemistry is illustrated in Route 2.



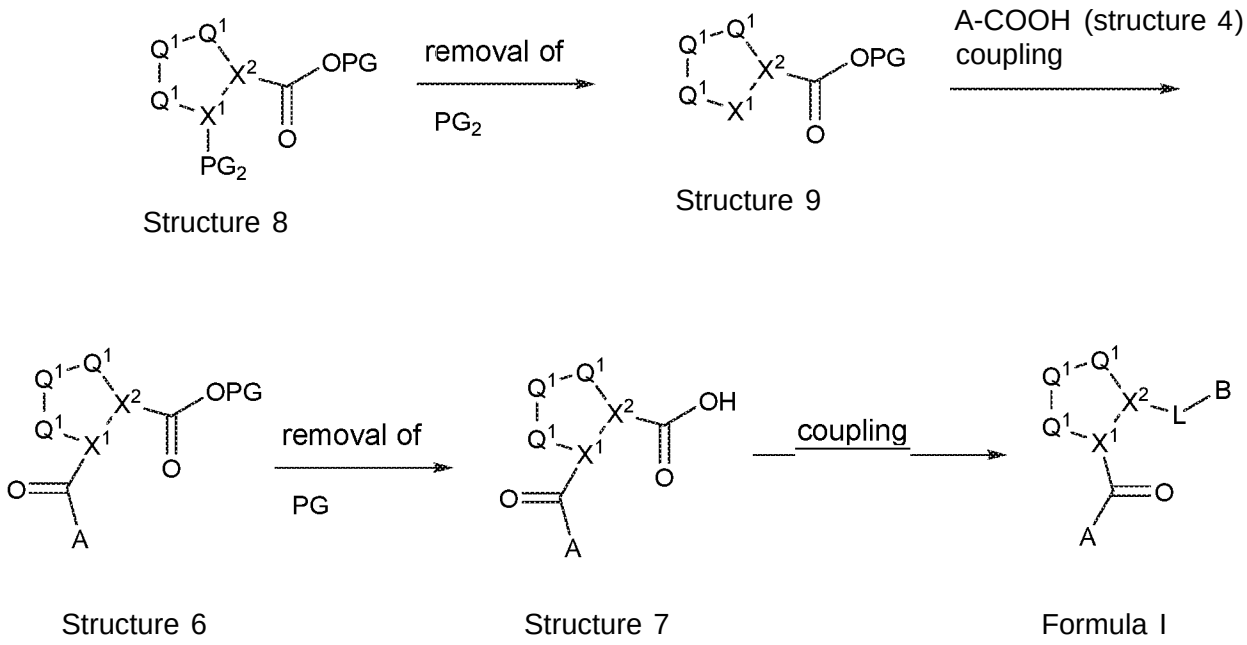
Structure 5 Structure 6



Structure 7 Formula I

Route 2

[0582] In an alternative embodiment, Structure 8 is deprotected to generate an amine which is Structure 9. Structure 9 is then coupled to generate an amide which is Structure 6. Structure 6 is then deprotected to generate a carboxylic acid which is Structure 7. Structure 7 is then coupled to form the amide which falls within Formula I. The chemistry is illustrated in Route 3.

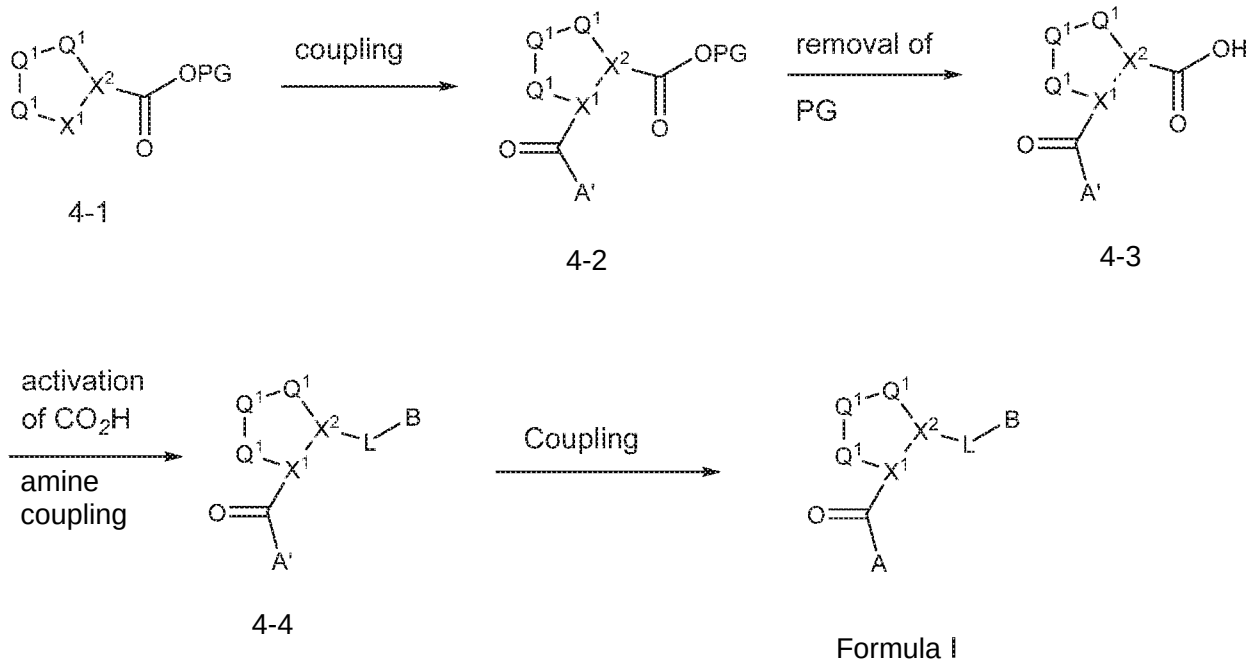


Structure 8 Structure 9

Structure 6 Structure 7 Formula I

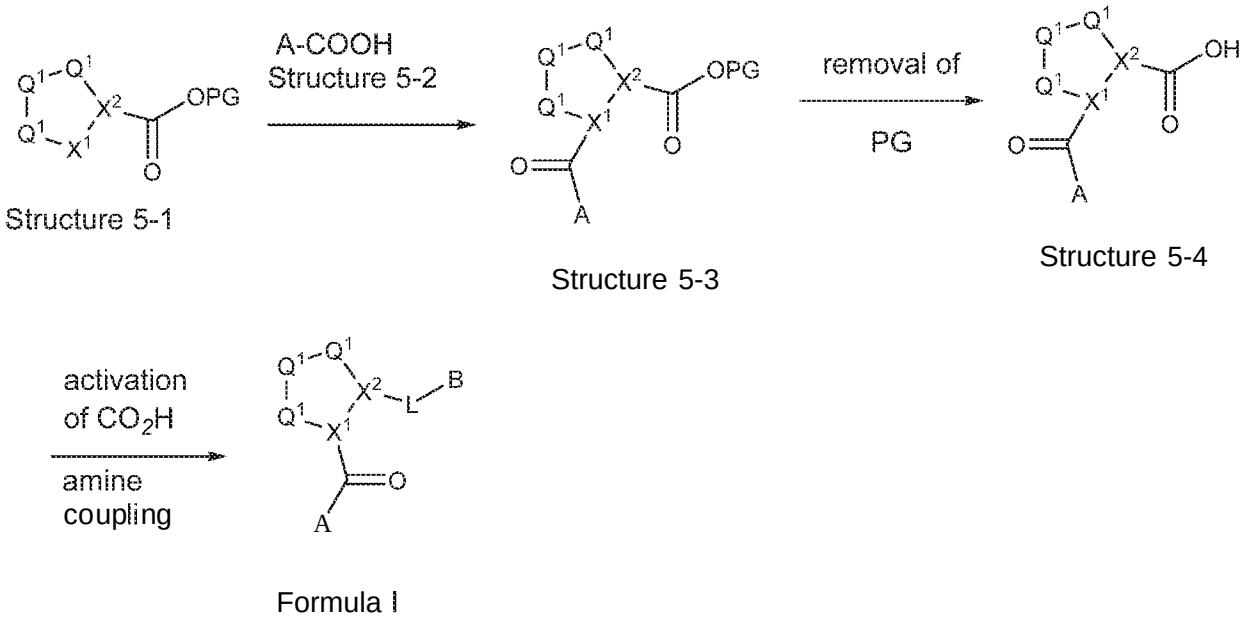
Route 3

[0583] In an alternate embodiment, a heteroaryl or aryl moiety, 4-1, is coupled to a central core to generate 4-2. The protected acid, 4-2 is deblocked to form the carboxylic acid, 4-3. The carboxylic acid is then coupled to form an amide (L-B) which is 4-4 . The heteroaryl or aryl moiety, A', can then be further derivitized to add substituents at the X^{11}, X^{12}, X^{13} and X^{14} positions to generate compounds of Formula I. This chemistry is illustrated in Route 4.



Route 4

[0584] In an alternate embodiment, Structure 5-1 is coupled to an acid, Structure 5-2, to generate Structure 5-3. The carboxylic acid, Structure 5-3, is deblocked to generate a carboxylic acid which is Structure 5-4. Carboxylic acid Structure 5-4 is coupled to an amine to form the product amide (L-B) which is a compound within Formula I. This chemistry is illustrated in Route 5.



Structure 5-1

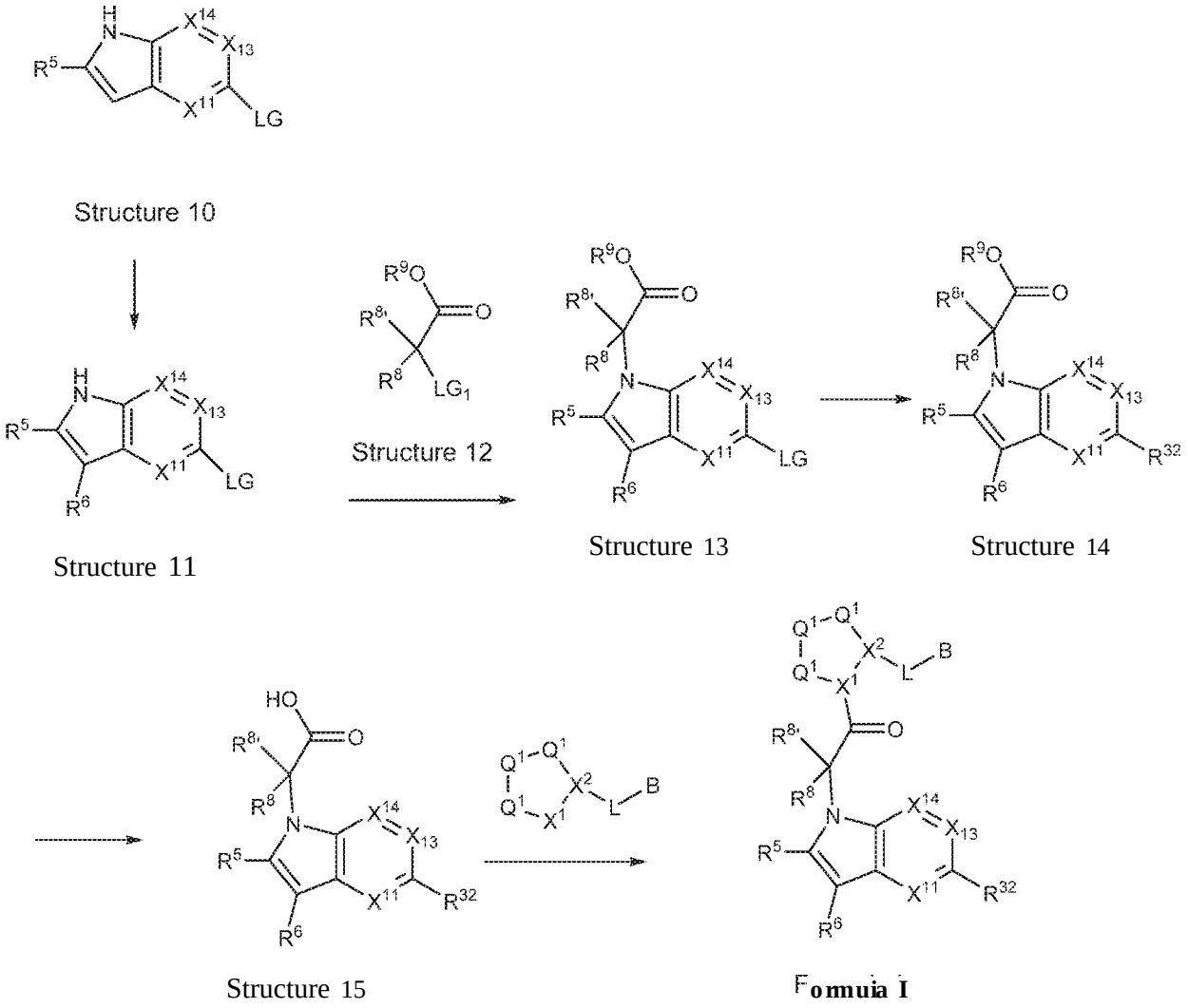
Structure 5-3

Structure 5-4

Formula I

Route 5

[0585] In an alternate embodiment, a heteroaryl compound of Structure 10 is acylated to generate a compound of Structure 11, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 11 is coupled to Structure 12 to generate Structure 13. In some embodiments, LGi is a leaving group. In some embodiments, the LGi is a halide. Structure 13 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 14. In some embodiments, Structure 13 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 14 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure 15. Structure 15 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 6.

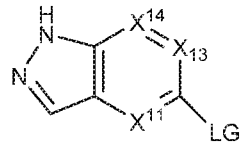


Route 6

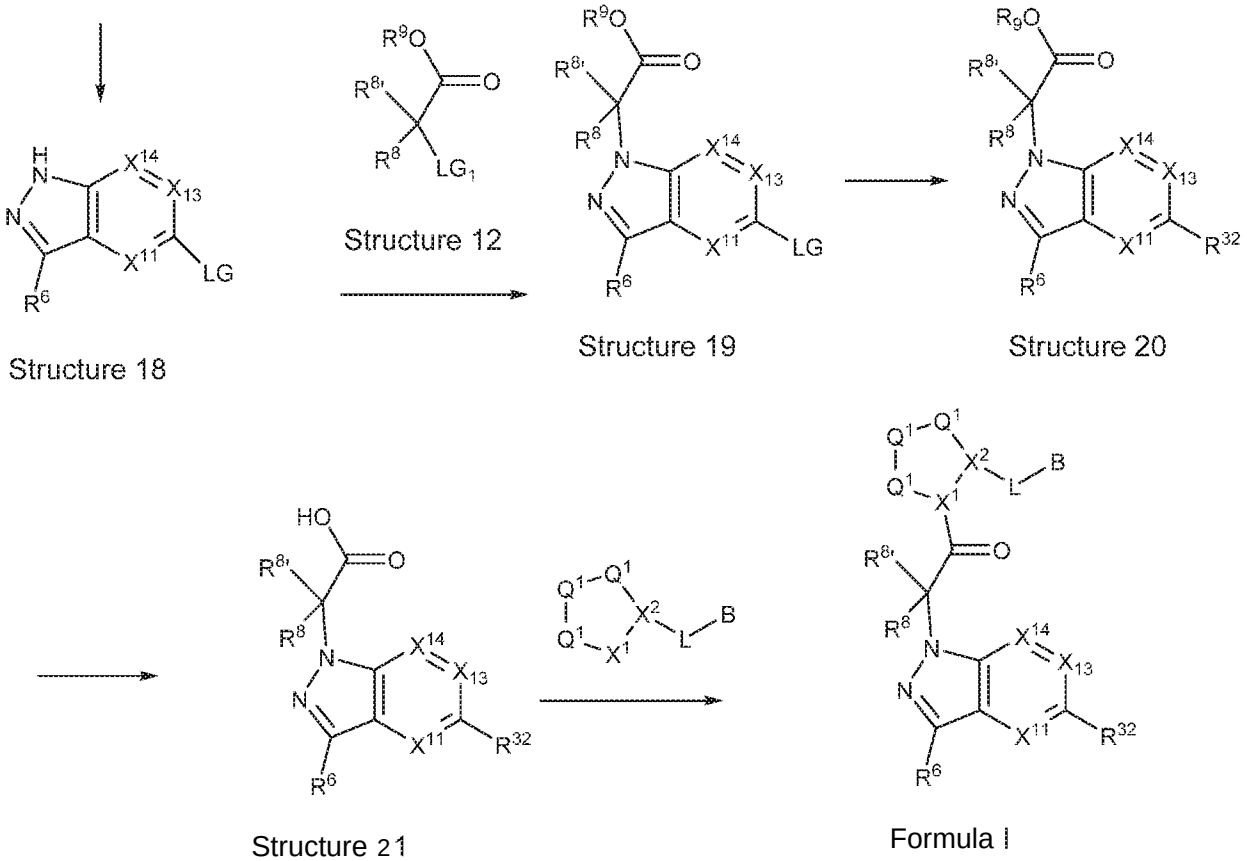
[0586] In an alternate embodiment, a heteroaryl compound of Structure 17 is acylated to generate a compound of Structure 18, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 18 is coupled to an activated ester, Structure 12 from Route 6, wherein LGi can be a halogen to generate Structure 19.

[0587] Structure 19 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 20. In some embodiments, Structure 19 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 20 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure

21. Structure 21 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 7.



Structure 17

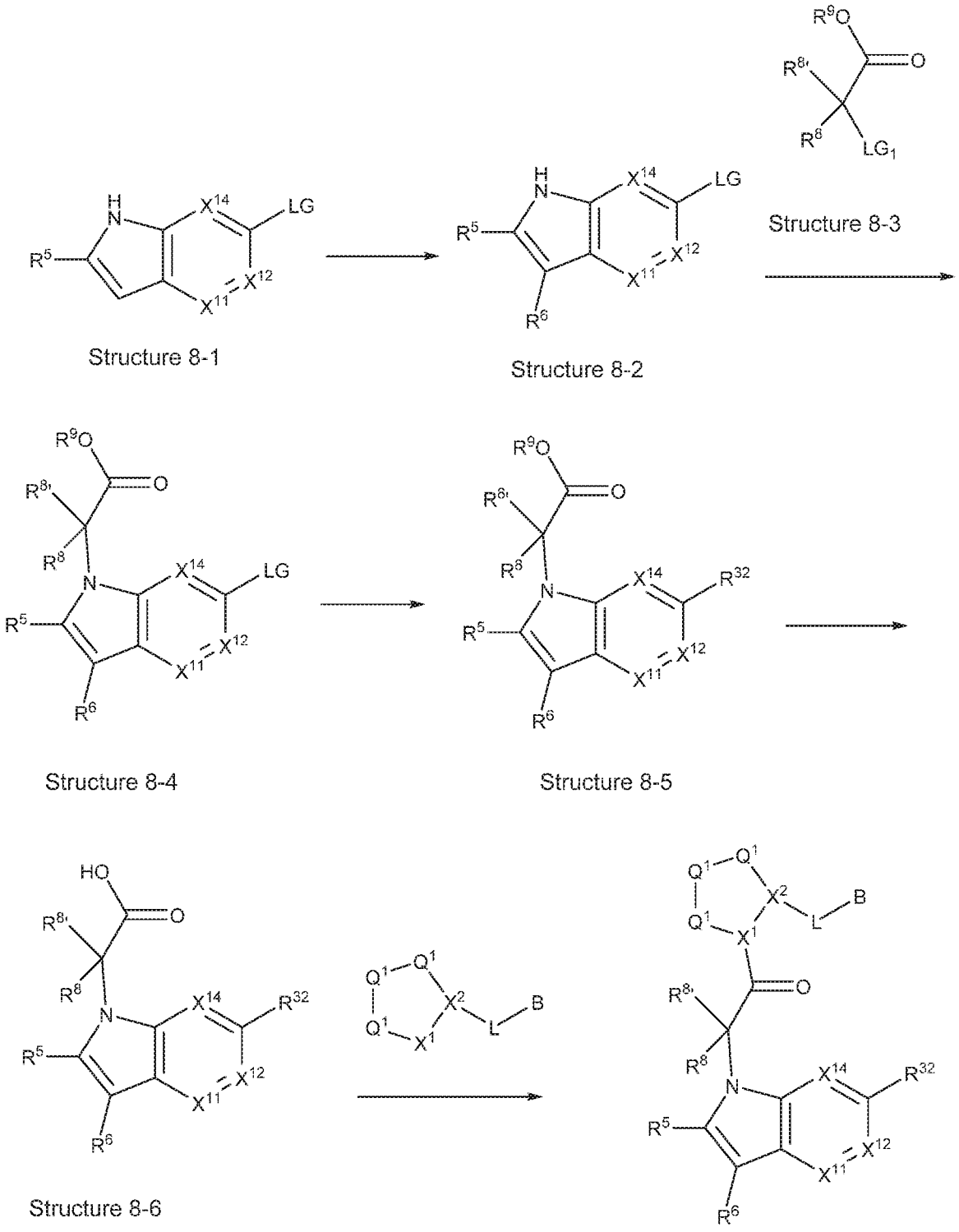


Route 7

[0588] In an alternate embodiment, a heteroaryl compound of Structure 8-1 is acylated to generate a compound of Structure 8-2, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 8-2 is coupled to Structure 8-3 to generate Structure 8-4. In some embodiments, LGi is a leaving group. In some embodiments, the LGi is a halide.

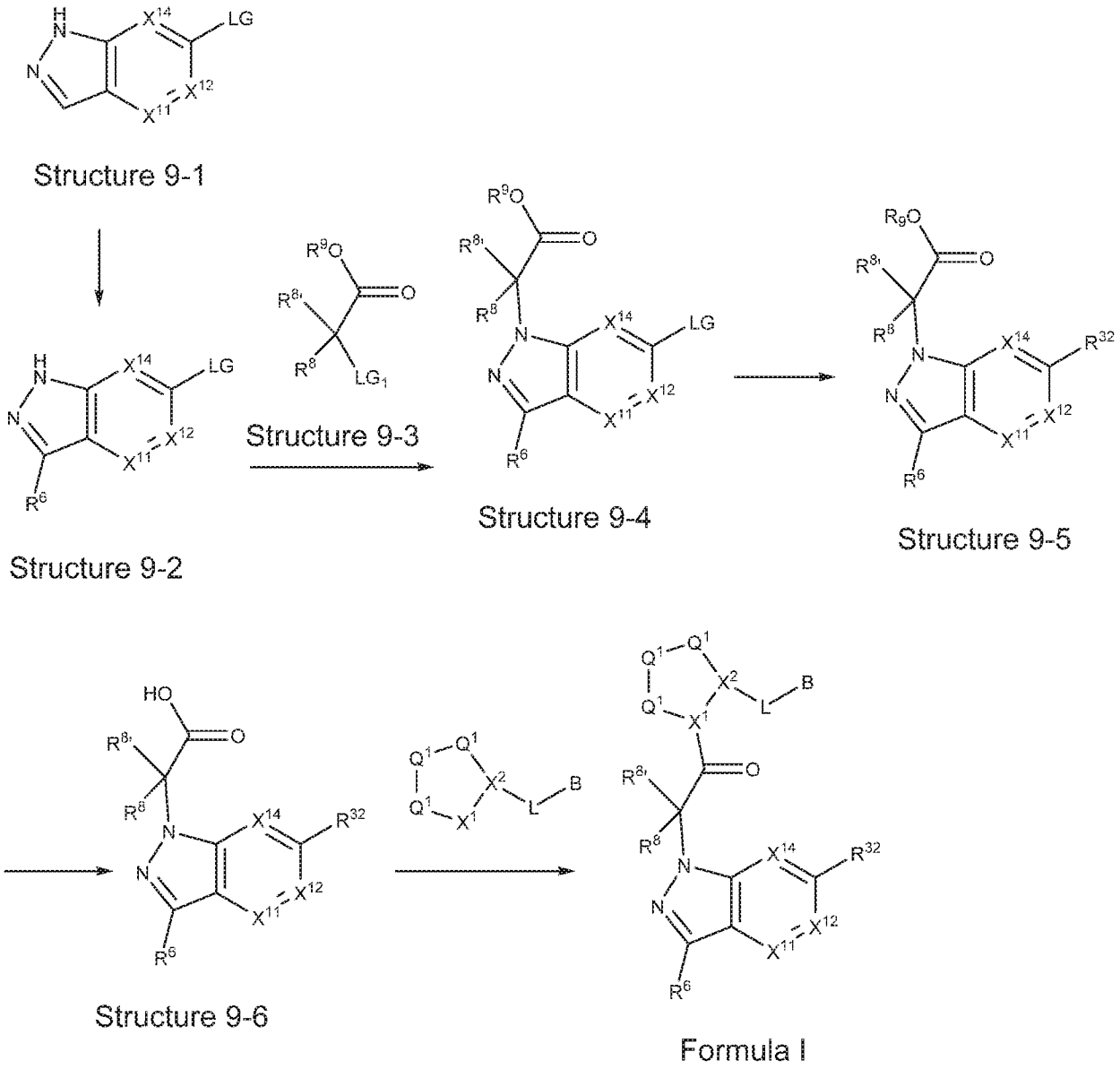
[0589] Structure 8-4 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 8-5. In some embodiments, Structure 8-4 is treated with an aryl, heteroaryl or heterocylic

boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 8-5 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure 8-6. Structure 8-6 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 8.


Structure 8-1
Structure 8-2
Structure 8-3
Structure 8-4
Structure 8-5
Structure 8-6
Formula I

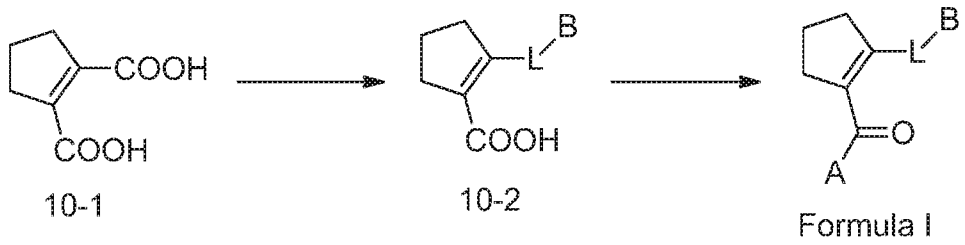
Route 8

[0590] In an alternate embodiment, a heteroaryl compound of Structure 9-1 is acylated to generate a compound of Structure 9-2, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 9-2 is coupled to an activated ester, Structure 9-3, wherein LGi can be a halide to generate Structure 9-4. Structure 9-4 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 9-5. In some embodiments, Structure 9-4 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 9-5 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure 9-6. Structure 9-6 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 9.



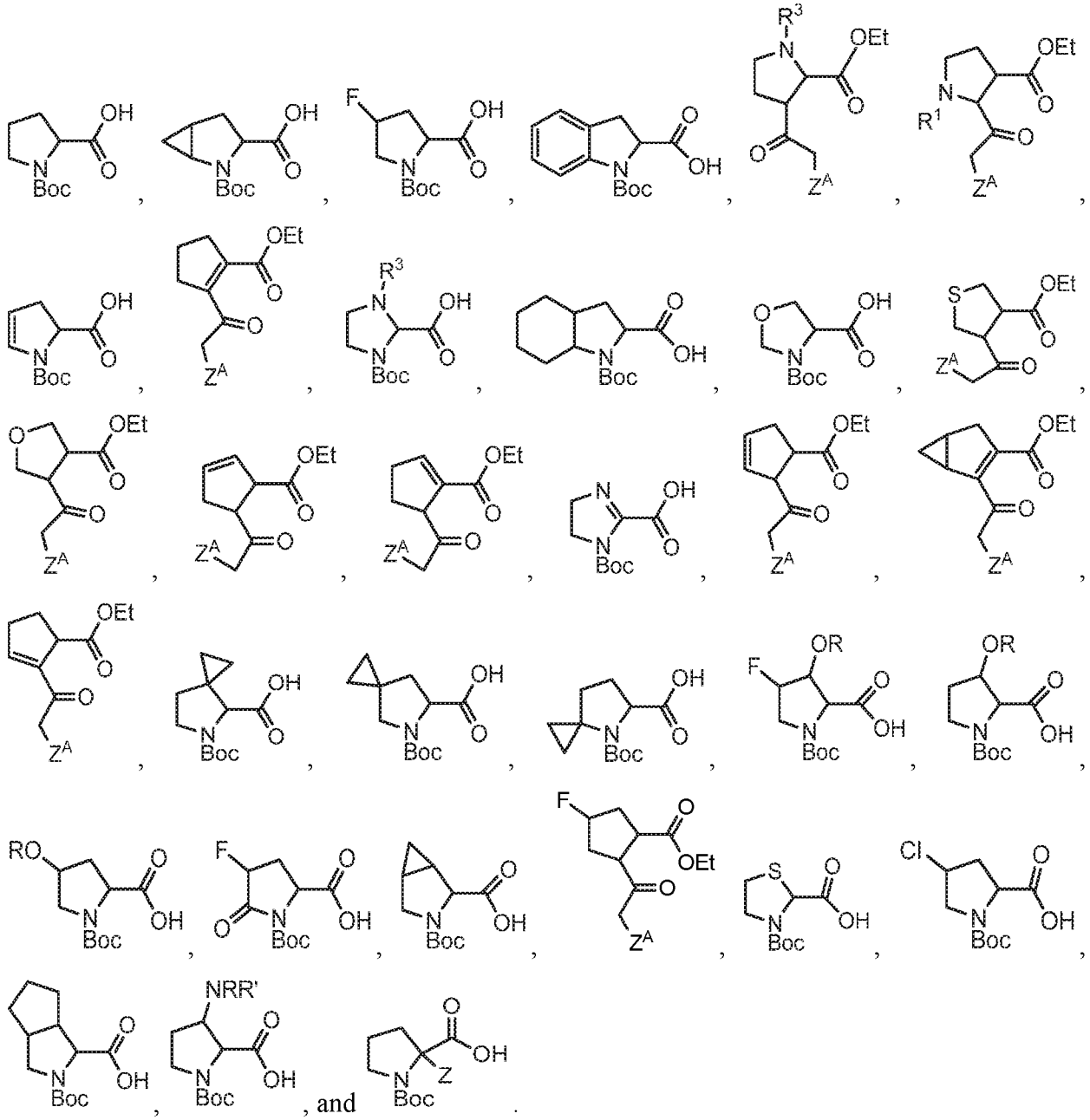
Route 9

[0591] In an alternate embodiment, Structure 10-1 is coupled to an amine to generate an amide (L-B), and Structure 10-2. Structure 10-2, is coupled to an amine to generate compounds within Formula I. This chemistry is illustrated in Route 10.



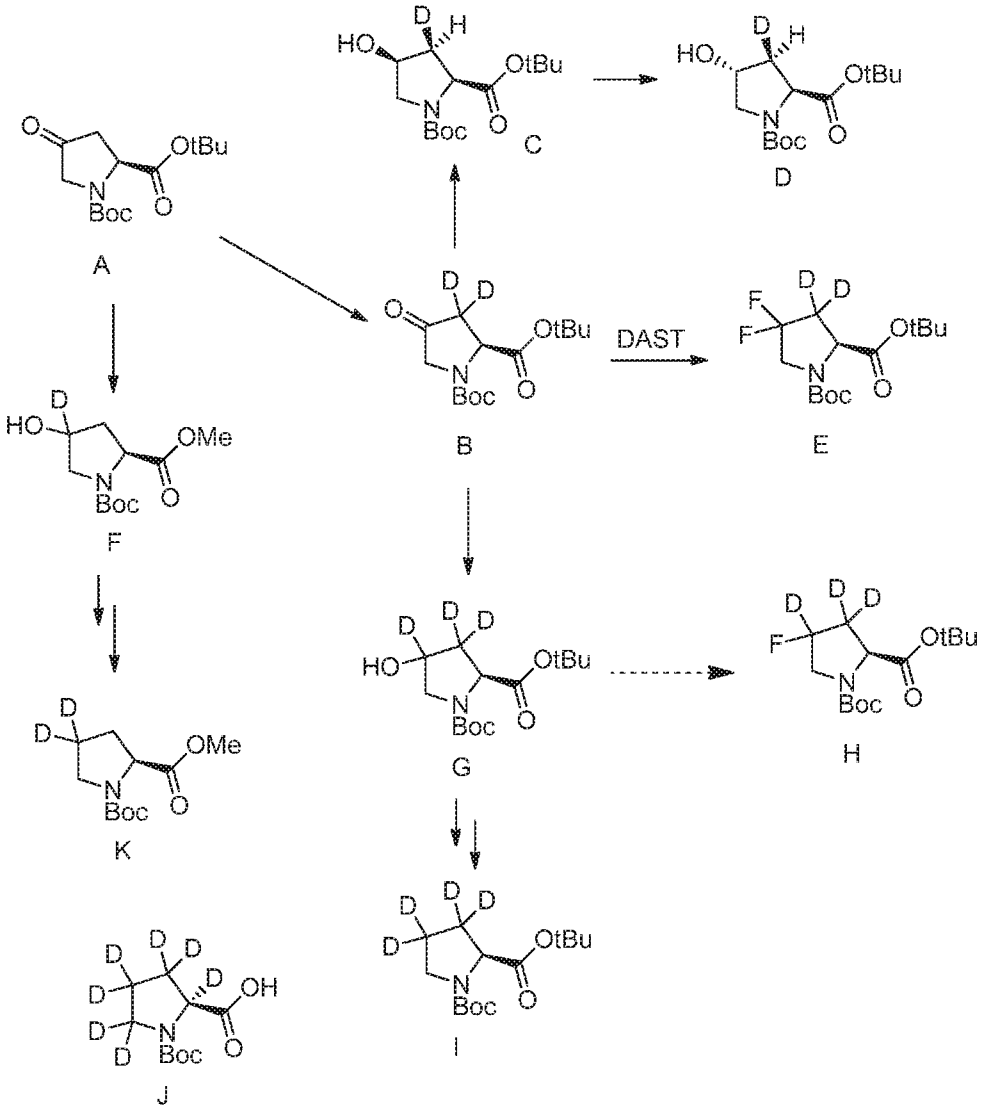
Route 10

EXAMPLE 2. EXAMPLES OF CENTRAL SYNTHONS



Z^A is halogen.

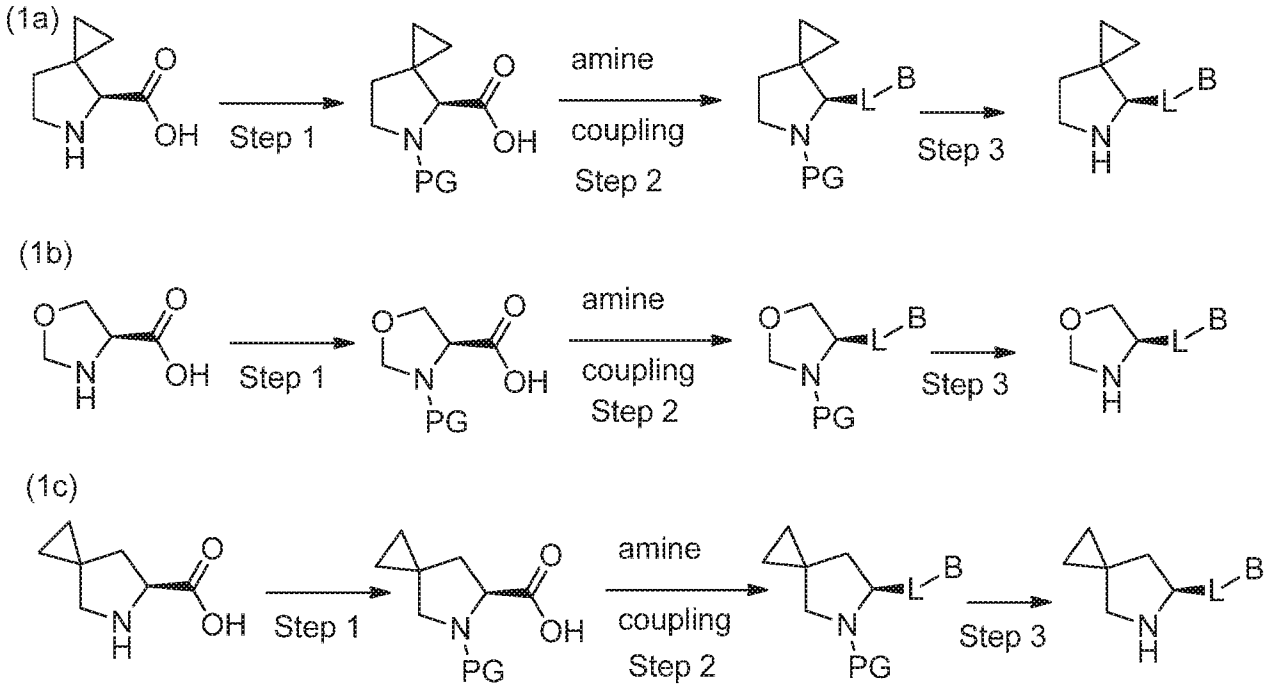
[0592] In one embodiment, deuterated L-proline synthons are disclosed. Deuterated synthons include, but are not limited to, for example, the following compounds:



[0593] Structure A can be treated with deuterium oxide to generate Structure B. See, Barraclough, P. et al. Tetrahedron Lett. **2005,** 46, 4653-4655; Barraclough, P. et al. Org. Biomol. Chem. **2006,** 4, 1483-1491 and WO 2014/037480 (p. 103). Structure B can be reduced to generate Structure C. See, Barraclough, P. et al. Tetrahedron Lett. **2005,** 46, 4653-4655; Barraclough, P. et al. Org. Biomol. Chem. **2006,** 4, 1483-1491 . Structure C can be treated with Mitsunobu reaction conditions to generate Structure D. Structure B can be treated with DAST to generate Structure E. See, WO 2014/037480. Structure A can be treated with sodium borodeuteride to generate

Structure F. See, Dormoy, J.-R; Castro, B. *Synthesis* **1986,** 81-82. Compound F can be used to generate Structure K. See, Dormoy, J.-R.; Castro, B. *Synthesis* **1986,** 81-82. Structure B can be treated with a deuterated reducing agent, for example sodium borodeuteride to generate Structure G. Structure G can be treated with DAST to generate Structure H. Structure F can be used to generate Structure K. See, Dormoy, J.-R; Castro, B. *Synthesis* **1986,** 81-82. Structure G can be used to generate Structure I. Structure J can be prepared according to Hruby, V. J. et al. *J. Am. Chem. Soc.* **1979,** *101,* 202-212. Structures A-J can be used to prepare compounds of Formula I.

EXAMPLE 3. PREPARATION OF CENTRAL-L-B SYNTHONS



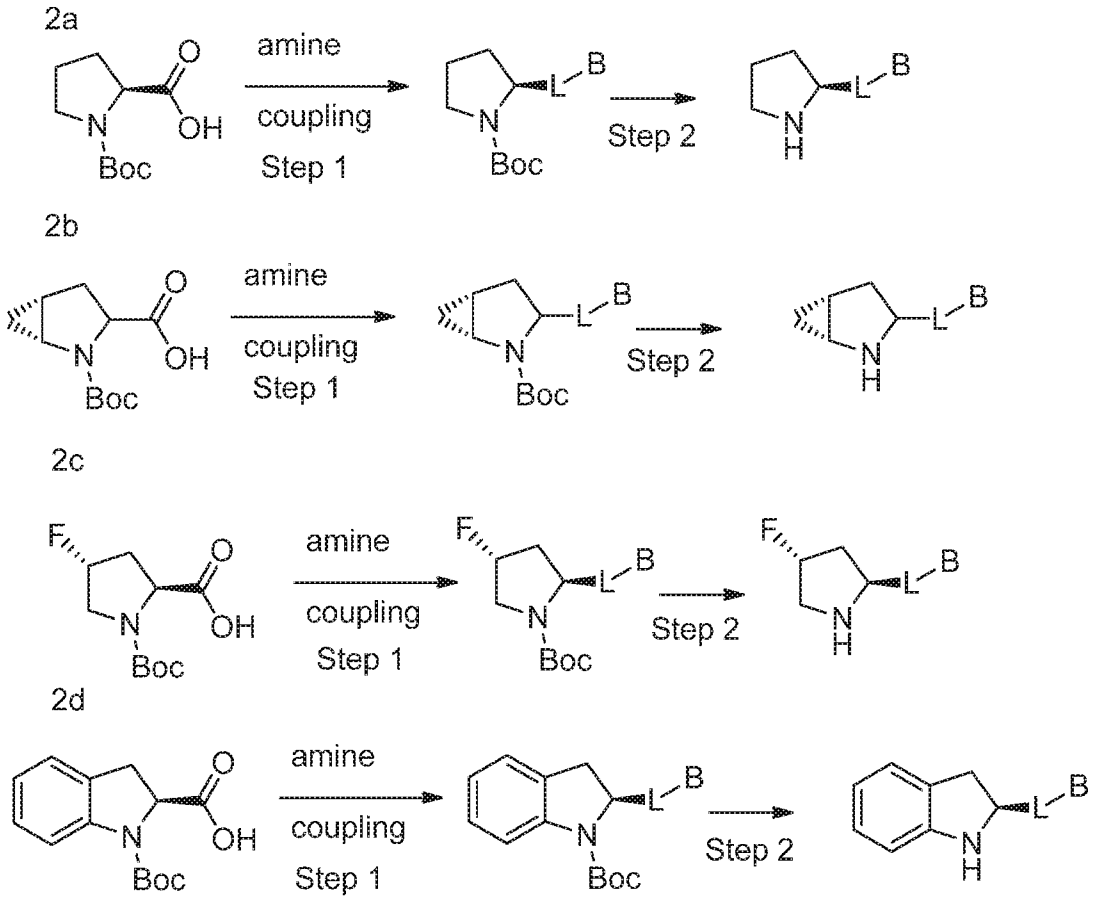
Routes la, 1b and lc.

[0594] In Route la, 5-azaspiro[2.4]heptane-4,5-dicarboxylic acid, 5-(l,l-dimethylethyl) ester, (45)-, CAS 209269-08-9, can be prepared as described in Tandon, M. et al. Bioorg. Med. Chem. Lett. 1998, 8, 1139-1 144. In Step 2, the protected azaspiro[2.4]heptane is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 3, the protecting group is removed. In one embodiment, the starting material is reacted with an acid in

the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0595] In Route lb, (4S) 4-oxazolidinecarboxylic acid, hydrochloride is treated with an amine protecting reagent. In one embodiment, the amine protecting reagent is di-*tert*-butyl dicarbonate. In another embodiment, 3,4-oxazolidinedicarboxylic acid, 3-(l,l-dimethylethyl) ester, (4S)-, is commercially available from JPM2 Pharmaceuticals. In one embodiment the reaction is carried out in an organic solvent in the presence of a base. In one embodiment, the organic solvent is acetonitrile. In one embodiment, the base is 4-dimentylaminopyridine (DMAP). In Step 2, the protected 4-oxazolidinecarboxylic acid is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 3, the protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0596] In Route lc, (S)-5-*(tert*-Butoxycarbonyl)-5-azaspiro[2.4]heptane-6-caboxylic acid, CAS 1129634-44-1, is commercially available from Ark Pharm. In Step 2, the carboxylic acid is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 3, the protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.



Routes 2a, 2b, 2c, and 2d.

[0597] In Route 2a, commercially available Boc-L-proline is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

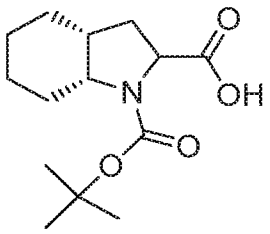
[0598] In Route 2b, commercially available (1R, 3S, 5R)-2-[(ter*t*-butoxy)carbonyl]-2-azabicyclo[3.1.0]hexane-3-carboxylic acid, from Enamine, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one

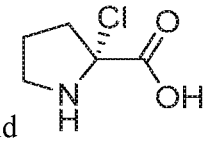
embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0599] In Route 2c, commercially available (2S,4R)-l -(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid, from Manchester Organics, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0600] In Route 2d, commercially available (S)-l -(*tert*-butoxycarbonyl)indoline-2-carboxylic acid, from Chem-Impex, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane. This chemistry is illustrated in Scheme 2.

[0601] Additional starting materials that can readily be converted to Central-L-B-Synthons include, but are not limited to: (S)-l -(*tert*-butoxycarbonyl)-2,3-dihydro-lH-pyrrole-2-carboxylic acid, CAS 90104-21-5, available from Ark Pharm; cyclopent-l-ene-l,2-dicarboxylic acid, CAS 3128-15-2, purchased from Ark Pharm; imidazole, lH-imidazole-l,2-dicarboxylic acid, 1-(1,1-dimethylethyl) 2-ethyl ester, CAS 553650-00-3, commercially available from FCH Group; Boc-L-octahydroindole-2-carboxylic acid can be purchased from Chem Impex. The compound,

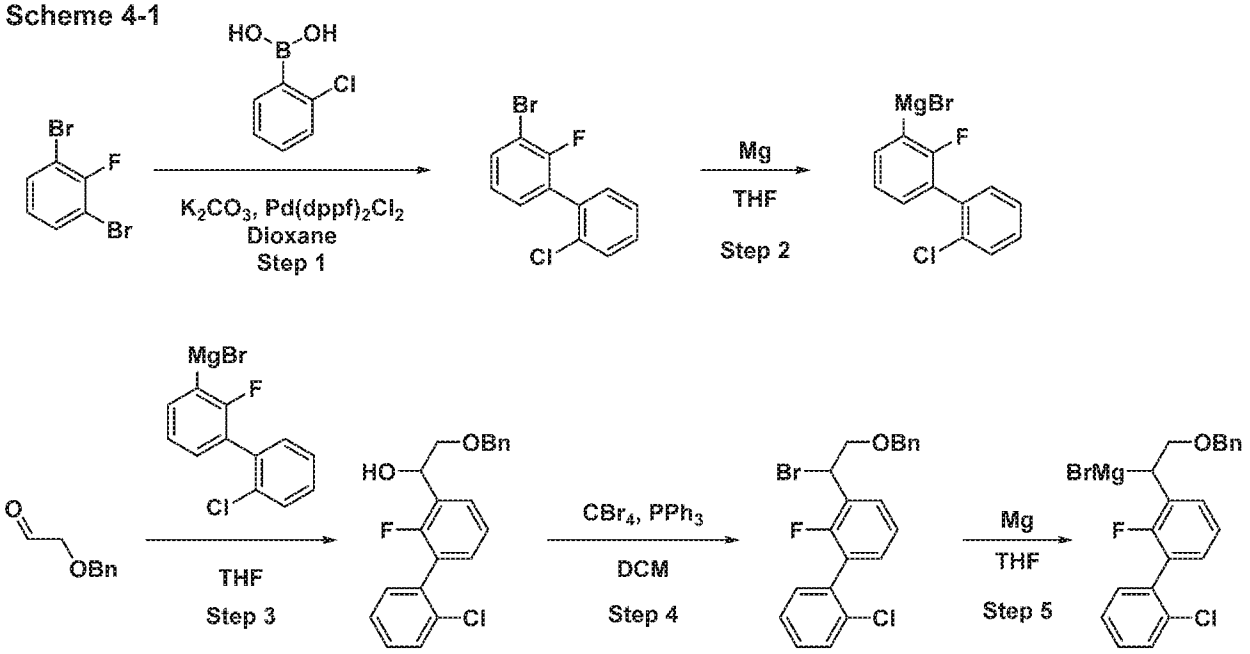
[0602]  can be prepared according to the procedures disclosed in WO 2004/1 11041; (S)-Boc-5-oxopyrrolidine-2-carboxylic acid is available from the Aldrich Chemical Co.; (lS,2S,5R)-3-(/er/-butoxycarbonyl)-3-azabicyclo[3.3.0]hexane-2-carboxylic acid is available from Ark Pharm; (S)-3-Boc-thiazolidine-2-carboxylic acid is available from Alfa Aesar; (2S,4R)-l-(/er/-butoxycarbonyl)-4-chloropyrrolidine-2-carboxylic acid is available from Arch Bioscience; (lS,3aR,6aS)-2-(/er/-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-l-carboxylic acid is available from Ark Pharm; 1,2-pyrrolidinedicarboxylic acid, 3-[[(phenylmethoxy)carbonyl]amino]-, l-(l,l-dimethylethyl) ester, (2S,3R) can be prepared as disclosed in WO 2004/007501. The Cbz group can be removed and the amino group can be alkylated to generate central core compounds of the present invention.

[0603] The compound  can be prepared as disclosed by Braun, J.V.; Heymons, Albrecht Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen (1930) 63B, 502-7.

[0604] The compounds (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-l,2-dicarboxylic acid 1-*tert*-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-l,2-dicarboxylic acid *l-tert*-butyl ester can be prepared as a mixture according to WO 2012/093101 to Novartis and the regioisomers can be ultimately separated once coupled to generate the central core-L-B synthons. The compound (S)-Boc-5-oxopyrrolidine-2-carboxylic acid is available from the Aldrich Chemical Co.

EXAMPLE 4. SYNTHESIS OF L-B MOIETIES

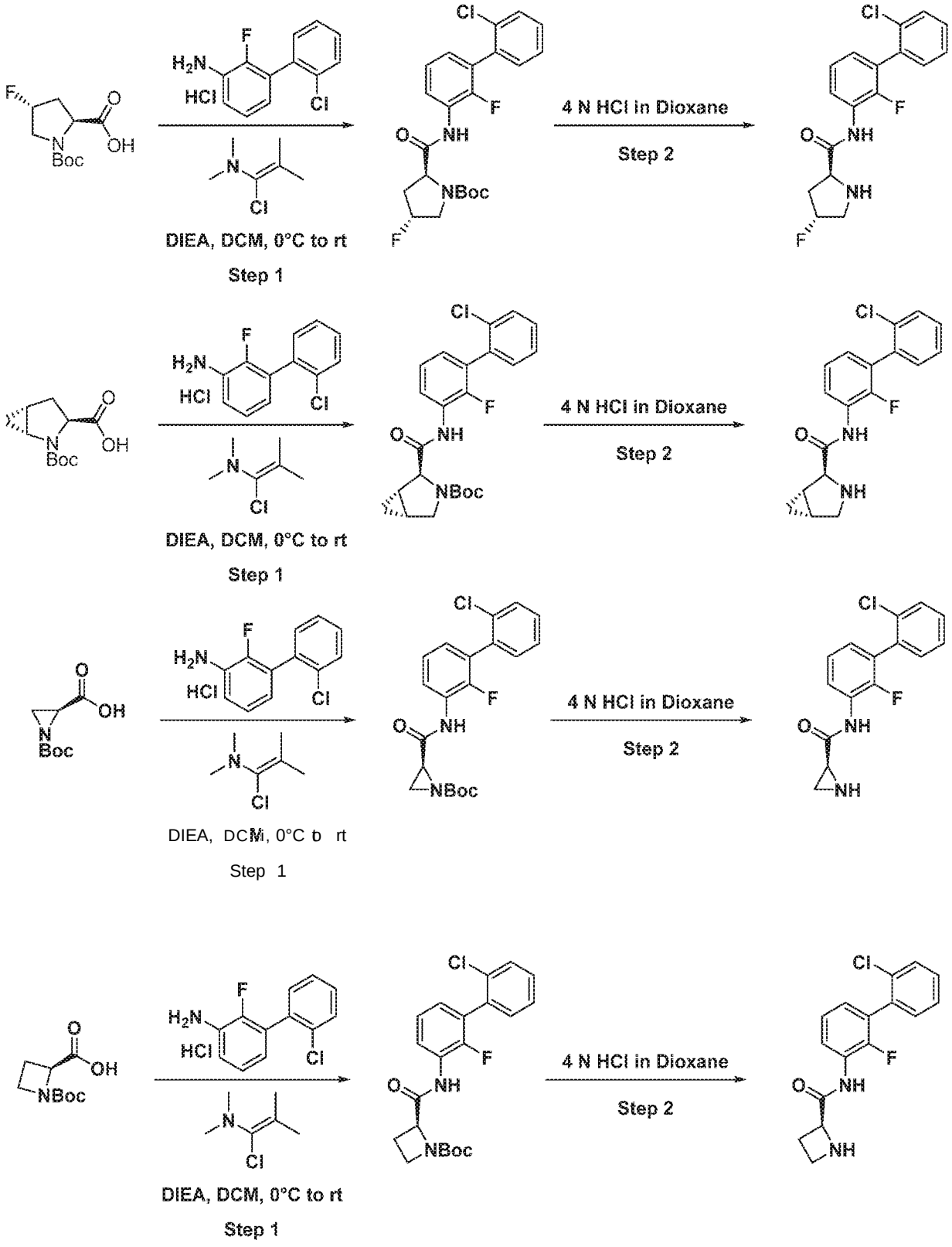
Scheme 4-1



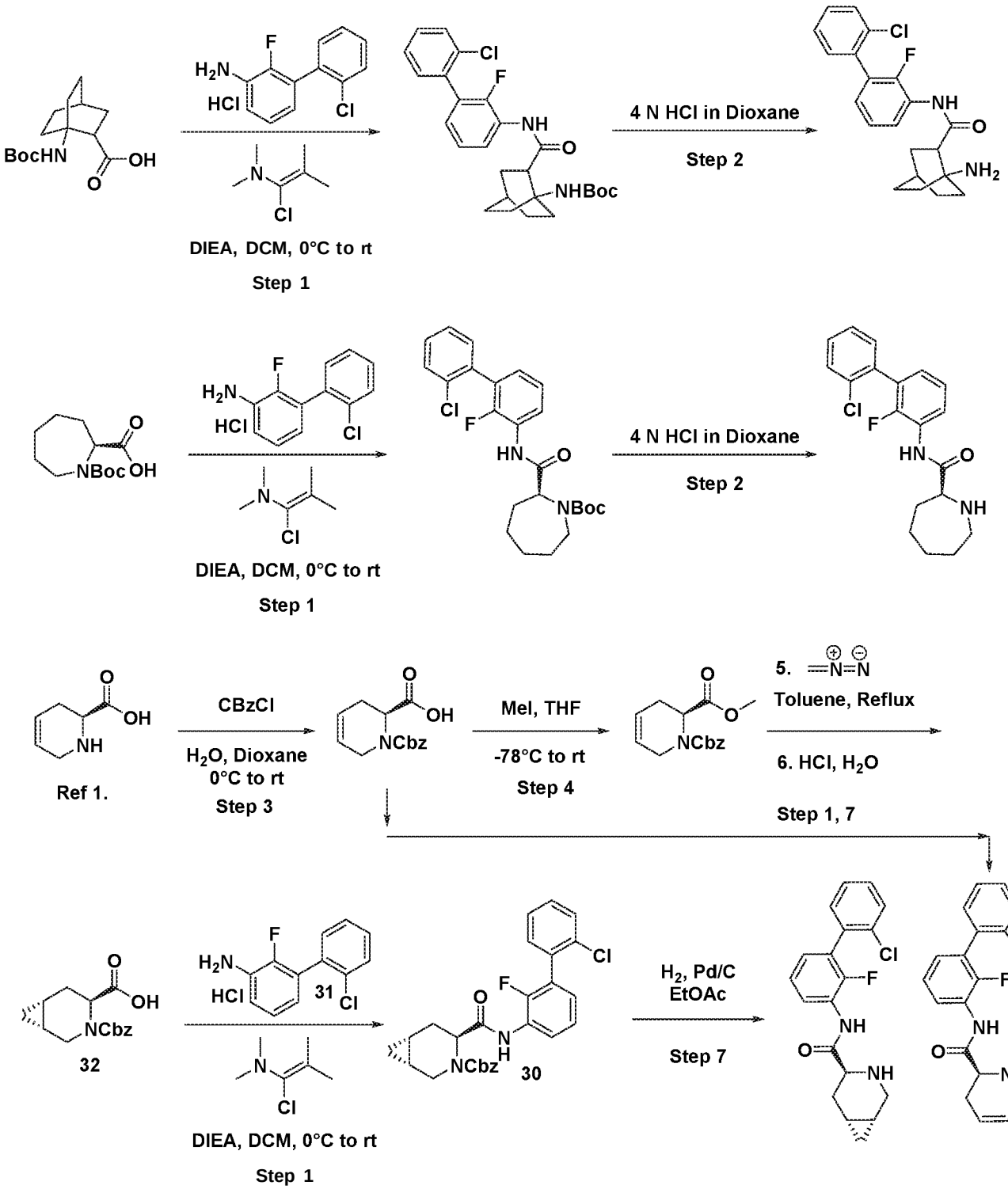
[0605] Scheme 4-1 : In Step 1 the appropriately substituted dibromo species is coupled with an appropriate boronic acid as known in the art to form a mixture of biaryl and triaryl products from which the desired biaryl compound is isolated. In Step 2 the appropriately substituted biaryl species is converted to the Grignard reagent with activated magnesium. In Step 3 the appropriately substituted aldehyde is treated with the previously prepared Grignard reagent to form an alcohol. In Step 4 the appropriately substituted alcohol is converted to a bromide as known in the art with carbon tetrabromide and triphenyl phosphine. In Step 5 the appropriately substituted bromide is converted to the Grignard reagent with activated magnesium.

EXAMPLE 5. SYNTHESIS OF C-L-B MOIETIES

Scheme 5-1



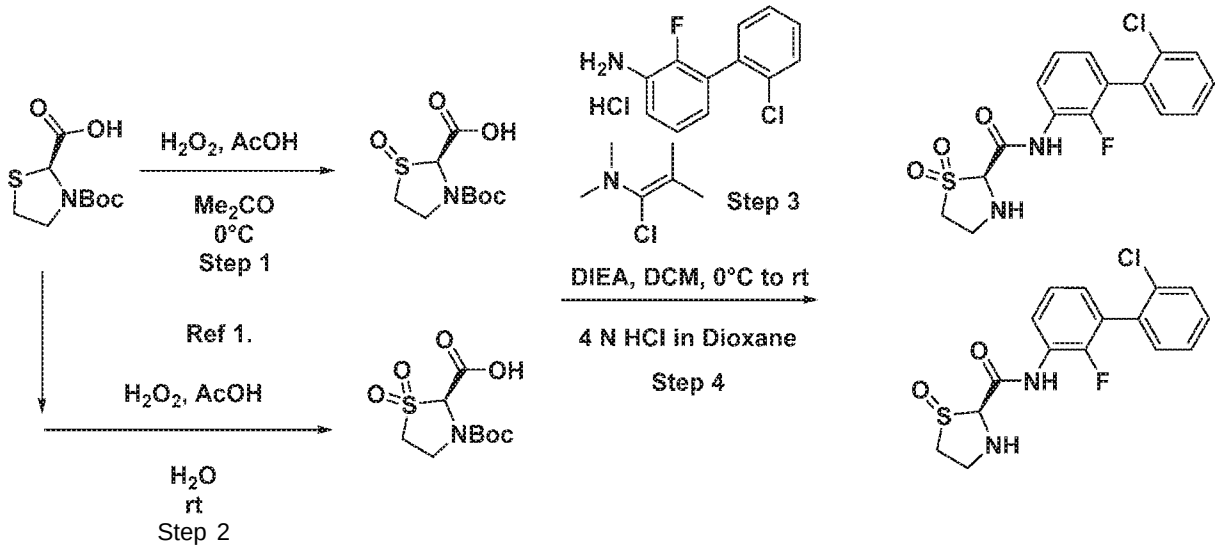
Scheme 5-1 cont.



1. Herdeis, C , et al. (1994). Liebigs Ann. Chem.(1 1): 1117-1 120.

[0606] Scheme 5-1: In Step 1 the appropriately substituted carboxylic acid is coupled to the appropriately substituted amine as known in the art to form an amide. In Step 2 the appropriately substituted Boc-protected species is deprotected with acid to liberate the free amine. In Step 3 the appropriately substituted amine is Cbz-protected as known in the art to form a protected carboxylic acid. In Step 4 the appropriately substituted carboxylic acid can be orthogonally protected as known in the art to form an ester. In Step 5 the appropriately substituted and protected alkene is subjected to a carbene to form a bicyclic ring. In Step 6 the appropriately substituted ester is saponified with acid to liberate the carboxylic acid. In Step 7 the appropriately substituted Cbz-protected species is deprotected with hydrogen to liberate the free amine.

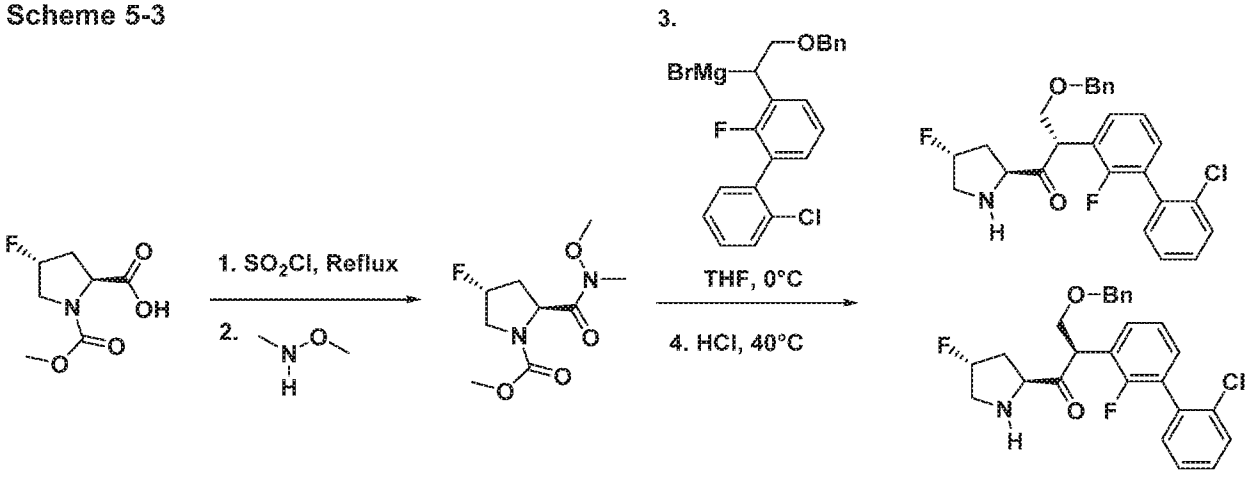
Scheme 5-2



1. Vasii'eva, T. P. (2003). Russ. Chem. Bull., 52(4): 958-960.

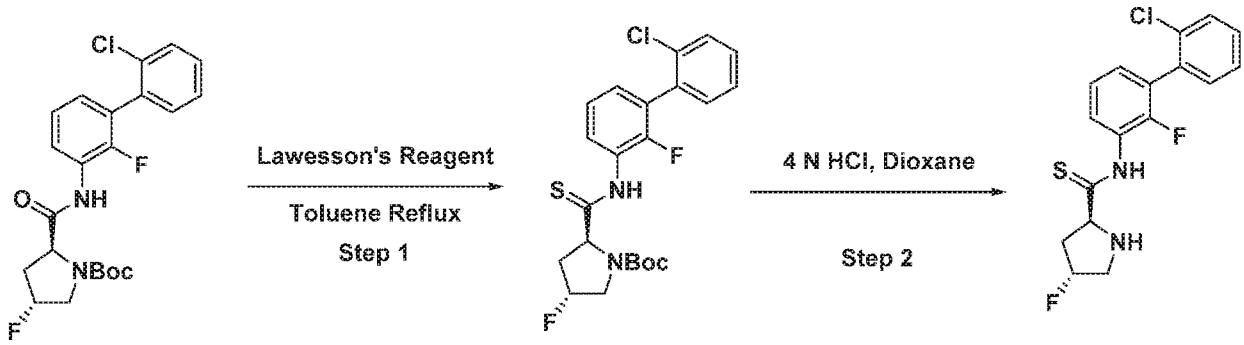
[0607] Scheme 5-2: In Step 1 the appropriately substituted sulfide is oxidized to a sulfoxide as known in the art. Alternatively, in Step 2 the appropriately substituted sulfide is oxidized to a sulfone as known in the art. In Step 3 the appropriately substituted carboxylic acid is coupled to the appropriately substituted amine as known in the art to form an amide. In Step 4 the appropriately substituted Boc-protected species is deprotected with acid to liberate the free amine.

Scheme 5-3



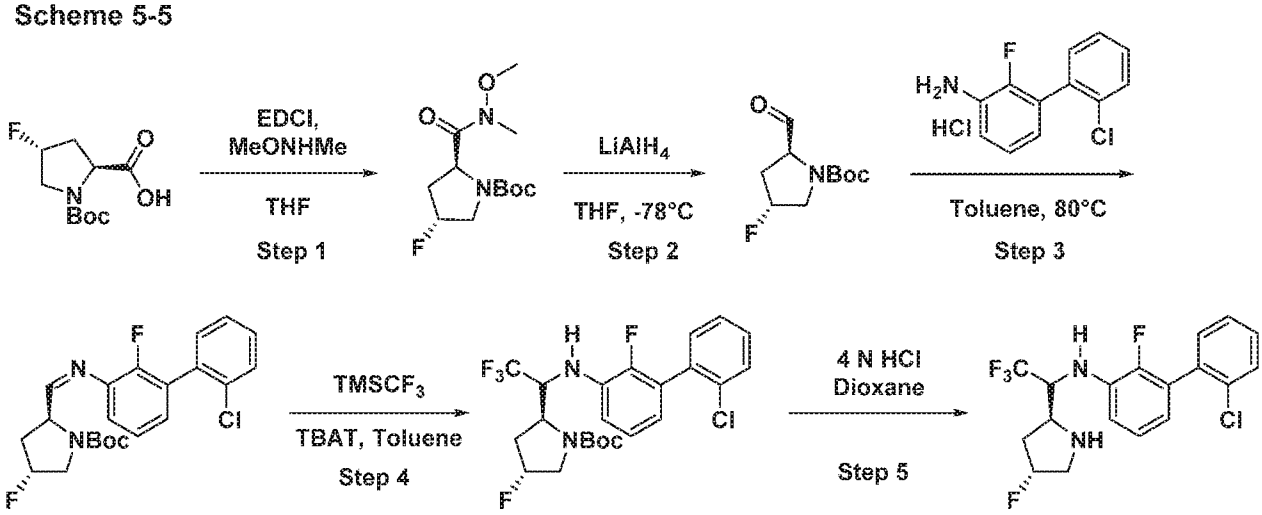
[0608] Scheme 5-3: In Step 1 the appropriately substituted carboxylic acid is converted to the acyl chloride as known in the art. In Step 2 the appropriately substituted acyl chloride is converted to the Weinreb amide as known in the art. In Step 3 the appropriately substituted Weinreb amide is reacted with a Grignard reagent to afford a ketone. The synthesis of complex Grignard reagents is described in Example 4. In Step 4 the appropriately substituted carbamate protected amine is deprotected to liberate the free amine.

Scheme 5-4



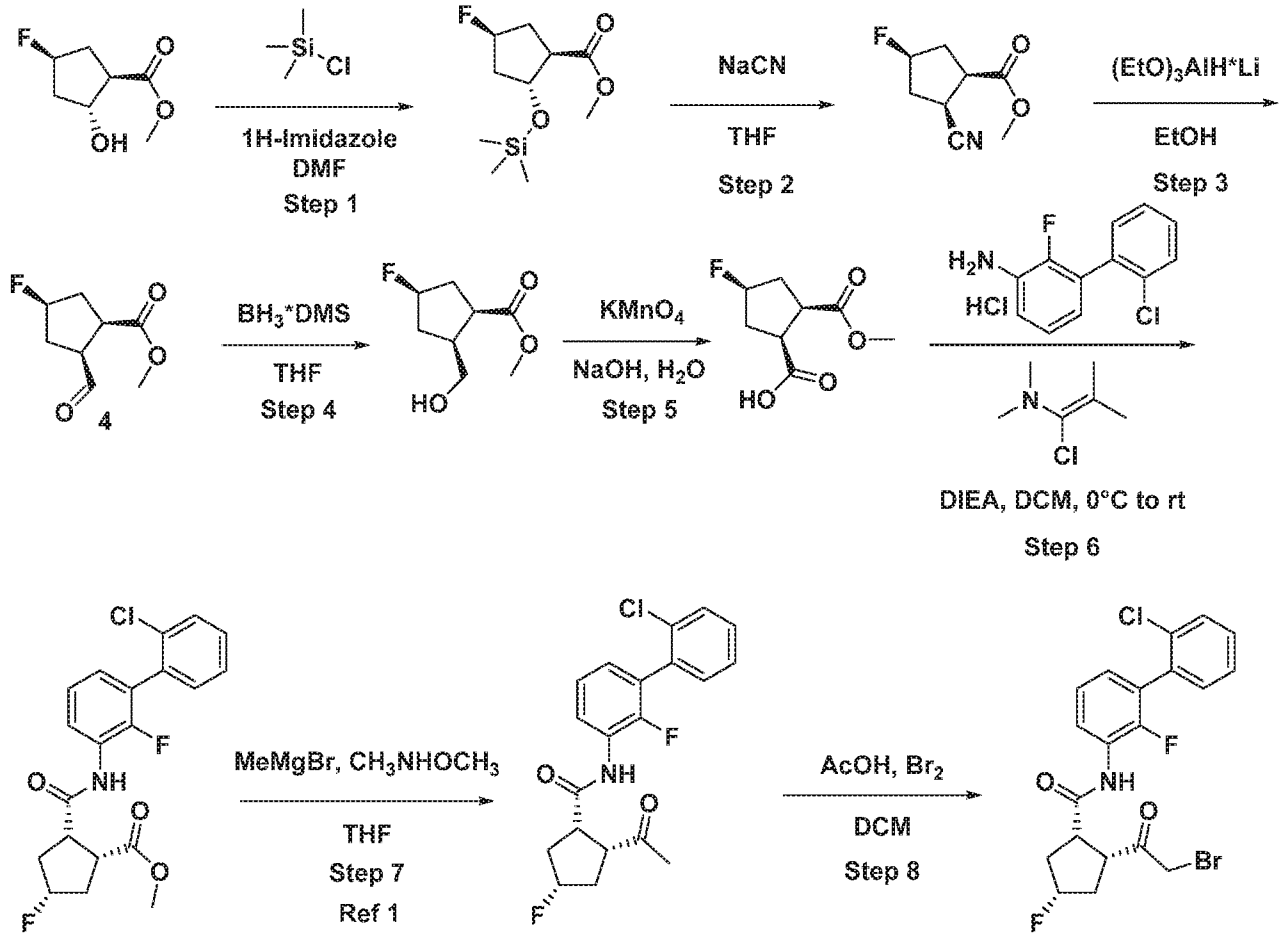
[0609] Scheme 5-4: In Step 1 the appropriately substituted amide is converted to a thioamide with Lawesson's reagent. In Step 2 the appropriately substituted Boc-protected amine is deprotected with acid to liberate the free amine.

Scheme 5-5



[0610] Scheme 5-5: In Step 1 the appropriately substituted carboxylic acid is converted to a Weinreb amide as known in the art. In Step 2 the appropriately substituted Weinreb amide is reduced as known in the art to afford an aldehyde. In Step 3 the appropriately substituted aldehyde is subjected to an amine to form a Schiff base which is subsequently quenched in Step 4. In Step 4 the appropriately substituted Schiff base is subjected to an appropriate nucleophile to form a complex amine. In Step 5 the appropriately substituted Boc-protected species is deprotected with acid to liberate the free amine.

Scheme 5-6

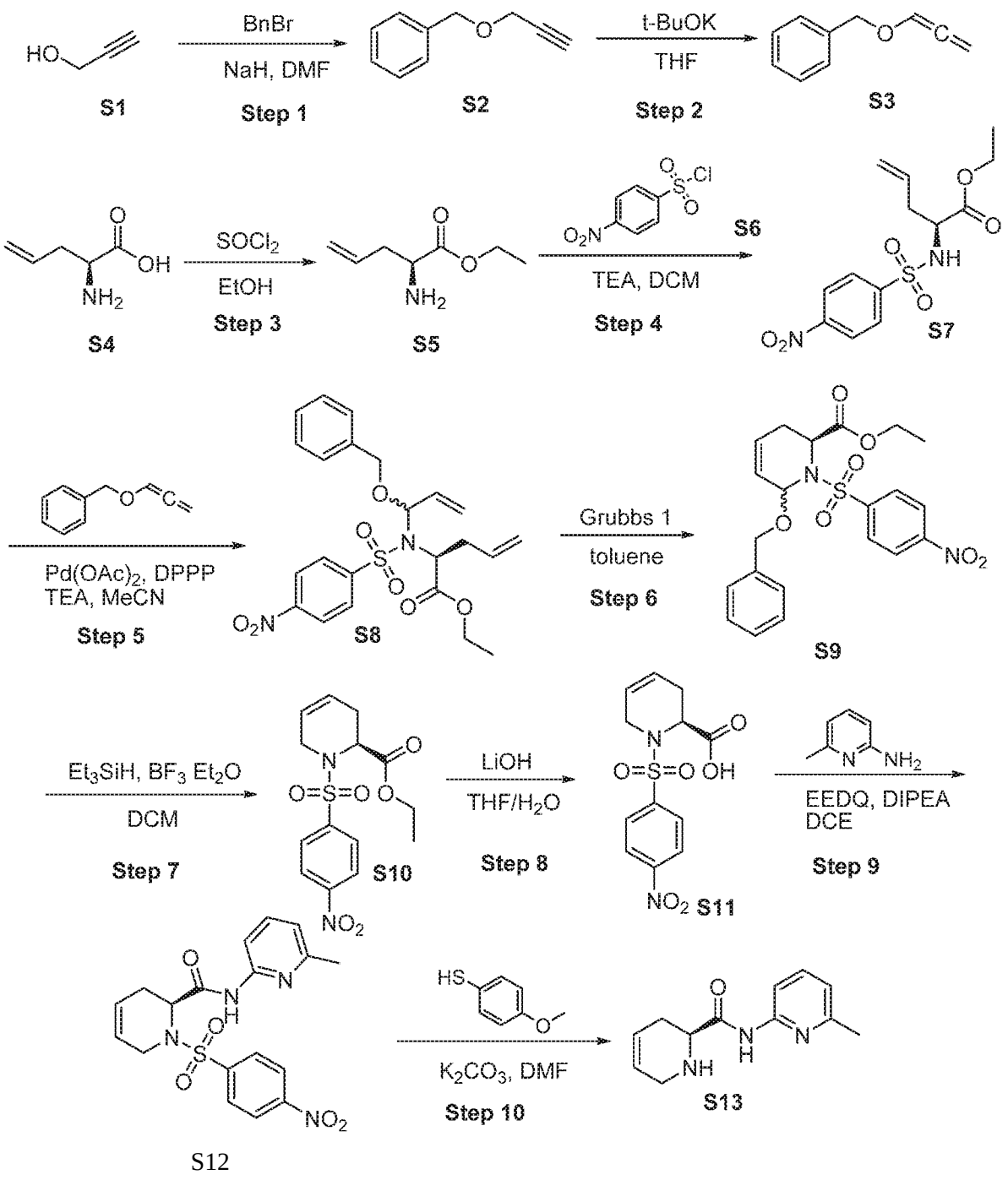


1. Prosser, A. R. and D. C. Liotta (2015). Tetrahedron Lett. 56(23): 3G05-3007.

[061 1] Scheme 5-6: In Step 1 the appropriately substituted alcohol is subjected to TMS-C1 as known in the art to afford a silyl ether. In Step 2 the appropriately substituted silyl ether is subjected with sodium cyanide to afford a cyano species. In Step 3 the appropriately substituted cyano species is reduced as known in the art to afford an aldehyde. In Step 4 the appropriately substituted aldehyde is further reduced with borane to afford an alcohol. In Step 5 the appropriately substituted alcohol is oxidized as known in the art to afford a carboxylic acid. In Step 6 the appropriately substituted carboxylic acid is coupled to the appropriately substituted amine as known in the art to form an amide. In Step 7 the appropriately substituted ester is converted to a methyl ketone by insitu formation of the Weinreb amide with subsequent attack by the methyl Grignard reagent. In Step 8 the appropriately substituted methyl ketone is subjected to bromine to

afford a bromide. By choice of the appropriate starting material all mixtures of chiral centers may be prepared as described.

Scheme 5-7



Step 1: ((Prop-2-ynyloxy)methyl)benzene (S2)

[0612] To a solution of scheme 5-7 compound **SI** (15.5 g, 0.277 mol) in dry DMF (150 mL) was added NaH (12 g, 305 mol) at 0 °C slowly. After stirring at 0 °C for 1 h, BnBr (52 g, 305 mol) was added to the mixture at 0 °C. The reaction was stirred at room temperature for 16 h. Then the mixture was quenched with saturated aqeuous NH_4Cl solution (150 mL) and extracted with DCM (300 mL). The organic layer was washed with aqeuous LiCl solution (150 mL x 3), dried over anhydrous Na_2S04,and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =100:0 to 100:1) to afford the title compound (21 g, 53.1 % yield) as a colorless oil.

Step 2: ((Propa-l,2-dienyloxy)methyl)benzene (S3)

[0613] To a solution of scheme 5-7 compound **S2** (21 g, 0.144 mol) in dry THF (120 ml) was added t-BuOK (4.84 g, 0.0432 mol). The reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. Et_20 (200 mL) was added and the resulting mixture was filtered. The filtrate was concentrated and purified by column chromatography on silica gel (eluted with petroleum ether) to afford the title compound (13.8 g, 66.3 % yield) as a colorless oil.

Step 3: (S)-Ethyl 2-aminopent-4-enoate (S5)

[0614] To a solution of scheme 5-7 compound **S4** (5 g, 43.5 mmol) in EtOH (70 mL) was added $SOCl_2$ (15.52 g, 130.5 mmol) dropwise at 0 °C. The reaction was stirred at room temperature for 16 h and concentrated. The residue was triturated with Et_20 (60 mL) and filtered to afford the title compound (7 g, yield 89 %) as a white powder, which was directly used in the next reaction without further purification. LC/MS (ESI) *mlz:* 144 $(M+H)^+$.

Step 4: (S)-Ethyl 2-(4-nitrophenylsulfonamido)pent-4-enoate (S7)

[0615] To a mixture of scheme 5-7 compound **S5** (7 g, 39 mmol) and TEA (9.85 g, 97.5 mmol) in DCM (80 mL) was added 4-nitrobenzene-l-sulfonyl chloride (8.63 g, 39 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with saturated aq.NaHCCb solution (100 mL). The resulting mixture was extracted with DCM (50 mL x 2). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with

petroleum ether: ethyl acetate =15:1 to 8:1) to afford the title compound (9.2 g, 71.84% yield) as a yellow oil. LC/MS (ESI) *mlz:* 327 $(M-H)^+$.

Step 5: (S)-Ethyl 2-(N-(l-(benzyloxy)allyl)-4-nitrophenylsulfonamido)pent-4-enoate (S8)

[0616] To a solution of scheme 5-7 compound **S7** (8.4 g, 25.6 mmol) in MeCN (90 mL) was added ((propa-l,2-dienyloxy)methyl)benzene (4.2 g, 28.17 mmol), DPPP (1.06 g, 2.56 mmol), TEA (5.17 g, 51.2 mmol) and $Pd(OAc)_2$ (576 mg, 2.56 mmol). The reaction was degassed and stirred at room temperature for 16 h under N_2 atmosphere. The mixture was concentrated to dryness and the residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =30:1 to 20: 1) to afford the title compound (8.1 g, 66.67% yield) as a yellow solid.

Step 6: (S)-Ethyl 6-(benzyloxy)-l-(4-nitrophenylsulfonyl)-l,2,3,6-tetrahydropyridine-2-carboxylate (S9)

[0617] To a solution of scheme 5-7 compound **S8** (8 g, 16.88 mmol) in dry degassed toluene (80 mL) was added Grubbs I catalyst (707 mg, 0.844 mmol) under N_2 atmosphere. The resulting mixture was degassed three times and stirred at 80 °C for 20 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =15: 1 to 6 :1) to afford the title compound (6.58 g, 87.3 1% yield) as a yellow oil. LC/MS (ESI) *mlz:* 447 $(M-H)^+$.

Step 7: (S)-Ethyl l-(4-nitrophenylsulfonyl)-l,2,3,6-tetrahydropyridine-2-carboxylate (S10)

[0618] To a mixture of scheme 5-7 compound **S9** (6.58 g, 14.72 mmol) and triethylsilane (5.17 g, 44.16 mmol) in dry DCM (80 mL) was added boron trifluoride etherate (6.27 g, 44.16 mmol) at -75 °C under N_2 atmosphere dropwise. The reaction was stirred at -75 °C for 1 h and then at room temperature for 3 h. The mixture was quenched with saturated NaHCCb solution (100 mL) and extracted with DCM (60 mL x 2). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =15:1 to 8:1) to afford the title compound (4.5 g, 89.8% yield) as a colorless oil.

Step 8: (S)-l-(4-Nitrophenylsulfonyl)-l,2,3,6-tetrahydropyridine-2-carboxylic acid (Sll)

[0619] To a mixture of scheme 5-7 compound **S10** (4.5 g, 13.22 mmol) in EtOH/THF/H_2O (40 mL, 1:2:1, V/V) was added LiOH (1.66 g, 39.66 mmol). The reaction mixture was stirred at room temperature for 4 h and then acidified with aqeuous HCl solution (1 M) to pH=5. The resulting mixture was extracted with DCM/MeOH (40 mL x 2, 20: 1, V/V). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound (3.3 g, 79.9% yield) as a yellow solid, which was directly used in the next reaction without further purification. LC/MS (ESI) *mlz:* 311 $(M-H)^+$.

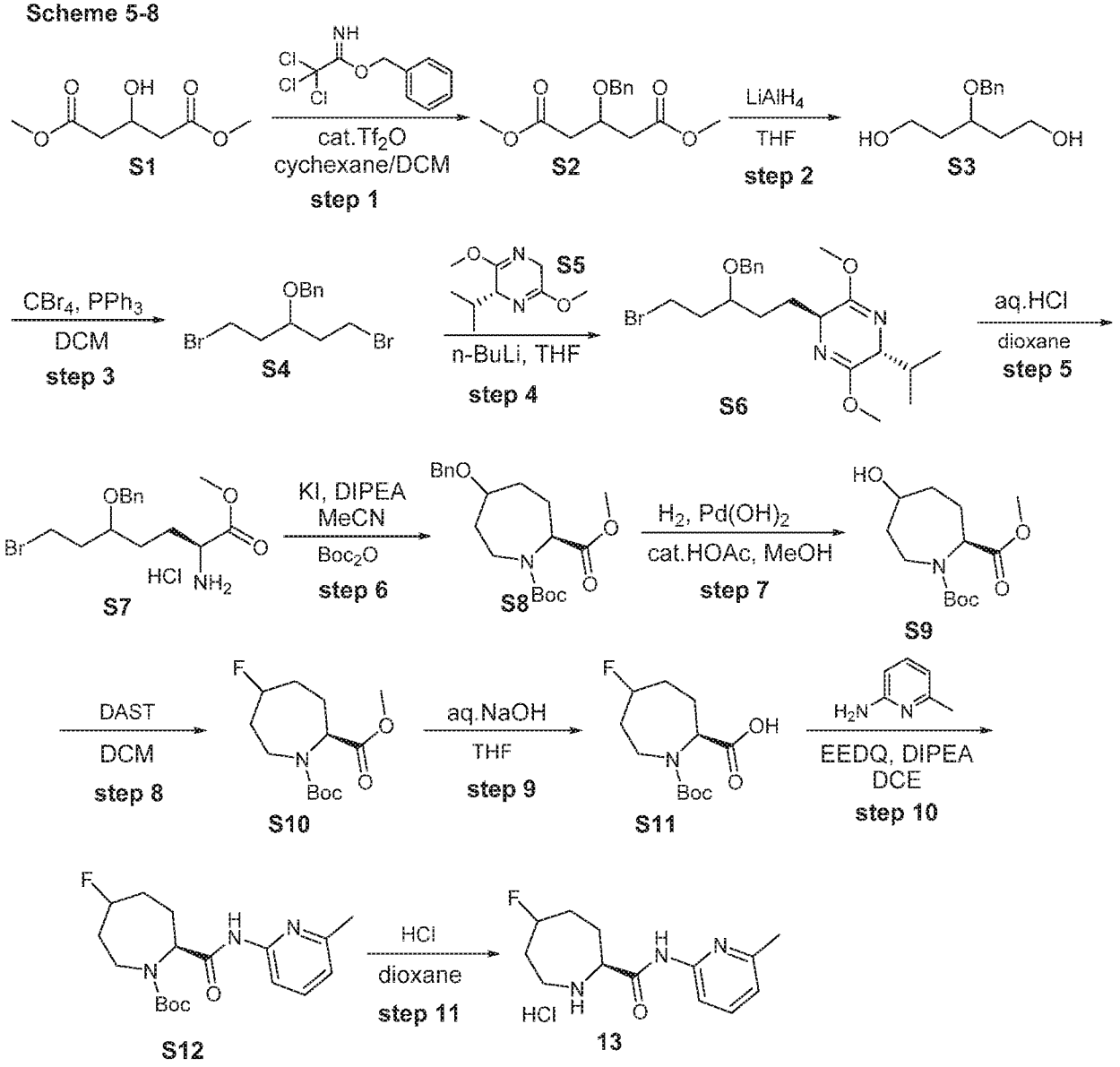
Step 9: (S)-N-(6-methylpyridin-2-yl)-l-(4-nitrophenylsulfonyl)-l,2,3,6-tetrahydropyridine-2-carboxamide (S12)

[0620] To a solution of scheme 5-7 compound **Sll** (1.77 g, 5.76 mmol) in dichloroethane (30 mL) was added 6-methylpyridin-2-amine (674 mg, 6.24 mmol), EEDQ (2.82 g, 11.34 mmol) and DIPEA (2.22 g, 17 mmol). The reaction was stirred at reflux overnight under N_2 atmosphere. After cooling, the mixture was concentrated and purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 8: 1 to 2: 1) to afford the title compound (1.4 g, 60.4% yield) as a yellow solid. LC/MS (ESI) *mlz:* 403 $(M+H)^+$.

Step 10: (S)-N-(6-methylpyridin-2-yl)-l,2,3,6-tetrahydropyridine-2-carboxamide (S13)

[0621] To a solution of scheme 5-7 compound **S12** (740 mg, 1.84 mmol) in DMF (8 mL) was added K_2CO_3 (762 mg, 5.52 mmol) and 4-methoxybenzenethiol (335 mg, 2.4 mmol). The reaction was stirred at room temperature for 24 h. Then the mixture was diluted with 10% of LiCl solution (40 ml) and extracted with DCM/MeOH (40 mL x 2, 20: 1, V/V). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM: MeOH =100:0 to 50:1) to afford scheme 5-7 compound **S13** (310 mg, 77.54% yield) as a yellow solid. LC/MS (ESI) *mlz:* 218 $(M+H)^+$.

Scheme 5-8



Step 1: Dimethyl 3-(benzyloxy)pentanedioate (S2)

[0622] To a solution of scheme 5-8 compound **SI** (24 g, 0.136 mol) and benzyl 2,2,2-trichloroacetimi date (51.3 g, 0.204 mol) in **cychexane/dichloromethane** (600 tnL/120 mL) at room temperature was added trifluoromethanesulfonic anhydride (cat. 1.2 mL) dropwise. The reaction mixture was stirred at room temperature overnight and filtered. The filtrate was washed with sat. NaHCOi and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =10: 1) to afford the title compound (35 g, 93.3% yield) as a yellow oil.

Step 2: 3-(Benzyloxy)pentane-l,5-diol (S3)

[0623] To a solution of scheme 5-8 compound S2 (35 g, 0.13 mol) in THF (anhydrous, 200 mL) was added lithium aluminium hydride (15 g, 0.39 mol) in portions at 0 °C. The mixture was heated to 65 °C for 4 h. The mixture was quenched by aqueous sodium hydroxide solution (15 mL, 15% wt) and water (15 mL+ 45 mL). The slurry was filtered and the filter cake was washed with dichloromethane twice. The combined filtrates were dried over sodium sulfate and concentrated to afford the title compound (22 g, 79.7% yield) as a yellow oil.

Step3: ((l,5-Dibromopentan-3-yloxy)methyl)benzene (S4)

[0624] To a mixture of scheme 5-8 compound S3 (22 g, 0.10 mol) and PPh_3 (82.3 g, 0.31 mol) in dry dichloromethane (200 mL) was added perbromomethane (86.95 g, 0.26 mol) in dry dichloromethane (50 mL) dropwise at 0°C. The reaction was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate=80:l) to afford the title compound (23 g, 66.7% yield) as a yellow oil.

Step4: (2S,5R)-2-(3-(Benzyloxy)-5-bromopentyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (S6)

[0625] To a dry-ice / acetone cooled solution of scheme 5-8 compound **S5** (5 g, 0.027 mol) in THF (50 ml), n-BuLi (2.5 M, 14.1 mL, 0.035 mol) was added dropwise for 30 min. After addition, the reaction was stirred at this temperature for 30 min, followed by dropwise addition of a solution of compound **S4** (13.6 g, 0.04 mol) in THF (20 mL). The reaction mixture was stirred at this temperature for another 30 min and allowed to stir at room temperature for 16 h. Then the reaction was quenched with aqeuous NH_4Cl (50 mL) and extracted with ethyl acetate (60 mL x 2). The combined organic layers were washed with brine, dried over anhydrous $Na_2SC"4$, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =10: 1) to afford the title compound (6 g, yield 50.4%) and scheme 5-8 compound **S4** (4.8 g) was recovered.

Step 5: (2S)-Methyl 2-amino-5-(benzyloxy)-7-bromoheptanoate hydrochloride salt (S7)

[0626] To a mixture of scheme 5-8 compound **S6** (6 g, 0.01 mol) in dioxane (30 mL) was added 0.5 M HC1 (30 mL, dropwise at 0 °C. The reaction was stirred at room temperature overnight and concentrated under reduced pressure to afford a residue, which was co-evaporated with toluene (15 mLx 2) to afford the title compound (crude HC1 salt, 8 g) as a brown oil. The residue was directly used in the next reaction without purification.

Step 6: (2S)-l-terf-Butyl 2-methyl 5-(benzyloxy)azepane-l,2-dicarboxylate (S8)

[0627] To a mixture of scheme 5-8 compound **S7** (8 g crude) in acetonitrile (80 mL) was added DIPEA (9.03 mL, 0.054 mol), followed by sodium iodide (2.05 g, 0.013 mol). The reaction was stirred at 90 °C for 16 h. Then $(Boc)_20$ (5.97 g, 0.027 mol) was added and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with ethyl acetate (100 mL) and washed twice with brine (30 mLx 2). The organic layer was dried over anhydrous Na_2S0_4, filtered and concentrated. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate =20:1) to afford the title compound (3.6 g, 72.4% yield) as a colorless oil.

Step 7: *tert*-Butyl (2S)-l-terf-butyl 2-methyl 5-hydroxyazepane-l,2-dicarboxylate (S9)

[0628] A solution of scheme 5-8 compound **S8** (1.6 g, 4.40 mmol) and cat. HOAc (1.5 mL) in methanol (35 mL) was degassed three times under N_2 atmosphere, and $Pd(OH)_2$ (240 mg) was added. The mixture was degassed again and stirred under a H_2 balloon at 50 °C over 12 h. The reaction was filtered through celite, and the filtrate was concentrated to afford the title compound (1.1 g, 91.3% yield) as a light yellow oil.

Step 8: (2S)-l-terf-Butyl 2-methyl 5-fluoroazepane-l,2-dicarboxylate (S10)

[0629] To a dry-ice/ ethanol cooled solution of scheme 5-8 compound **S9** (1.1 g, 4.03 mmol) in DCM (20 mL) was added DAST (0.79 mL, 6.04 mmol) dropwise. The reaction mixture was warmed up slowly and stirred at room temperature overnight. After quenching with saturated aq.NaHCCb solution, the mixture was extracted with DCM (20 mL x 2). The combined organic phases were washed with water and brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford crude product. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate =10:1) to afford the title compound (750 mg, 68.1% yield) as a colorless oil.

Step 9: (2S)-l-(terf-Butoxycarbonyl)-5-fluoroazepane-2-carboxylic acid (Sll)

[0630] To a mixture of scheme 5-8 compound **S10** (750 mg, 2.72 mmol) in THF (7 mL) was added aqeuous NaOH solution (4 M, 2.7 mL, 10.8 mmol). The reaction was stirred at 40 °C overnight and concentrated under reduced pressure. The residue was diluted with water (10 mL) and washed with Et_20 (3 ml x2). The aqueous layer was acidified with diluted hydrochloric acid (1 M) to pH= 3. The resulting mixture was extracted with DCM (10 mLx 2). The combined organic layers were washed with brine, dried over anhydrous Na_2S0_4 and concentrated under reduced pressure to afford the title compound (700 mg, 98.4% yield) as a white solid.

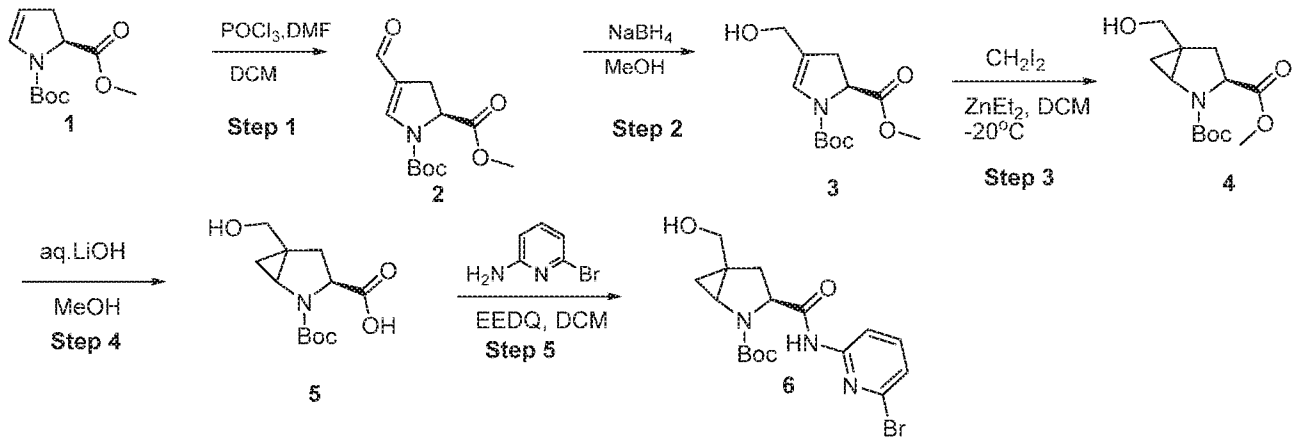
Step 10: (2S)-terf-Butyl 5-fluoro-2-(6-methylpyridin-2-ylcarbamoyl)azepane -l-carboxylate (S12)

[0631] To a solution of scheme 5-8 compound Sll (500 mg, 1.91 mmol) and 6-methylpyridin-2-amine (248 mg, 2.29 mmol) in DCE (10 ml) was added DIPEA (0.95 mL, 5.73 mmol) and EEDQ (943.5 mg, 3.82 mmol). The reaction mixture was stirred at 90 °C overnight and concentrated under high vacuum. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate =10:1) to afford the title compound (500 mg, 74.4% yield) as a white solid.

Step 11: (2S)-5-Fluoro-N-(6-methylpyridin-2-yl)azepane-2-carboxamide hydrochloride (S13)

[0632] To a mixture of scheme 5-8 compound **S12** (500 mg, 1.42 mmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 5 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to afford scheme 5-8 **S13** (550 mg, 100% yield) as a white solid, which was directly used in the next reaction without purification.

Scheme 5-9



Step 1: (S)-Methyl 4-formyl-2,3-dihydro-lH-pyrrole-2-carboxylate (S2)

[0633] POCh (2.7 g, 17.6 mmol) was added dropwise to ice-cooled DMF (2.6 g, 35.2 mmol) under N2 atmosphere. The reaction was stirred at 0 °C for 30 min and then diluted with dry DCM (50 mL). A solution of scheme 5-8 compound SI (2 g, 8.8 mmol) in DCM (20 mL) was added to the above mixture dropwise at 0 °C for 30 min. The reaction mixture was stirred at room temperature for 1 h and slowly poured into ice cooled 2 M aqeuous NaOH solution. The resulting mixture was extracted with DCM (50 mL x 2). The combined organic layers were washed with water and brine, dried, and concentrated to afford a residue that was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 5:1) to afford the title compound (1.9 g, 84.6% yield) as a light yellow oil.

Step 2: (S)-l-tert-Butyl 2-methyl 4-(hydroxymethyl)-2,3-dihydro-lH-pyrrole-l,2-dicarboxylate (S3)

[0634] To a solution of the scheme 5-8 compound **S2** (1.9 g, 7.44 mmol) in DCM (20 mL) and MeOH (10 mL) was added $NaBH_4$ (23 mg, 1.44 mmol) in portions at -70 °C. The reaction was stirred at 0 °C for 30 min and quenched with saturated aqeuous NH_4C1 solution (10 mL). The resulting mixture was extracted with DCM twice and the combined organic layers were washed with brine, dried over anhydrous Na_2S04, filtered, and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 3:1) to afford the title compound (1.7 g, 88.8% yield) as a colorless oil.

Step 3: (3S)-2-terf-Butyl 3-methyl 5-(hydroxymethyl)-2-azabicyclo [3.1.0] hexane-2,3-dicarboxylate (S4)

[0635] To a solution of the scheme 5-8 compound **S3** (1.5 g, 5.83 mmol) in DCM (20 mL) was added diethylzinc hexane solution (1 M, 17.5 mL, 17.5 mmol) dropwise followed by diiodomethane (4.68 g, 17.5 mmol) at -20 °C under N_2 atmosphere. The reaction was stirred at -20 °C for 2 h and quenched with aqueous NH_4Cl solution. The resulting mixture was extracted with DCM twice. The combined organic layers were washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford a residue. This residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 3:1) to afford the title compound (1.2 g, 75.8% yield) as a colorless oil.

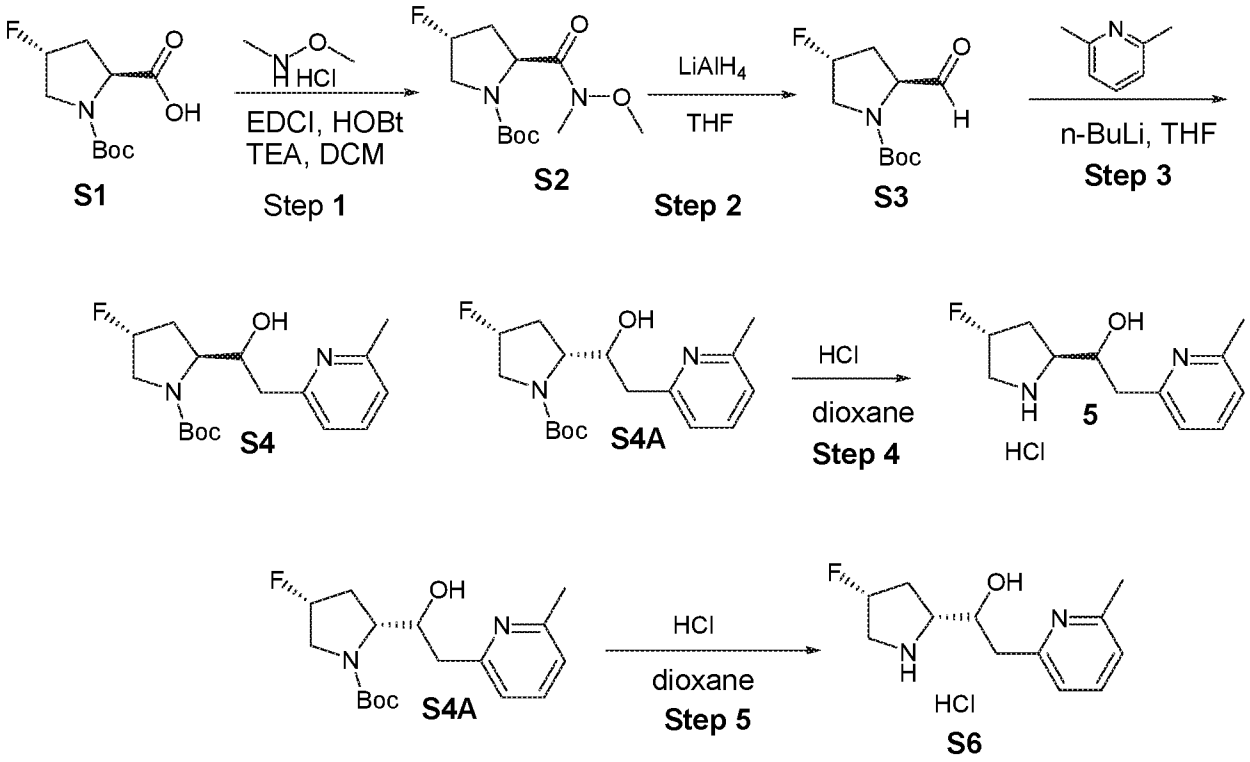
Step 4: (3S)-2-(ieri-Butoxycarbonyl)-5-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (S5)

[0636] To a solution of scheme 5-8 compound **S4** (150 mg, 0.55 mmol) in THF (5 mL) was added aqeuous LiOH solution (3 mL, 3 mmol). The reaction was stirred at room temperature for 2 h and concentrated. The residue was acidified with 1 N HC1 solution to pH= ~3. The resulting mixture was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over anhydrous Na_2S04, filtered and concentrated to afford the title compound (110 mg, 78.2% yield) as a white solid.

Step 5: (3S)-terf-Butyl 3-(6-bromopyridin-2-ylcarbamoyl)-5-(hydroxymethyl)-2-azabicyclo [3.1.0] hexane-2-carboxylate (S6)

[0637] To a mixture of the scheme 5-8 compound **S5** (110 mg, 0.43 mmol), 6-bromopyridin-2-amine (74 mg, 0.43 mmol and EEDQ (210 mg, 0.85 mmol) in 1,2-DCE (5 mL) was added DIPEA (165 mg, 1.29 mmol). The reaction was stirred at 90 °C for 16 h and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 2:1) to afford the title scheme 5-8 compound **S6** (120 mg, 67.7% yield) as a yellow solid. LC/MS (ESI) *m/z*: 412(M+H)$^+$.

Scheme 5-10



Step 1: (2S,4R)-ferf-Butyl 4-fluoro-2-(methoxy(methyl)carbamoyl)pyrrolidine-l-carboxylate (S2)

[0638] To a solution of scheme 5-10 compound **SI** (5 g, 21.43 mmol) in DCM (100 mL) was added N,O-dimethylhydroxylamine hydrochloride (2.5 g, 25.72 mmol), EDCI (6.16 g, 32.14 mmol) and HOBt (2.9 g, 21.43 mmol) followed by TEA (5.4 g, 53.58 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM and washed with water and brine, dried over anhydrous Na_2S04 and concentrated to afford crude product that was washed with petroleum ether/EtOAc (2/1) to afford the title compound (5.5 g, 92.88% yield) as a white solid.

Step 2: (2S,4R)-ferf-Butyl 4-fluoro-2-formylpyrrolidine-l-carboxylate (S3)

[0639] To a solution of scheme 5-10 compound **S2** (5 g, 18.12 mmol) in THF (40 mL) was added $LiAlH_4$ (1.38 g, 36.23 mmol). The reaction was stirred at 0 °C for 2 h. The reaction was quenched with water (1.38 mL), aqeuous NaOH solution (1.38 mL, 15% wt) and water (4 mL) successively. The mixture was filtered and the filter cake was washed with THF twice. The

combined filtrates were concentrated to dryness to afford crude product. The crude product was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =30:1 to 10:1) to afford the title compound (2.7 g, 68.7 % yield) as a white solid .

Step 3: (2S,4R)-tert-Butyl 4-fluoro-2-((R)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidine-l-carboxylate (S4A) & (2R,4R)-tert-butyl 4-fluoro-2-((S)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidine-l-carboxylate (S4)

[0640] To a stirred solution of 2,6-dimethylpyridine (2.46 g, 23.04mmol) in THF (50 mL) was added n-butyllithium (1.6 M in THF, 7.2 mL, 11.52 mmol) dropwise at -70 °C. The reaction mixture was stirred at this temperature for 1 h. and then scheme 5-10 compound **S3** (2.5 g, 1.52 mmol) in THF (10 mL) was added at -70 °C for 30 min. The mixture was continued to stir at this temperature for 1 h and quenched with aqeuous NH_4Cl solution. The resulting mixture was extracted with EtOAc (100 mL). The organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =20:1 to 10:1) to afford the title compound **S4** (1.2 g, 26.3% yield) and **S4A** (1.3 g, 28.56% yield) as a white solid.

Step 4: (R)-l-((2S,4R)-4-Fluoropyrrolidin-2-yl)-2-(6-methylpyridin-2-yl)ethanol (S5)

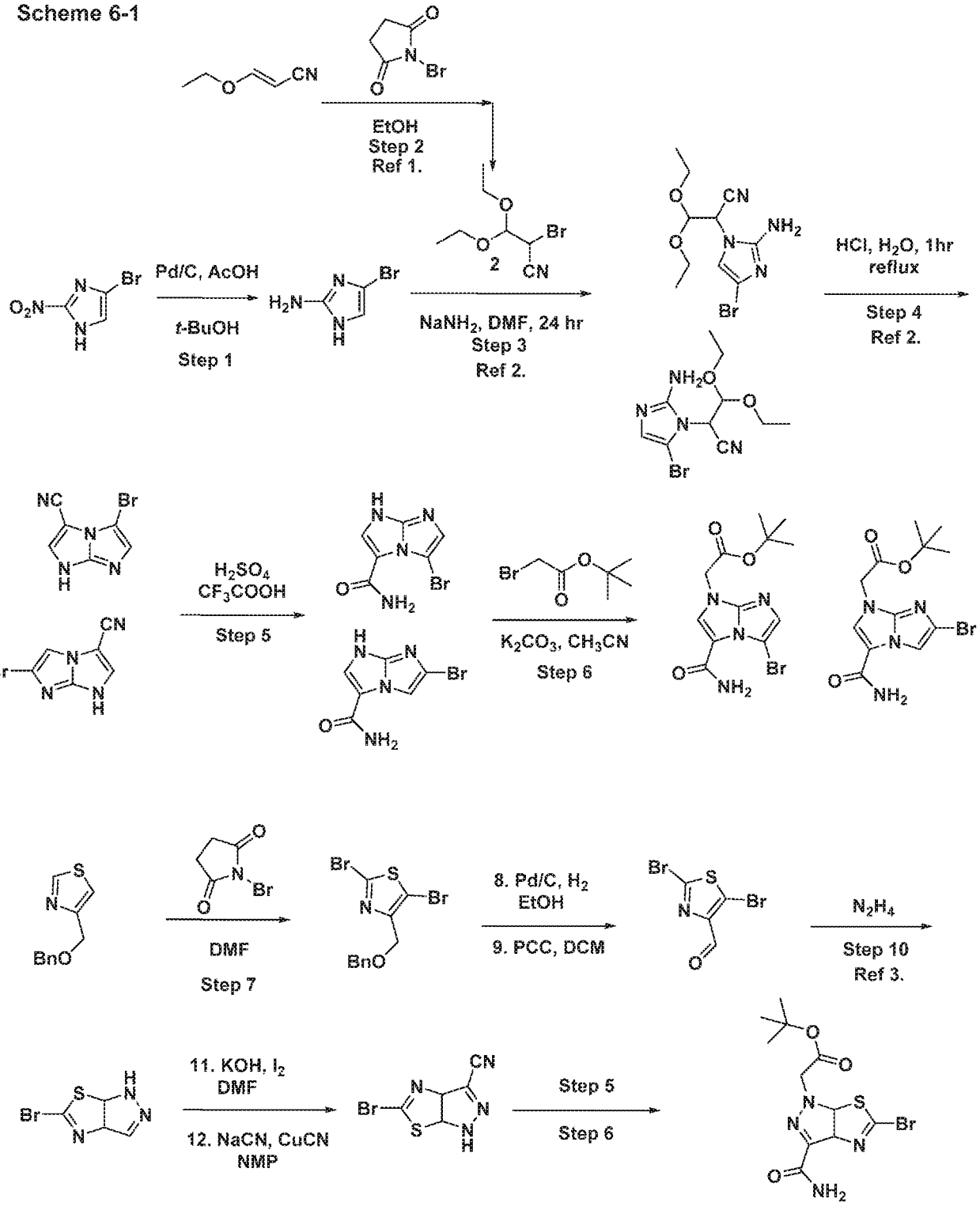
[0641] To a solution of scheme 5-10 compound **S4** (1.2 g, 3.7 mmol) in dioxane (10 mL) was added HCl/dioxane (4 M, 5 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction solution was concentrated to afford scheme 5-10 compound **S5** (1.3 g, 100% yield) as a white solid. This compound was carried forward without any further purification.

Step 5: (S)-l-((2R,4R)-4-Fluoropyrrolidin-2-yl)-2-(6-methylpyridin-2-yl)ethan-l-ol (S6)

[0642] To a solution of scheme 5-10 compound **S4A** (1.3 g, 4 mmol) in dioxane (10 mL) was added HCl/dioxane (4 M, 5 mL). The reaction mixture was stirred at room temperature for lhr and concentrated to dryness to afford scheme 5-10 compound **S6** (1.4 g, *100%* yield) as a white solid. This compound was carried forward without further purification.

EXAMPLE 6. SYNTHESIS OF A MOIETIES

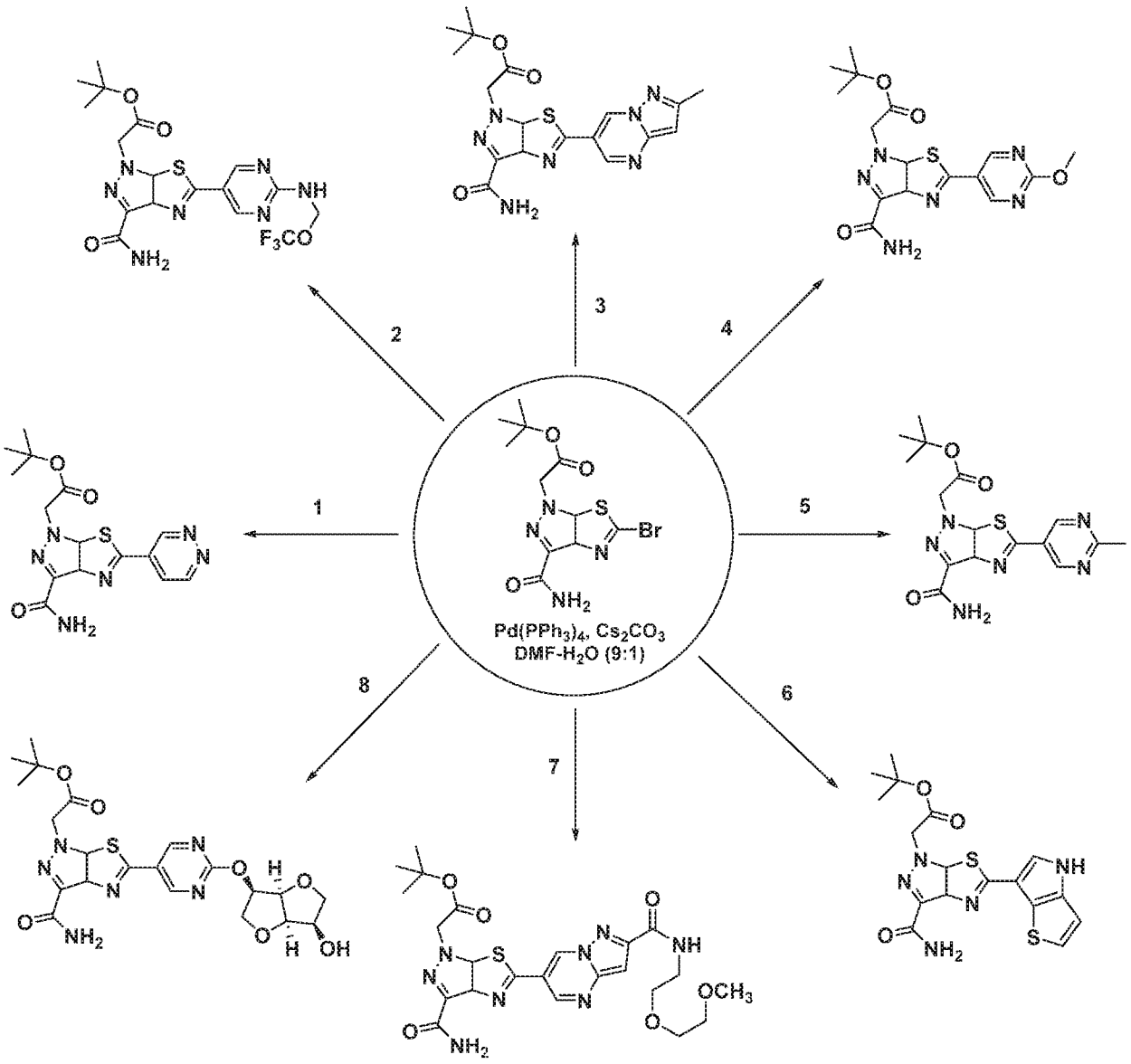
Scheme 6-1

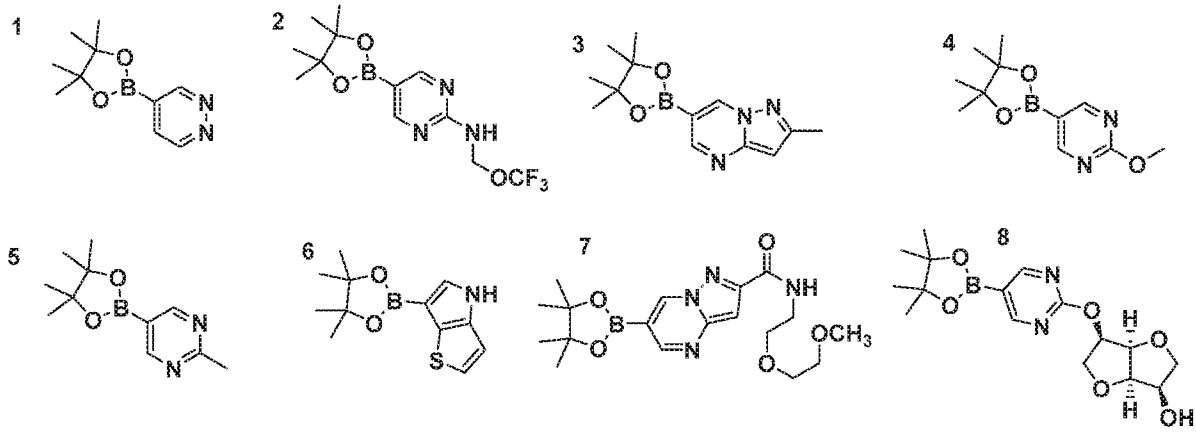


1. Babler, J. H. (1987). Synth. Commun. 17(1): 77-84.
2. Mas, T., et al. (2002). ARKiVOC (Gainesville, FL, U. S.)(5): 48-61.
3. Lebedev, A, Y., et al. (2005). J. Org. Chem. 70(2): 596-802.

[0643] Scheme 6-1: In Step 1 the appropriately substituted nitro species is reduced with palladium as known in the art to afford an amine. In Step 2 the appropriately substituted alkene species is brominated with concurrent addition of ethanol as known in the art to afford the bromide species. In Step 3 the appropriately substituted mixture of tautomers is subjected to the previously prepared bromide species as known in the art to afford the two isomers. The appropriately substituted isomers corresponding to each tautomer may either be separated or used as a mixture in the subsequent reactions with separation at a later step. In Step 4 the appropriately substituted ketal species is deprotected and subsequently cyclized in the presence of acid as known in the art. In Step 5 the appropriately substituted cyano species is subjected to strong acid to afford a primary amide. In Step 6 the appropriately substituted heterocycle is subjected to a bromide species of the appropriate linker to afford the appropriately protected species. Various 5-5 fused bicyclic systems can be appropriately prepared by slight modifications of this synthetic protocol, another non-limiting example is presented in Steps 5 through 12 with the same conditions for formation of a primary amide and installation of linker. In Step 7 the appropriately substituted aryl species is brominated as known in the art. In Step 8 the appropriately substituted ether species is deprotected with palladium as known in the art to afford an alcohol. In Step 9 the appropriately substituted alcohol is oxidized as known in the art to afford an aldehyde. In Step 10 the appropriately substituted aldehyde is subjected to hydrazine to first form a Schiff base and subsequently cyclize to afford a bicyclic system. In Step 11 the appropriately substituted bicyclic system is iodinated as known in the art. In Step 12 the appropriately substituted iodide is subjected to sodium cyanide to afford the cyano species.

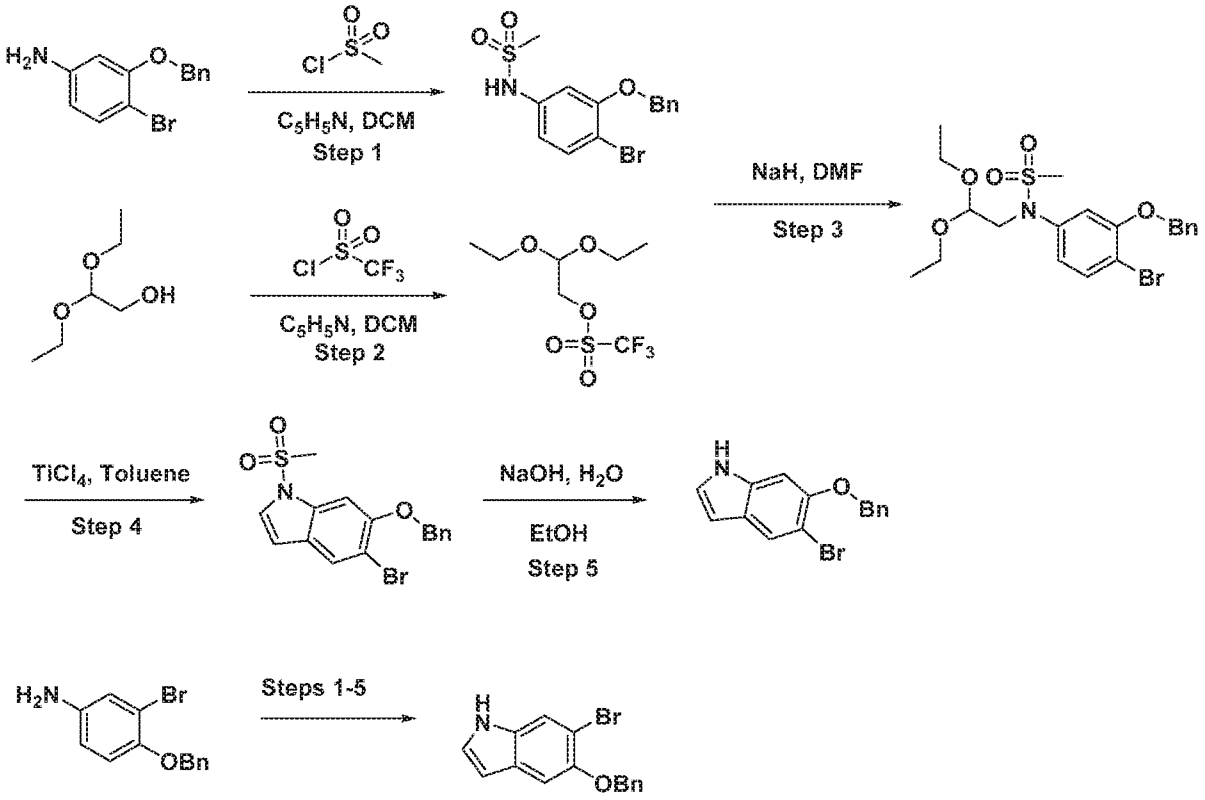
Scheme 6-2



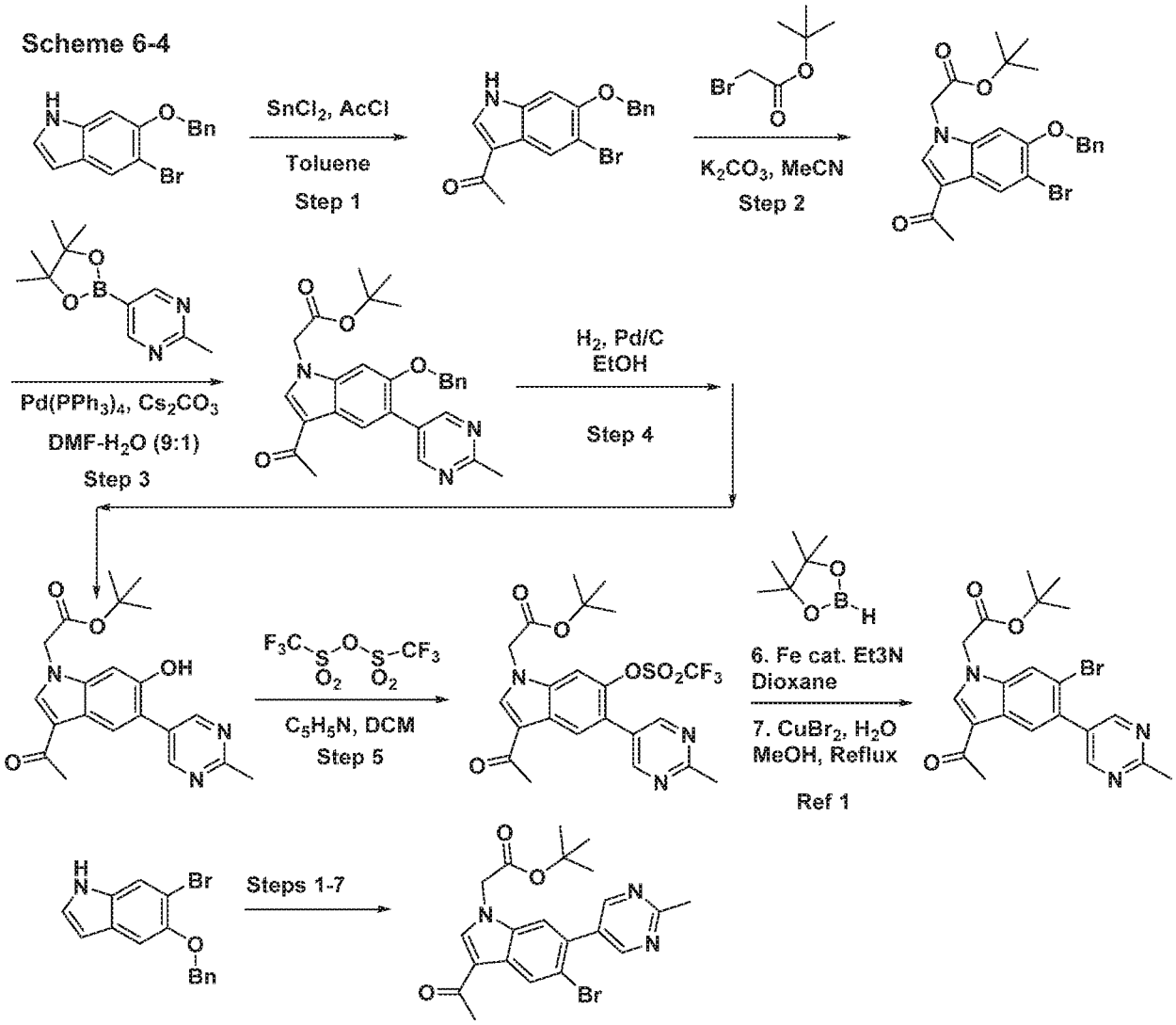


[0644] Scheme 6-2: Non-limiting examples of aryl substituents are provided demonstrating the robust nature of the synthetic protocol. Boronic acids 1-8 are subjected to an appropriately substituted aryl bromide to afford a biaryl system.

Scheme 6-3



[0645] Scheme 6-3: In Step 1 the appropriately substituted and protected aniline is converted as known in the art to a sulfonamide. In Step 2 the appropriately substituted alcohol is converted as known in the art to a triflouro sulfonamide. In Step 3 the previously prepared reagents are subjected to sodium hydride to afford their adduct. In Step 4 the appropriately substituted ketal is subjected to a strong lewis acid to afford deprotection and subsequent cyclization to a biaryl species. In Step 5 the appropriately substituted sulfonamide is deprotected in the presence of base to afford a free amine. In an alternative embodiment this synthetic protocol can be applied to other aniline isomers to afford substituents on alternative positions.

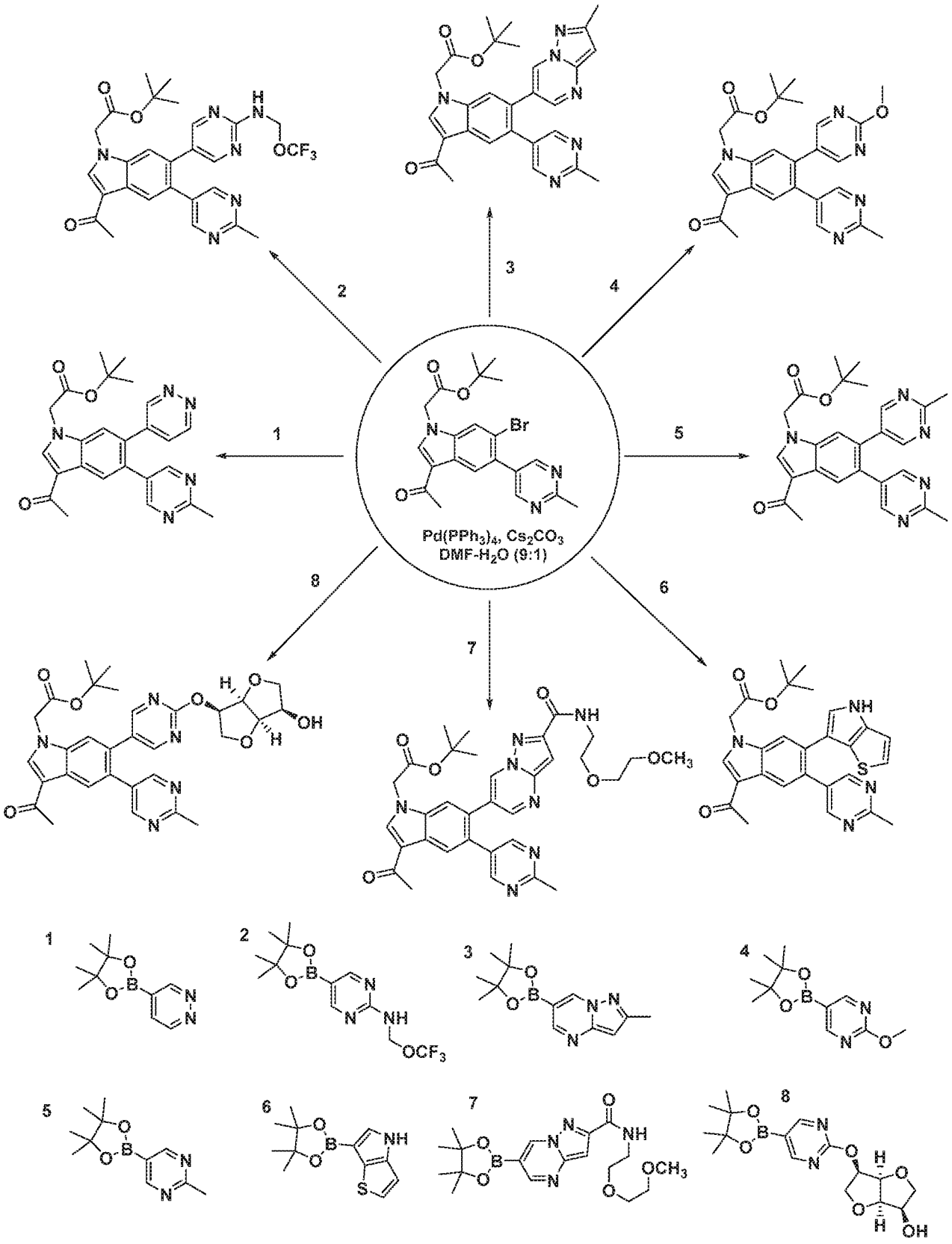


1. Thompson, A. L. S., et al. (2005). Synthesis (4): 547-550.

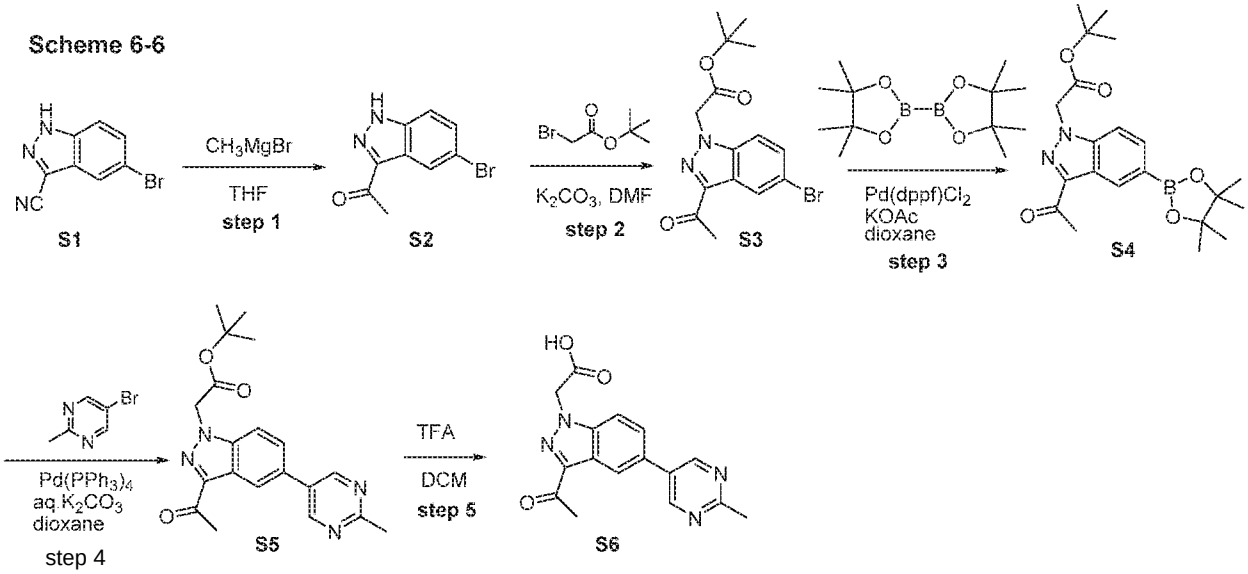
[0646] Scheme 6-4: In Step 1 the appropriately substituted indole is acylated as known in the art. In Step 2 the appropriately substituted heterocycle is subjected to a bromide species of the appropriate linker to afford the appropriately protected species. In Step 3 the appropriately substituted aryl bromide is subjected to a boronic acid to afford an aryl species. In Step 4 the appropriately substituted benzyl alcohol is deprotected in the presence of hydrogen gas and palladium to afford a free alcohol. In Step 5 the appropriately substituted phenol is subjected to a sulfonic anhydride to afford a leaving group. In Step 6 the appropriately substituted aryl species is converted to a boronic acid as known in the art. In Step 7 the appropriately substituted boronic acid is subjected to copper bromide to afford an aryl bromide species. In an alternative embodiment

this synthetic protocol can simply be applied to other indole isomers to afford substituents on alternative positions.

Scheme 6-5



[0647] Scheme 6-5: Non-limiting examples of aryl substituents are provided demonstrating the robust nature of the synthetic protocol. Boronic acids 1-8 are subjected to an appropriately substituted aryl bromide to afford an aryl system.



Step 1: l-(5-Bromo-lH-indazol-3-yl)ethanone (S2)

[0648] To a stirred solution of scheme 6-6 compound **SI** (10 g, 57.5 mmol) in THF (150 mL) under nitrogen was added methyl magnesium bromide solution (63.2 mL, 126.5 mmol) dropwise at 0 °C under N2 atmosphere. The reaction mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqeuous NH_4C1 solution and extracted with EtOAc (200 mL). The organic phase was washed with brine, dried with anhydrous Na_2S04 and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 5:1) to afford the title compound (5.1 g, 37.1 % yield) as a white solid.

Step 2: *tet* -Butyl 2-(3-acetyl-5-bromo-lH-indazol-l-yl)acetate (S3)

[0649] To a mixture of scheme 6-6 compound **S2** (5 g, 20.9 mmol) and *tert*-butyl bromoacetate (4.9 g, 25.1 mmol) in DMF (40 mL) was added K2CO3 (5.78 g, 41.8 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate (100 mL). The organic phase was washed with brine, dried with anhydrous Na_2S04 and concentrated, the residue was purified by silica gel cloumn

chromatography (eluted with petroleum ether: ethyl acetate =50:1 to 5:1) to afford the title compound (6.5g, 88.0 % yield) as a white solid.

Step 3: *tert-Butyl* 2-(3-acetyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-indazol-l-yl)acetate (S4)

[0650] A mixture of scheme 6-6 compound **S3** (5.5 g, 15.57 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (3.99 g, 18.67 mmol), KOAc (4.58 g, 46.71 mmol) in dioxane (70 mL) was degassed under N2 for three times. Pddppf (1.14 g, 1.56 mmol) was added to the mixture and the resulting mixture was degassed again and stirred at 120 °C under N2 atmosphere for 2 h. The mixture was diluted with EtOAc and washed with water and brine, dried, and concentrated to afford a residue. The crude material was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =10:1 to 1:1) to afford the title compound (3.5 g, 56.2% yield) as a white solid.

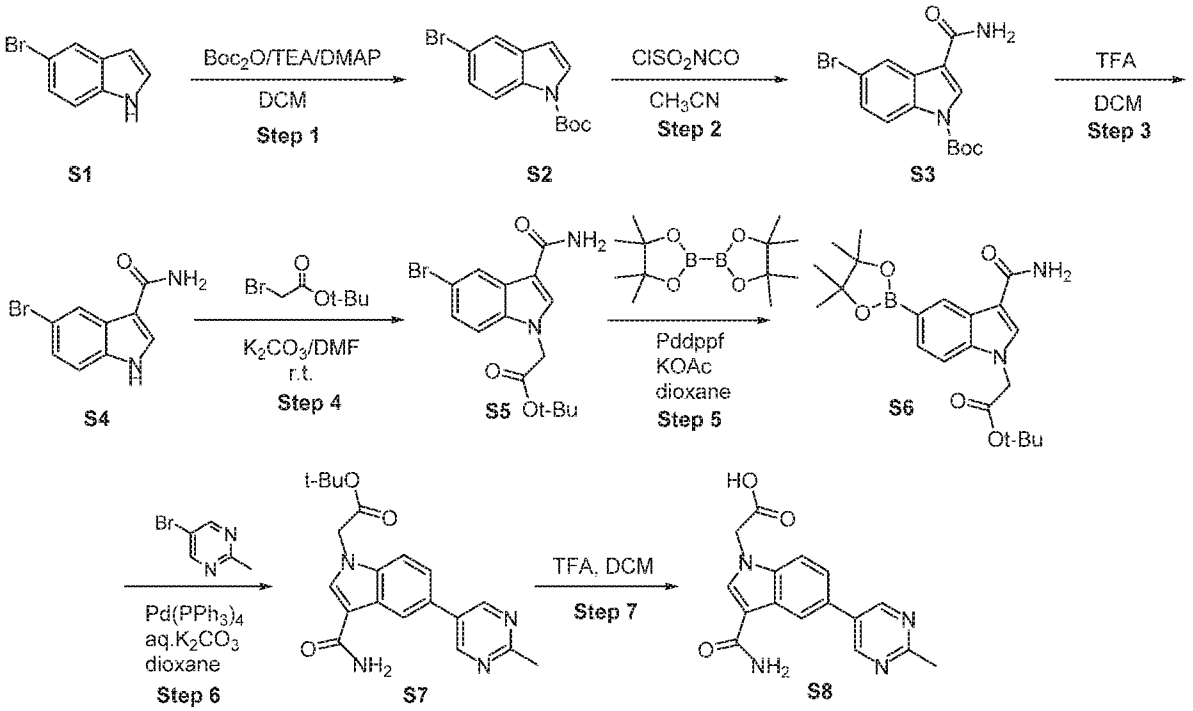
Step 4: *tert-Butyl* 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetate (S5)

[0651] The mixture of scheme 6-6 compound **S4** (3.5 g, 8.744 mmol), 5-Bromo-2-methylpyrimidine (1.666g, 9.681mmol), $Pd(PPh_3)_4$ (1 g, 0.87 mmol) and K_2C0_3 (3.63 g, 26.23 mmol) in dioxane (150 mL) and water (50 mL) was degassed under N_2 atmosphere for three times and then stirred at 100 °C for 4 h under N2 atmosphere. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2S04, filtered, and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =50: 1 to 5:1) to afford the title compound (2.4 g, 74.9% yield) as a white solid.

Step 5: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (S6)

[0652] To a solution of scheme 6-6 compound **S5** (2 g, 5.46 mmol) in DCM (20 mL) was added TFA (10 mL). The reaction was stirred at room temperature for 2 h. Then the reaction solution was concentrated to afford scheme 6-6 compound **S6** (1.6 g, 100% yield) as a yellow solid. This compound was carried forward without any further purification.

Scheme 6-7



Step 1: *tert*-Butyl 5-bromo-lH-indole-l-carboxylate (S2)

[0653] To a solution of scheme 6-7 compound **SI** (30 g, 0.15 mol) in DCM (300 mL) at 0 °C was added Et_3N (64 mL, 0.46mol) and DMAP (5.6g, 0.046 mol). This was followed by portion-wise addition of B0C2O (50 g, 0.23 mol) and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM (200 mL) and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 50: 1) to afford the title compound (44 g, 97 % yield) as a white solid. LC/MS (ESI) ***m/z:*** 240 (M-56+H)$^+$.

Step 2: *tert-Butyl* 5-bromo-3-carbamoyl-lH-indole-l-carboxylate (S3)

[0654] To a solution of scheme 6-7 compound **S2** (10 g, 33.7 mmol) in MeCN (100 mL) was added chlorosulfonyl isocyanate (3.1 mL, 35.6 mmol) dropwise at 0 °C. The reaction was stirred at room temperature overnight. Acetone (200 mL) and H2O (25 mL) was dropwise added at 0 °C, followed by dropwise addition of aqeuous KOH solution (5 mL, 10% wt). The reaction was stirred at room temperature for 30 min and extracted with EtOAc (50 mL x 2). The combined organic phases are washed with brine, dried over anhydrous Na_2S04, and then

concentrated to afford the title compound (7.4 g, 64.8% yield) as a white solid. LC/MS (ESI) *mlz:* 339 $(M+H)^+$.

Step 3: 5-Bromo-lH-indole-3-carboxamide (S4)

[0655] To a solution of scheme 6-7 compound **S3** (7.4 g, 21.8 mmol) in DCM (100 mL) was dropwise added TFA (15 mL) and the reaction was stirred at room temperature for 2 h. The reaction mixture was concentrated, and co-evaporated with toluene twice to afford the title compound (7.5 g, 100% yield) as a yellow solid, which was directly used in the next reaction without further purification. LC/MS (ESI) *mlz:* 239 $(M+H)^+$

Step 4: *tert*-Butyl 2-(5-bromo-3-carbamoyl-lH-indol-l-yl)acetate (S5)

[0656] To a mixture of scheme 6-7 compound **S4** (7.5 g, 21.8 mmol) and K2CO3 (9.04 g, 65.45 mmol) in DMF (100 mL) was added *tert*-butyl 2-bromoacetate (6.2 mL, 43.5 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was washed with petroleum ether and dried under vacuum to afford the title compound (6.7 g, 87.0%> yield) as a white solid. LC/MS (ESI) *mlz:* 353 $(M+H)^+$.

Step 5: *tert*-Butyl 2-(3-carbamoyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-indol-l-yl)a- cetate (S6)

[0657] To a solution of scheme 6-7 compound **S5** (4 g, 11.36 mmol) in dioxane (40 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (4.4 g, 17.04 mmol), KOAc (2.2 g, 22.72 mmlo), and $PdCl_2$(dppf) (416 mg, 0.568 mmol). The reaction mixture was stirred at 90 °C under N_2 for overnight. After filtration, water was added and the resulting mixture was extracted with ethyl acetate (20 mL x 3). The organic phase was washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM/ MeOH =50: 1 to 30: 1) to afford scheme 5-7 compound **S6** (4.2 g, 92.3% yield) as a white solid. LC/MS (ESI) *mlz:* 401 $(M+H)^+$.

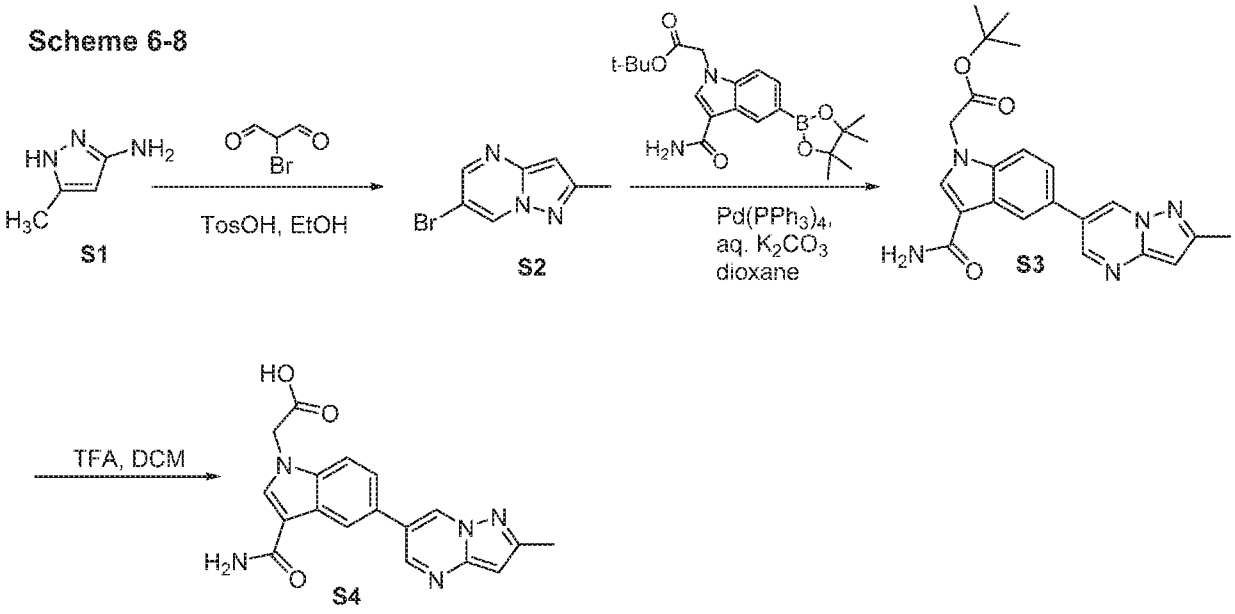
Step 6: *tert*-Butyl 2-(3-carbamoyl-5-(2-methylpyrimidin-5-yl)-lH-indol-l-yl)acetate (S7)

[0658] To a mixture of scheme 6-7 compound **S6** (2 g, 4.99 mmol) and 5-bromo-2-methyl pyrimidine (1.04 g, 5.98 mmol) in dioxane (20 mL) was added aq.K_2C03 solution (7.5 mL, 7.5 mmol,l M) and the mixture was degassed under N_2 atmosphere three times. $Pd(PPh_3)_4$ (289 mg, 0.25 mmol) was added under N_2 atmosphere and the reaction was stirred at 100 °C under N_2 atmosphere for 16 h. The reaction mixture was cooled and diluted with EtOAc, washed with water and brine, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel eluted with petroleum ether/EtOAc (10:1 to 1:1) to afford the title compound (1.49 g, 81.6% yield) as a white solid. LC/MS (ESI) *mlz:* 367 $(M+H)^+$.

Step 7: *tert*-Butyl 2-(3-carbamoyl-5-(2-methylpyrimidin-5-yl)-lH-indol-l-yl)acetate (S8)

[0659] To a solution of scheme 6-7 compound **S7** (1.49 g, 4.06 mmol) in DCM was added TFA dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness and washed with diethyl ether and dried under vacuum to afford scheme 6-7 compound **S8** (1.1 g, 87.3% yield) as a yellow solid. LC/MS (ESI) *mlz:* 311 $(M+H)^+$.

Scheme 6-8



Step 1: 6-Bromo-2-methylpyrazolo [1, 5-a] pyrimidine (S2)

[0660] To a solution of 5-methyl-lH-pyrazol-3-amine (1.0 g, 10.31 mmol) in EtOH (2 mL) was added 2-bromomalonaldehyde (1.56 g, 10.31 mmol), followed by 4-

methylbenzenesulfonic acid (91 mg, 0.52 mmol). The reaction mixture was stirred at 80 °C overnight and concentrated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/ EtOAc (50: 1 to 5:1) to afford the title compound (540 mg, 25.0 % yield); LC/MS (ESI) *mlz:* 212 $[M+H]^+$.

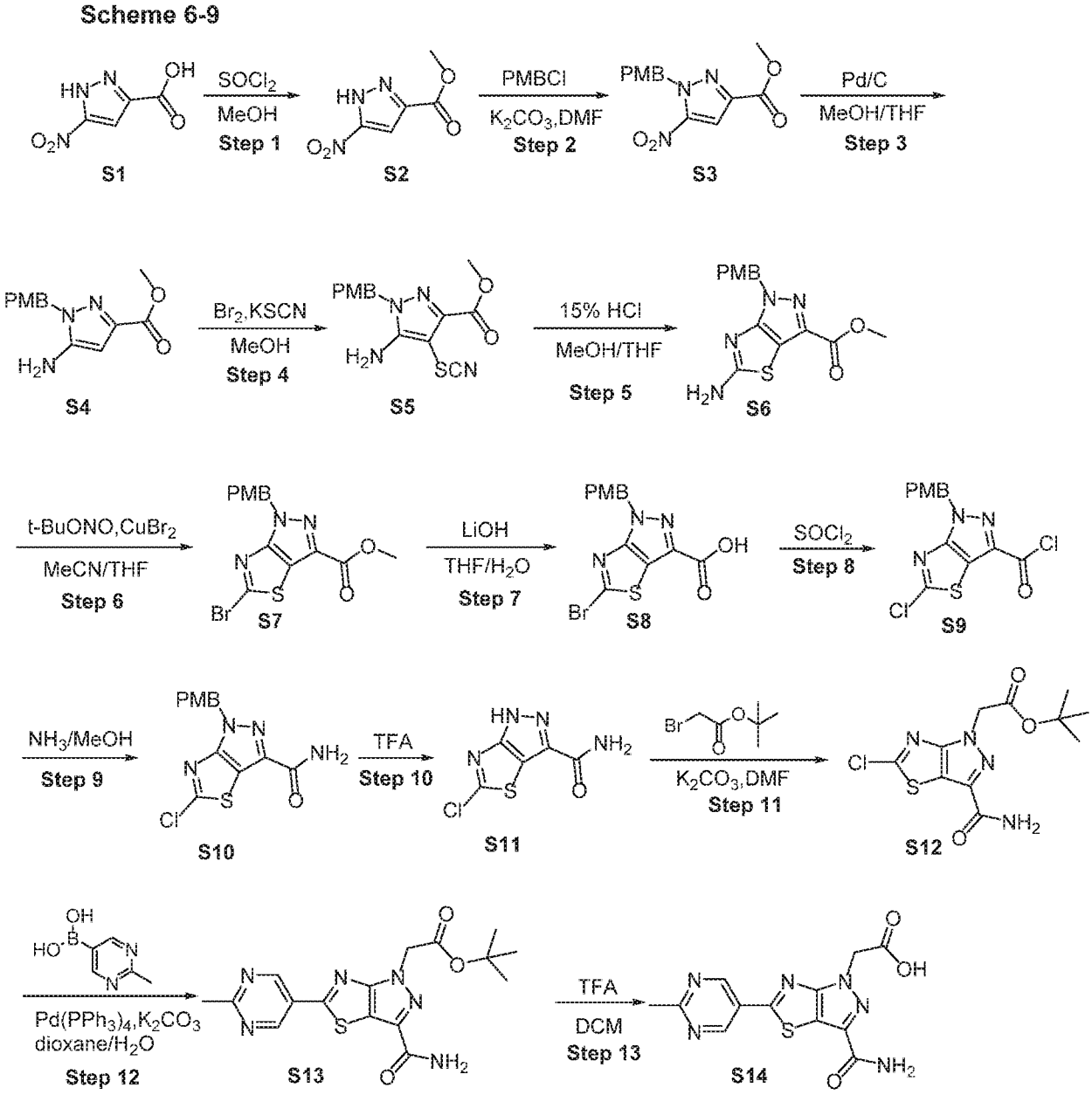
Step 2: *tert*-Butyl 2-(3-carbamoyl-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-indol-l-yl)acetate (S3)

[0661] To a mixture of scheme 6-8 compound **S2** (490 mg, 1.22 mmol) and 6-bromo-2-methylpyrazolo [1, 5-a] pyrimidine (286 mg, 1.35 mmol) in dioxane (10 mL) was added aqeuous K2CO3 solution (2 mL, 2 mmol, 1 M) and the mixture was degassed under N2 atmosphere for three times. After addition of $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) under N2 atmosphere, the reaction mixture was stirred at 100 °C under N2 atmosphere for 16 h. The reaction mixture was cooled and diluted with EtOAc. The resulting mixture was washed with water and brine, dried over anhydrous $Na2S0_4$ and concentrated to dryness. The residue was purified by column chromatography on silica gel eluted with DCM/ MeOH (100: 1 to 40: 1) to afford the title compound (290 mg, 58.6% yield) as a white solid. LC/MS (ESI) *mlz:* 406 $(M+H)^+$.

Step 3: 2-(3-Carbamoyl-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-indol-l-yl)acetic acid (S4)

[0662] To a solution of *tert*-butyl 2-(3-carbamoyl-5-(2-methylpyrazolo [1, 5-a] pyrimidin-6-yl)-lH- indol-l-yl) acetate (290 mg, 0.72 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction mixture was stirred at at room temperature for 2 h and concentrated to dryness to afford scheme 6-8 compound **S4** (240 mg, 96 % yield) as a yellow solid, which was used directly in the next step; LC-MS: LC/MS (ESI) *mlz:* 350 $[M+H]^+$.

Scheme 6-9



Step 1: Methyl 5-nitro-lH-pyrazole-3-carboxylate (S2)

[0663] To a mixture of scheme 6-9 compound **SI** (50 g, 0.318 mol) in MeOH (500 mL) was added SOCh (190 g, 1.59 mol) dropwise at 0 °C. The reaction mixture was stirred at 80 °C for 6 h and then concentrated under reduced pressure to afford the title compound (54.0 g, 98.2 % yield) as a white solid. This compound was carried forward without further purification. LC/MS (ESI) *mlz*: 170 $(M-H)^-$.

Step 2: Methyl l-(4-methoxybenzyl)-5-nitro-lH-pyrazole-3-carboxylate (S3)

[0664] To a mixture of scheme 6-9 compound **S2** (54.0 g, 0.316 mol) and K2CO3 (87.1 g, 0.63 mol) in DMF (400 mL) was added PMBC1 (59.2 g, 0.38 mol). Then the reaction mixture was stirred at 80 °C for 3 h. After cooling, the mixture was diluted with aqeuous LiCl (500 mL, 10%) and extracted with EtOAc (400 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2S0_4, filtered and concentrated. The residue was recrystallized with petroleum ether/ EtOAc (2/ 1) to afford the title compound (40.4 g, 43.9 % yield) as a yellow solid.

Step 3: Methyl 5-amino-l-(4-methoxybenzyl)-lH-pyrazole-3-carboxylate (S4)

[0665] To a mixture of scheme 6-9 compound **S9** (40.4 g, 138.8 mmol) in MeOH/THF (400 mL, 1:1) was added 10% Pd/C (4 g). The reaction mixture was stirred at room temperature overnight under a H_2 balloon. After filtration, the filtrate was concentrated to dryness to afford the title compound (33.7 g, yield 93.1 %) as yellow oil. The compound was carried forward without further purification. LC/MS (ESI) *m/z*: 262 $(M+H)^+$.

Step 4: Methyl 5-amino-l-(4-methoxybenzyl)-4-thiocyanato-lH-pyrazole-3-carboxylate (S5)

[0666] To a mixture of scheme 6-9 compound **S4** (33.7 g, 128.6 mmol) and KSCN (37.4 g, 385.9 mmol) in EtOH (300 mL) was added a solution of Br_2 (41. lg, 257.2 mmol) in EtOH (200 mL) dropwise to maintain the internal temperature below 0 °C under N2 atmosphere. Then the reaction mixture was stirred at 0 °C for 16 h. The mixture was basified with aqeuous Na_2C0_3 solution to pH=9 at 0 °C and extracted with EtOAc (400 ml x2). The combined organic phases were dried over anhydrous Na_2S0_4 and concentrated. The residue was recrystallized with THF/petroleum ether (1/ 1) to afford the title compound (23.0 g, 55.9 % yield) as a white solid. LC/MS (ESI) *m/z:* 319 $(M+H)^+$.

Step 5: Methyl 5-amino-l-(4-methoxybenzyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxylate (S6)

[0667] To a mixture of scheme 6-9 compound **S5** (23.0 g, 72.1 mmol) in EtOH (160 mL) and H2O (108 mL) was added cone. HC1 (60 mL). The reaction was stirred at 90 °C for 2 h and concentrated under reduced pressure. The residue was recrystallized with EtOAc/ petroleum

ether (1/ 2) to afford the title compound (12.2 g, yield 53. 1 %) as a white solid. LC/MS (ESI) *mlz:* 319 $(M+H)^+$.

Step 6: Methyl 5-bromo-l-(4-methoxybenzyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxylate (S7)

[0668] To a mixture of scheme 6-9 compound **S6** (12.2 g, 38.3 mmol) and $CuBr_2$ (17.2 g, 76.6 mmol) in dry MeCN/THF (175 mL, 1:4) was added t-BuONO (5.92 g, 57.45 mmol) at 0 °C under N_2 atmosphere dropwise. After stirring for 1 h at 0 °C, the resulting mixture was quenched with aqeuous Na_2S_20 3(150 mL, 5%) and extracted with DCM (80 mL x 2). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =30: 1 to 10: 1) to afford the title compound (4.59 g, 31.4 % yield) as yellow oil. LC/MS (ESI) *mlz:* 382 $(M+H)^+$.

Step7: 5-Bromo-l-(4-methoxybenzyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxylic acid (S8)

[0669] To a mixture of scheme 6-9 compound **S7** (4.59 g, 12.0 mmol) in THF/ H_20 (50 mL, 4:1, v/v) was added $LiOH·H_2O$ (1.01 g, 24.0 mmol). The reaction mixture was stirred at room temperature for 1 h and then acidified with aqeuous HC1 solution (1 M) to pH=5. The mixture was extracted with DCM/MeOH (30 mL x 2, 20: 1, v/ v). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford the title compound (4.04 g, 91.5 % yield) as a white solid.LC/MS (ESI) *mlz:* 368 $(M+H)^+$.

Step 8: 5-Chloro-l-(4-methoxybenzyl)-lH-pyrazolo[3,4-d]thiazole-3-carbonyl chloride (S9)

[0670] A solution of scheme 6-9 compound S8 (4.04 g, 10.98 mmol) in SOCI2 (30 mL) was stirred at 70 °C for 4 h. After cooling, the mixture was concentrated to dryness and the residue was co-evaporated with toluene twice to afford the title compound (3.75 g, 100% yield) as yellow oil. The compound was carried forward without further purification.

Step 9: 5-Chloro-l-(4-methoxybenzyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxamide (S10)

[0671] To a solution of scheme 6-9 compound **S9** (3.75 g, 10.97 mmol) in dry THF (25 mL) at 0 °C was added NH3/MeOH solution (2 M, 15 mL) dropwise. The reaction mixture was

stirred at 0 °C for 30 min and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =15:1 to 3:1) to afford the title compound (3.25 g, 92.1 % yield) as a white solid. LC/MS (ESI) *mlz:* 323 $(M+H)^+$.

Step 10: 5-Chloro-lH-pyrazolo[3,4-d]thiazole-3-carboxamide (11)

[0672] A solution of scheme 6-9 compound **S10** (3.25 g, 10.1 mmol) in TFA (30 mL) was stirred at 70 °C for 4 h. The mixture was concentrated to dryness and the residue was co-evaporated with toluene twice, dried under vacuum to afford the title compound (3.03 g, 94.9 % yield) as a brown solid. The compound was carried forward without further purification. LC/MS (ESI) *mlz:* 203 $(M+H)^+$.

Step 11: *tert*-Butyl 2-(3-carbamoyl-5-chloro-lH-pyrazolo[3,4-d]thiazol-l-yl)acetate (S12)

[0673] To a mixture of scheme 6-9 compound **Sll** (3.03 g, 9.59 mmol) and K2CO3 (3.97 g, 28.77 mmol) in DMF (30 mL) was added *tert*-butyl bromoacetate (2.62 g, 13.43 mmol.). The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with 10% aq.LiCl solution and brine successively, dried over anhydrous Na_2S04, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =10:1 to 3:1) to afford the title compound (2.01 g, 66.2 % yield) as a yellow solid. LC/MS (ESI) *mlz:* 317 $(M+H)^+$.

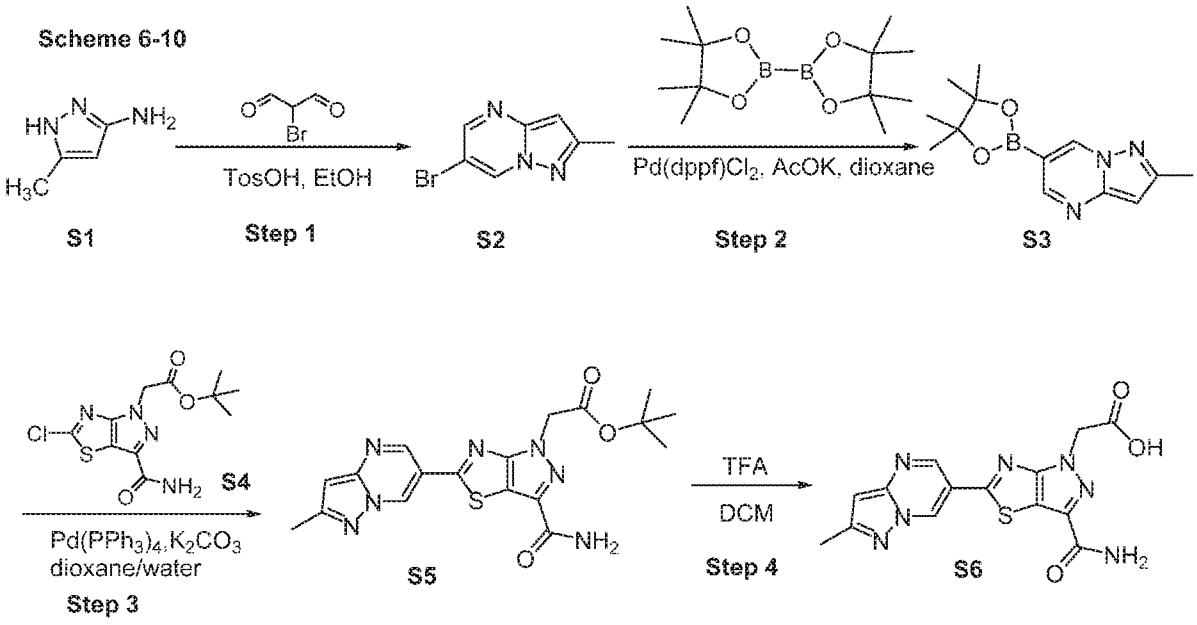
Step 12: *tert*-Butyl 2-(3-carbamoyl-5-(2-methylpyrimidin-5-yl)-lH-pyrazolo[3,4-d]thiazol-l-yl)acetate (S13)

[0674] To a mixture of scheme 6-9 compound **S12** (300 mg, 0.84 mmol) and K2CO3 (292 mg, 2.1 mmol) in dioxane/LbO (10 mL, 9:1) was added 2-methylpyrimidin-5-ylboronic acid (138 mg, 1 mmol.) and $Pd(PPh_3)_4$ (100 mg, 0.08 mmol). The reaction was degassed under N2 three times and stirred at 90 °C for 4 h under N2 atmosphere. After cooling, the mixture was diluted with saturated aqeuous NaHCCb (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM: MeOH=50: 1 to 20: 1) to afford the title compound (121 mg, 38.4 % yield) as a white solid. LC/MS (ESI) *mlz:* 375 $(M+H)^+$.

Step 13: 2-(3-Carbamoyl-5-(2-methylpyrimidin-5-yl)-lH-pyrazolo[3,4-d]thiazol-l-yl)acetic acid (S14)

[0675] To a mixture of scheme 6-9 compound **S13** (121 mg, 0.32 mmol) in DCM (2 mL) was added TFA (1 mL) and the reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to afford compound **S14** (130 mg, 100% yield) as a brown solid. The compound was carried forward without further purification. LC/MS (ESI) *mlz:* 319 $(M+H)^+$.

Scheme 6-10



Step 1: 6-Bromo-2-methylpyrazolo[l,5-a]pyrimidine (S2)

[0676] To a mixture of 5-methyl-lH-pyrazol-3-amine (6.43 g, 0.066 mol) in EtOH (40 mL) in the presence of 4-methylbenzenesulfonic acid (0.63 g, 3.0 mmol) was added 2-bromomalonaldehyde (10.0 g, 0.066 mol). The reaction mixture was stirred at 80 °C overnight under a N_2 atmosphere and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ EtOAc (100: lto 10: 1) to afford the title compound (3.0 g, 21.4 % yield). LC/MS (ESI) *mlz:* 212 $(M+H)^+$.

Step 2: 2-Methyl-6-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrazolo[l,5-a]pyrimidine (S3)

[0677] A round-bottom flask was charged with 6-bromo-2-methylpyrazolo [1, 5-a] pyrimidine (2.97 g, 14.08 mmol), 4, 4, 4', 4', 5, 5, 5', 5'-octamethyl-2, 2'-bi(l, 3, 2-dioxaborolane) (4.29 g, 16.89 mmol), AcOK (4. 14 g, 42.23 mmol), Pd(dppf)Cl_2 (0.52 g, 0.70 mmol) and 1, 4-dioxane (40 mL). The reaction mixture was stirred at 85 °C for 2 h under N_2 atmosphere. After dilution with with EtOAc, the resulting mixture was washed with water and brine, dried over anhydrous Na_2S04 and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ EtOAc=100: 1 to 5: 1) to afford the title compound (3.05 g, 83.7 % yield) as a white solid. LC/MS (ESI) *mlz:* 260 $(M+H)^+$.

Step 3: ***tert*-Butyl 2-(3-carbamoyl-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-pyrazolo [3,4-d] thiazol- l-yl)acetate** (S5)

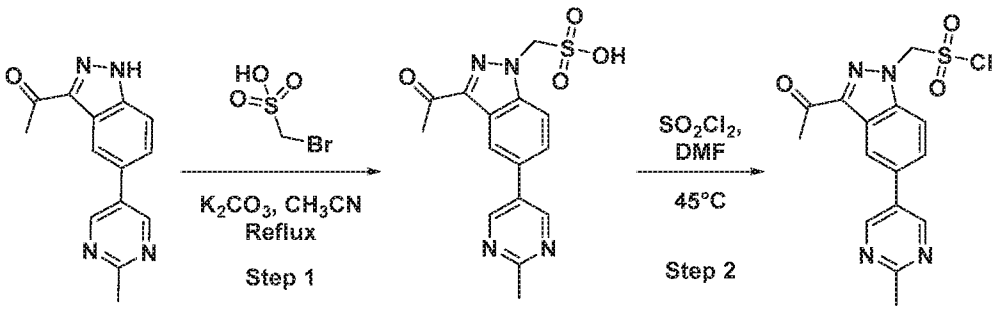
[0678] To a mixture of scheme 6-9 compound S3 (230 mg, 0.88 mmol) and **K2CO3** (276 mg, 2 mmol) in dioxane/H_20 (15 mL, 4:1) was added *tert*-butyl 2-(3 -carbamoyl-5-chloro-lH-pyrazolo[3,4-d]thiazol-l-yl)acetate (253 mg, 0.8 mmol.) and Pd$(PPh_3)_4$ (93 mg, 0.08 mmol). The mixture was degassed under **N2** atmosphere for three times and stirred at 95 °C for 5 h under **N2** atmosphere. After dilution with saturated aqeuous NaHCCb (10 mL), the mixture was extracted with EtOAc (20 mL x 2). The combined organic phases were washed with brine, dried over anhydrous Na_2S0_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: EtOAc =20: 1 to 3: 1) to afford the title compound (211 mg, 63.7 % yield) as a white solid. LC/MS (ESI) *mlz:* 414 $(M+H)^+$.

Step 4: **2-(3-Carbamoyl-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-pyrazolo [3,4-d]thiazol-l-yl)acetic acid** (S6)

[0679] To a mixture of scheme 6-9 compound S4 (140 mg, 0.34 mmol) in DCM (3 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to afford scheme 6-9 compound S6 (142 mg, 100% yield) as a brown solid. The compound was carried forward without further purification. LC/MS (ESI) *mlz:* 358 $(M+H)^+$.

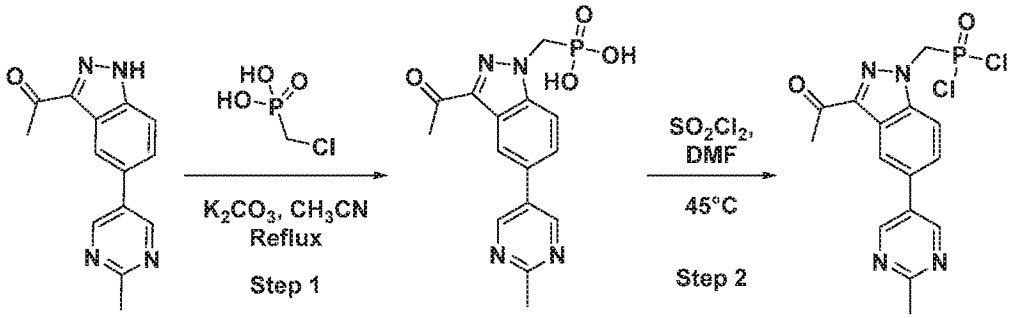
EXAMPLE 7. SYNTHESIS OF L3-A MOIETIES

Scheme 7-1



[0680] Scheme 7-1: In Step 1 the appropriately substituted aryl compound is subjected to a bromide to afford a sulfonic acid substituted species. In Step 2 the appropriately substituted sulfonic acid species is chlorinated as known in the art.

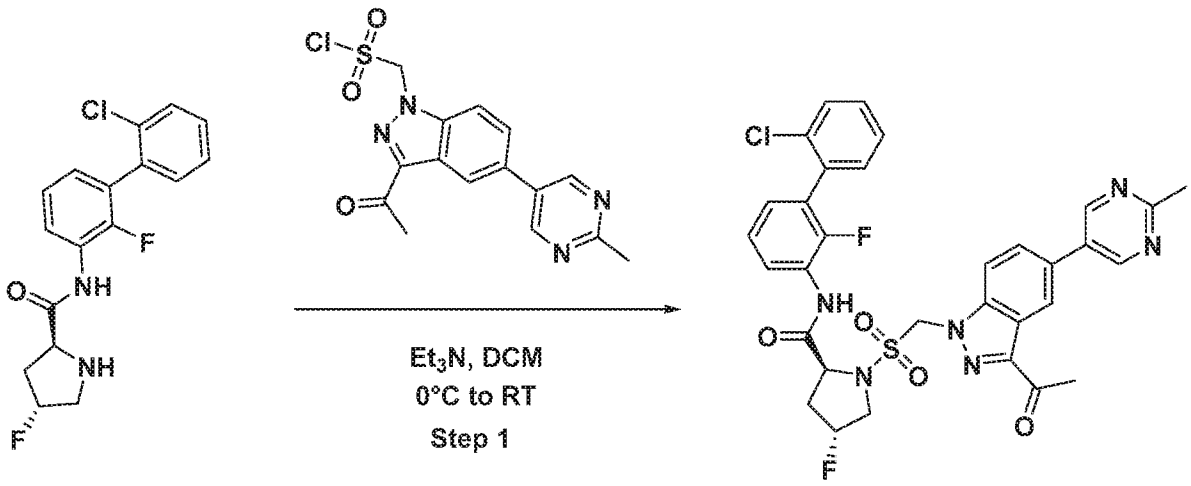
Scheme 7-2



[0681] Scheme 7-2: In Step 1 the appropriately substituted aryl compound is subjected to a chloride to afford a phosphonic acid substituted species. In Step 2 the appropriately substituted phosphonic acid species is chlorinated as known in the art.

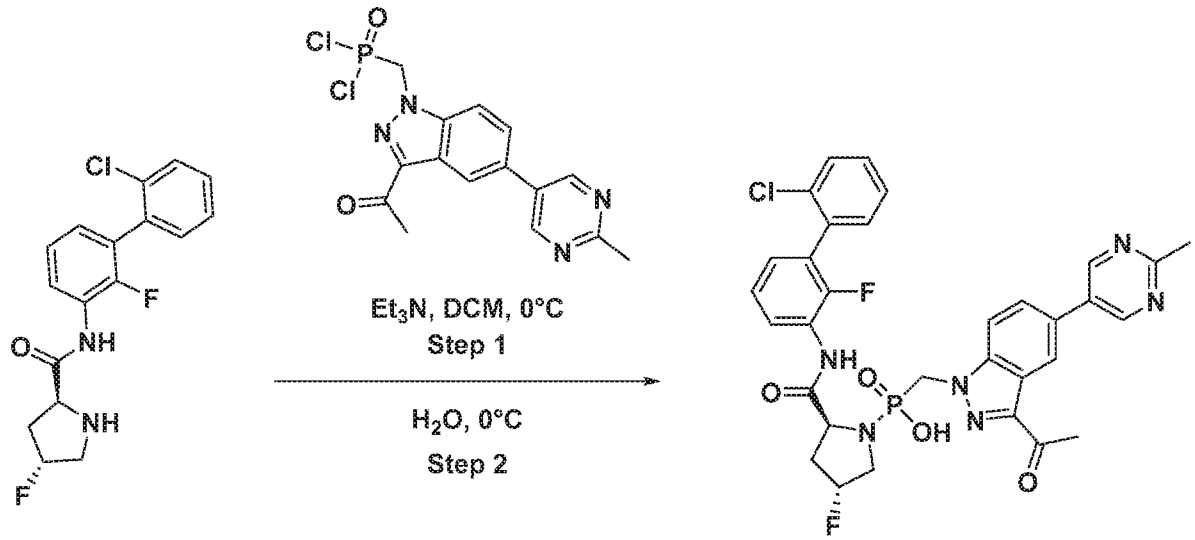
EXAMPLE 8. COUPLING OF L3-A TO C-L-B

Scheme 8-1



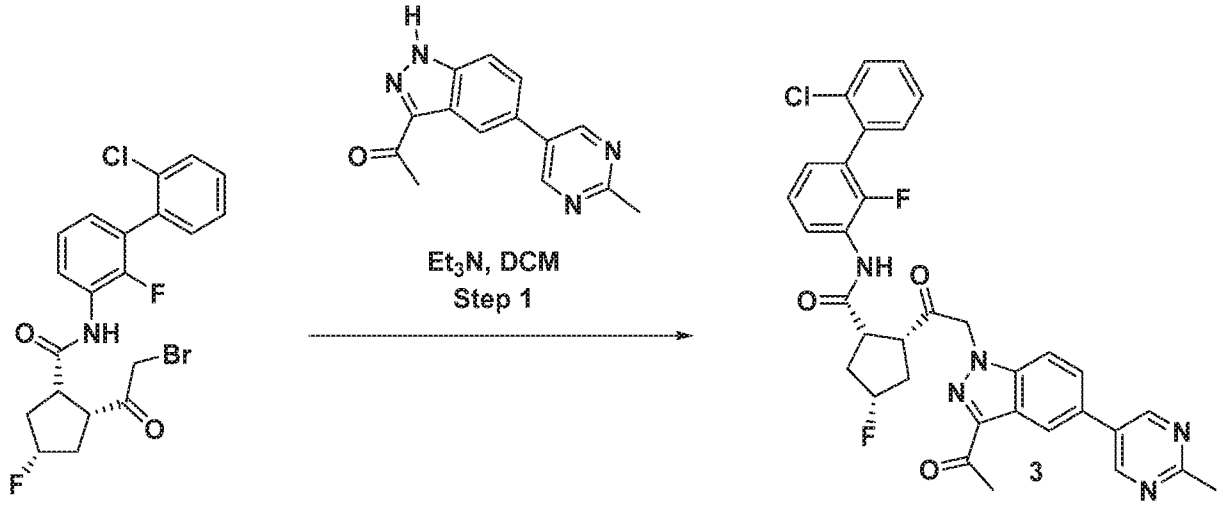
[0682] Scheme 8-1: In Step 1 the appropriately substituted amine is subjected to a sulfonyl chloride which can be prepared as described in Scheme 7-1 to afford a compound of Formula I.

Scheme 8-2



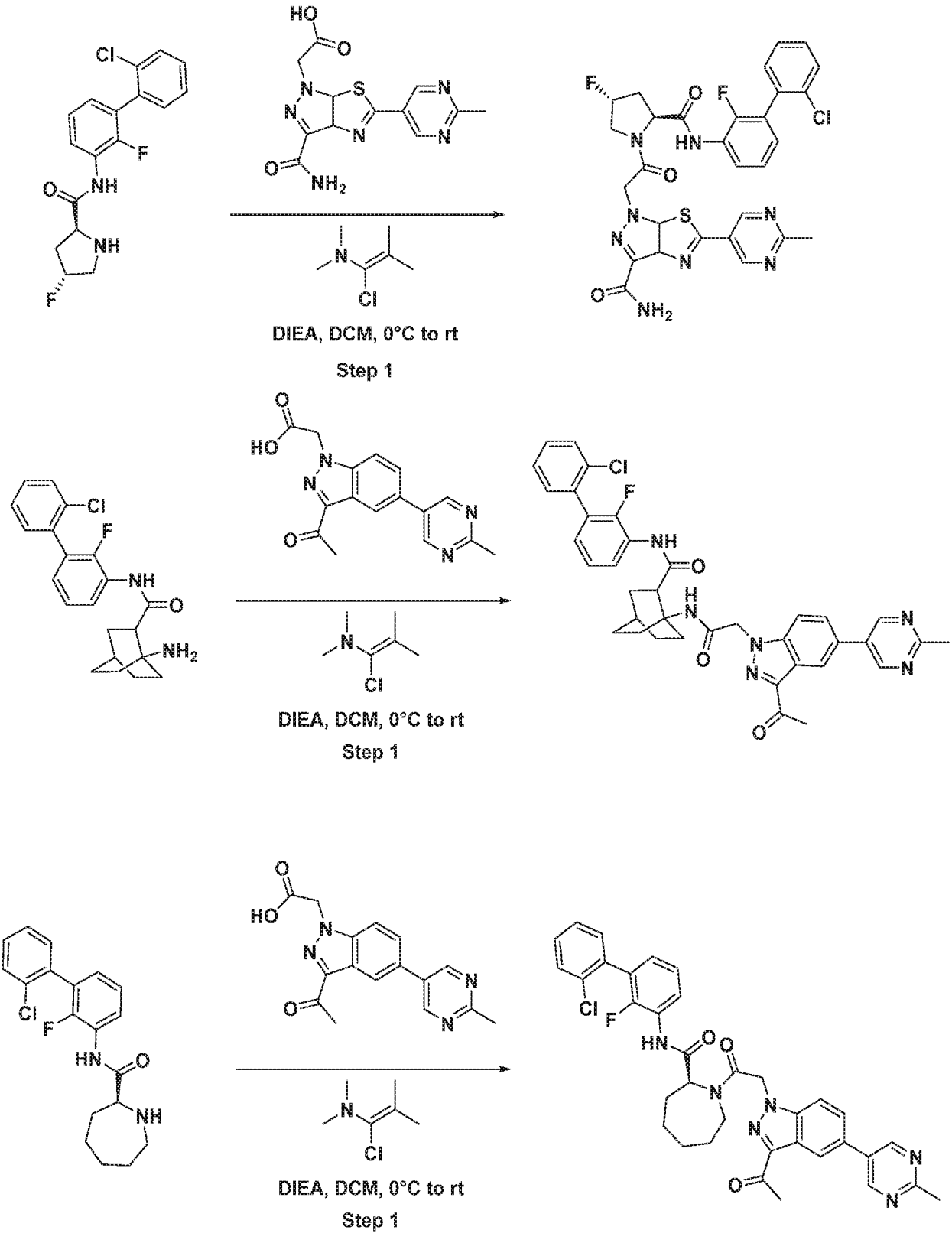
[0683] Scheme 8-2: In Step 1 the appropriately substituted amine is subjected to a phosphonic dichloride which can be prepared as described in Scheme 7-2 followed by a subsequent quench with water to afford a compound of Formula I.

Scheme 8-3

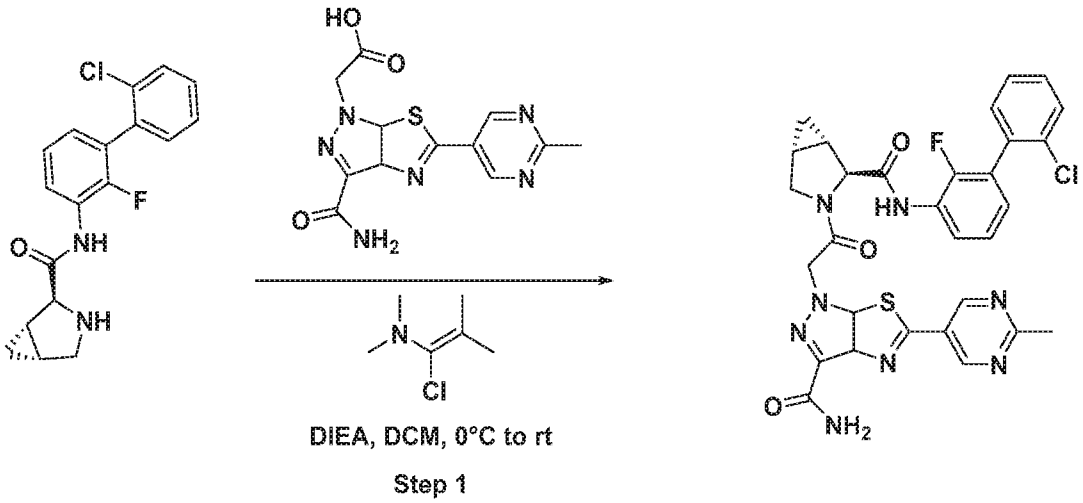


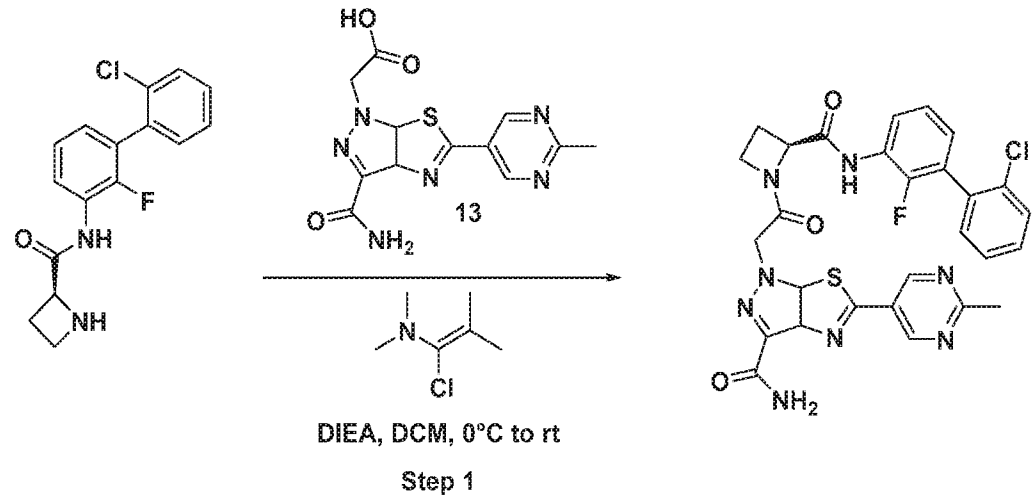
[0684] Scheme 8-3: In Step 1 the appropriately substituted bromide is subjected to a heteroaryl species to afford a compound of Formula I.

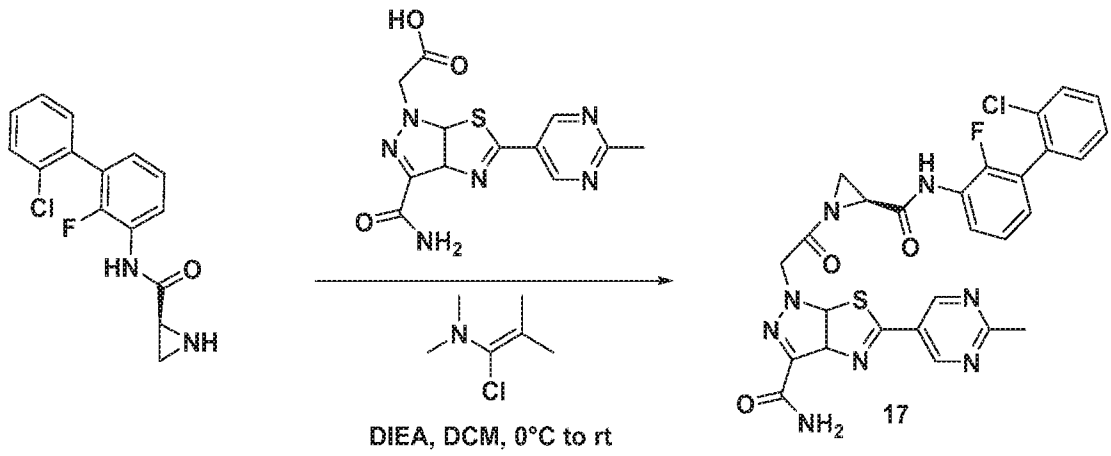
Scheme 8-4


DIEA, DCM, 0°C to rt
Step 1
DIEA, DCM, 0°C to rt
Step 1
DIEA, DCM, 0°C to rt
Step 1

Scheme 8-4 cont.

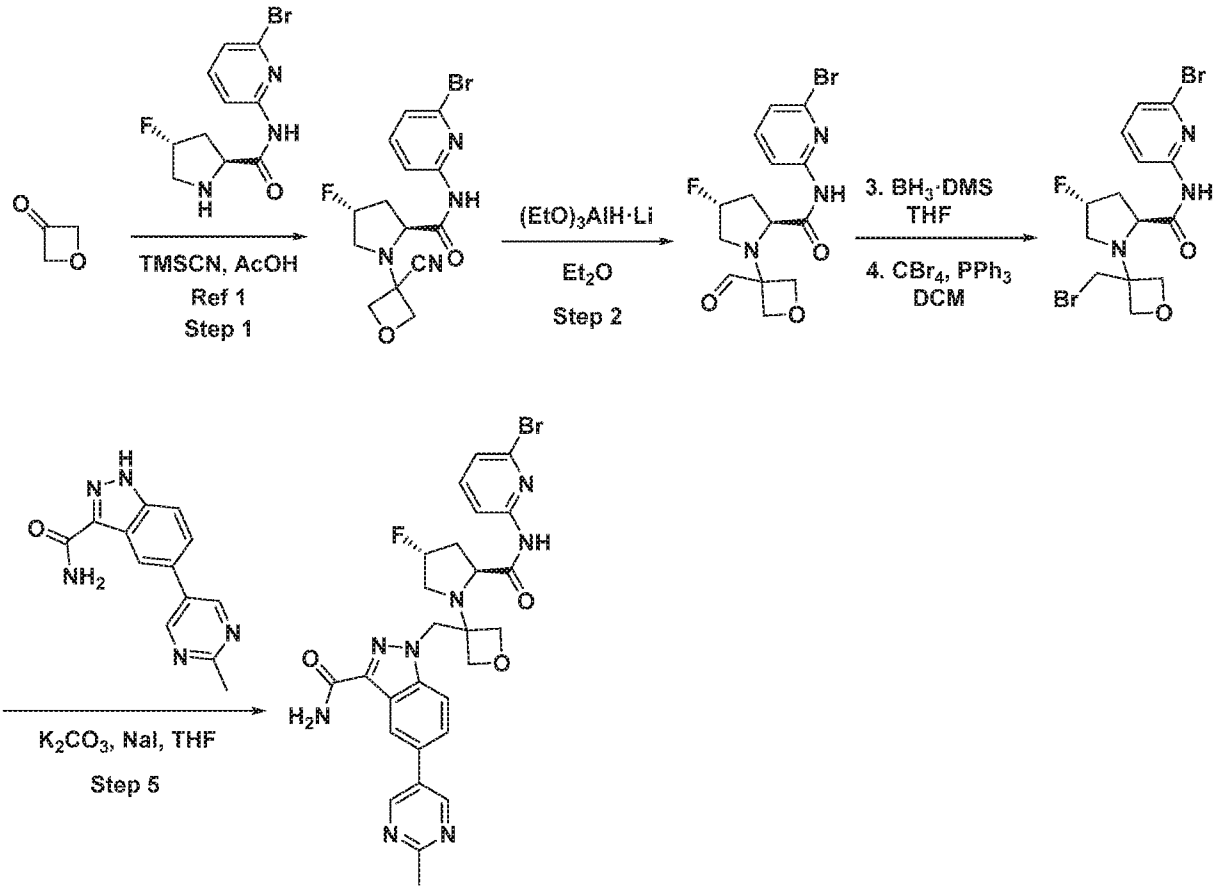






[0685] Scheme 8-4: In Step 1 the appropriately substituted carboxylic acid is coupled to the appropriately substituted amine as known in the art to form a compound of Formula I.

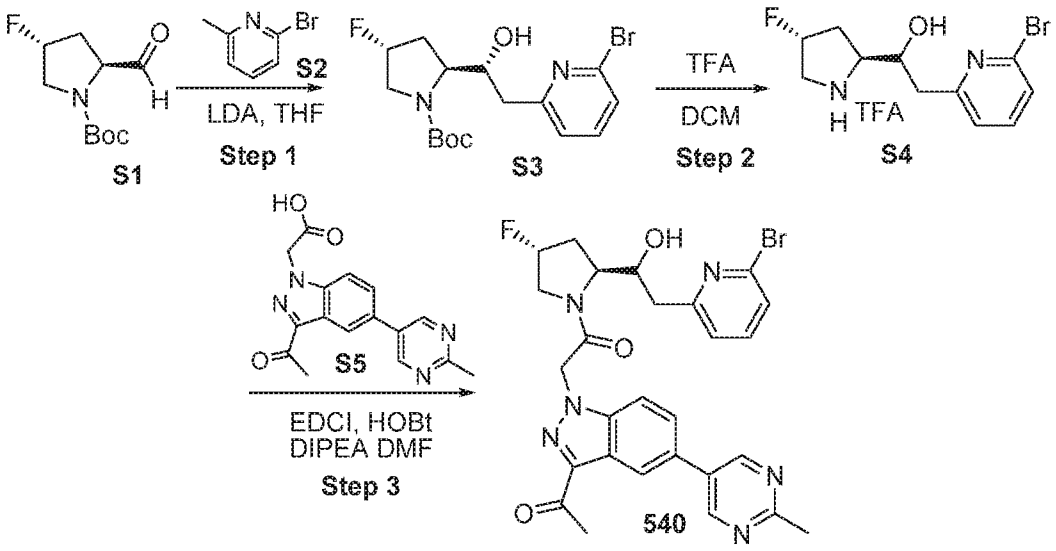
Scheme 8-5



1. Wuitsehik, Georg. Thesis, http://dx.doi.org/10.3929/eihz-a-005697432, ETH (2008)

[0686] Scheme 8-5: In Step 1 the appropriately substituted oxetane is subjected to conditions known in the art to form an amino/cyano substituted species. In Step 2 the appropriately substituted cyano species is reduced as known in the art to afford an aldehyde. In Step 3 the appropriately substituted aldehyde is reduced with borane to afford an alcohol. In Step 4 the appropriately substituted alcohol is converted to a bromide as known in the art. In Step 5 the appropriately substituted bromide is subjected to a heteroaryl species as known in the art to afford a compound of Formula I.

Scheme 8-6



Step 1: (2S,4R)-tert-Butyl 2-((R)-2-(6-bromopyridin-2-yl)-l-hydroxyethyl)-4-fluoropyrrolidine-l-carboxylate (S3)

[0687] To a stirred solution of 2-bromo-6-methylpyridine (800 mg, 4.60 mmol) in THF (30 mL) under nitrogen was added LDA (5.1 mL, 5.1 mmol) dropwise at -70 °C. The reaction was stirred at -70 °C for 30 min. A solution of scheme 8-6 compound **SI** (1 g, 4.60 mmol) in THF (5 mL) was added to the mixture dropwise for 30 min and the reaction was stirred at -70 °C for another 1 h. The reaction was quenched with aq.NH4Cl solution (20 mL) and the mixture was extracted with EtOAc twice. The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel cloumn chromatography (eluted with petroleum ether: ethyl acetate =20:1 to 10:1) to afford the title compound (300 mg, 17 % yield) as a white solid.

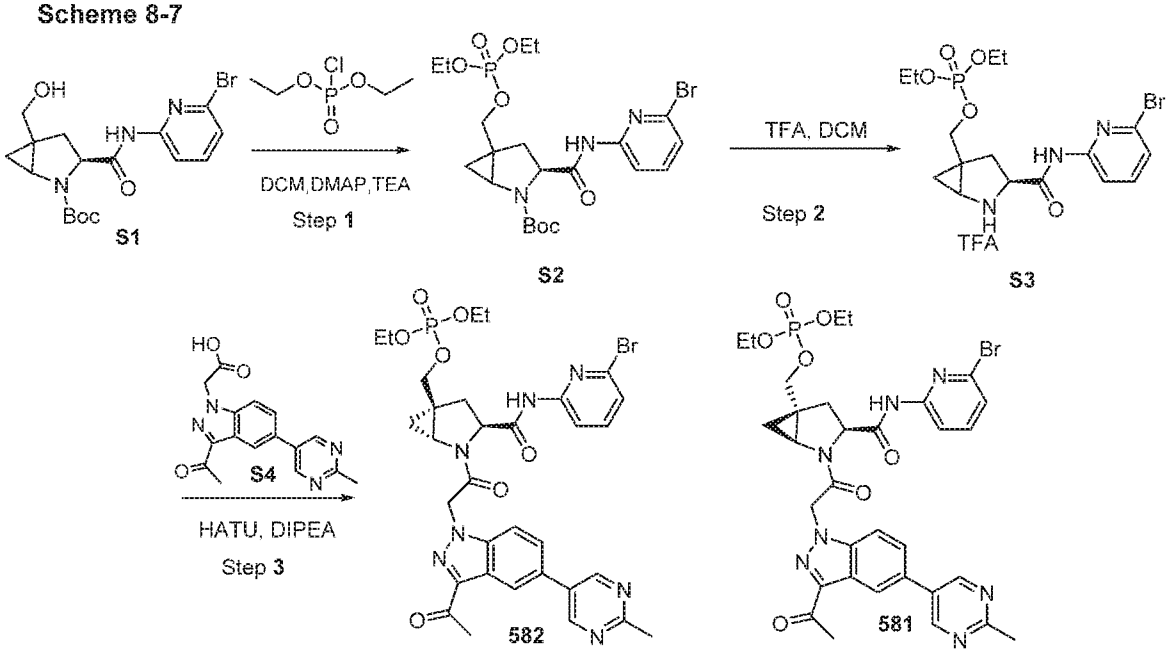
Step 2: (R)-2-(6-Bromopyridin-2-yl)-l-((2S,4R)-4-fluoropyrrolidin-2-yl)ethanol (S4)

[0688] To a solution of scheme 8-6 compound **S3** (120 mg, 0.311 mmol) in DCM (2 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to afford scheme 8-6 compound **S4** (110 mg, 100 % yield) as a yellow solid. The compound was carried forward without further purification.

Step 3: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-((R)-2-(6-bromopyridin-2-yl)-l-hydroxyethyl)-4-fluoropyrrolidin-l-yl)ethanone (540)

[0689] To a mixture of scheme 8-6 compound **S4** (90 mg, 0.23 mmol), scheme 8-6 compound **S5** (80 mg, 0.25 mmol) and DIPEA (150 mg, 1.165 mmol) in DMF (2 mL) was added EDCI (98 mg, 0.51 mmol) and HOBt (70 mg, 0.513mmol). The resulting mixture was stirred at room temperature overnight. The mixture was diluted with water and extracted with EtOAc twice. The combined organic phases were washed with 10% aqeuous LiCl solution and brine successively, dried over anhydrous $Na_2SC"4$ and concentrated. The residue was purified with preparative HPLC to afford the title compound (20 mg, 15 % yield) as a white solid. ¾ NMR (400 MHz, DMSO-d_6) δ 9.06 - 9.03 (m, 1H), 9.00 (dd, *J* = 9.6, 3.8 Hz, 1H), 8.44 (t, *J* = 5.9 Hz, 1H), 7.99 - 7.74 (m, 2H), 7.66 - 7.53 (m, 1H), 7.52 - 7.39 (m, 1H), 7.26 (dd, *J* = 16.0, 7.5 Hz, 1H), 5.83 - 5.70 (m, 1H), 5.60 (dd, *J* = 34.2, 16.1 Hz, 1H), 5.41 (t, *J* = 20.1 Hz, 1H), 5.06 (d, *J* = 60.6 Hz, 1H), 4.44 (dt, *J* = 10.7, 9.8 Hz, 1H), 4.36 - 4.04 (m, 2H), 3.85 - 3.53 (m, 1H), 2.68 (d, *J* = 4.2 Hz, 3H), 2.65 (d, *J* = 2.5 Hz, 3H), 2.33 (dd, *J* = 6.4, 4.6 Hz, 1H), 2.21 (dd, *J* = 19.0, 12.6 Hz, 1H), 2.00 (d, *J* = 57.5 Hz, 1H), 1.26 - 0.96 (m, 1H). LC/MS (ESI) *m/z:* 581 $(M+H)^+$.

Scheme 8-7



Step 1: (lR,3S,5S)-tert-Butyl 3-((6-bromopyridin-2-yl)carbamoyl)-5-(((diethoxyphosphoryl)oxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (S2)

[0690] To a solution of scheme 8-7 compound **SI** (120 mg, 0.29 mmol) in THF (5 mL) was added TEA (100 mg, 1 mmol) and DMAP (12 mg, 0.1 mmol). This was followed by dropwise addition of diethyl phosphorochloridate (78 mg, 0.45 mmol) at 0 °C under **N2** atmosphere. The reaction was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and washed with 10% aq.NaHCCb solution and brine. The organic layer was washed with brine, dried over anhydrous Na_2S04, and concentrated under reduced pressure. The crude product was purified by silica gel cloumn chromatography eluted with (DCM / MeOH= 100: 1 to 30: 1) to afford the title compound (40 mg, 25% yield) as a white solid. LC/MS (ESI) *mlz:* 548 $(M+H)^+$.

Step 2: (3S)-terf-Butyl 3-(6-bromopyridin-2-ylcarbamoyl)-5-((diethoxyphosphoryloxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (S3)

[0691] To a solution of scheme 8-7 compound **S2** (40 mg, 0.07 mmol) in DCM (1 mL) was added TFA (0.5 mL). The reaction was stirred at room temperature for 1.5 h and concentrated to afford the title compound (50 mg, 100% yield) as a grey solid. LC/MS (ESI) *mlz:* 448 $(M+H)^+$.

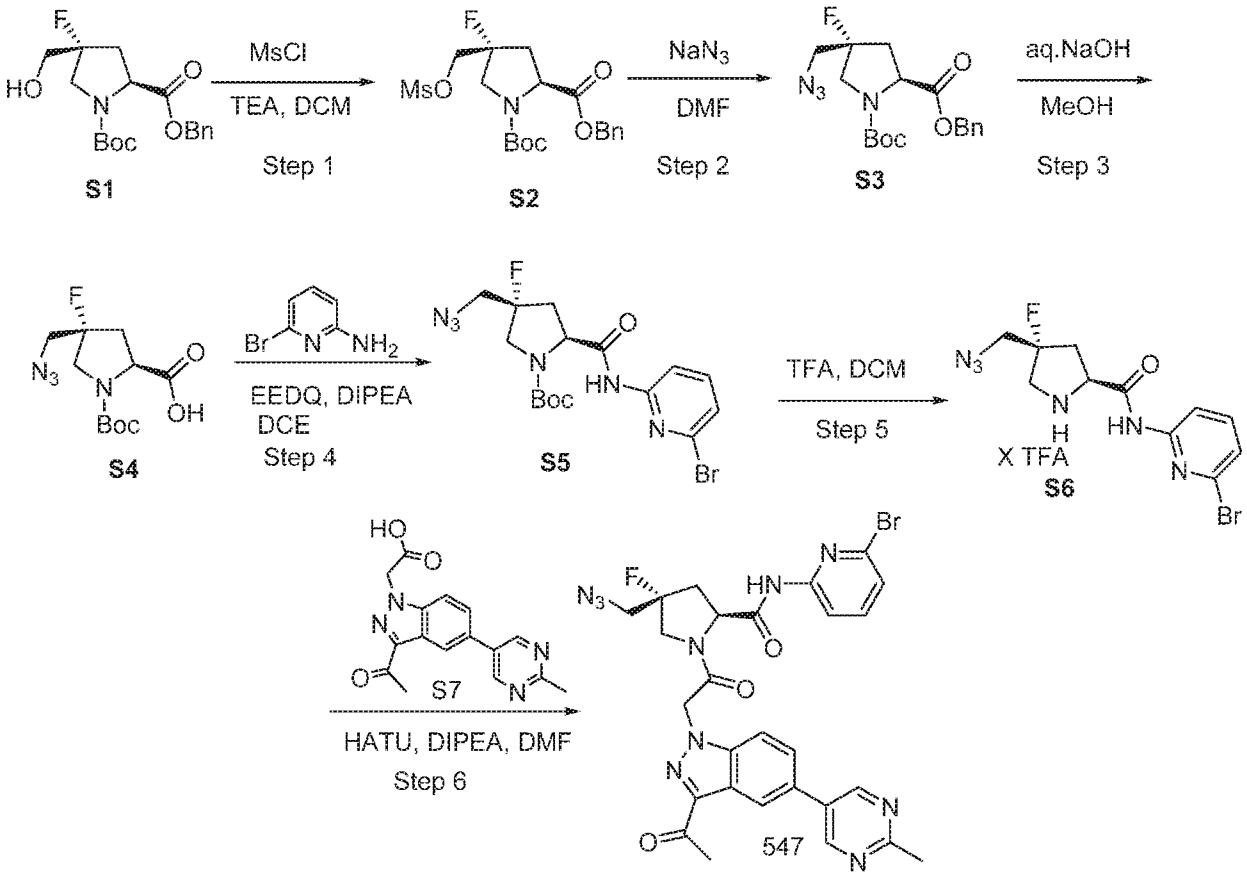
Step 3: ((lR,3S,5S)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-3-(6-bromopyridin-2-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate (582) & ((lS,3S,5R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-3-(6-bromopyridin-2-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate (581)

[0692] To a solution of the scheme 8-7 compound **S3** (50 mg, 0.07 mmol), scheme 8-7 compound **S4** (28 mg, 0.09 mmol) and HATU (50 mg, 0.13 mmol) in DMF (2 mL) was added DIPEA (30 mg, 0.23 mmol). The reaction was stirred at room temperature for 16 h. The mixture was partitioned with EtOAc and water. The organic layer was washed with brine, dried over anhydrous Na_2S0_4 and concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford **582** (4.5 mg, 8.68% yield) and **581** (2 mg, 3.8% yield) as a white solid.

[0693] **582:** ¾ NMR (400 MHz, CD3OD) δ 9.03 (d, *J* = 14.3 Hz, 2H), 8.56 (s, 1H), 8.09 (d, *J* = 5.1 Hz, 1H), 7.77 (d, *J* = 41.4 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 5.85 (d, *J* = 17.2 Hz, 1H), 5.68 (d, *J* = 17.2 Hz, 1H), 4.63 (s, 1H), 4.24 (dd, *J* = 11.0, 7.1 Hz, 1H), 4.18 - 3.98 (m, 5H), 3.84 (dd, *J* = 5.7, 2.7 Hz, 1H), 2.80 - 2.62 (m, 6H), 2.62 - 2.46 (m, 2H), 1.42 - 1.20 (m, 8H). LC/MS (ESI) *mlz:* 740 $(M+H)^+$.

[0694] **581:** ¾ NMR (400 MHz, CD3OD) δ 9.06 - 8.97 (m, 2H), 8.53 (d, *J* = 15.5 Hz, 1H), 8.05 (dd, *J* = 16.9, 7.6 Hz, 1H), 7.84 - 7.65 (m, 2H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 5.83 (d, *J* = 17.1 Hz, 1H), 5.72 - 5.59 (m, 1H), 5.03 (d, *J* = 7.8 Hz, 1H), 4.29 - 4.08 (m, 6H), 3.96 - 3.85 (m, 1H), 2.87 - 2.65 (m, 6H), 2.26 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.64 (dd, *J* = 6.0, 2.8 Hz, 1H), 1.34 (dt, *J* = 26.0, 9.4 Hz, 7H), 1.21 (t, *J* = 5.7 Hz, 1H). LC/MS (ESI) *mlz:* 740 $(M+H)^+$.

Scheme 8-8



Step 1: (2S,4R)-4-Azidomethyl-4-fluoro-pyrrolidine-l,2-dicarboxylic acid 2-benzyl ester 1-*tert*-butyl ester (S2)

[0695] A solution of MsCl (371 mg, 3.2 mmol) in DCM (2 mL) and TEA (0.75 mL, 5.4 mmol) was added to (2S,4R)-4-fluoro-4-hydroxymethyl-pyrrolidine-l,2-dicarboxylic acid 2-benzyl ester 1-*ter**t*-butyl ester (scheme 8-8 compound **SI,** 950 mg, 2.7 mmol) in DCM (10 mL) at 0 °C. Then the reaction was stirred at room temperature for 1 h. The mixture was poured into ice water (30 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2S0_4 and concentrated under reduced pressure to afford scheme 8-8 compound **S2** (1.0 g, crude). The compound was carried forward without further purification.

Step 2: (2S,4R)-2-Benzyl *1-tert-butyl* 4-(azidomethyl)-4-fluoropyrrolidine -1,2-dicarboxylate (S3)

[0696] To a solution of (2S,4R)-4-azidomethyl-4-fluoro-pyrrolidine-l,2-dicarboxylic acid 2-benzyl ester 1-*ter**t*-butyl ester (scheme 8-8 compound **S2,** 950 mg, 2.2 mmol) in DMF (30 mL) was added NaN_3 (900 mg, 13.2 mmol) and the reaction was stirred at 80 °C overnight. The mixture was poured into ice water (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2S0_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (PE: EtOAc =15: 1 to 5: 1) to afford scheme 8-8 compound **S3** (690 mg, 83.0% yield) as a light oil .

Step 3: (2S,4R)-4-(Azidomethyl)-l-(ieri-butoxycarbonyl)-4-fluoropyrrolidine-2 -carboxylic acid (S4)

[0697] To a solution of (2S,4R)-2-benzyl 1-*ter**t*-butyl 4-(azidomethyl)-4-fluoropyrrolidine -1,2-dicarboxylate (scheme 8-8 compound **S3,** 690 mg, 1.8 mmol) in MeOH (8 mL) was added a 1 M aqeuous NaOH solution (3.6 mL, 3.6 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water (15 mL), the volatiles were removed under reduced pressure. The residue was washed with Et_20 (2 x 10 mL) and acidified with 2 N HC1 to pH= ~3. The resulting mixture was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried over anhydrous Na_2S0_4 and concentrated under reduced pressure to afford scheme 8-8 compound **S4** (480 mg, 92.5% yield) as a light oil .

Step 4: (2S,4R)-ferf-Butyl 4-(azidomethyl)-2-((6-bromopyridin-2-yl)carbamoyl)-4 -fluoropyrrolidine-l-carboxylate (S5)

[0698] A mixture of (2S,4R)-4-(azidomethyl)-l-(fer *t*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 8-8 compound **S4,** 480 mg, 1.67 mmol), 6-bromopyridin-2-amine (316 mg, 1.84 mmol), DIPEA (539 mg, 4.18 mmol) and EEDQ (825 mg, 3.34 mmol) in DCE (10 mL) was stirred at 90 °C overnight. The mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (PE: EtOAC =20: 1 to 4: 1) to afford scheme 8-8 compound **S5** (510 mg, 69.1% yield) as a light oil .

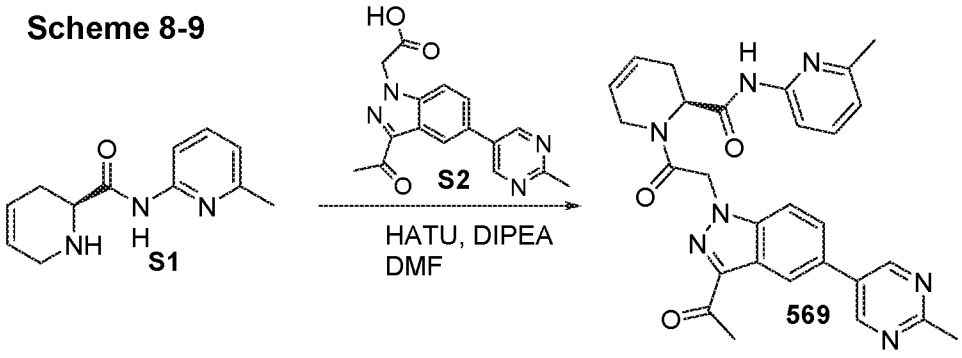
Step 5: (2S,4R)-4-(Azidomethyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine -2-carboxamide (S6)

[0699] To a solution of (2S,4R)-fer *t*-butyl 4-(azidomethyl)-2-((6-bromopyridin-2-yl) carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 8-8 compound **S5,** 200 mg) in DCM (3.0 mL) was added TFA (1 mL) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The mixture was evaporated under reduced pressure to afford scheme 8-8 compound **S6** (180 mg, 100% yield). The compound was carried forward without further purification.

Step 6: (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl) -4-(azidomethyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (547)

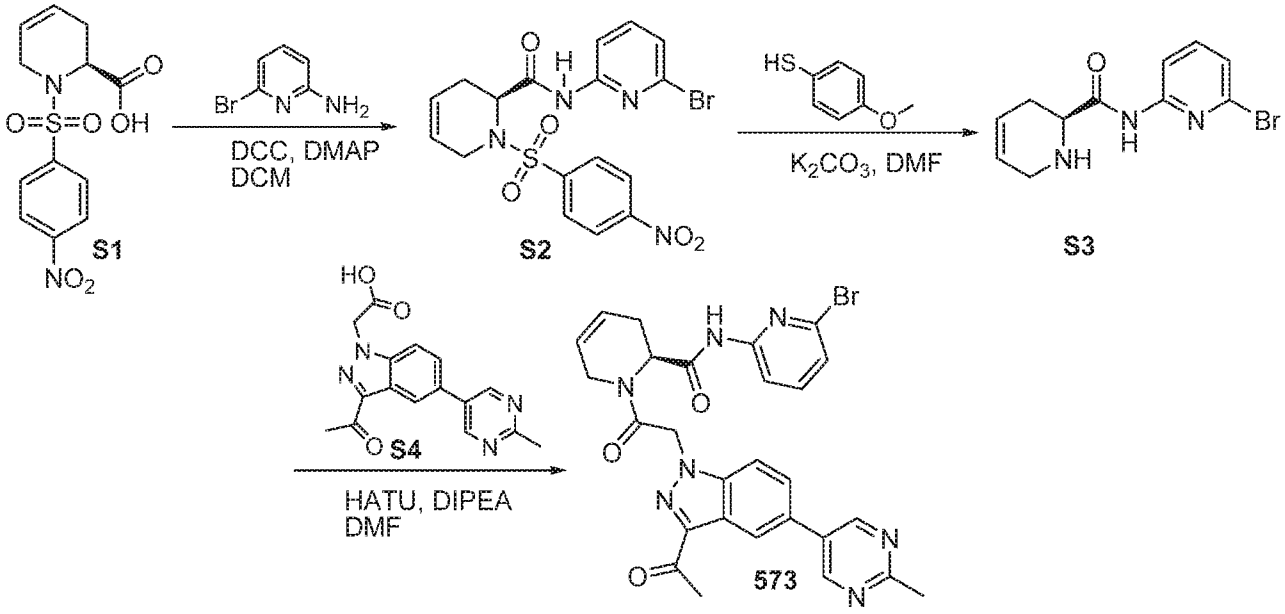
[0700] A mixture of (2S,4R)-4-(azidomethyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine -2-carboxamide (scheme 8-8 compound **S6,** 180 mg, 0.47 mmol), 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH -indazol-l-yl)acetic acid (161 mg, 0.52 mmol), HATU (270 mg, 0.71 mmol) and DIPEA (0.24 mL, 1.41 mmol) in DMF (4 mL) was stirred at room temperature overnight. The mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over anhydrous Na_2S04 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (DCM: MeOH=80:l to 60:1) to afford **547** (200 mg, yield 67. 1% yield) as a white solid. ¾ NMR (400 MHz, DMSO-^e) δ 11.02 (s, 1H), 9.03 (s, 2H), 8.42 (d, *J* = 1.0 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.85 (dd, *J* = 7.3, 5.2 Hz, 2H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 5.87 (d, *J* = 17.3 Hz, 1H), 5.64 (d, *J* = 17.2 Hz, 1H), 4.71 (t, *J* = 8.6 Hz, 1H), 4.32 (m, 1H), 4.07 - 3.92 (m, 2H), 3.90 - 3.79 (m, 1H), 2.66 (d, *J* = 15.0 Hz, 6H), 2.62 - 2.55 (m, 1H), 2.17 (m, 1H). LC/MS (ESI) *mlz*: 635 $(M+H)^+$.

Scheme 8-9



[0701] **(S)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-methylpyridin-2-yl)-l,2,3,6-tetrahydropyridine-2-carboxamide (569):** To a solution of scheme 8-9 compound **SI** (53 mg, 0.165 mmol), scheme 8-9 compound **S2** (30 mg, 0.15 mmol) and DIPEA (60 mg, 0.45 mmol) in DMF (2 mL) was added HATU (114 mg, 0.3 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with 10% aqeuous LiCl solution and brine successively, dried over anhydrous Na_2S04, filtered and then concentrated. The residue was purified by preparative HPLC (eluted with CftCN/water) to afford compound **569** (15 mg, 19.6% yield) as a white solid. ¾ NMR (400 MHz, DMSO-d_6) δ: 10.52 (s, 1H), 9.06 (s, 2H), 8.44 (d, J = 4.7 Hz, 1H), 7.64 - 7.91 (m, 4H), 7.00 (d, J =7.5 Hz, 1H), 5.95 (d, J = 17.3 Hz, 1H), 5.80 (m, 3H), 5.33 (d, J = 6.2 Hz, 1H), 4.41 (m, 2H), 2.81 (m, 1H), 2.66 (d, J = 8.3 Hz, 6H), 2.55 (m, 1H), 2.42 (d, J = 17.3 Hz, 3H).LC/MS (ESI) mlz: 510 $(M+H)^+$.

Scheme 8-10



Step 1: (S)-N-(6-Bromopyridin-2-yl)-l-(4-nitrophenylsulfonyl)-l,2,3,6-tetrahydropyridine-2-carboxamide (S2)

[0702] To a solution of scheme 8-10 compound **SI** (250 mg, 0.8 mmol) in DCM (20 mL) was added 6-bromopyridin-2-amine (153 mg, 0.88 mmol), DCC (332 mg, 1.6 mmol) and DMAP (99 mg, 0.8 mmol). The reaction was stirred at room temperature overnight. The mixture was washed water and brine, dried over anhydrous Na_2S04, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 8: 1 to 2: 1) to afford the title compound (80 mg, 22% yield) as a yellow solid. LC/MS (ESI) *mlz:* 489 $(M+Na)^+$.

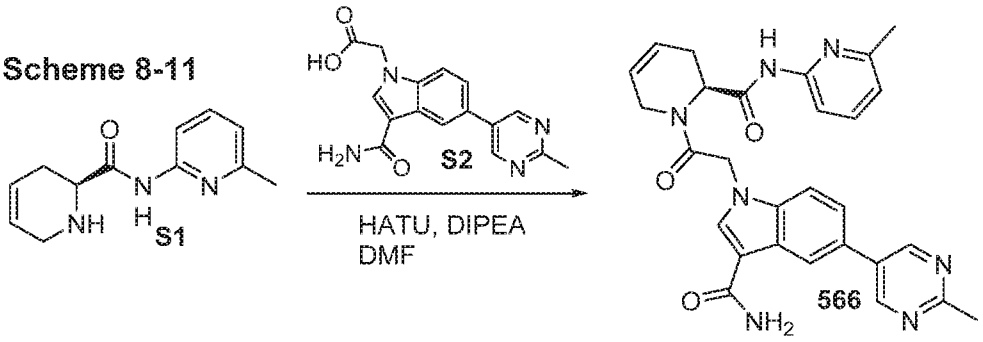
Step 2: (S)-N-(6-Bromopyridin-2-yl)-l,2,3,6-tetrahydropyridine-2-carboxamide (S3)

[0703] To a solution of scheme 8-10 compound **S2** (80 mg, 0.17 mmol) in DMF (4 mL) was added K2CO3 (71 mg, 0.51 mmol) and 4-methoxybenzenethiol (31 mg, 0.22 mmol). The reaction was stirred at room temperature for 24 h. The mixture was diluted with EtOAc and washed with 10% aqeuous LiCl solution and brine, dried over anhydrous Na_2S04, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM: MeOH =100:0 to 50: 1) to afford the title compound (40 mg, 83% yield) as a yellow solid. LC/MS (ESI) *mlz:* 282 $(M+H)^+$.

Step 3: (S)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-l,2,3,6-tetrahydropyridine-2-carboxamide (573)

[0704] To a solution of scheme 8-10 compound **S3** (20 mg, 0.071 mmol), scheme 8-10 compound **S4** (25 mg, 0.078 mmol) and DIPEA (28 mg, 0.213 mmol) in DMF (1 mL) was added HATU (54 mg, 0.142 mmol). The reaction was stirred overnight and diluted with EtOAc. The resulting mixture was washed with 10% aqeuous LiCl solution and brine, dried over anhydrous Na_2S04, filtered and then concentrated. The residue was purified by preparative HPLC (eluted with CftCN/water) to afford compound **573** (8 mg, 19.6 % yield) as a white solid. ¾NMR (400 MHz, DMSO-d_6) δ: 10.95 (s, 1H), 9.05 (s, 2H), 8.44 (s, 1H), 7.99 - 8.08 (m, 1H), 7.83 - 7.91 (m, 2H), 7.74 (m, 1H), 7.36 (m, 1H), 5.95 (d, *J* = 17.2 Hz, 1H), 5.87 (s, 1H), 5.75 (m, 2H), 5.31 (m, 1H), 4.25 - 4.45 (m, 2H), 2.82 (s, 1H), 2.54 - 2.73 (m, 7H). LC/MS (ESI) *mlz*: 574 $(M+H)^+$.

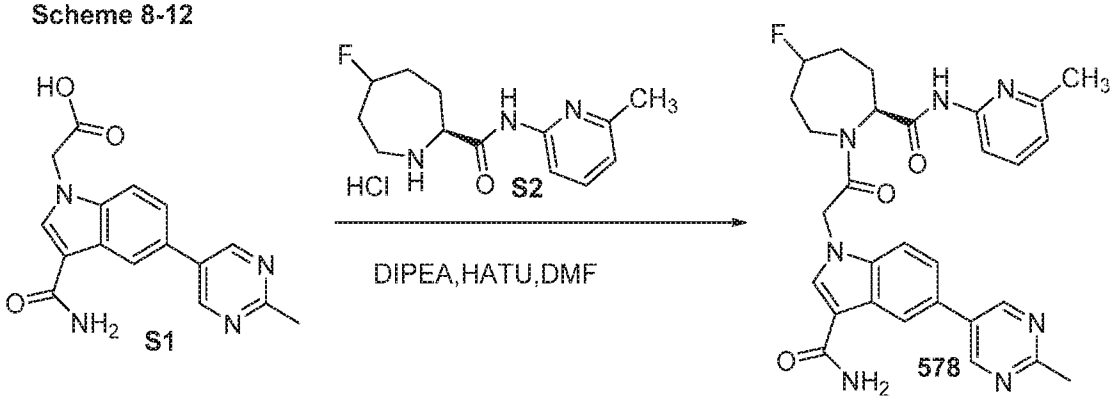
Scheme 8-11



[0705] **(S)-l-(2-(2-((6-Methylpyridin-2-yl)carbamoyl)-3,6-dihydropyridin-l(2H)-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indole-3-carboxamide (566):** To a solution of scheme 8-1 1 compound **SI** (30 mg, 0.15 mmol), scheme 8-1 1 compound **S2** (53 mg, 0.165 mmol), and DIPEA (60 mg, 0.45 mmol) in DMF (2 mL) was added HATU (114 mg, 0.3 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 10% aqeuous LiCl solution and brine successively, dried over anhydrous **Na_2S0_4**, filtered and then concentrated. The residue was purified by preparative HPLC (eluted with CftCN/water) to afford compound **566** (10 mg, 13 % yield) as a white solid. ¾ NMR (400 MHz, CDCh) δ: 10.49 (s, 1H), 9.01 (s, 2H), 8.42 (s, 1H), 8.01 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.52 - 7.61 (m, 2H), 6.97 (d, *J* = 7.5 Hz, 1H), 5.86 (s, 2H), 5.55 (d, *J* =

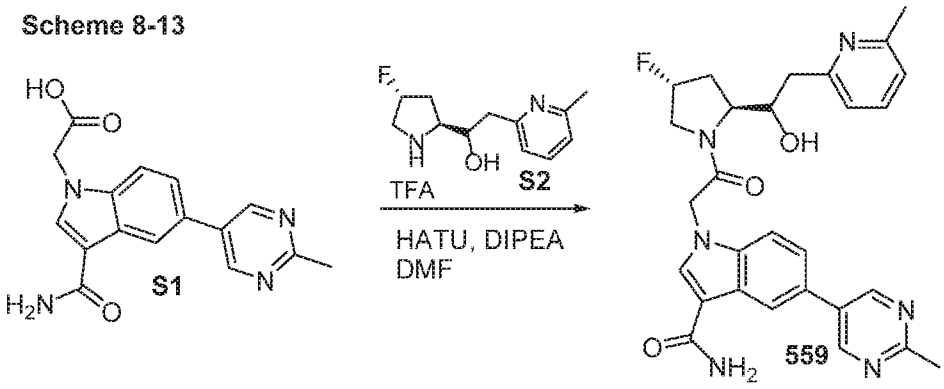
17.5 Hz, 1H), 5.33 (d, *J* = 17.5 Hz, 2H), 5.09 - 5.25 (m, 1H), 4.40 (s, 2H), 4.31 (d, *J* = 24.9 Hz, 1H), 2.68 (s, 3H), 2.57 (m, 1H), 2.42 (s, 3H), 2.33 (m, 1H).

Scheme 8-12



[0706] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indole-3-carboxamide (578):** The titled compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, CD_3OD) δ: 8.98 (d, *J* = 8.0 Hz, 2H), 8.41 (d, *J* = 21.6 Hz, 1H), 8.21 (s, 1H), 7.96 (d, *J* = 9.4 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 2.6 Hz, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.31 (dt, *J* = 107.5, 17.1 Hz, 2H), 4.24 - 3.97 (m, 1H), 3.77 - 3.56 (m, 1H), 2.73 (s, 3H), 2.44 (d, *J* = 11.0 Hz, 1H), 2.41 (d, *J* = 4.8 Hz, 3H), 2.29 (d, *J* = 25.2 Hz, 2H), 1.97 (dd, *J* = 25.3, 10.9 Hz, 2H), 1.84 - 1.72 (m, 1H), 1.51 - 1.23 (m, 4H). LC/MS (ESI) *mlz*: 544 $(M+H)^+$.

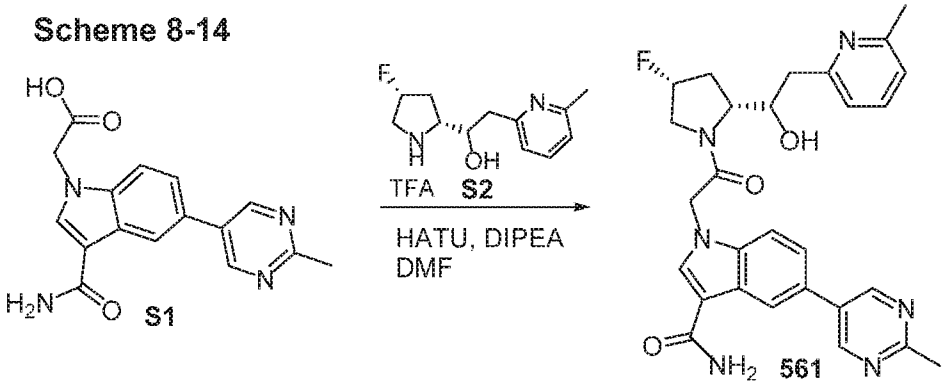
Scheme 8-13



[0707] **l-(2-((2S,4R)-4-Fluoro-2-((S)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indole-3-carboxamide**

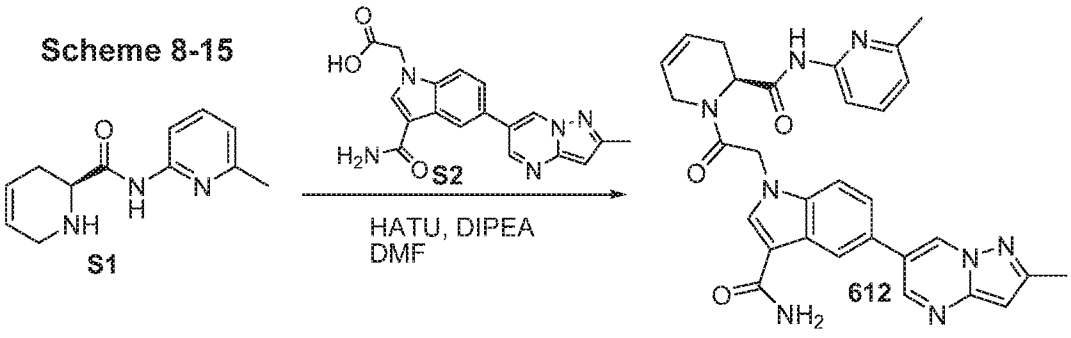
(559): The titled compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, CDCh) δ: 8.81 (s, 2H), 8.26 (d, *J* = 7.9 Hz, 1H), 8.14 (s, 1H), 7.68 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46 - 7.28 (m, 2H), 7.02 (t, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.70 (d, *J* = 23.1 Hz, 2H), 5.40 (d, *J* = 52.6 Hz, 1H), 4.95 (d, *J* = 13.3 Hz, 2H), 4.63 (s, 1H), 3.89 (dd, *J* = 38.3, 17.5 Hz, 3H), 2.86 (dd, *J* = 25.1, 12.2 Hz, 2H), 2.68 (d, *J* = 31.3 Hz, 3H), 2.46 (d, *J* = 14.7 Hz, 3H), 2.32 (dt, *J* = 23.5, 11.4 Hz, 2H). LC/MS (ESI) *mlz:* 517 $(M+H)^+$.

Scheme 8-14



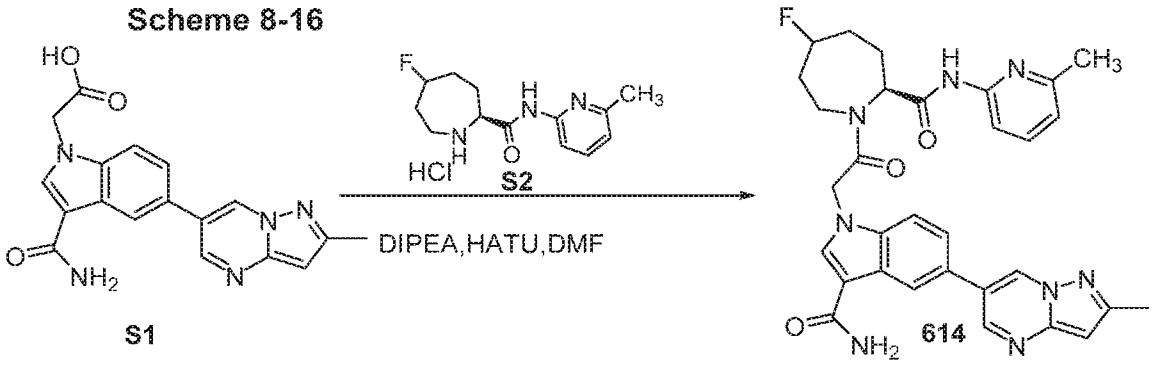
[0708] **l-(2-((2R,4R)-4-Fluoro-2-((R)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indole-3-carboxamide (561):** The titled compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, CDCh) δ: 9.02 (d, *J* = 4.8 Hz, 2H), 8.42 (d, *J* = 1.2 Hz, 1H), 8.32 (t, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.77 - 7.65 (m, 2H), 7.64 - 7.51 (m, 2H), 7.50 - 7.29 (m, 1H), 7.12 - 6.89 (m, 1H), 5.62 - 5.24 (m, 3H), 5.06 (d, *J* = 17.6 Hz, 1H), 4.66 - 4.38 (m, 2H) 4.22 - 4.17 (m, 1H), 4.16 - 4.09 (m, 1H), 3.04 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.83 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.70 - 2.66 (m, 6H), 2.37 - 2.18 (m, 1H). LC/MS (ESI) *mlz:* 517 $(M+H)^+$.

Scheme 8-15



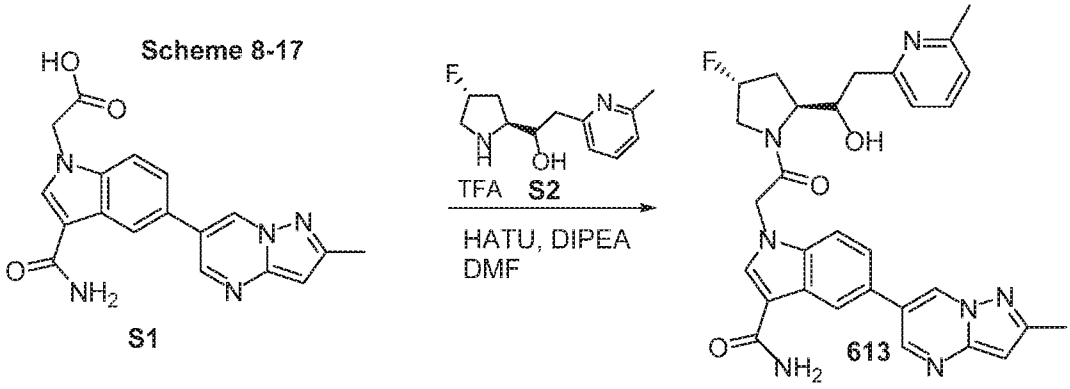
[0709] **(S)-5-(2-Methylpyrazolo[l,5-a]pyrimidin-6-yl)-l-(2-(2-((6-methylpyridin-2-yl)carbamoyl)-3,6-dihydropyridin-l(2H)-yl)-2-oxoethyl)-lH-indole-3-carboxamide (612):** The titled compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾NMR (400 MHz, CDCh) δ: 10.48 (s, 1H), 9.27 (s, 1H), 8.86 (d, *J* = 2.1 Hz, 1H), 8.43 (s, 1H), 8.32 (s, 1H), 8.00 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.53 - 7.75 (m, 3H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.56 (s, 1H), 5.86 (s, 2H), 5.55 (d, *J* = 17.5 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 2H), 5.09 - 5.24 (m, 1H), 4.28 - 4.44 (m, 2H), 3.80 (m, 1H), 2.81 (m, 1H), 2.65 (m, 1H), 2.32 - 2.48 (m, 6H). LC/MS (ESI) *mlz:* 549 $(M+H)^+$.

Scheme 8-16



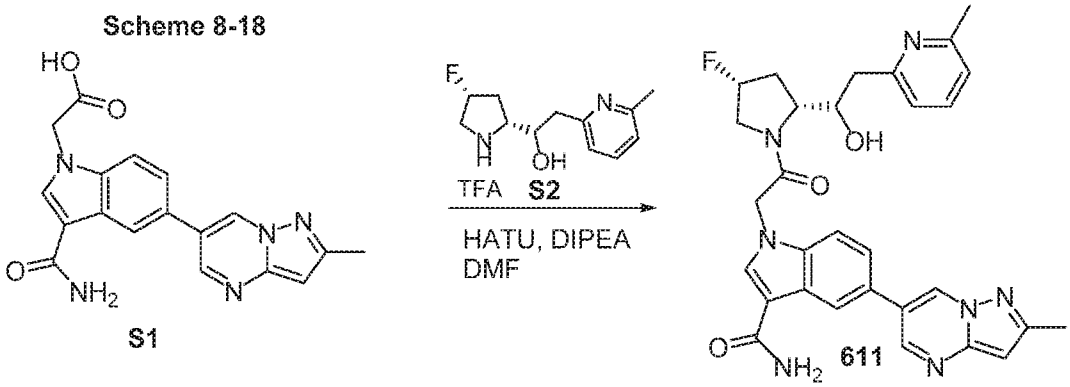
[0710] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(2-methylpyrazolo [1,5-a]pyrimidin-6-yl)- lH-indole-3-carboxamide (614):** The titled compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, **DMSO-d_6)** δ: 10.43 (s, 1H), 9.25 (d, *J* = 1.6 Hz, 1H), 8.85 (d, *J* = 2.4 Hz, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.01 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.76 - 7.35 (m, 4H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.55 (s, 1H), 5.52 (d, *J* = 17.6 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 4.94 - 4.65 (m, 2H), 3.98 (d, *J* = 16.4 Hz, 1H), 3.57 - 3.42 (m, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 2.34 - 2.08 (m, 3H), 2.02 - 1.75 (m, 2H), 1.68 - 1.46 (m, 1H); LCMS (ESI) *mlz:* 583 $[M+H]^+$.

Scheme 8-17



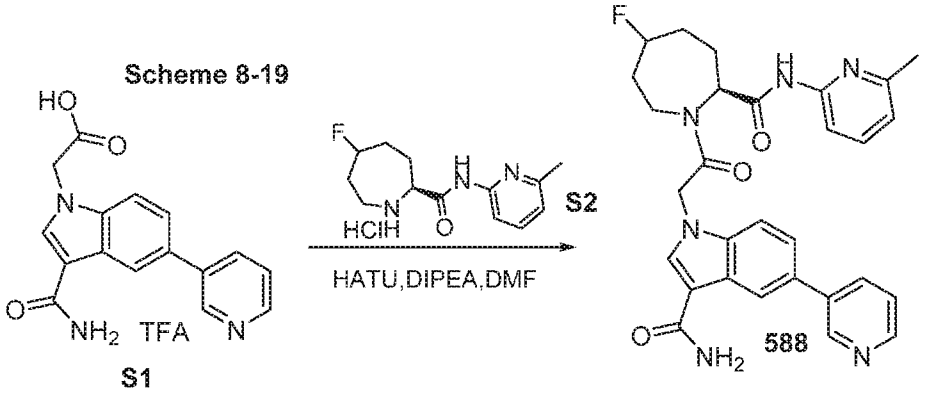
[071 1] **l-(2-((2S,4R)-4-fluoro-2-((S)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-indole-3-carboxamide (613):** The title compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, DMSO-d_6) δ 9.34 - 9.25 (m, 1H), 8.90 - 8.86 (m, 1H), 8.44 (s, 1H), 8.3 1 (s, 1H), 8.05 - 7.93 (m, 1H), 7.83 - 7.53 (m, 4H), 7.48 - 7.32 (m, 1H), 7.28 - 6.92 (m, 1H), 6.56 (s, 1H), 5.74 - 5.28 (m, 3H), 5.27 - 5.07 (m, 1H), 4.52 - 4.38 (m, 1H), 4.26 - 4.12 (m, 2H), 3.13 - 3.06 (m, 2H), 2.93 - 2.80 (m, 1H), 2.66 (s, 3H), 2.47 (s, 3H), 2.40 - 2.21 (m, 2H); LCMS (ESI) *mlz:* 556 $[M+H]^+$.

Scheme 8-18



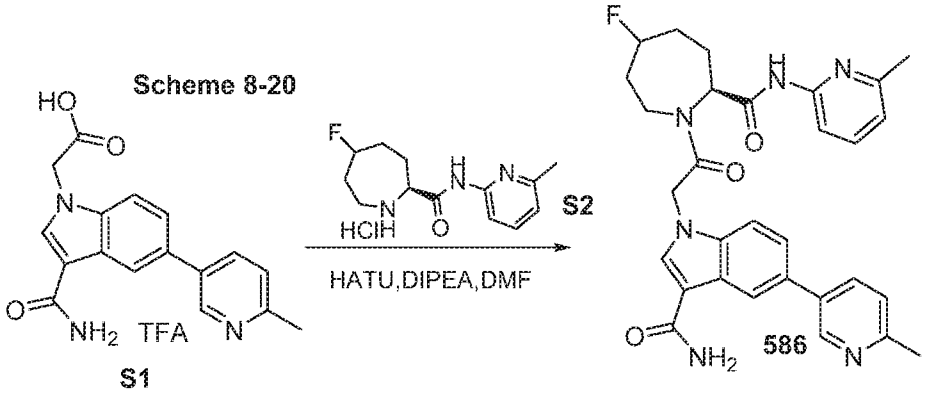
[0712] **l-(2-((2R,4R)-4-Fluoro-2-((R)-l-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-indole-3-carboxamide (611):** The title compound was prepared according to the procedure for Scheme 8-1 1 from appropriate starting materials. ¾ NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 2.0 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.43 (s, 1H), 8.36 - 8.13 (m, 2H), 7.98 (s, 1H), 7.76 - 7.51 (m, 4H), 7.50- 6.73 (m, 2H), 6.56 (s, 1H), 5.80 - 5.14 (m, 3H), 5.07 (d, J = 17.2 Hz, 1H), 4.52- 4.42 (m, 1H), 4.23 - 4.09 (m, 2H), 3.04 (d, J = 10.8 Hz, 1H), 2.83 (dd, J = 14.0, 10.4 Hz, 1H), 2.66 (s, 3H), 2.47 (s, 3H), 2.36 - 2.16 (m, 2H); LCMS (ESI) *mlz:* 556 $[M+H]^+$.

Scheme 8-19



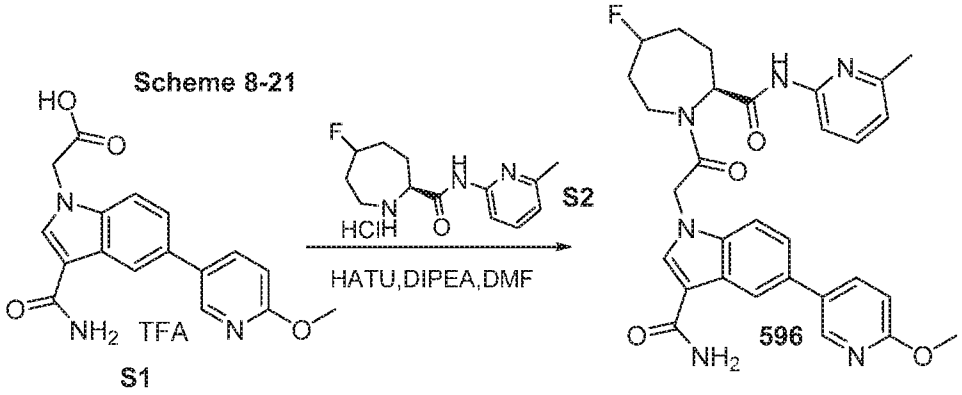
[0713] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(pyridin-3-yl)-lH-indole-3-carboxamide (588):** To a solution of scheme 8-19 compound **SI,** scheme 8-19 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **588** as a white solid. ¾ NMR (400 MHz, CD3OD) δ 8.82 (dd, *J* = 8.8, 1.8 Hz, 1H), 8.47 (d, *J* = 4.8 Hz, 1H), 8.43 - 8.33 (m, 1H), 8.28 (s, 1H), 8.12 (ddd, *J* = 7.0, 4.4, 1.9 Hz, 1H), 7.95 - 7.80 (m, 2H), 7.65 (dt, *J* = 27.1, 7.9 Hz, 1H), 7.52 - 7.37 (m, 3H), 6.98 (dd, *J* = 26.1, 7.5 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.26 (dd, *J* = 17.0, 5.0 Hz, 1H), 5.10 - 4.90 (m, 1H), 4.05 - 3.71 (m, 2H), 2.48 - 2.24 (m, 6H), 2.21 - 1.61 (m, 3H). LCMS (ESI) *mlz*: 529 $[M+H]^+$.

Scheme 8-20



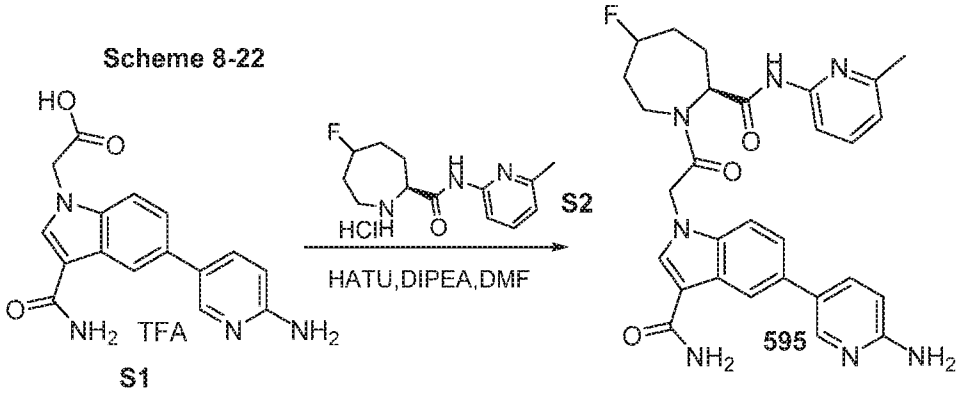
[0714] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(6-methylpyridin-3-yl)-lH-indole-3-carboxamide (586):** To a solution of scheme 8-20 compound **SI,** scheme 8-20 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with

EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford the title compound as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.52 (s, 1H), 8.41 (s, 1H), 8.13 (m, 1H), 7.82-7.91 (m, 2H), 7.56-7.62 (m, 1H), 7.51 (s, 1H), 7.35-7.37 (m, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.44-5.49 (m, 1H), 5.28-5.34 (m, 1H), 4.61-4.81 (m, 1H), 3.90-4.12 (m, 1H), 3.62-3.72 (m, 1H), 3.19-3.29 (m, 1H), 2.58 (s, 3H), 2.40 (s, 3H), 1.69-1.97 (m, 4H), 1.32-1.37 (m, 2H). LC/MS (ESI) *mlz:* 543 $(M+H)^+$.



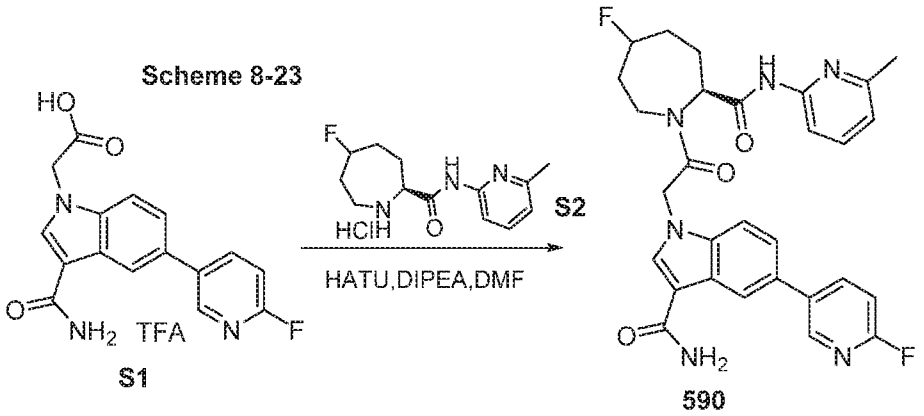
[0715] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(6-methoxypyridin-3-yl)-lH-indole-3-carboxamide (596):** To a solution scheme 8-21 compound **SI,** scheme 8-21 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **596** as a white solid. ¾ NMR (400 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 8.48 - 8.41 (m, 1H), 8.35 - 8.29 (m, 1H), 8.04 - 7.94 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.51 - 7.34 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.96 - 6.89 (m, 2H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 4.90 - 4.65 (m, 2H), 3.97 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 3H), 3.55 - 3.44 (m, 1H), 2.37 (s, 3H), 2.34 - 2.07 (m, 3H), 2.02 - 1.73 (m, 2H), 1.69 - 1.47 (m, 1H); LCMS (ESI) *mlz:* 559 $[M+H]^+$.

Scheme 8-22



[07 16] **5-(6-Aminopyridin-3-yl)-l-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-lH-indole-3-carboxamide (595):** To a solution of scheme 8-22 compound **SI,** scheme 8-22 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous $Na_2SC"4$, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **595** as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.79-7.87 (m, 2H), 7.59-7.63 (m, 1H), 7.39-7.42 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.42-5.47 (m, 1H), 5.28-5.33 (m, 1H), 4.57 (s, 2H), 3.97-4.02 (m, 1H), 3.56-3.63 (m, 1H), 2.40 (s, 3H), 1.71-2.05 (m, 4H), 1.24-1.37 (m, 2H). LCMS (ESI) *mlz*: 544 $[M+H]^+$.

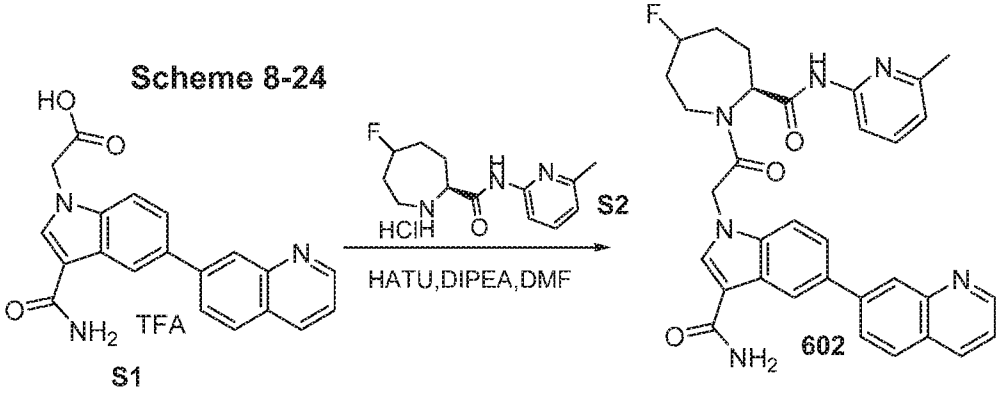
Scheme 8-23



[0717] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(6-fluoropyridin-3-yl)-lH-indole-3-carboxamide (590):** To a solution of scheme 8-23 compound **SI,** scheme 8-23 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford

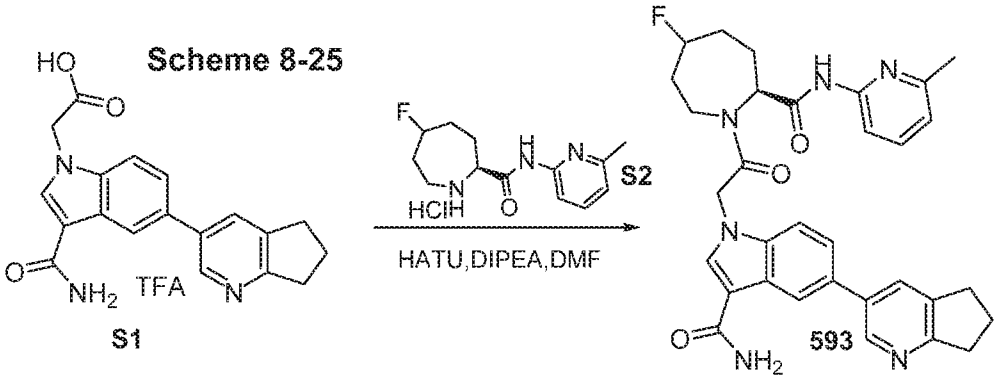
compound **590** as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.46 (t, *J* = 6.1 Hz, 1H), 8.38 (s, 1H), 8.26 - 8.19 (m, 1H), 7.95 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.53 - 7.44 (m, 2H), 7.14 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 5.49 (d, 1H), 5.33 (dd, 1H), 4.90 (s, 1H), 4.57 (s, 1H), 4.02 (d, 1H), 3.71 - 3.54 (m, 1H), 2.40 (s, 3H), 2.27 (s, 1H), 2.06 (dd, *J* = 95.2, 10.0 Hz, 3H), 1.80 (s, 1H), 0.90 (s, 1H). LC/MS (ESI) *mlz:* 547 $(M+H)^+$

Scheme 8-24



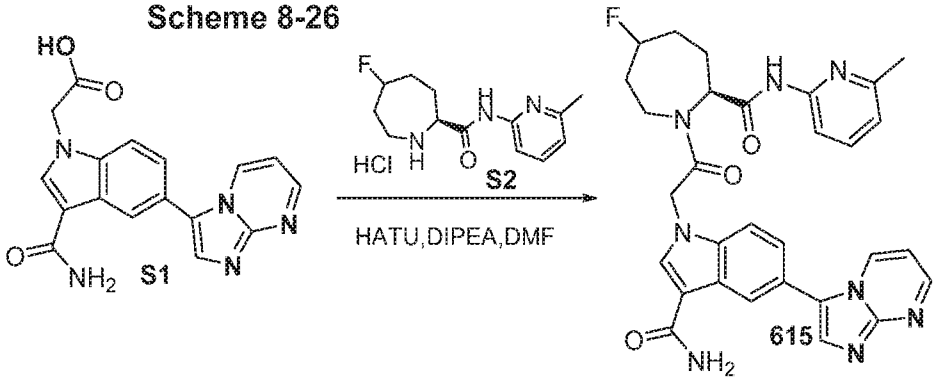
[0718] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(quinolin-7-yl)-lH-indole-3-carboxamide (602):** To a solution of scheme 8-24 compound **SI,** scheme 8-24 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford the compound **602** as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.95 - 8.67 (m, 1H), 8.57 (d, *J* = 1.4 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 8.28 (s, 1H), 8.02 (d, *J* = 4.2 Hz, 2H), 7.95 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 - 7.57 (m, 2H), 7.56 - 7.46 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 1H), 5.50 (d, 1H), 5.35 (d, 1H), 4.92 (dd, *J* = 11.3, 5.2 Hz, 1H), 4.67 (s, 1H), 4.03 (d, 1H), 3.68 - 3.55 (m, 1H), 2.40 (s, 3H), 2.38 - 2.14 (m, 2H), 2.08 - 1.89 (m, 2H), 1.79 (dd, 1H). LC/MS (ESI) *mlz:* 579 $(M+H)^+$.

Scheme 8-25



[07 19] **5-(6,7-Dihydro-5H-cyclopenta[b] pyridin-3-yl)-l-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-lH-indole-3-carboxamide (593):** To a solution of scheme 8-25 compound **SI,** scheme 8-25 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **593** as a white solid. ^1H NMR (400 MHz, DMSO-^e) δ 10.51 (s, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 8.45 (d, *J* = 1.7 Hz, 1H), 8.12 - 8.00 (m, 1H), 7.96 - 7.86 (m, 2H), 7.72 (t, *J* = 7.9 Hz, 1H), 7.62 - 7.46 (m, 2H), 7.03 (d, *J* = 7.5 Hz, 2H), 5.64 (d, *J* = 17.3 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.02 - 4.81 (m, 2H), 4.06 (d, *J* = 17.4 Hz, 1H), 3.65 - 3.51 (m, 1H), 3.05 (dt, *J* = 18.1, 7.5 Hz, 4H), 2.48 (d, *J* = 20.4 Hz, 3H), 2.32 (d, *J* = 28.2 Hz, 2H), 2.20 (h, *J* = 8.1, 7.5 Hz, 3H), 1.97 (ddd, *J* = 59.4, 24.1, 11.6 Hz, 2H), 1.72 (d, *J* = 13.0 Hz, 1H), 1.33 (s, 1H). LC/MS (ESI) *mlz:* 569 $(M+H)^+$.

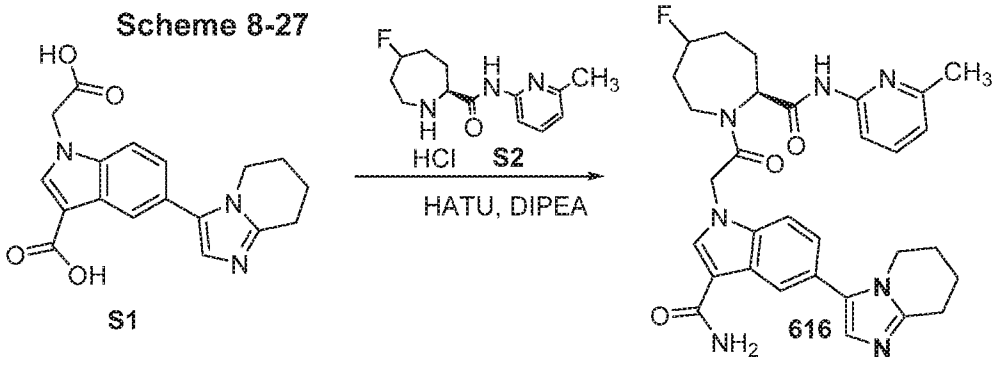
Scheme 8-26



[0720] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(imidazo[l,2-a]pyrimidin-3-yl)-lH-indole-3-carboxamide (615):** To a solution of scheme 8-26 compound **SI,** scheme 8-26 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **615** as a white solid. ¾NMR (400 MHz, CD_3OD) δ: 9.00 (d, *J* = 6.5 Hz, 1H), 8.57 (t, *J* = 12.5 Hz, 2H), 8.37 (d, *J* = 17.0 Hz, 1H), 7.97 (d, *J* = 10.6 Hz, 1H), 7.84 (t, *J* = 11.4 Hz, 2H), 7.61 (t, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 6.8, 4.2 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 5.53 (d, *J* = 17.3 Hz, 1H), 5.37 (d, *J* = 17.3 Hz, 1H), 4.63 (d, *J* = 40.3 Hz, 3H),

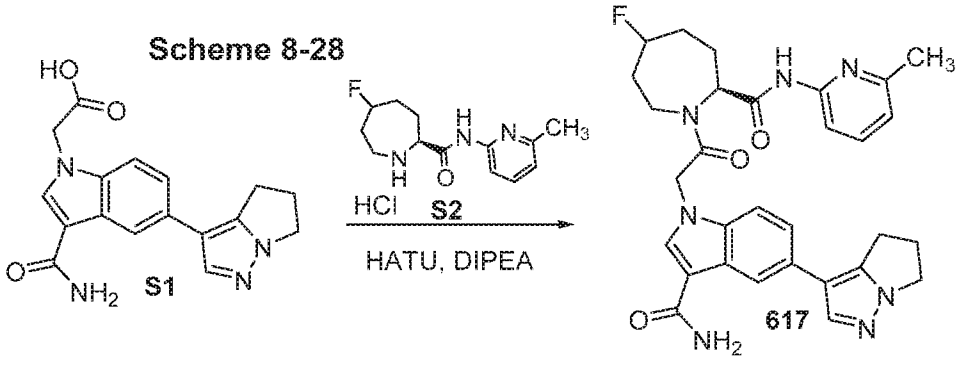
4.03 (d, *J* = 15.8 Hz, 1H), 3.59 (dd, *J* = 44.1, 27.4 Hz, 1H), 3.10 (dd, *J* = 48.0, 14.5 Hz, 1H), 2.42 (d, *J* = 13.5 Hz, 4H), 2.24 (d, *J* = 26.8 Hz, 1H), 1.99 (d, *J* = 11.8 Hz, 2H), 1.80 (s, 1H), 1.31 (d, *J* = 14.1 Hz, 1H). LC/MS (ESI) *mlz*: 569 (M+H) $^{+}$.

Scheme 8-27



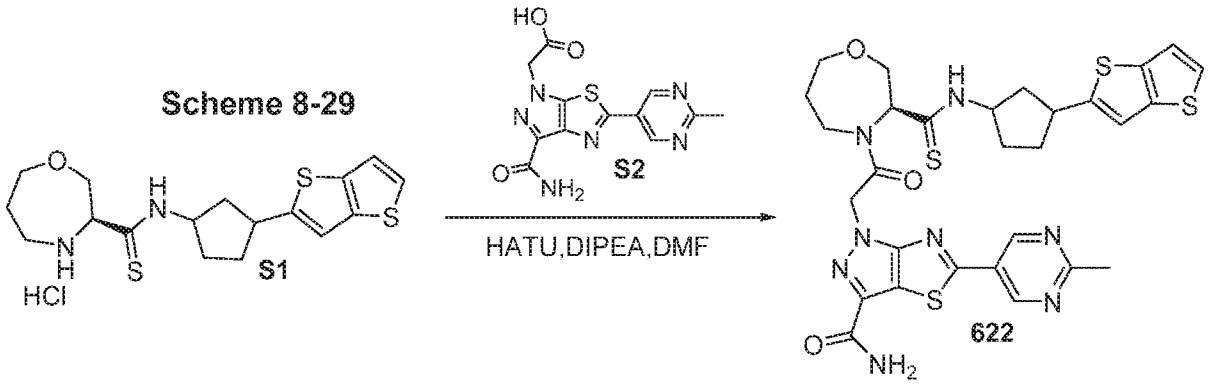
[0721] **l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(5,6,7,8-tetrahydroimidazo[l,2-a]pyridin-3-yl)-lH-indole-3-carboxamide (616):** To a solution of scheme 8-27 compound **SI,** scheme 8-27 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **616** as a white solid. ¾ NMR (400 MHz, CD_3OD) δ: 8.44 (s, 2H), 8.25 (t, *J* = 4.9 Hz, 1H), 7.96 (d, *J* = 9.6 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.35 - 7.24 (m, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 5.43 (dd, *J* = 63.5, 17.3 Hz, 2H), 4.67 (s, 2H), 4.02 (d, *J* = 18.0 Hz, 3H), 3.67 - 3.44 (m, 1H), 3.16 - 2.99 (m, 2H), 2.51 (d, *J* = 42.9 Hz, 1H), 2.41 (s, 3H), 2.38 - 2.19 (m, 2H), 2.08 - 1.92 (m, 6H), 1.88 - 1.69 (m, 1H). LC-MS (ESI) found: 572 [M+l] $^{+}$.

Scheme 8-28



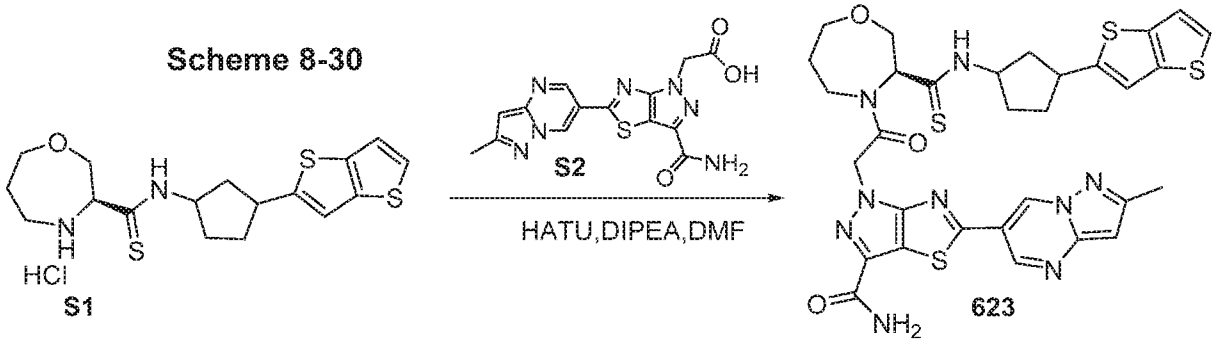
[0722] **5-(5,6-Dihydro-4H-pyrrolo[l,2-b]pyrazol-3-yl)-l-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-lH-indole-3-carboxamide (617):** To a solution of scheme 8-28 compound **SI,** scheme 8-28 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **617** as a white solid. ¾ NMR (400 MHz, DMSO-^e) δ 10.42 (s, 1H), 8.22 (s, 1H), 7.92 (s 1H), 7.79 (s, 2H), 7.65 - 7.60 (m, 1H), 7.34 (m,2H), 6.94 (d, *J* = 7.4 Hz, 1H), 5.47 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 4.83 (m, 2H), 4.70 (s, 1H), 4.09 (t, *J* = 7.3 Hz, 2H), 3.96 (d, *J* = 15.7 Hz, 1H), 3.09 - 3.03 (m, 2H), 2.67 - 2.59 (m, 2H), 2.39 (d, *J* = 19.4 Hz, 3H), 2.18 (m 3H), 1.93 - 1.78 (m, 2H), 1.62 (m 1H). LC-MS (ESI) found: 558 $[M+l]^+$.

Scheme 8-29



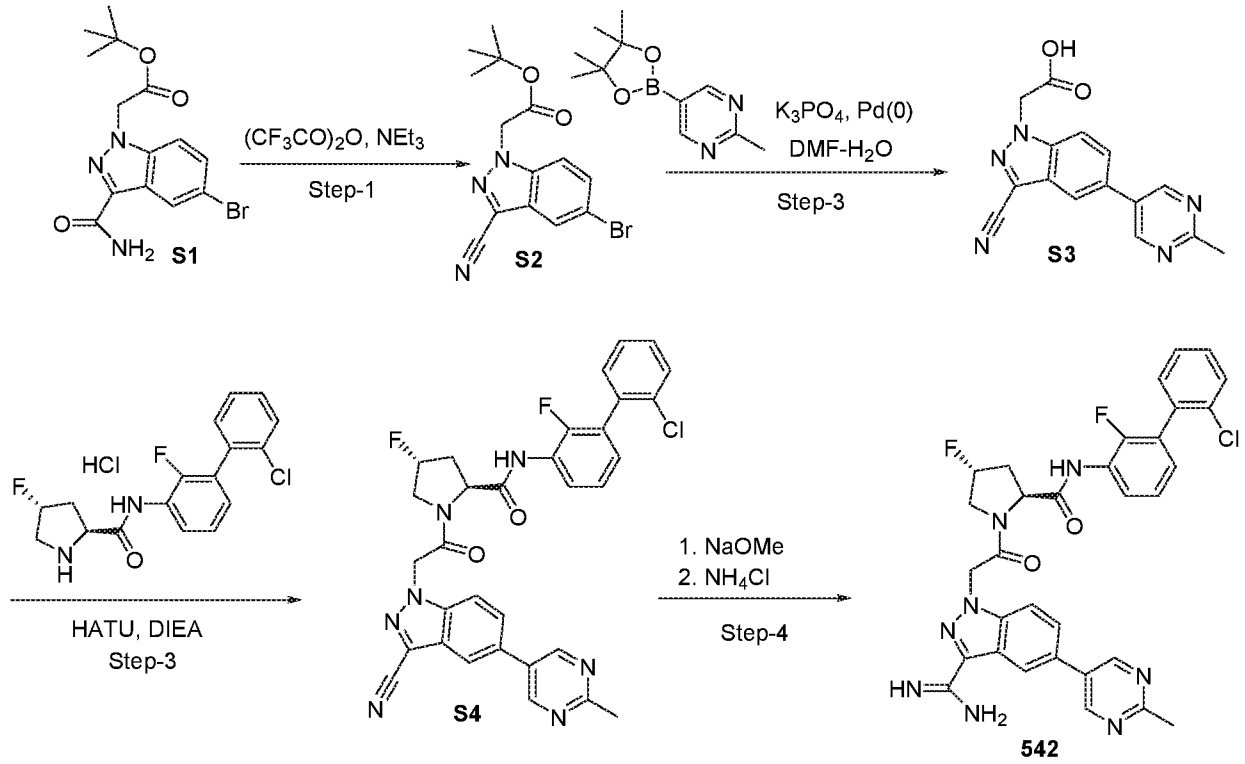
[0723] **5-(2-Methylpyrimidin-5-yl)-l-(2-oxo-2-((3S)-3-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)-l,4-oxazepan-4-yl)ethyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxamide (622):** To a solution of scheme 8-29 compound **SI,** scheme 8-29 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S0_4, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **622** as a white solid. ¾ NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 9.32 - 9.16 (m, 2H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.61 (s, 1H), 7.53 (dd, *J* = 11.8, 5.2 Hz, 1H), 7.38 - 7.25 (m, 1H), 7.22 - 7.08 (m, 1H), 5.75 (dd, *J* = 16.8, 3.8 Hz, 1H), 5.46 (d, *J* = 17.0 Hz, 1H), 5.08 - 4.87 (m, 1H), 4.65 (s, 1H), 4.14 (ddd, *J* = 44.2, 26.4, 13.3 Hz, 4H), 3.68 (ddd, *J* = 97.6, 51.4, 7.3 Hz, 3H), 3.31 (s, 1H), 2.72 (d, *J* = 6.3 Hz, 3H), 2.18 - 1.99 (m, 2H), 1.87 (s, 2H), 1.63 (d, *J* = 6.3 Hz, 2H). LC/MS (ESI) *mlz*: 667 $(M+H)^+$.

Scheme 8-30



[0724] **5-(2-Methylpyrazolo[l,5-a]pyrimidin-6-yl)-l-(2-oxo-2-((3S)-3-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)-l,4-oxazepan-4-yl)ethyl)-lH-pyrazolo[3,4-d]thiazole-3-carboxamide (623):** To a solution of the scheme 8-30 compound **SI,** scheme 8-30 compound **S2,** and HATU in DMF (3 mL) was added DIPEA at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2S04, filtered and concentrated to afford crude product, which was purified by preparative HPLC to afford compound **623** as a white solid. ¾ NMR (400 MHz, DMSO-d_6) δ: 10.21 (d, *J* = 7.1 Hz, 1H), 9.56 - 9.67 (m, 1H), 8.96 (d, *J* = 2.3 Hz, 1H), 7.87 - 7.97 (m, 1H), 7.58 (s, 1H), 7.46 (d, *J* = 5.2 Hz, 1H), 7.07 - 7.31 (m, 2H), 6.68 (s, 1H), 5.72 (d, *J* = 17.1 Hz, 1H), 5.49 (d, *J* = 17.0 Hz, 1H), 5.01 - 5.12 (m, 1H), 4.63 - 4.79 (m, 1H), 4.23 - 4.41 (m, 1H), 3.97 - 4.16 (m, 3H), 3.70 - 3.86 (m, 1H), 3.45 - 3.65 (m, 2H), 2.48 (s, 3H), 1.52 - 2.28 (m, 8H). LC/MS (ESI) *mlz*: 706 $(M+H)^+$.

Scheme 8-31



Step-1 *tert*-Butyl 2-(5-bromo-3-cyano-lH-indazol-l-yl)acetate (S2)

[0725] To the solution of *tert*-butyl 2-(5-bromo-3-carbamoyl-lH-indazol-l-yl)acetate (scheme 8-31 compound **SI,** 1.06g, 3.0mmol) in DCM (15.0 mL), trifluoroacetic anhydride (756 mg, 3.6mmol) was added, followed by addition of triethyl amine at 0°C. The mixture was warmed up to room temperature and stirred overnight. The reaction was quenched with HCl (IN, 15mL). The DCM layer was collected and the aqueous phase was extracted with DCM (15mLx2). The combined DCM solution was washed with brine and dried over $MgS0_4$. The solution was filtered and the filtrate was concentrated. The remaining material was purified to afford 965 mg of title compound. ¾ NMR (400 MHz, DMSO-d_6) δ: 1.41 (s, 9H), 5.51 (s, 2H), 7.76 (d, J=8.8Hz, 1H), 7.89 (d, J=8.8Hz, 1H), 8.20 (s, 1H). LC (method A): t_R = 2.55min. LC/MS (EI) *mlz:* $[M + H]^+$ 280.08, 282. 11.

Step-2 2-(3-Cyano-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (S3)

[0726] *tert*-Butyl 2-(5-bromo-3-cyano-lH-indazol-l-yl)acetate (scheme 8-31 compound **S2,** 965 mg, 2.86mmol), 2-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidine (692 mg, 3.15mmol) andK_3P04 (1.82g, 8.58mmol) are mixed in co-solvent of DMF

(16ml) and+ H2O (4ml). The mixture was degassed and refilled with argon. To the mixture, $Pd(PPh_3)_4$ (O.leq) was added under Ar. The reaction was heated in an oil bath (125°C) for 5.5 h. The reaction was cooled to rt and the volatiles were evaporated. The remaining materials are purified to afford 845 mg of title product. ^{1}H NMR (400 MHz, DMSO-^e) δ: 2.69 (s, 3H), 5.50 (s, 2H), 7.99-8.07 (m, 2H), 8.32 (s, 1H), 9.15 (s, 2H)ppm. LC (method A): t_R = 0.88 min. LC/MS (EI) *mlz:* $[M + H]^+$ 294.23.

Step-3 (2S,4R)-N-(2'-chloro-2-fluoro-[l,l'-biphenyl]-3-yl)-l-(2-(3-cyano-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide (S4)

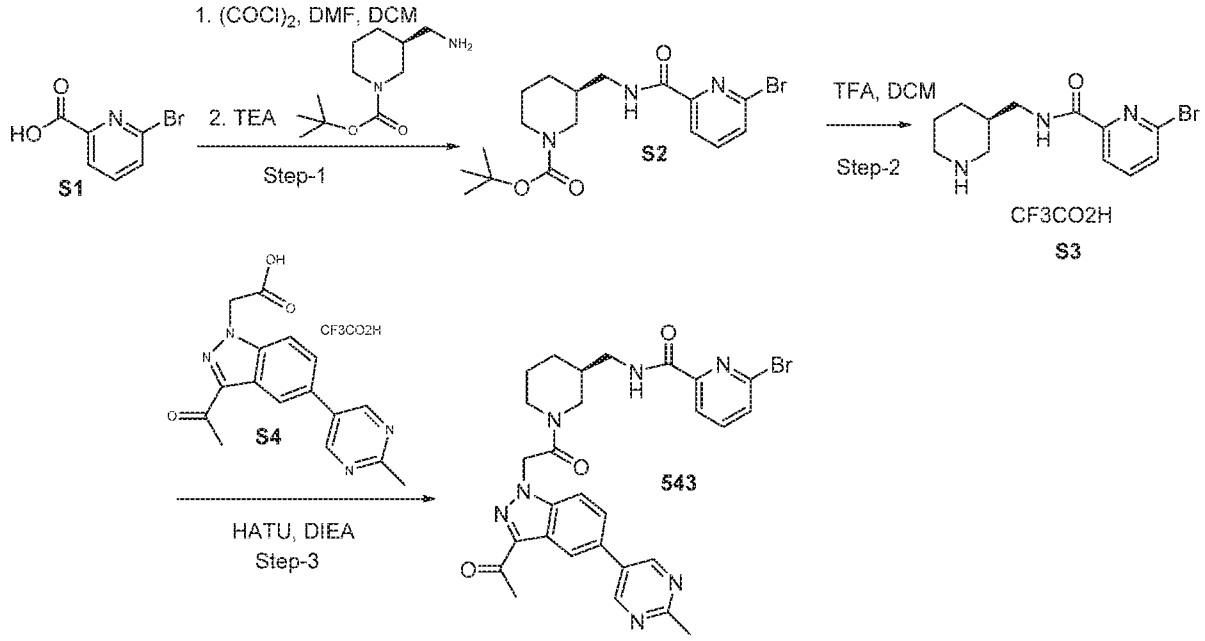
[0727] 2-(3-cyano-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-31 compound **S3,** 293 mg, l.Ommol), HATU (418 mg, 1.1 mmol) and (2S,4R)-N-(2'-chloro-2-fluoro-[l **,**1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (336 mg, 0.90mmol) are dissolved in DMF (2mL). To the solution, DIEA (0.5 mL) was dropwise added at room temperature. The mixture was stirred for 1 h at rt and the volatiles were evaporated. The residue was partitioned between ethyl acetate and saturated aqueous NaHCCb. The combined ethyl acetate solution was collected and washed with water, brine and dried over MgS04. The solution was concentrated and the remaining residue was purified to afford 453 mg of desire title compound. ¾ NMR (400 MHz, **DMSO**-d_6)**:** (major rotamer) 6:2.12-2.29(m, 1H), 2.51-2.63(m, 1H), 2.69 (s, 3H), 3.95-4.07 (m, 1H), 4.18-4.27 (m, 1H), 4.77 (t, J=8.4Hz, 1H), 5.50-5.91 (m, 3H), 7.06 (t, J=6.80Hz, 1H), 7.22 (t, J=6.80Hz, 1H), 7.35-7.47 (m, 3H), 7.56(d, J=7.2Hz, 1H), 7.95 (m, 3H), 8.32(s, 1H), 9.13(s, 2H), 9.99 (s, lH)ppm. ^{19}F NMR (376 MHz, DMSO-^e): (major rotamer) δ -126.70, -176.15. LC (method A): t_R = 2.21min. LC/MS (EI) *mlz:* $[M + H]^+$ 612.38

Step-4 (2S,4R)-l-(2-(3-Carbamimidoyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(2'-chloro-2-fluoro-[l,l'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide TFA (542)

[0728] (2S,4R)-N-(2'-chloro-2-fluoro-[l **,**1'-biphenyl]-3-yl)-l-(2-(3-cyano-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide (scheme 8-3 1 compound **S4,** 339 mg,0.55mml) was dissolved in dry methyl alcohol (3.0mL) and treated with NaOMe in MeOH (25%)(1.5mL). The reaction was stirred overnight at room temperature. Then NH4CI (400 mg) was added in one portion. The mixture was stirred overnight at room temperature. The mixture was purified by preparative HPLC to afford 41.6 mg of compound **542.** ¾ NMR (400 MHz, **DMSO**-d_6)**:** (major rotamer) δ: 2.06-2.23(m, 1H), 2.47-2.57(m, 1H), 2.63 (s, 3H), 3.87-3.98 (m, 1H), 4.15-4.23 (m, 1H), 4.71 (t, J=8.4Hz, 1H), 5.44-5.83 (m, 3H), 6.99 (t, J=6.80Hz, 1H), 7.14

(t, J=6.80Hz, 1H), 7.26-7.41 (m, 3H), 7.48-7.54(m, 1H), 7.82-7.94 (m, 3H), 8.3 l(s, 1H), 9.06-9.09 (m, 2H),9.22 9s, 2H), 9.30 (s, 2H), 9.93 (s, lH)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -126.64, -175.87. LC (method A): t_R = 1.64min. LC/MS (EI) *mlz:* [M + H]$^+$ 629.46

Scheme 8-32



Step-1 *tert*-Butyl (S)-3-((6-bromopicolinamido)methyl)piperidine-l-carboxylate (S2)

[0729] To the suspension of 6-bromopicolinic acid (scheme 8-32 compound **SI,** 606 mg, 3.0mmol) in DCM (15.0mL), a catalytic amount of DMF was added, followed by dropwise addition of oxalyl chloride (495 mg, 3.9mmol, 0.34mL) at 0°C. The reaction mixture was warmed up to rt and kept stirring for additional 1 h. The volatiles were evaporated and the remaining material was dissolved in DCM (15.0 mL). The solution was cooled in an ice bath. To the solution, *tert*-butyl (S)-3-(aminomethyl)piperidine-l-carboxylate (535 mg, 2.5mmol) was added, followed by addition of TEA. The mixture was stirred overnight and quenched with saturated NaHCCb. The two layers are separated and the organic phase was dried over $MgS0_4$, filtered and concentrated. The residue was purified to afford the title compound (900 mg). LC (method A): t_R = 2.21min. LC/MS (EI) *mlz:* [M + H]$^+$ 398.34, 400.37

Step-2 (R)-6-Bromo-N-(piperidin-3-ylmethyl)picolinamide TFA (S3)

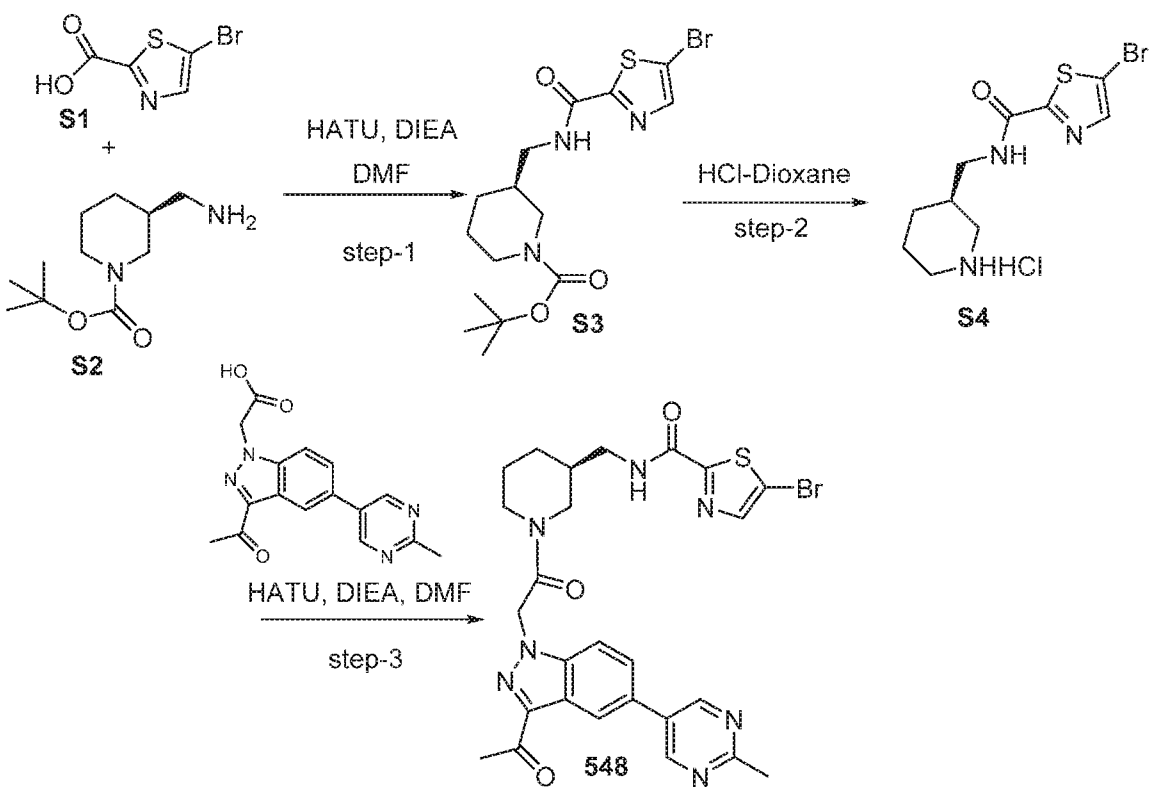
[0730] *tert*-butyl (S)-3-((6-bromopicolinamido)methyl)piperidine-l-carboxylate (scheme 8-32 compound **S2,** 900 mg) was dissolved in DCM (8 mL) and treated with TFA (2mL).

The mixture was stirred overnight at room temperature. The volatiles were evaporated under reduced pressure. The remaining material was co-evaporated with toluene twice. The residue was used for next step without further purification.

Step-3 (S)-N-((l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)piperidin-3-yl)methyl)-6-bromopicolinamide (S4)

[0731] 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid TFA salt (288 mg, 0.68mmol), (R)-6-bromo-N-(piperidin-3-ylmethyl)picolinamide TFA (scheme 8-32 compound **S3,** 280 mg, 0.68mmol) are dissolved in DMF (10 mL) and HATU (310 mg, 0.82 equiv) was added, followed by addition of DIEA (0.59 mL, 5 equiv). The reaction mixture was stirred overnight at rt. The volatiles were evaporated under reduced pressure. The remaining material was treated with saturated NaHCCb. The resulting solid was collected and dried. The solid was dissolved in minimum co-solvent MeOH-DCM (15%) and loaded on silica gel for chromatography. Purification afforded compound **543** (13.1 mg). ¾ NMR (400 MHz, **DMSO-de):** (major rotamer) 5:1.17-1.29 (m, 2H), 1.47-1.65 (m, 1H), 1.68-1.79 (m, 2H), 2.56 (s, 3H), 2.61 (s, 3H), 2.78-2.94 (m, 1H), 3.08-3.25 (m, 3H), 3.77-4.14(m, 2H), 5.59 (s, 2H), 7.74-7.78 (m, 3H),7.82-7.87 (m, 1H), 7.93-8.0 (m, 1H), 8.35(s, 1H), 8.66-8.73 (m, 1H), 8.96 (s, 2H) ppm; LC (method A): t_R = 1.72min. LC/MS (EI) *mlz:* $[M + H]^+$ 590.41, 592.37

Scheme 8-33



Step-1 ***tert-Butyl*** **(S)-3-((5-bromothiazole-2-carboxamido)methyl)piperidine-l-carboxylate (S3)**

[0732] To the solution of 5-bromothiazole-2-carboxylic acid (scheme 8-33 compound **SI,** 458 mg, 2.2mmol) and *ter t*-butyl (S)-3-(aminomethyl)piperidine-l-carboxylate (scheme 8-33 compound **S2,** 429 mg, 2.0mmol) in DCM (15.0 mL) at 0°C, HATU (912 mg, 2.4mmol) was added, followed by addition of DIEA (3.6mmol). The mixture was stirred for 1 h. The volatiles were evaporated under reduced pressure. The residue was diluted with ethyl acetate (60mL) and washed with saturated NaHCCb, water and brine. The organic solution was dried over MgS04. The solution was filtered and the filtrate was concentrated. The remaining material was purified to afford 513 mg of title product. LC (method A): t_R = 2.30 min. LC/MS (EI) *m/z: [M* + H]$^+$ 404.06, 406.09.

Step-2 (R)-5-Bromo-N-(piperidin-3-ylmethyl)thiazole-2-carboxamide hydrochloride (S4)

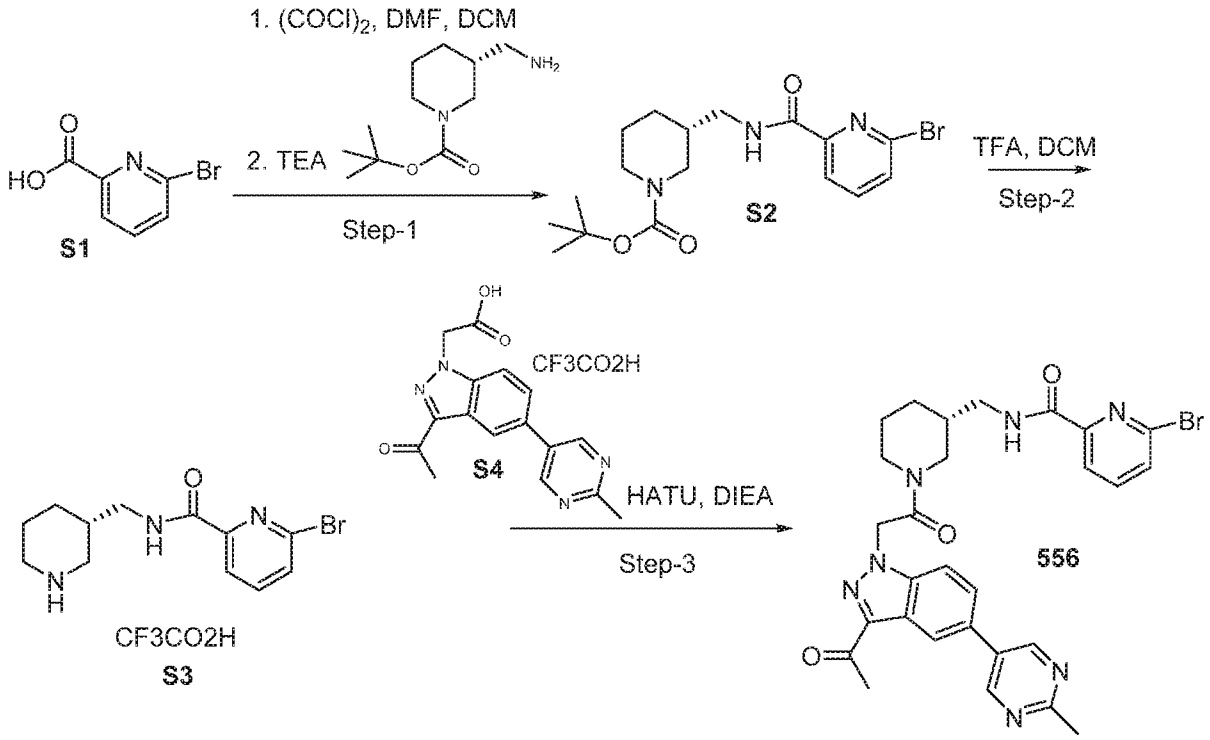
[0733] *ter t*-Butyl (S)-3-((5-bromothiazole-2-carboxamido)methyl)piperidine-l-carboxylate (scheme 8-33 compound **S3,** 513 mg) was taken up in 4N HC1 dioxane (6 mL) and the resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction monitored by

HPLC, the solvent was removed under reduced pressure. The remaining residue was used directly without further purification.

Step-3 (S)-N-((l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)piperidin-3-yl)methyl)-5-bromothiazole-2-carboxamide (548)

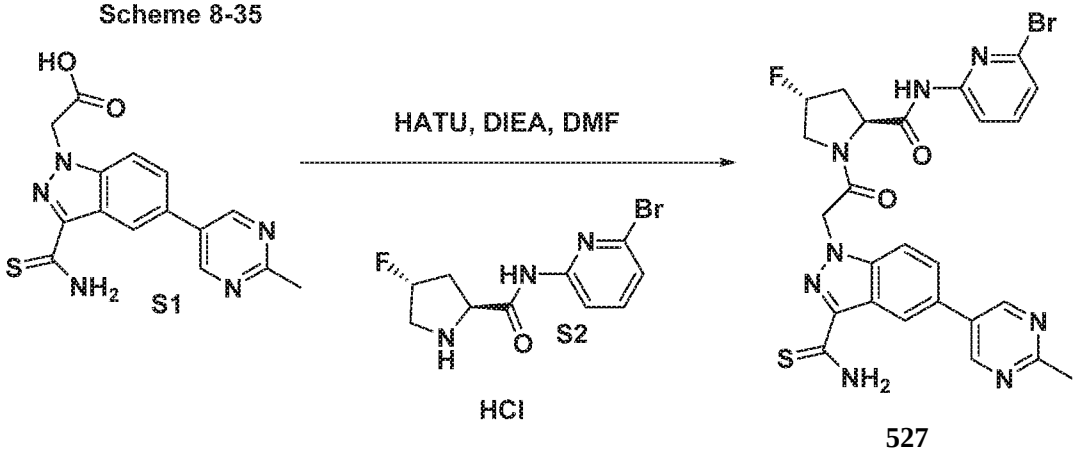
[0734] 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid TFA salt (scheme 8-33 compound **S4,** 220 mg, 0.5mmol), (R)-5-bromo-N-(piperidin-3-ylmethyl)thiazole-2-carboxamide hydrochloride (170 mg, 0.5mmol) was dissolved in DMF (5.0 mL), and HATU (228 mg, 0.60 mmol) was added, followed by addition of DIEA (5 equiv). The reaction mixture was stirred overnight at room temperature. The volatiles were evaporated under reduced pressure. The residue was diluted with ethyl acetate (60mL) and washed with saturated NaHCCb, water and brine. The organic solution was dried over MgS04. The solution was filtered and the filtrate was concentrated. The remaining material was purified to afford 125.7 mg of compound **548.** ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) 61.1 1-1.31 (m, 2H), 1.46-1.60 (m, 1H), 1.62-1.72 (m,2H), 2.56 (s, 3H), 2.62 (s, 3H), 2.77-2.98 (m, 1H), 3.02-3.18 (m, 2H), 3.20-3.35 (m, 1H), 3.80- 4.1 1 (m, 2H), 5.60 (s, 2H), 7.77 (s, 2H), 8.04 (s, 1H), 8.35 (s, 1H), 8.96 (s, 2H), 8.91 (t, J=6.0Hz, lH) ppm. LC (method A): ₹ = 1.78 min. LC/MS (EI) *mlz:* $[M + H]^+$ 598.04.

Scheme 8-34



[0735] **(R)-N-((l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)piperidin-3-yl)methyl)-6-bromopicolinamide (556):** Compound **556** was prepared following the procedure for the synthesis of compound **543** (Scheme 8-32). ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) 5:1.15-1.29 (m, 2H), 1.47-1.55 (m, 1H), 1.68-1.79 (m, 2H), 2.56 (s, 3H), 2.61 (s, 3H), 2.78-3.06 (m, 1H), 3.08-3.20 (m, 3H), 3.77-4. 14(m, 2H), 5.59 (s, 2H), 7.74-7.78 (m, 3H),7.82-7.87 (m, 1H), 7.93-8.0 (m, 1H), 8.35(s, 1H), 8.66-8.73 (m, 1H), 8.96 (s, 2H) ppm; LC (method A): t_R = 1.72min. LC/MS (EI) *mlz:* $[M + H]^+$ 592.09.

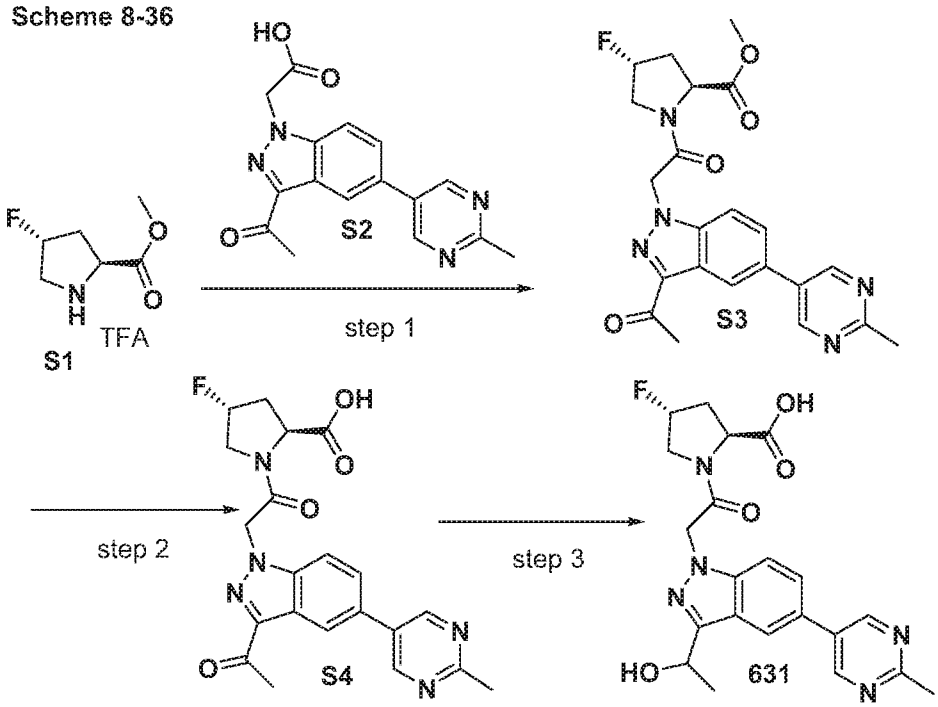
Scheme 8-35



Step 1: (2S,4R)-N-(6-Bromopyridin-2-yl)-l-(2-(3-carbamothioyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide (527)

[0736] 2-(3-carbamothioyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-35 compound **SI,** 327 mg) was dissolved in DMF (10 mL) and DIEA (0.3 mL) was added. This was followed by the addition of (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (324 mg) at 5 °C. HATU (456 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then added to water (50 mL + 5 g solid NaCl) and extracted with DCM (2 x 20 mL). The organic layer was washed successively with an aqueous solution of NaHCCb (20 mL), water (20 mL), and brine (20mL), then dried over $\mathbf{Na_2S04}$ and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to afford **527.** ¾NMR (400 MHz, DMSO-^e) δ 0.78 - 0.90 (m, 1H), 1.24 (s, 1H), 2.05 - 2.26 (m, 0.5H), 2.15 - 2.26 (m, 0.5H), 3.93 (d, *J* = 12.1 Hz, 0.5H), 4.02 (d, *J* = 12.6 Hz, 0.5H), 4.17 - 4.31 (m, 1H), 4.67 (t, *J* = 8.5 Hz, 1H), 5.46 - 5.60 (m, 4H), 5.74 (d, *J* = 17.3 Hz,

1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.83 (s, 2H), 8.03 (d, *J* = 8.2 Hz, 1H), 8.98 (d, *J* = 12.7 Hz, 3H), 9.45 (s, 1H), 9.71 (s, 1H), 11.02 (s, 1H). ^{19}F NMR (376 MHz, DMSO) δ -175.70.; LC (method A): t_R = 1.58 min. LC/MS (EI) *m/z*: $[M + H]^+$ 597.



Step 1 Methyl (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate (S3)

[0737] To a solution of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-36 compound **S2,** 310 mg) in DMF (5 mL) was added DIEA (0.5 mL) followed by methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (scheme 8-36 compound **SI,** 150 mg). HATU (456 mg) was then added slowly and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then added to water (10 mL) and extracted with EtOAc (2 x 15 mL). The organic layer was washed successively with an aqeuous solution of NaHCCb (10 mL), water (10 mL), and brine (10 mL), dried over $Na_2SC"4$, and concentrated under reduced pressure. The remaining residue was purified by HPLC to afford the title compound.

Step 2 (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (S4)

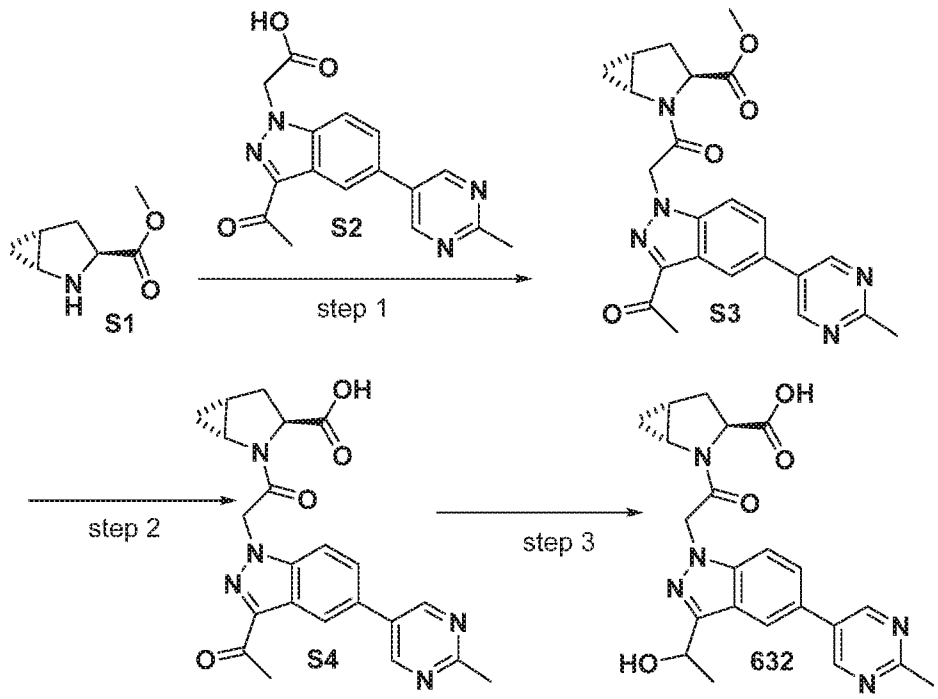
[0738] To a solution of methyl (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate (scheme 8-36 compound **S3,** 439 mg) in MeOH (5 mL) was added LiOH (48 mg) in 2 mL water solution. The reaction was then stirred for

3 h at room temperature. The reaction mixture was then added HCl/water (pH ~3) and removed all solvent. The remaining residue was purified by HPLC to afford the title compound.

Step 3 (2S,4R)-4-Fluoro-l-(2-(3-(l-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)pyrrolidine-2-carboxylic acid (631)

[0739] To a solution of methyl (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 8-36 compound **S4,** 425 mg) in MeOH (5 mL) was added $NaBH_4$ (40 mg) then stirred for 3 h at room temperature. AcOH was added to the reaction mixture and solvent was removed in vacuo. The residue was purified by HPLC to afford compound **631.** ¾ NMR (400 MHz, DMSO) δ 1.59 (dd, *J* = 1.8, 6.6 Hz, 3H), 2.08 (s, 1H), 2.01 - 2.23 (m, 1H), 2.57 (td, *J* = 7.1, 12.2, 13.4 Hz, 1H), 2.69 (s, 3H), 3.87 - 4.07 (m, 1H), 4.17 (dd, *J* = 12.5, 21.7 Hz, 1H), 4.32 (t, *J* = 8.5 Hz, 1H), 5.16 (m, 1H), 5.33 (dd, *J* = 2.6, 17.3 Hz, 1H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.48 - 5.60 (m, 1H), 6.35 (s, 1H), 7.60 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.71 - 7.80 (m, 1H), 8.28 (s, 1H), 9.05 (s, 2H); ^{19}F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -176.06. LC (method A): t_R = 0.72 min. LC/MS (EI) *mlz*: $[M + H]^+$ 428.

Scheme 8-37



Step 1 Methyl (lR,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-2-azabicyclo [3.1.0] hexane-3-car boxylate (S3)

[0740] To a solution of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-37 compound **S2,** 310 mg) in DMF (5 mL) was added DIEA (0.5 mL) followed by methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate (scheme 8-37 compound **SI,** 141 mg). HATU (456 mg) was then added slowly and the reaction mixture was stirred for 18 h at rt. The reaction mixture was then added to water (10 mL) and extracted with EtOAc (2 **x** 15 mL). The organic layer was washed successively with an aqeuous solution of NaHCCb (10 mL), water (10 mL), and brine (10 mL), dried overNa $_2$**S04** and concentrated under reduced pressure. The remaining residue was purified by HPLC to afford the title compound.

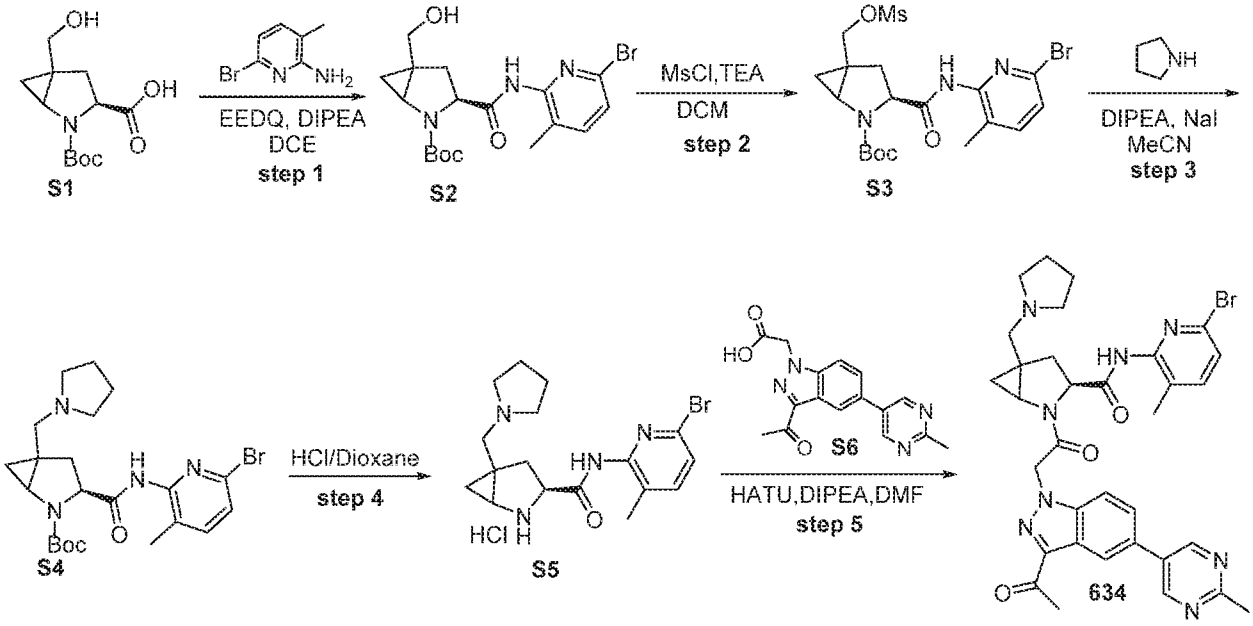
Step 2 (lR,3S,5R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (S4)

[0741] To a solution of methyl methyl (lR,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylate (scheme 8-37 compound **S3,** 433 mg) in MeOH (5 mL) was added LiOH (48 mg) in 2 mL water solution then stirred for 3 h at room temperature. The reaction mixture was then added HCl/water (pH ~3) and removed all solvent. The remaining residue was purified by HPLC to afford the title compound.

Step 3 (lR,3S,5R)-2-(2-(3-(l-Hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (632)

[0742] To a solution of (lR,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (scheme 8-37 compound **S4,** 419 mg) in MeOH (5 mL) was added $NaBH_4$ (40 mg). The reaction was then stirred for 3 h at room temperature. AcOH was added to the reaction mixture and solvent was removed in vacuo. The remaining residue was purified by HPLC to afford compound **632.** ¾ NMR (400 MHz, DMSO) δ 0.83 (m, 1H), 1.01 (m, 1H), 1.89 (m, 1H), 2.09 - 2.48 (m, 3H), 2.68 (m, 5H), 3.80 (m, 1H), 4.18 - 4.31 (m, 1H), 5.60 (d, *J* = 17.2 Hz, 1H), 5.98 (d, *J* = 17.3 Hz, 1H), 7.81 - 7.93 (m, 2H), 8.45 (s, 1H), 9.06 (s, 2H), 12.56 (s, 1H). LC (method **A):** t_R = 1.11 min. LC/MS (EI) *m/z*: $[M + H]^+$ 420.

Scheme 8-38



Step 1: (3S)-ferf-Butyl 3-(6-bromo-3-methylpyridin-2-ylcarbamoyl)-5-(hydroxymethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (S2)

[0743] To a solution of scheme 8-38 compound **SI** (1 g, 3.89 mmol) and 6-bromo-3-methylpyridin-2-amine (870 mg, 4.67 mmol) in DCE (10 ml) was added DIPEA (2.56 mL, 15.56 mmol) and EEDQ (1.92 g, 7.78 mmol). The reaction was stirred at 90 °C overnight. The solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate =2: 1) to afford scheme 8-38 compound **S2** (710 mg, 43.0% yield) as a white solid. LC/MS (ESI) *mlz*: 426 $(M+H)^+$.

Step 2: (3S)-terf-Butyl 3-(6-bromo-3-methylpyridin-2-ylcarbamoyl)-5-((methylsulfonyloxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (S3)

[0744] Methanesulfonyl chloride (0.08 mL, 1.05 mmol) was added to a solution of scheme 8-38 compound **S2** (300 mg, 0.70 mmol) and triethylamine (0.19 mL, 1.41 mmol) in DCM (6 mL) dropwise at 0 °C. After the addition was complete, the reaction was stirred at 0 °C for 2 h. The mixture was poured into ice-water. The organic layer was separated, washed with brine, dried over anhydrous Na_2S04 and filtered. The filtrate was concentrated to afford the crude scheme 8-38 compound **S3** (320 mg, 90.2% yield) as a yellow solid. The compound was carried forward without any further purification.

Step 3: (3S)-terf-Butyl 3-((6-bromo-3-methylpyridin-2-yl)carbamoyl)-5-(pyrrolidin-l-ylmethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (S4)

[0745] To a mixture of (lR,3S,5S)-*tert*-butyl 3-((6-bromo-3-methylpyridin-2-yl)carbamoyl)-5-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (scheme 8-38 compound **S3,** 25 mg, 0.05 mmol) in CftCN (2 mL) was added DIPEA (0.035 mL, 0.2 mmol) and pyrrolidine (4 mg, 0.055 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with DCM and washed with water and brine. The organic layer was dried over anhydrous Na_2S04, filtered and concentrated to afford scheme 8-38 compound **S4** (15 mg, 62.6 % yield) as a brown solid. LC/MS (ESI) *mlz:* 479 $(M+H)^+$.

Step 4: (3S)-N-(6-Bromo-3-methylpyridin-2-yl)-5-(pyrrolidin-l-ylmethyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (S5)

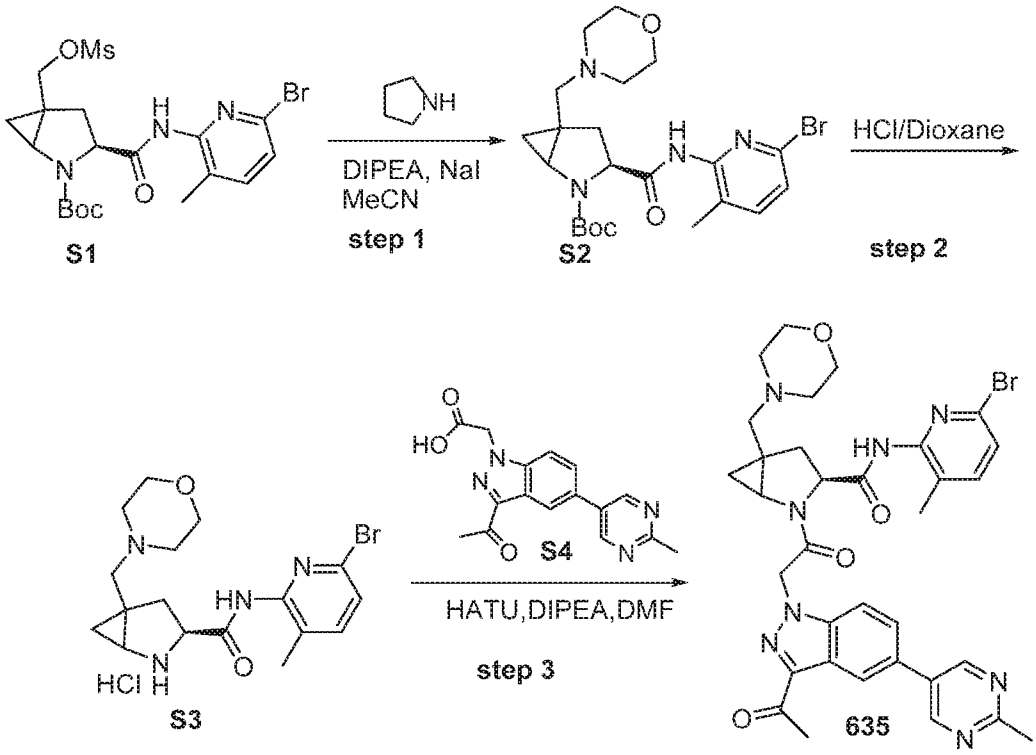
[0746] To a solution of (3S)-ter*t*-butyl 3-((6-bromo-3-methylpyridin-2-yl)carbamoyl)-5-(pyrrolidin-l-ylmethyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (scheme 8-38 compound **S4,** 15 mg, 0.03 mmol) in dioxane (1 mL) was added HCl/dioxane (1 mL) at 0 °C. The reaction was stirred at room temperature for 1 h. The mixture was concentrated to afford scheme 8-38 compound **S5** (17 mg, yield 100 %) as a brown solid, which was directly used in the next reaction without further purification. LC/MS (ESI) *mlz:* 379 $(M+H)^+$.

Step 5: (3S)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-(pyrrolidin-l-ylmethyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (634)

[0747] To a mixture of 2-(3-acetyl-5-(lH-benzo[d]imidazol-2-yl)-lH-indazol-l-yl)acetic acid (scheme 8-38 compound **S6,** 17 mg, 0.03 mmol), 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-38 compound **S5,** 9.3 mg, 0.03 mmol) and HATU (22.8 mg, 0.06 mmol) in DMF (1 mL) was added DIPEA (0.09 mL, 0.02 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with 10% aqeuous LiCl solution and brine. The organic layer was dried over anhydrous Na_2S0_4, filtered and concentrated. The residue was purified by preparative HPLC to afford compound **634** (2.2 mg, 10.9 % yield) as a white solid. ^{1}H-NMR (400 MHz, CD_3OD) δ 9.02 (s, 2H), 8.56 (s, 1H), 7.83 (d, J = 3.7 Hz, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 5.86 (d, J = 17.3

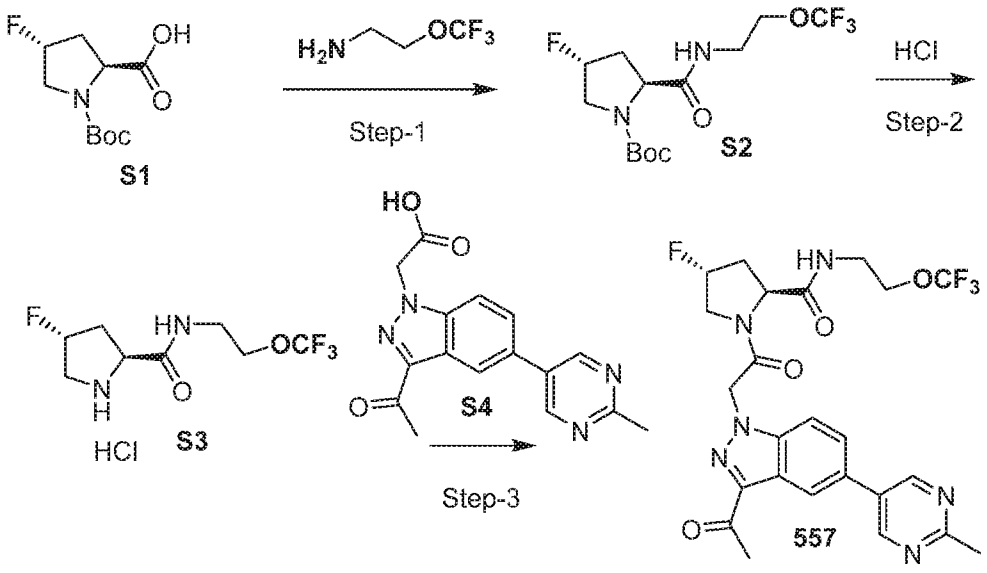
Hz, 1H), 5.70 (s, 1H), 5.34 (t, J = 4.7 Hz, 3H), 2.76 (s, 3H), 2.70 (d, J = 3.3 Hz, 3H), 2.23 - 2.17 (m, 3H), 2.13 (s, 5H), 2.03 (s, 4H), 1.60 (s, 4H), 0.91 (s, 2H). LC/MS (ESI) *mlz:* 671 $(M+H)^+$.

Scheme 8-39



[0748] **(3S)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-5-(morpholinomethyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (635):** Compound **635** was prepared according to the procedure for example 8-38 from appropriate starting materials. ^{1}HNMR (400 MHz, MeOD) δ 9.00 (s, 2H), 8.54 (s, 1H), 7.83 (t, J = 8.0, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 17.2 Hz, 1H), 5.63 (d, J = 17.2 Hz, 1H), 3.74 (t, J = 4.8 Hz, 4H), 3.65 (dd, J = 2.4, 2.4 Hz, 1H), 3.35 (s, 1H), 2.87 (s, J = 8.8 Hz, 1H), 2.75 (s, 3H), 2.70 (s, 3H), 2.55 (d, J = 17.6 Hz, 4H), 2.44 (d, J = 12.8 Hz, 1H), 2.35 - 2.27(m, 1H), 2.20(t, J = 3.6 Hz ,1H), 2.06 (d, J = 17.6 Hz, 3H), 1.62 - 1.60 (m, 1H), 1.03 (t, J = 5.6 Hz ,1H), 0.89 (d, J = 6.0 Hz, 1H). LC/MS (ESI) *mlz:* 687 $(M+H)^+$.

Scheme 8-40



Stepl: *tert-Butyl* (2S,4R)-4-fluoro-2-((2-(trifluoromethoxy)ethyl)carbamoyl)pyrrolidine-l-carboxylate (S2)

[0749] To a stirred solution of (2S, 4R)-l -(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 8-40 compound **SI,** 160 mg, 0.7 mmole) in 10 mL of DMF was added 2-(trifluoromethoxy)ethan-l -amine (116 mg, 1 equiv) , DIEA (0.4 mL, 3 equiv). This was followed by addition of HATU (319 mg, 1.2 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature. Water (10 mL) and ethyl acetate (15mL) were added to the reaction mixture, layers were separated and the aqueous layer was extracted with EtOAc (lxlOmL). The combined organic layer was washed with IN HCl (10 mL), saturated NaHCCb (lOmL), and brine (lOmL). Combined organic layers were dried overNa_2S04, concentrated and 250 mg (quantitative yield) of 557 was obtained.

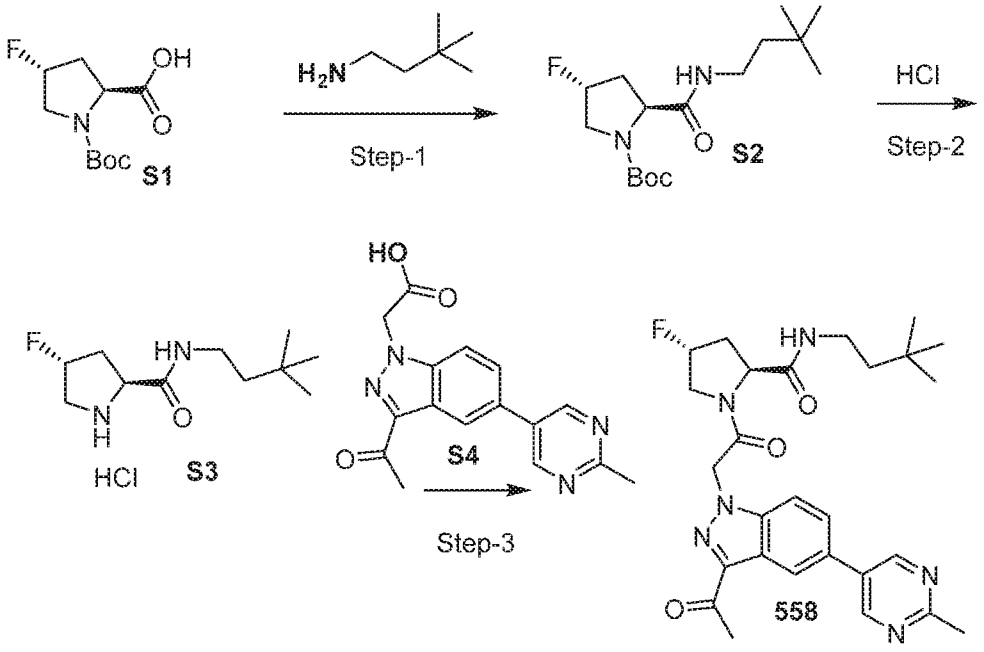
Step-2 : (2S,4R)-4-Fluoro-N-(2-(trifluoromethoxy)ethyl)pyrrolidine-2-carboxamide (S3)

[0750] To *tert*-butyl (2S,4R)-4-fluoro-2-((2-(trifluoromethoxy)ethyl)carbamoyl)pyrrolidine-l-carboxylate (scheme 8-40 compound **S2)** was added 10 ml of 4N HCl in dioxane. The resulting solution was stirred at room temperature for 6 h. The reaction mixture was then concentrated in vacuuo and carried forward without further purification.

Step-3: (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoro-N-(2-(trifluoromethoxy)ethyl)pyrrolidine-2-carboxamide (557)

[0751] To a stirred solution of (2S,4R)-4-fluoro-N-(2-(trifluoromethoxy)ethyl)pyrrolidine-2-carboxamide (hydrochloride salt, scheme 8-40 compound **S3,** 118 mg) in DMF (10 mL) was added 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-40 compound **S4,** 119 mg, 1.0 equiv.), HATU (173 mg,1.2 equiv), and DIEA (0.4 mL, 5.0 equiv). The reaction was stirred at room temperature and then diluted with EtOAC (15mL), and water (lOmL). The organic layer was washed with brine (3xl5mL), dried over Na_2S04 and concentrated in vacuuo. The resulting oil was purified by silica gel column chromatography (silica gel, eluted with 10 % MeOH in DCM gradient) to yield 109 mg (54%) of compound **557.** 1HNMR (400 MHz, DMSO-i¾): (major rotamer) δ 1.96-2.14 (m, 1H), 2.53-2.61 (m, 1H), 2.65 (s, 3H), 2.69 (s, 3H), 3.23-3.32 (m, 2H), 3.95-4.05 (m, 3H), 4.15-4.26 (m, 1H), 4.40 (t, 1H, J= 8.2 Hz), 5.43-5.83 (m, 3H), 7.76-7.90 (m, 2H), 8.45 (s, 1H), 9.06 (s, 2H); 19F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -58.86 (3F), -176.24 (IF). LC (method A): tR = 1.42 min. LC/MS (EI) *mlz*: [M+H]+ 537.

Scheme 8-41



Stepl: *tert*-Butyl (2S,4R)-2-((3,3-dimethylbutyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S2)

[0752] To a stirred solution of (2S, 4R)-l -*(tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 8-41 compound **SI,** 157 mg, 0.7 mmole) in 10 mL of DMF was added 3,3-dimethylbutan-l-amine (0.1 mL, 1 equiv) and DIEA (0.4 mL, 3 equiv). This was followed by addition of HATU (319 mg, 1.2 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature. Water (10 mL) and ethyl acetate (15mL) were added to the reaction mixture, layers were separated and the aqueous layer was extracted with EtOAc (lxlOmL). The combined organic layer was washed with IN HC1 (10 mL), saturated NaHCCb (lOmL) and brine (lOmL). Combined organic layers were dried over Na_2S04 and concentrated to yield 225 mg (quantative yield) of the title compound.

Step-2 : (2S,4R)-N-(3,3-Dimethylbutyl)-4-fluoropyrrolidine-2-carboxamide (S3)

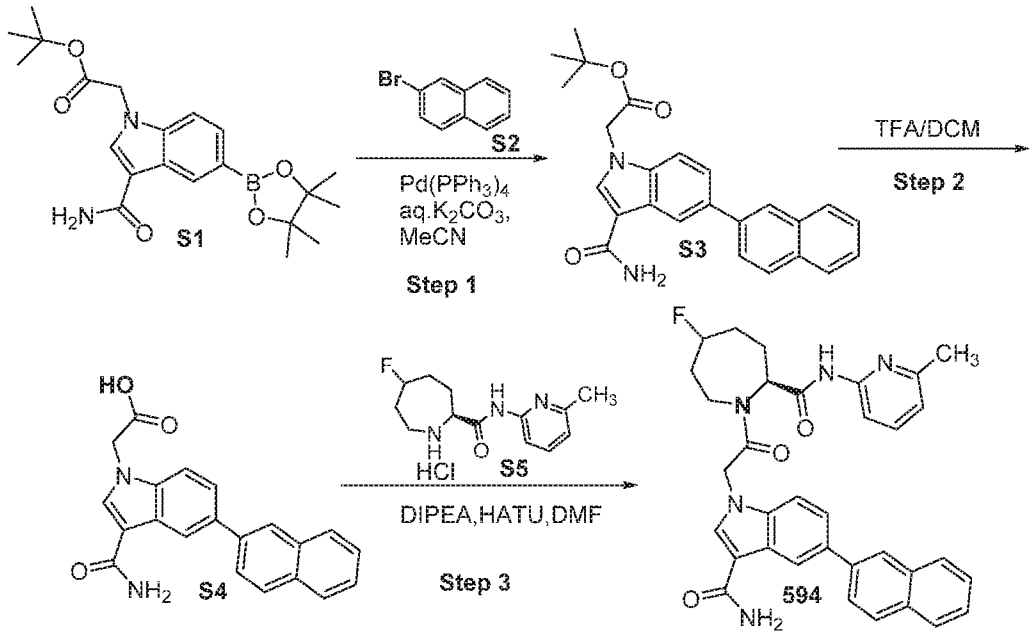
[0753] To ter*t*-butyl (2S,4R)-2-((3,3-dimethylbutyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 8-41 compound **S2)** was added 10 ml of 4N HC1 in Dioxane. The resulting solution was stirred at room temperature for 6 h. Then, the reaction mixture was concentrated in vacuuo and used for the following step.

Step-3: (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(3,3-dimethylbutyl)-4-fluoropyrrolidine-2-carboxamide (558)

[0754] To a stirred solution of (2S,4R)-N-(3,3-dimethylbutyl)-4-fluoropyrrolidine-2-carboxamide (scheme 8-41 compound **S3,** hydrochloride salt, 125 mg) in DMF (10 mL) was added 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-41 compound **S4,** 155 mg, 1.0 equiv.), HATU (228 mg,1.2 equiv), and DIEA (0.5 mL, 5.0 equiv). The reaction was stirred at room temperature for 2 h then diluted with EtOAC (15mL) and water (lOmL). The organic layer was washed with brine (3x15mL), dried over Na_2S0_4 and concentrated in vacuuo. The resulting oil was purified by silica gel column chromatography (silica gel, eluted with 10 % MeOH in DCM gradient) to yield 125 mg (49%) of compound **558.** 1H NMR (400 MHz, DMSO-*d6)*: (major rotamer) δ 0.93 (s, 9H), 1.31-1.38 (m, 2H), 2.03-2.22 (m, 1H), 2.41-2.55 (m, 1H), 2.74 (s, 3H), 2.78 (s, 3H), 2.97-3.21 (m, 2H), 3.95-4.09 (m, 1H), 4.21-4.32 (m, 1H), 4.41 (t, 1H, J= 8.2 Hz), 5.51-5.92 (m, 3H), 7.89-8.04 (m, 2H), 8.53 (s, 1H), 9.15 (s, 2H); 19F NMR (376 MHz,

OMSO-de): (major rotamer) -176.13 (IF). LC (method A): tR = 1.69 min. LC/MS (EI) *mlz:* [M+H]+ 509.

Scheme 8-42



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(naphthalen-2-yl)-lH-indol-l-yl)acetate (S3)

[0755] To a mixture of scheme 8-42 compound **SI** (200 mg , 0.5 mmol) and scheme 8-42 compound **S2** (123 mg , 0.6 mmol) in CH_3CN (5 mL) and water (2 mL) was added K2CO3 (206 mg , 1.5 mmol) and $Pd(PPh_3)_4$ (20 mg) at 0 °C. The reaction was degassed under N2 atmosphere three times and stirred at 80 °C under N2 atmosphere for 8 h. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous $Na2S0_4$, filtered and concentrated. The residue was purified by silica gel column chromatography (dichloromethane: methanol =100: 1) to afford scheme 8-42 compound **S3** (104 mg, 52.0% yield) as a white solid. LC/MS (ESI) *mlz:* 401 $(M+l)^+$.

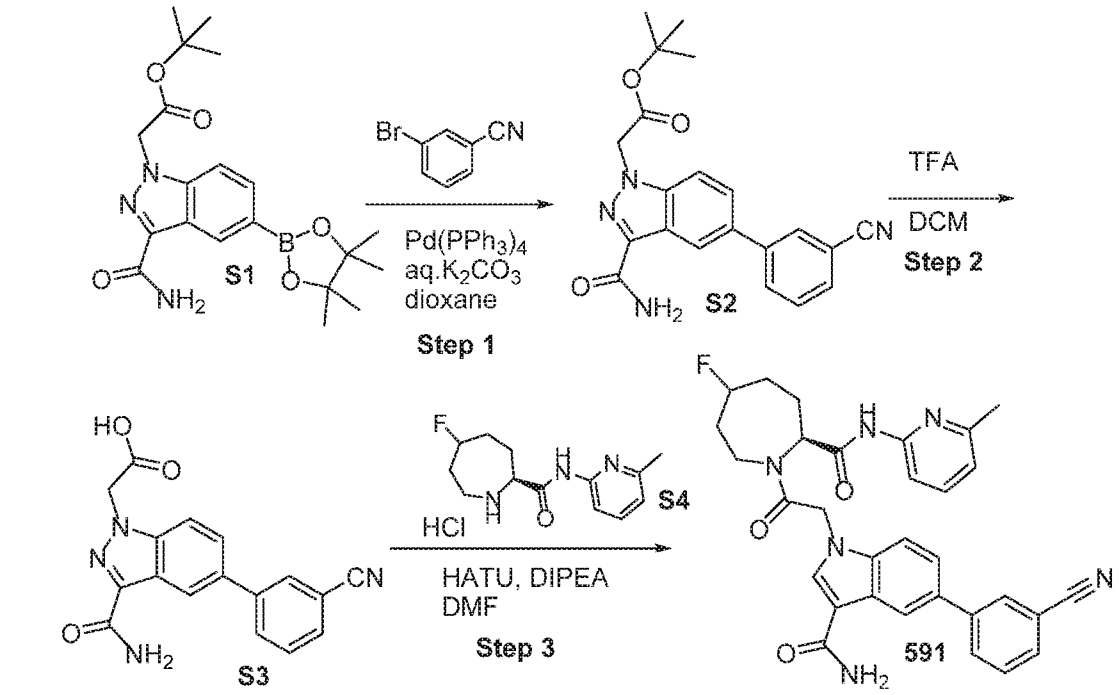
Step 2: 2-(3-Carbamoyl-5-(naphthalen-2-yl)-lH-indol-l-yl)acetic acid (S4)

[0756] TFA (0.5 mL) was added dropwise to a solution of scheme 8-42 compound **S3** (52 mg, 0.13 mmol) in DCM (1 mL) at 0 °C. The reaction was stirred at room temperature for 3 h. The resulting mixture was concentrated under vacuum to afford compound **S4** (60 mg, 100% yield) as a brown soild. LC/MS (ESI) *mlz:* 345 $(M+l)^+$.

Step 3: l-(2-((2S)-5-Fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(naphthaalen-2-yl)-lH-indole-3-carboxamide (S6)

[0757] To a mixture of scheme 8-42 compound **S4** (60 mg , 0.13 mmol) and scheme 8-42 compound **S5** (33 mg , 0.13 mmol) in DMF (1 mL) was added DIPEA (67 mg , 0.52 mmol) and HATU (99 mg , 0.26 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with 10% aqeuous LiCl solution and brine successively. The organic layer was dried over anhydrous Na_2S04, filtered and concentrated to dryness. The residue was purified by prep-TLC (DCM/ MeOH = 20: 1) to afford **594** (6 mg, 8.0 % yield) as a white solid. ¾ NMR (400 MHz, MeOD) δ: 8.53 (d, *J* = 1.3 Hz, 1H), 8.12 (s, 1H), 7.96 - 7.89 (m, 3H), 7.85 (dd, *J* = 8.5, 1.9 Hz, 3H), 7.72 - 7.58 (m, 2H), 7.48 (dd, *J* = 11.1, 5.1 Hz, 3H), 6.96 (d, *J* = 7.5 Hz, 1H), 5.41 (dd, *J* = 55.4, 17.2 Hz, 2H), 4.92 (d, *J* = 6.6 Hz, 1H), 4.03 (d, *J* = 16.4 Hz, 1H), 3.81 - 3.62 (m, 2H), 3.25 - 3.20 (m, 1H), 2.41 (d, *J* = 5.2 Hz, 3H), 2.37 - 2.13 (m, 2H), 1.97 (t, *J* = 11.1 Hz, 2H), 1.79 (d, *J* = 9.8 Hz, 1H). LC/MS (ESI) *mlz*: 578 (M+l) $^+$.

Scheme 8-43



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-indazol-l-yl)acetate (S2)

[0758] To a mixture of scheme 8-43 compound **SI** (200 mg, 0.498 mmol), 3-bromobenzonitrile (100 mg, 0.548mmol) and potassium carbonate (147 mg, 1.06 mmol) in dioxane (9 mL) and water (2 mL) was added tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol). The reaction was degassed under N_2 atmosphere three times and stirred at 100 °C for 2 h under N_2 atmosphere. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2S04, filtered and concentrated to dryness. The residue was purified by silica gel cloumn chromatography (eluted with Petroleum ether: Ethyl acetate =5:1 to 3:1) to afford scheme 8-43 compound **S2** (140 mg, 74.8% yield) as a white solid. LC/MS (ESI) *mlz:* 377 $(M+H)^+$.

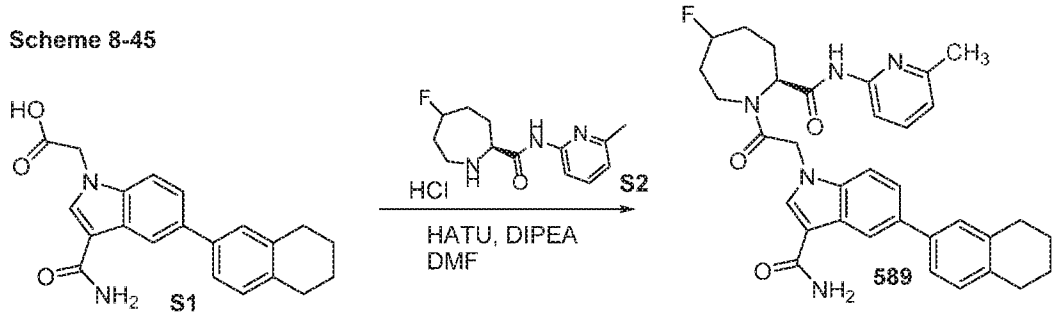
Step 2: 2-(3-Carbamoyl-5-(3-cyanophenyl)-lH-indazol-l-yl)acetic acid (S3)

[0759] To a solution of scheme 8-42 compound **S2** (140 mg, 0.372 mmol) in DCM (2 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 2 h. The mixture was concentrated to dryness to afford scheme 8-43 compound **S3** (110 mg, 92.4% yield) as a white solid. LC/MS (ESI) *mlz:* 321 $(M+H)^+$.

Step 3: 5-(3-Cyanophenyl)-l-(2-((2S)-5-fluoro-2-(6-methylpyridin-2-ylcarbamoyl)azepan-l-yl)-2-oxoethyl)-lH-indole-3-carboxamide (591)

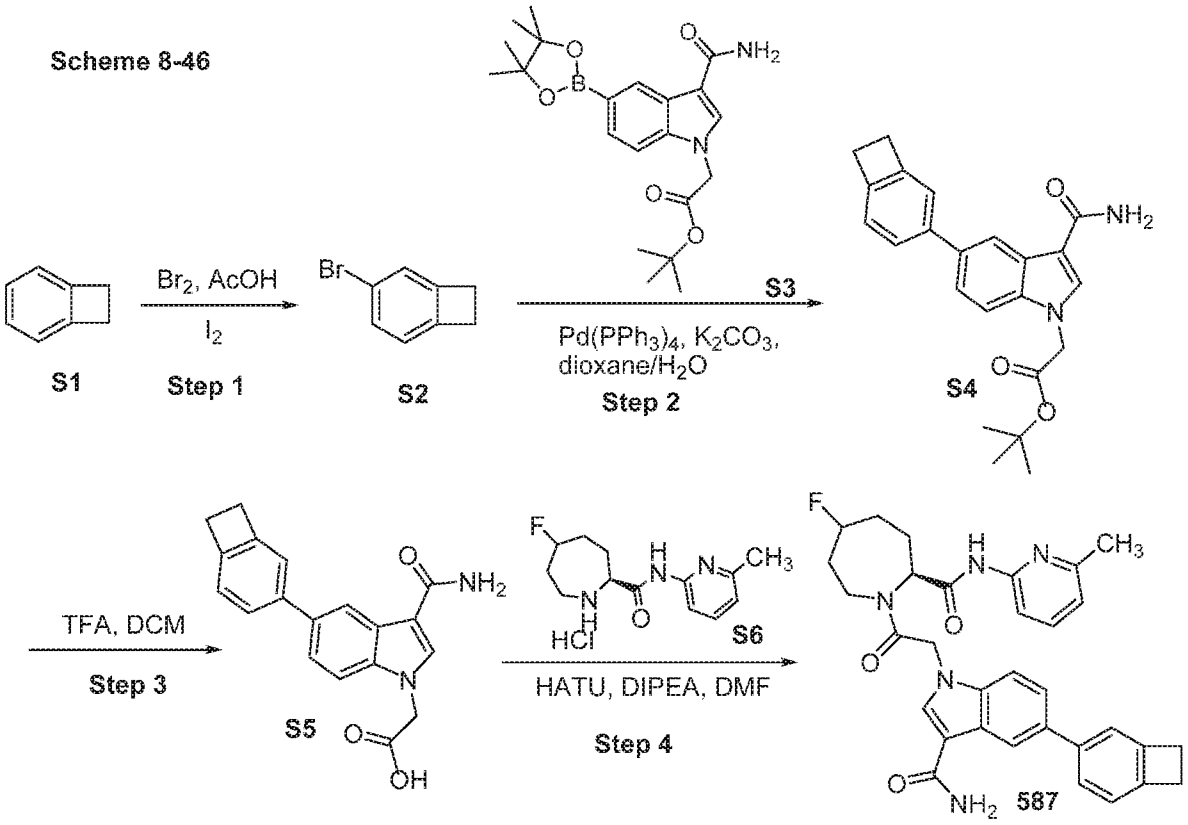
[0760] **l-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-lH-indole-3-carboxamide (591):** Compound **591** was prepared according to the procedure for the synthesis from example 8-46 from appropriate starting materials. ¾ NMR (400 MHz, DMSO-d_6) δ: 10.44 (d, J = 11.9 Hz, 1H), 8.41 (s, 1H), 8.12 (s, 1H), 8.06 - 7.94 (m, 2H), 7.77 (ddd, J = 25.4, 18.1, 7.9 Hz, 2H), 7.62 (ddd, J = 45.1, 25.2, 5.0 Hz, 3H), 6.94 (d, J = 7.5 Hz, 1H), 5.57 (d, J = 17.2 Hz, 1H), 5.13 (dd, J = 71.9, 31.9 Hz, 2H), 4.79 (d, J = 9.6 Hz, 1H), 3.96 (d, J = 14.6 Hz, 1H), 3.69 - 3.58 (m, 1H), 2.51 (s, 3H), 2.39 (d, J = 20.7 Hz, 2H), 2.17 (dd, J = 44.9, 27.6 Hz, 4H), 1.65 (d, J = 42.0 Hz, 2H). LC/MS (ESI) *mlz:* 553 $(M+H)^+$.

Scheme 8-45



[0761] **l-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-l-yl)-2-oxoethyl)-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-lH-indole-3-carboxamide (589):** Compound **589** was prepared according according to the procedure for the synthesis from Example 8-46 from appropriate starting materials. ¾NMR (400 MHz, MeOD) δ: 8.32 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.91 - 7.78 (m, 2H), 7.64 (dt, *J* = 25.8, 7.9 Hz, 1H), 7.46 - 7.25 (m, 4H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 25.4, 7.5 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.08 - 4.89 (m, 1H), 3.96 - 3.74 (m, 2H), 2.80 (d, *J* = 15.6 Hz, 4H), 2.46 - 2.19 (m, 6H), 2.11 (td, *J* = 16.1, 15.0, 7.6 Hz, 1H), 1.90 - 1.60 (m, 6H). LC/MS (ESI) *mlz*: 582 $(M+H)^+$.

Scheme 8-46



Step 1: 4-Bromo-l, 2-dihydrocyclobutabenzene (S2)

[0762] Br_2 (1.10 g, 6.88 mmol) dropwise to a mixture of 1, 2-dihydrocyclobutabenzene (scheme 8-46 compound **SI,** 650 mg, 6.25 mmol) and I2 (14 mg, 0.056 mmol) in AcOH/H_20 (8 mL/ 0.4 mL) at 0 °C for 20 min. The reaction was stirred at room temperature overnight. The mixture was poured into water and extracted with petroleum ether (50 mL). The organic layer was washed with aqeuous Na_2C0_3 solution and water, dried over anhydrous Na_2S04, and concentrated. The residue was purified by column chromatography on silica gel eluted with petroleum ether to afford scheme 8-46 compound **S2** (490 mg, 51.1 %) as a light yellow oil.

Step 2: *tert*-Butyl 2-(3-carbamoyl-5-(l, 2-dihydrocyclobutabenzen-4-yl)-lH-indol-l-yl) acetate (S4)

[0763] To a solution of 4-bromo-l, 2-dihydrocyclobutabenzene (scheme 8-46 compound **S2,** 490 mg, 2.68 mmol) in dioxane/H_20 (10 mL, v/v = 9:1) was added scheme 8-43 compound S3 (1.07 g, 2.68 mmol), K_2C0_3 (924 mg, 6.69 mmol), and tetrakis(triphenylphosphine) palladium (154 mg, 0.13 mmol) under N2 atmosphere. The reaction was stirred at 80 °C overnight. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na_2S0_4 and concentrated. The residue was purified by column chromatography on silica gel eluted with DCM/MeOH (100:1 to 50:1) to afford scheme 8-43 compound **S4** (700 mg, 69.5 % yield) as a light yellow solid. LC/MS (ESI) *mlz:* 377 $(M+H)^+$.

Step 3: 2-(3-Carbamoyl-5-(l, 2-dihydrocyclobutabenzen-4-yl)-lH-indol-l-yl) acetic acid (S5)

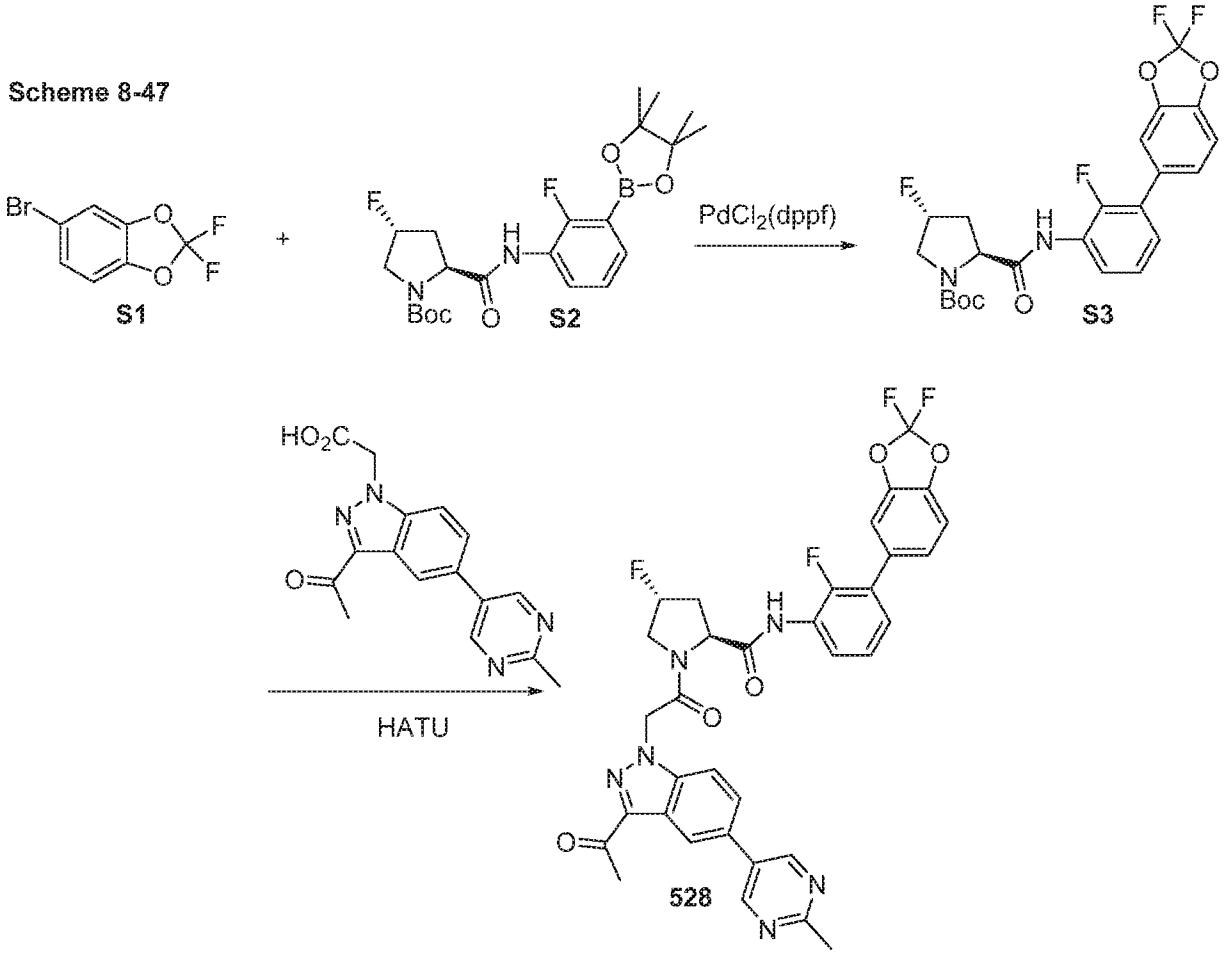
[0764] To a solution of ter*t*-butyl 2-(3-carbamoyl-5-(l, 2-dihydrocyclobutabenzen-4-yl)-lH-indol-l-yl) acetate (scheme 8-46 compound **S4,** 340 mg, 0.91 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was stirred at room temperature for 2 h. The mixture was concentrated to afford scheme 8-46 compound **S5** (170 mg, 58.8 % yield) as a yellow solid, which was used directly in the next step. LC/MS (ESI) *mlz:* 321 $(M+H)^+$.

Step 4: 5-(l,2-Dihydrocyclobutabenzen-4-yl)-l-(2-((2S)-5-fluoro-2-(6-methylpyridin-2-ylcarbamoyl)azepan-l-yl)-2-oxoethyl)-lH-indole -3-carboxamide (587)

[0765] Compound **587** was prepared according the procedure for according to the procedure from Example 8-46 from appropriate starting materials. ¾ NMR (400 MHz, DMSO-*d_6)* 5:10.42 (s, 1H), 8.30 (d, *J* = 1.2 Hz, 1H), 8.00 - 7.92 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.62 (t,

J = 8.0, Hz, 1H), 7.56 - 7.22 (m, 5H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 4.88 - 4.62 (m, 2H), 3.97 (d, *J* = 16.2 Hz, 1H), 3.68 - 3.43 (m, 1H), 3.18 (d, *J* = 2.8 Hz, 4H), 2.39 (s, 3H), 2.33 - 2.08 (m, 3H), 2.03 - 1.75 (m, 2H), 1.68 - 1.50 (m, 1H); LC/MS (ESI) *mlz*: 554 $(M+H)^+$.

Scheme 8-47

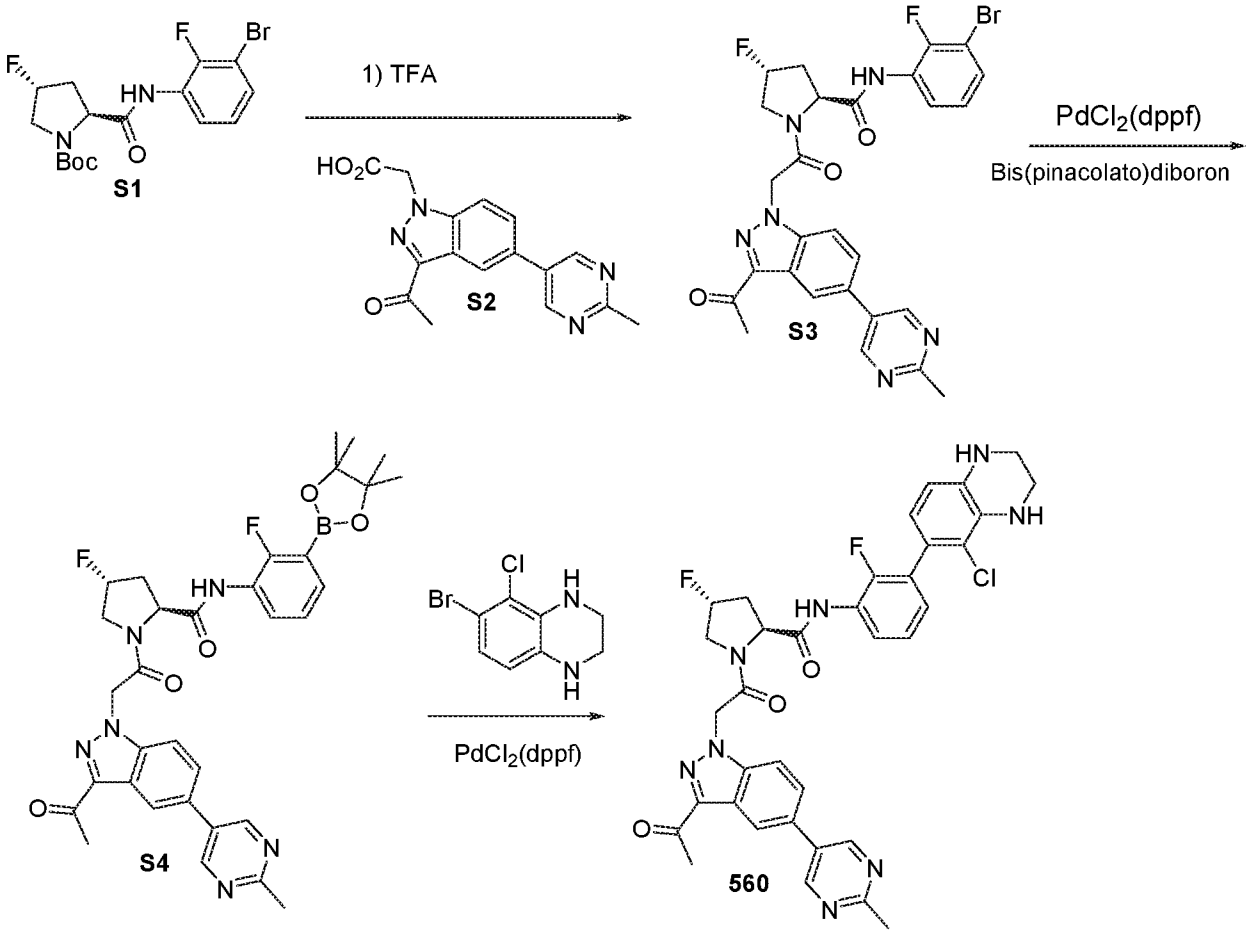


[0766] **teri-Butyl(2S,4R)-2-((3-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S3):** *ter t*-Butyl (2S,4R)-4-fluoro-2-((2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)pyrrolidine-l-carboxylate (scheme 8-47 compound **S2,** 0.100 g), 5-bromo-2,2-difluorobenzo[d][l,3]dioxole (scheme 8-46 compound **SI,** 0.05 g), $Pd(PPh_3)_4$ and sodium carbonate were mixed in a pressure tube under argon. To this mixture, 4 mL of dioxane and 1 mL of water were added. The mixture was bubbled with argon for 5 min and the vial stoppered and subjected to microwave irradiation at 100 °C for 45 min. The volatiles were removed under

reduced pressure and the residue was purified by silica gel column chromatography (0-1.5 % MeOH in CH2CI2) to afford the desired product.

[0767] **(2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl *)-N*-(3-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide (528):** *ter t*-Butyl (2S,4R)-2-((3-(2,2-difluorobenzo[d][l,3]dioxol-5-yl)-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 8-46 compound **S3,** 60 mg) was dissolved in CH2CI2 (1 mL) and an equal volume of TFA was added. The mixture was stirred for 30 min at room temperature. Then the volatiles were removed under reduced pressure. The residue was dissolved in DMF (1.0 mL) and ^{i}Pn NEt (160 μL) was added, followed by the sequential addition of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (38 mg) and HATU (57 mg) slowly at 5 °C. The reaction mixture was then stirred for 30 min at room temperature and poured into water (10 mL). The solid was isolated by filtration, washed with water and dried in *vacuo.* The solid was then purified by silica gel column chromatography (eluent: 0-2.5 % MeOH in CH2CI2) to afford compound **528.** ¾ NMR (400 MHz, CD_3OD) (major rotamer): δ 2.29-2.46 (m, 1H), 2.67 (s, 3H), 2.71-2.26 (m, 1H), 2.74 (s, 3), 3.99-4.12 (m, 1H), 4.27 (dd, J = 20.4, 12 Hz, 1H), 4.87 (t, J = 8.4 Hz, 1H), 5.53 (d, J = 52 Hz, 1H), 5.53 (d, J = 16.8 Hz, 1H), 5.64 (d, J = 16.8 Hz, 1H), 7.09-7.37 (m, 5 H), 7.62 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 8.44 (s, 1H), 8.89 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) (major rotamer): δ -52.3, -132.1, -178.5.

Scheme 8-48



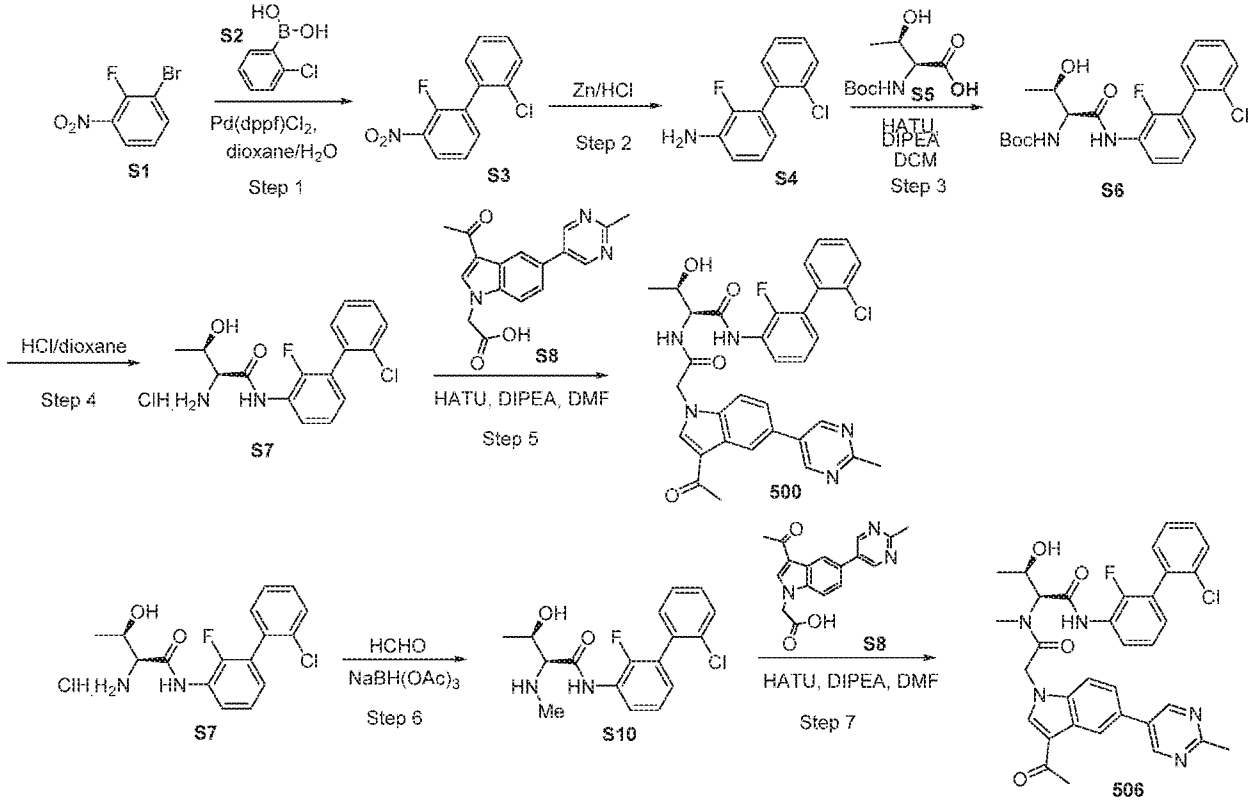
[0768] **(2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(3-bromo-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide (S3):** *ter t*-Butyl (2S,4R)-2-((3-bromo-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 8-48 compound **SI,** 0.653 g) was dissolved in CH_2Cl_2 (6 mL) and an equal volume of TFA was added. The mixture was stirred for 30 min at room temperature. Then the volatiles were removed under reduced pressure. The residue was dissolved in DMF (5 mL) and $^{i}Pr_2NEt$ (1.4 mL) was added, followed by the sequential addition 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 8-48 compound **S2,** 0.450 g) and HATU (0.735 g, 1.2 equiv) slowly at 5 °C. The reaction mixture was then stirred for 30 min at room temperature, poured into water (10 mL) and the solid was isolated by filtration, washed with water and dried in *vacuo.* The solid was then purified by silica gel column chromatography (eluent: 0-2.5 % MeOH in CH_2Cl_2) to get a white solid, scheme 8-48 compound **S3.**

[0769] **(2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoro-*N*-(2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-2-carboxamide (S4):** (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(3-bromo-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide (scheme 8-48 compound **S3,** 0.82 g), bis(pinacolato)diboron (0.875 g), Pd(dppf)Cl2 (0.225 g) and potassium acetate (0.406 g) were taken up in a pressure tube under argon. To this mixture, 20 mL of dioxane was added. The mixture was bubbled with argon for 5 min and the vial stoppered and heated at 90 °C overnight. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-5 % MeOH in CH2CI2) to afford the desired product.

[0770] **(2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(3-(5-chloro-l,2,3,4-tetrahydroquinoxalin-6-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide (560):** (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoro-N-(2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-2-carboxamide (scheme 8-48 compound **S4,** 0.196 g), 6-bromo-5-chloro-1,2,3,4-tetrahydroquinoxaline (0.05 g), Pd(dppf)Cl2 (33 mg) and potassium carbonate (0.140 g) were taken in a pressure tube under argon. To this mixture, 4 mL of dioxane and 1 mL of water were added. The mixture was bubbled with argon for 5 min and the vial stoppered subjected to microwave irradiation at 100 °C for 45 min. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (0-3 % MeOH in CH2CI2) to afford the desired product. ¾ NMR (400 MHz, DMSO) (major rotamer) δ 2.04-2.28 (m, 1H), 2.50-2.57 (m, 1H), 2.57 (s, 3H), 2.61 (s, 3H), 3.12-3.18 (m, 2H), 3.29-3.32 (m, 2H), 3.88-3.99 (m, 1H), , 4.1 1 - 4.22 (m, 1H), 4.71 (**t, *J*** = 8.4 Hz, 1H), 5.21 (s, 1H), 5.42-5.79 (m, 3H), , 6.22 (**d, *J*** = 8.0 Hz, 1H), **6.32** (**d, *J*** = 7.8 Hz, 1H), 6.86 (**t, *J*** = 7.1 Hz, 1H), 7.01 (**t, *J*** = 6.4 Hz, 1H), 7.67 - 7.78 (m, 3H), , 8.36 (s, 1H), 8.96 (s, 2H), 9.80 (s, 1H). ^{19}F NMR (376 MHz, DMSO) (major rotamer): ₡ -126.5, -175.9.

EXAMPLE 9. SYNTHESIS OF ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I, FORMULA I' AND FORMULA I"

Scheme 9-1



Step 1: 2'-Chloro-2-fluoro-3-nitrobiphenyl (S3)

[0771] To a solution of scheme 9-1 compound **SI** (10.0 g, 45.68 mmol) and scheme 9-1 compound **S2** (9.26 g, 59.38 mmol) in dioxane (100 mL)/water (20 mL) is added K2CO3 (15.78 g, 114.2 mmol) and Pd(dppf)C12 (3.34 g, 4.59 mmol). The reaction was stirred at 120 °C overnight under nitrogen. After cooling to room temperature, the catalyst was removed by filtration and the filtrate is concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 500: 1 to 100: 1) to afford compound 3 (10 g, yield 80%) as a yellow solid.

Step 2: 2'-Chloro-2-fluorobiphenyl-3-amine (S4)

[0772] To a solution of scheme 9-1 compound **S3** (10 g, 39.8 mmol) in MeOH (250 mL) was added zinc powder (23.5g, 358.6 mmol) and 3 M HC1 (133 mL, 398 mmol). The resulting mixture was stirred at room temperature overnight and then filtered through Celite. The filtrate was concentrated to afford compound 4 (5 g, yield 60%), which was used in the next step without further purification. LC-MS: *mlz* 222 (M+H)+.

Step 3: *(tert-Butyl* (2S,3R)-l-(2'-chloro-2-fluorobiphenyl-3-ylamino)-3-hydroxy-l-oxobutan-2-ylcarbamate (S6)

[0773] To a solution of scheme 9-1 compound **S4** (1.0 g, 4.5 mmol), scheme 9-1 compound **S5** (1.09 g, 4.98 mmol) and DIPEA (1.17 g, 9.05 mmol) in DCM (4 mL) was added HATU (2.06 g, 5.4 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated. The residue is purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford compound 6 (0.5 g, yield 30%) as a white solid.

Step 4: (2S,3R)-2-Amino-N-(2'-chloro-2-fluorobiphenyl-3-yl)-3-hydroxybutanamide (S7)

[0774] A mixture of scheme 9-1 compound **S6** (840 mg, 1.99 mmol) and HCl/dioxane (40 mL) was stirred at room temperature overnight, and then concentrated to afford the crude compound 7 (700 mg), which was used in the next step without further purification. LC-MS: ***m/z*** 323 (M+H)+.

Step 5: (2S,3R)-2-(2-(3-Acetyl-lH-indol-l-yl)acetamido)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-3-hydroxybutanamide (500)

[0775] To a solution of scheme 9-1 compound **S7** (80 mg, 0.25 mmol), scheme 9-1 compound **S8** (92 mg, 0.29 mmol) and DIPEA (160 mg, 1.24 mmol) in DMF (3 mL) was added HATU (208 mg, 0.55 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H20 as eluent) to afford scheme 9-1 compound **500** as a white solid (37 mg, yield 24%). LC-MS: ***m/z*** 614 (M+H)+. 1H-NMR: δ 9.83 (s, 1H), 8.97 (s, 2H), 8.62 (d, J = 8.0 Hz, 1H), 8.44 (d, 2H), 8.01 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.59 (m, 2H), 7.54-7.36 (m, 3H), 7.27 (t, J = 8.0 Hz, 1H), 7.1 1 (t, J = 8.0 Hz, 1H), 5.14-5.25 (m, 3H), 4.57 (dd, J = 31.2, 4.3 Hz, 1H), 4.16 (s, 1H), 2.68 (s, 3H), 2.47 (s, 3H), 1.15 (d, J = 11.2 Hz, 3H).

Step 6: (2S,3R)-N-(2'-Chloro-2-fluorobiphenyl-3-yl)-3-hydroxy-2-(methylamino)butanamide (S10)

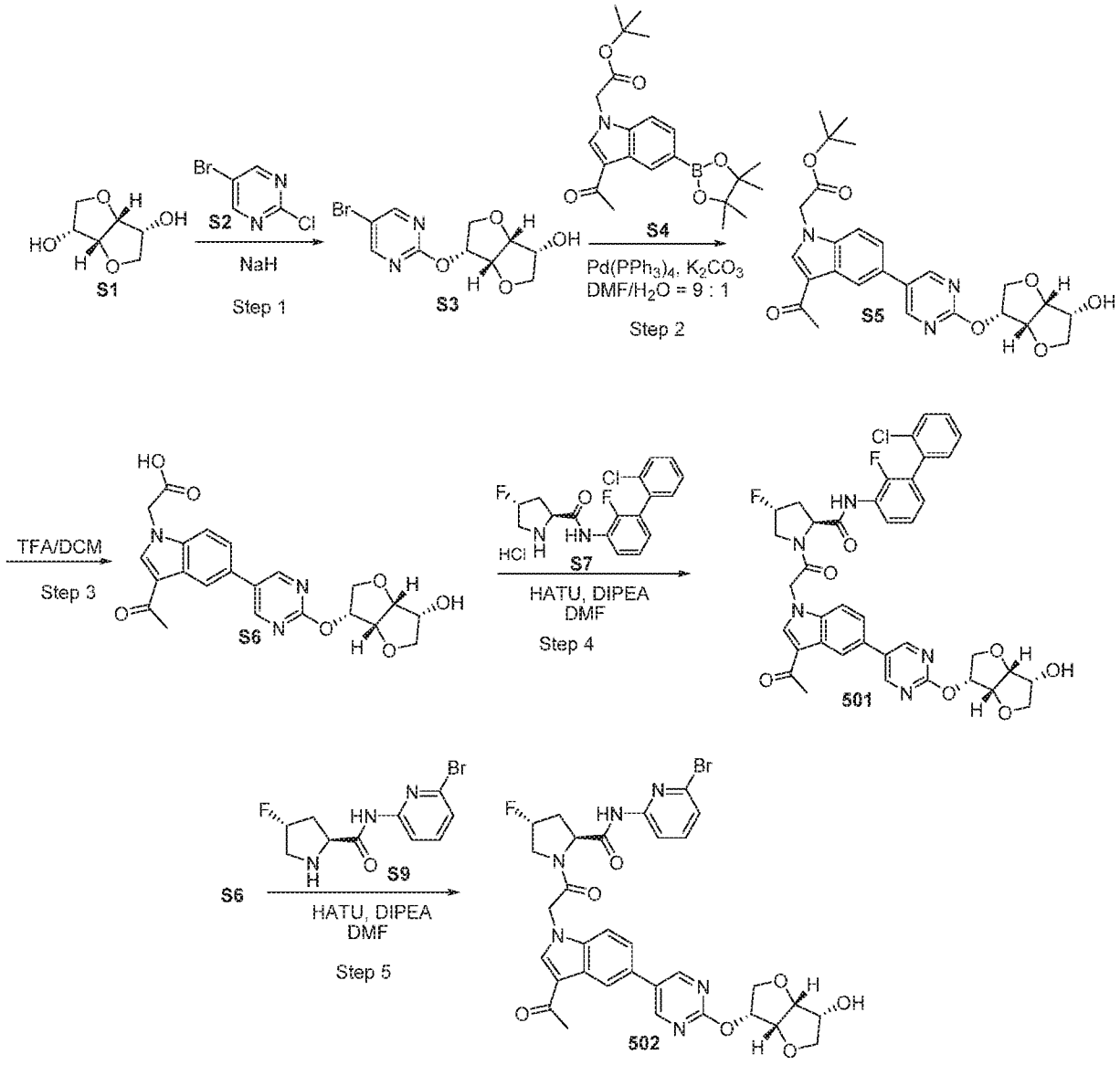
[0776] To a solution of scheme 9-1 compound **S7** (0.35 g, 1.08 mmol) in CICH2CH2CI (10 mL) was added $(CH20)_n$ (16.3 mg, 0.54 mmol). The resulting mixture was stirred at 80 °C overnight and concentrated under high vacuum. The residue was dissolved in methanol (5 mL)

followed by the addition of $NaBH(OAc)_3$. The resulting mixture was stirred at room temperature overnight and then concentrated to afford the crude scheme 9-1 compound **S10** (0.35 g), which was used in the next step without further purification.

Step 7: (2S,3R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indol-l-yl)-N-methylacetamido)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-3-hydroxybutanamide (Sll)

[0777] To a solution of scheme 9-1 compound **S10** (170 mg, 0.50 mmol), scheme 9-1 compound **S8** (187 mg, 0.61 mmol), and DIPEA (423 mg, 1.1 1 mmol) in DMF (3 mL) was added HATU (326 mg, 2.5 mmol). The reaction mixture is stirred at room temperature overnight and concentrated. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H20 as eluent) to afford scheme 9-1 compound **506** as a white solid (5 mg, yield 2%). LC-MS: *mlz* 628 (M+H)+. 1H-NMR: δ 8.83 (s, 2H), 8.49 (s, 2H), 8.09 (t, J = 6.4 Hz, 1H), 7.78 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.29 - 7.21 (m, 5H), 7.15 (m, 2H), 7.03 (t, J = 6.4 Hz, 1H), 5.08 (s, 2H), 4.98 (d, J = 3.6 Hz, 1H), 4.49 (s, 1H), 3.32 (s, 3H), 2.78 (s, 3H), 2.39 (s, 3H), 1.29 (d, J = 6.0 Hz, 3H).

Scheme 9-2



Step 1: (3R,3aR,6R,6aR)-6-(5-Bromopyrimidin-2-yloxy)hexahydrofuro[3,2-b]furan-3-ol (S3)

[0778] To an ice-water cooled solution of scheme 9-2 compound **SI** (5.0 g, 13.69 mmol) in DMF (20 mL) was added NaH (1.09 g, 27.37 mmol) under nitrogen protection. The reaction mixture was stirred at this temperature for 30 min and compound 2 (2.65 g, 13.69 mmol) was added. The reaction mixture was stirred at 60 °C for 2 h and then the reaction waspoured carefully into saturated NH4CI solution. The resulting mixture was extracted with ethyl acetate (200 mL). The organic layer was dried over anhydrous **Na_2S04** and concentrated. The residue was purified

by preparative HPLC (acidic condition, using CH3CN/H20 as eluent) to afford scheme 9-2 compound **S3** (0.75 g, yield 20%) as a white solid.

Step 2: *tert-Butyl* 2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetate (S5)

[0779] To a solution of scheme 9-2 compound **S3** (0.75 g, 2.47 mmol) and scheme 9-2 compound **S4** (1.09 g, 2.72 mmol) in DMF (18 mL)/water (2 mL) was added K2CO3 (0.68 g, 4.95 mmol) and $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol). The reaction mixture was stirred at 120 °C under N_2 protection for 2 h and then quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine, dried over anhydrous Na_2S04, filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 100:1 to 5:1) to afford scheme 9-2 compound **S5** (0.4 g, yield 35%) as a yellow solid. LC-MS: *mlz* 496 (M+H)+.

Step 3: 2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy) pyrimidin-5-yl)-lH-indol-l-yl)acetic acid (S6)

[0780] To a solution of scheme 9-2 compound **S5** (400 mg, 0.81 mmol) in DCM (5 mL), TFA (5 mL) was added. The resulting mixture was stirred at room temperature for 4 h and then concentrated to afford crude product 6 (300 mg). The compound was carried forward without further purification. LC-MS: *mlz* 440 (M+H)+.

Step 4: (2S,4R)-l-(2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide (501)

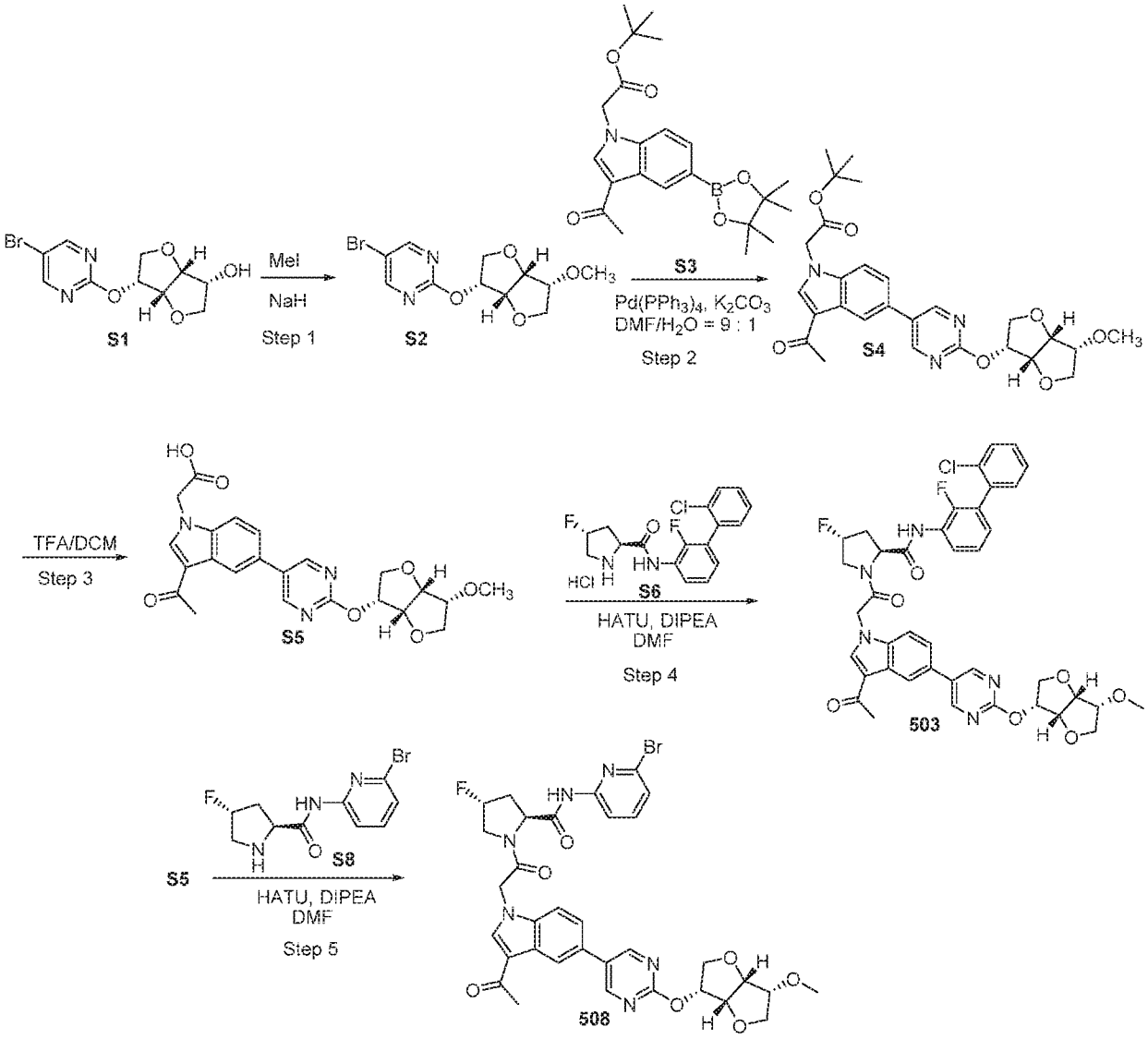
[0781] To a solution of scheme 9-2 compound **S6** (100 mg, 0.23 mmol), scheme 9-2 compound **S7** (76 mg, 0.23 mmol), and DIPEA (60 mg, 0.46 mmol) in DMF (2 mL) was added HATU (175 mg, 0.46 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated under high vacuum. The residue was purified by preparative FIPLC (acidic condition, using CH3CN/H20 as eluent) to afford the desired product **501** as a white solid (50 mg, yield 29%). LC-MS: *mlz* 758 (M+H)+. 1H-NMR: δ 10.00 (s, 1H), 8.86 (s, 2H), 8.40 (s, 1H), 8.32 (s, 1H), 7.96 (t, 1H), 7.30-7.64 (m, 7H), 7.22 (t, 1H), 7.01-7.13 (m, 1H), 5.01-5.81 (m, 5H), 4.96

(d, IH), 4.83 (t, IH), 4.77 (t, IH), 4.37 (t, IH), 3.84-4.28 (m, 5H), 3.74 (t, IH), 2.56-2.66 (m, IH), 2.45 (s, 3H), 2.1 1-2.31 (m, IH).

Step 5: (2S,4R)-l-(2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (502)

[0782] To a solution of scheme 9-2 compound **S6** (100 mg, 0.23 mmol), scheme 9-2 compound **S8** (66 mg, 0.23 mmol), and DIPEA (60 mg, 0.46 mmol) in DMF (2 mL) was added HATU (175 mg, 0.46 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford the desired product **502** as a white solid (65 mg, yield 40%). LC-MS: *mlz* 709 (M+H)+. IH-NMR: δ 8.80 (s, 2H), 8.47 (d, IH), 8.20 (d, IH), 7.89-8.00 (m, IH), 7.57 (d, IH), 7.43-7.52 (m, 2H), 7.25-7.41 (m, 3H), 7.17 (t, IH), 7.00-7.09 (m, IH), 5.34-5.58 (m, 3H), 5.24 (d, IH), 4.95-4.99 (m, IH), 4.84 (d, IH), 4.64 (t, IH), 4.20-4.29 (m, IH), 3.88-4.19 (m, 5H), 3.60-3.66 (m, IH), 3.47 (s, 3H), 2.84-3.00 (m, IH), 2.66-2.78 (m, IH), 2.51 (s, 3H), 2.24-2.43 (m, IH).

Scheme 9-3



Step 1: 5-Bromo-2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidine (S2)

[0783] To an ice-water cooled solution of scheme 9-3 compound **SI** (0.15 g, 0.2 mmol) in DMF (5 mL) was added NaH (16 mg, 0.4 mmol, 60 % wt) under nitrogen protection. The reaction was stirred at this temperature for 30 min followed by the addition of MeI (60 mg, 0.4 mmol). The reaction mixture was stirred at 0 °C for 2 h and then poured carefully into a saturated NH_4Cl solution. The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by preparative

HPLC (acidic condition, using CH3CN/H2O as eluent) to afford scheme 9-3 compound **S2** (80 mg, yield 53%) as a white solid.

Step 2: *tert-Butyl* 2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetate (S4)

[0784] To a solution of scheme 9-3 compound **S2** (0.08 g, 0.25 mmol) and scheme 9-3 compound S3 (0.2 g, 0.5 mmol) in DMF (5 mL)/water (1 mL) was added K2CO3 (0.07 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.025 mmol). The mixture was stirred at 120 °C under N2 protection for 2 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford scheme 9-3 compound **S4** (0.06 g, yield 50%) as a yellow solid. LC-MS: *mlz* 510 (M+H)+.

Step 3: 2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy) pyrimidin-5-yl)-lH-indol-l-yl)acetic acid (S5)

[0785] To a solution of scheme 9-3 compound **S4** (60 mg, 0.12 mmol) in DCM (1 mL), TFA (1 mL) was added dropwise. The resulting solution was stirred at room temperature for 4 h and then concentrated to afford crude product 6 (60 mg), which was used in the next step without further purification. LC-MS: *mlz* 454 (M+H)+.

Step 4: (2S,4R)-l-(2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide (503)

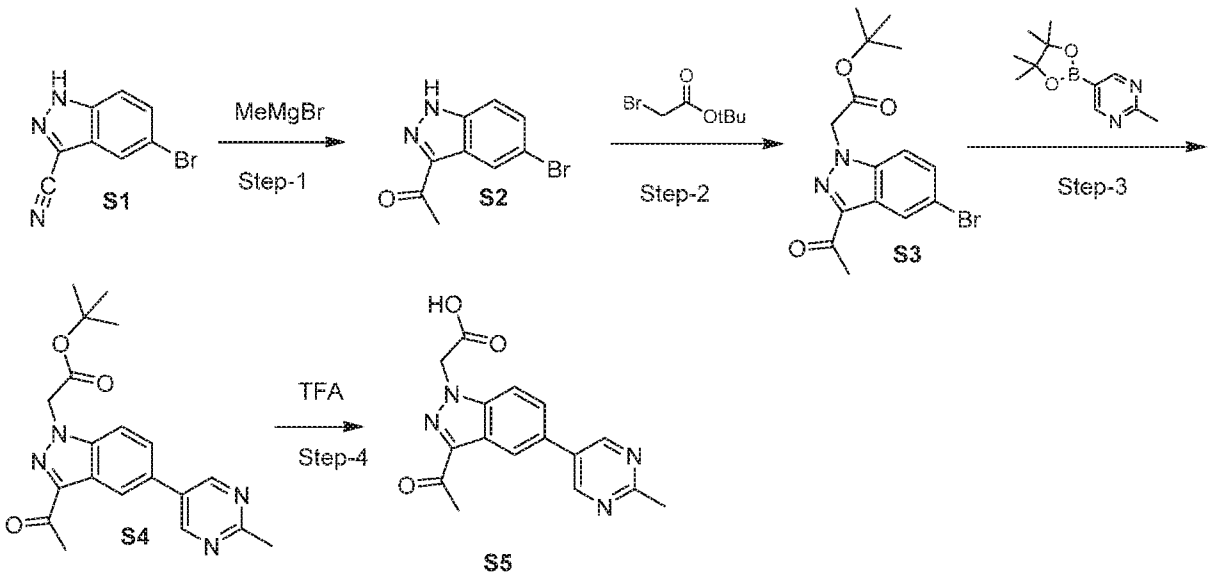
[0786] To a solution of scheme 9-3 compound **S5** (30 mg, 0.06 mmol), scheme 9-3 compound **S6** (23 mg, 0.06 mmol), and DIPEA (15 mg, 0.12 mmol) in DMF (2 mL) was added HATU (45 mg, 0.12 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated under vacuum. The residue was purified by preparative HPLC (acidic condition, using CH_3CN/H20 as eluent) to afford the desired product **503** as a white solid (10 mg, yield 22%). LC-MS: *mlz* 772 (M+H)+. 1H-NMR: δ 11.05 (s, 1H), 8.87 (s, 2H), 8.38 (s, 1H), 8.34 (d, 1H), 8.04 (d, 1H), 7.71 (t, 1H), 7.59 (q, 2H), 7.33 (d, 1H), 5.08-5.67 (m, 5H), 4.96 (s, 1H), 4.83 (t, 1H), 4.68

(t, 1H), 4.37 (t, 1H), 4.06-4.22 (m, 4H), 3.91 (dd, 1H), 3.74 (t, 1H), 2.57 (m, 1H), 2.47 (s, 3H), 2.05-2.25 (m, 1H).

Step 5: (2S,4R)-l-(2-(3-Acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-lH-indol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (508)

[0787] To a solution of scheme 9-3 compound **S5** (30 mg, 0.06 mmol), scheme 9-3 compound **S8** (17 mg, 0.06 mmol), and DIPEA (15 mg, 0.12 mmol) in DMF (2 mL) was added HATU (45 mg, 0.12 mmol). The resulting solution was stirred at room temperature overnight and concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford the desired product **508** as a white solid (5 mg, yield 12%). LC-MS: *mlz* 723 (M+H)+. 1H-NMR: δ 8.79 (s, 2H), 8.39 (s, 1H), 8.07 (s, 1H), 7.95 (d, 1H), 7.39-7.47 (m, 3H), 7.14 (d, 1H), 4.85-5.46 (m, 5H), 4.75 (t, 1H), 4.64 (t, 1H), 4.54 (t, 1H), 3.77-4.12 (m, 7H), 3.5 6 (t, 1H), 3.39 (s, 3H), 2.52-2.53 (m, 1H), 2.42(s, 3H), 2.09-2.15 (m, 1H).

Scheme 9-4



Step-1: l-(5-Bromo-l *H*-indazol-3-yl)ethan-l-one (S2)

[0788] To an ice-cold solution of 5-bromo-lH-indazole-3-carbonitrile (scheme 9-4 compound **SI,** 110 g) in a mixture of 1.1 L THF and 3.3 L diethyl ether, methyl magnesium

bromide (1 M in THF, 1.48 L, 3 equiv) was added dropwise. After completion of addition, the reaction mixture was brought to room temperature and stirred for 3 h (monitored by HPLC). Then the reaction was cooled to 0 °C and the pH was adjusted to 5 using 1.5 N HC1 (pH ~ 5, not <5). The reaction was stirred at room temperature for another 30 min. The reaction mixture was diluted with EtOAc and the layers were separated. The aqueous layer was again extracted with EtOAc. The combined organic layer was washed with water, washed with brine, dried over $Na_2SC"4$, and concentrated. The crude residue was recrystallized with a mixture of DCM:hexane (1:2, total 10 volume based on crude weight) to afford brown solid (100 g).

Step-2: *tert*-Butyl 2-(3-acetyl-5-bromo-l *H*-indazol-l-yl)acetate (S3)

[0789] Br_2 (1.10 g, 6.88 mmol) dropwise to l-(5-bromo-lH-indazol-3-yl)ethan-l-one (scheme 9-4 compound **S2,** 155 g, 1 equiv) and potassium carbonate (225.6 g, 2.5 equiv) in DMF (1.6 L) at room temperature. The resulting mixture was stirred at 50 °C for 3 h. Then the reaction mixture was poured into water (16 L) and the precipitated solid was collected by filtration and dried to afford 186 g of the title product. The obtained material was used in the next step without further purification.

Step-3: *tert-Butyl* 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-l *H*-indazol-l-yl)acetate (S4)

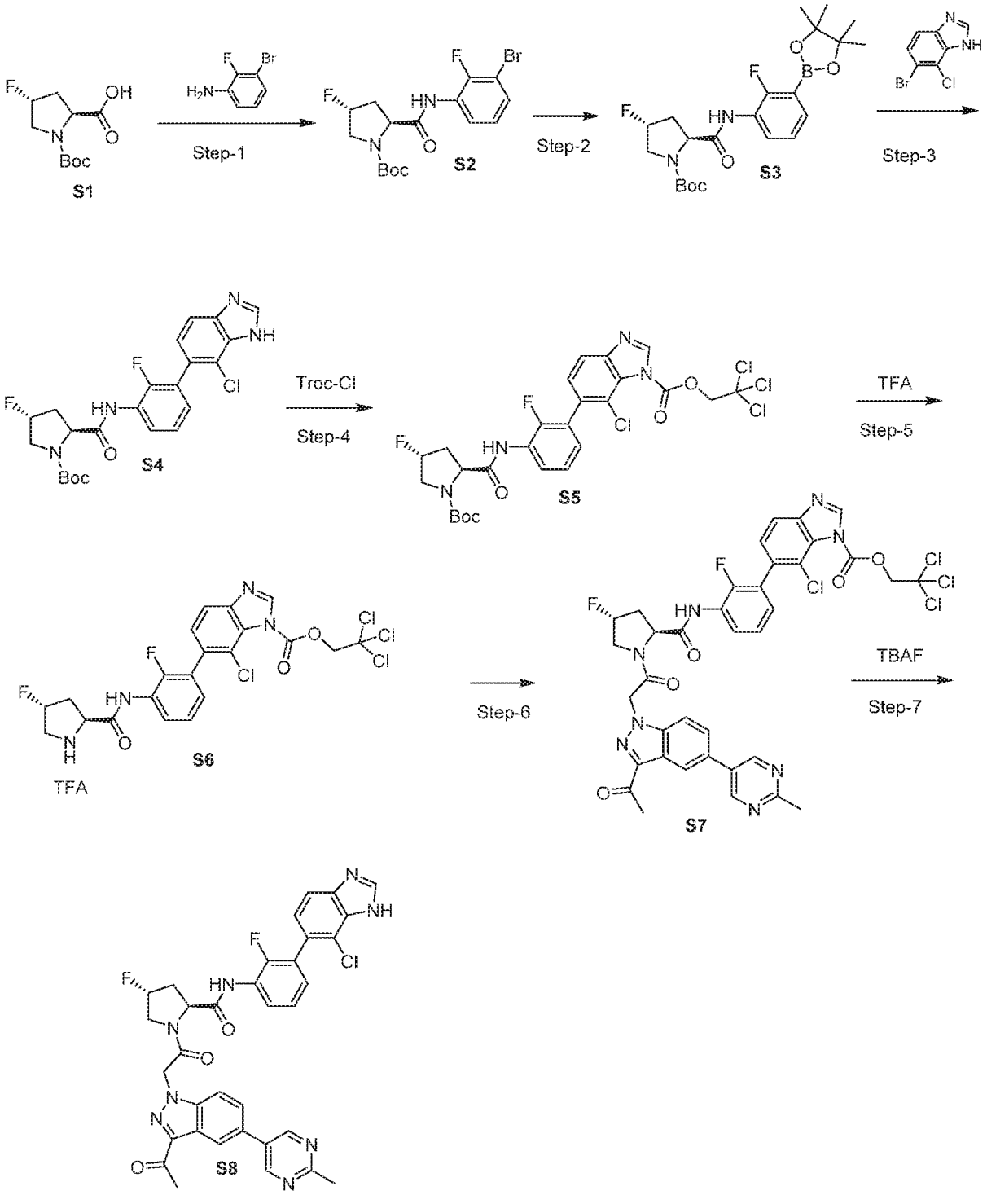
[0790] A mixture of *tert*-butyl 2-(3-acetyl-5-bromo-lH-indazol-l-yl)acetate (scheme 9-4 compound **S3,** 150 g , 1 equiv), 2-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidine (112.2 g, 1.2 equiv), cesium carbonate (166.1 g, 1.2 equiv) in DMF (1.5 L) and water (150 mL) was purged with nitrogen gas for 30 min. Tetrakis(triphenylphosphine)palladium(0) (24.5 g, 0.05 equiv) was then added under an atmosphere of nitrogen and the reaction mixture was heated at 95 °C for 2 h. The reaction mixture was cooled to room temperature and added slowly to water (15 L). The solid was collected by filtration and dried. The crude residue was purified by column chromatography (silica gel, ethyl acetate/methanol) to afford the title compound as an off-white solid (135 g).

Step-4: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (S5)

[0791] ter*t*-Butyl 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetate (scheme 9-4 compound **S4,** 134 g, 1 equiv) was taken in a mixture of 1340 mL DCM and 670 mL

TFA and heated at 50 °C for 2 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The remaining crude material was stirred over MTBE for 30 min, collected by filtration and dried. The obtained solid was used in the next step without further purification.

Scheme 9-5


S1
Step-1
S2
Step-2
S3
Step-3
S4
Troc-Cl
Step-4
S5
TFA
Step-5
S6
TFA
Step-6
S7
TBAF
Step-7
S8

Step-1: *tert-Butyl* (2S,4R)-2-((3-bromo-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S2)

[0792] To a stirred solution of N-Boc-trans-4-fluoro-proline (scheme 9-5 compound **SI,** 25 g, 1 equiv), 3-bromo-2-fluoroaniline (14.5 mL, 1.2 equiv) and HATU (53 g, 1.3 equiv) in DMF (250 mL) was added DIPEA (37 mL, 2 equiv). The resulting solution was stirred at room temperature under an atmosphere of nitrogen. The reaction mixture was poured into water and filtered. The collected solid was washed with excess water and the solid was dissolved in DCM and washed with 10% NaHCCb, 1.5 N HC1, and brine. The solvent was removed under vacuum, hexane was added, and the precipitated solid was collected by filtration to afford the title product (27 g).

Step-2: *tert-Butyl* (2*S*,4*R*)-4-fluoro-2-((2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)pyrrolidine-l-carboxylate (S3)

[0793] A stirred solution of ter*t*-butyl (2S,4R)-2-((3-bromo-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 9-5 compound **S2,** 30 g, 1 equiv), bis(pinacolato)diboron (47 g, 2.5 equiv), PdC12(dppf) (12 g, 0.22 equiv) and KOAc (21.8 g, 3 equiv) in 570 mL dioxane was purged with nitrogen gas for 10 min and then heated at 90 °C for 12 h. Then the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to afford the title product as a viscous liquid (31.5 g).

Step-3: *tert-Butyl* (2*S*,4*R*)-2-((3-(7-chloro-li/-benzo[</|imidazol-6-yl)-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S4)

[0794] A solution of 6-bromo-7-chlorobenzimidazole (scheme 9-5 compound **S3,** 6.5 g, 1 equiv), *ter**t*-butyl (2S,4R)-4-fluoro-2-((2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)pyrrolidine-l-carboxylate (25.4 g, 2 equiv), tetrakis(triphenylphosphine)palladium(0) (4.5 g, 0.14 equiv), and K2CO3 (19.4 g, 5 equiv) in 358 mL dioxane and 88 mL water was purged with nitrogen gas for 10 min. The reaction mixture was heated at 100 °C for 12 h. Then the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title product as an off-white solid (7.8 g).

Step-4: 2,2,2-Trichloroethyl 6-(3-((2*S*,4*R*)-l-(teri-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxamido)-2-fluorophenyl)-7-chloro-lH-benzo[</|imidazole-l-carboxylate (S5)

[0795] Troc-Cl (2.65 mL, 1.2 equiv) was added dropwise to a mixture of ter*t*-butyl (2S,4R)-2-((3-(7-chloro-lH-benzo[d]imidazol-6-yl)-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (scheme 9-5 compound **S4,** 7.8 g, 1 equiv) and K2CO3 (3.4 g, 1.5 equiv) in DCM (98 mL) cooled to 0 °C. This mixture was stirred for 1 h at the same temperature. Then the cooling bath was removed and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the title product as an off-white solid (8.4 g).

Step-5: 2,2,2-Trichloroethyl 7-chloro-6-(2-fluoro-3-((2*S*,4*R*)-4-fluoropyrrolidine-2-carboxamido)phenyl)-l *H*-benzo[</|imidazole-l-carboxylate (S6)

[0796] 2,2,2-Trichloroethyl 6-(3-((2S,4R)-l-(ter *t*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxamido)-2-fluorophenyl)-7-chloro-lH-benzo[d]imidazole-l-carboxylate (scheme 9-5 compound **S5,** 1 g) was stirred in a mixture of DCM (10 mL) and TFA (5 mL) for 30 min. Then the volatiles were removed under reduced pressure. The residue was triturated with MTBE and decanted. The solid obtained was dried to afford the title product and this material was used in the next step without further purification.

Step-6: 2, 2, 2-Trichloroethyl 6-(3-((2*S*,4*R*)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-l *H*-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)-2-fluorophenyl)-7-chloro-l *H*-benzo[</|imidazole-l-carboxylate (S7)

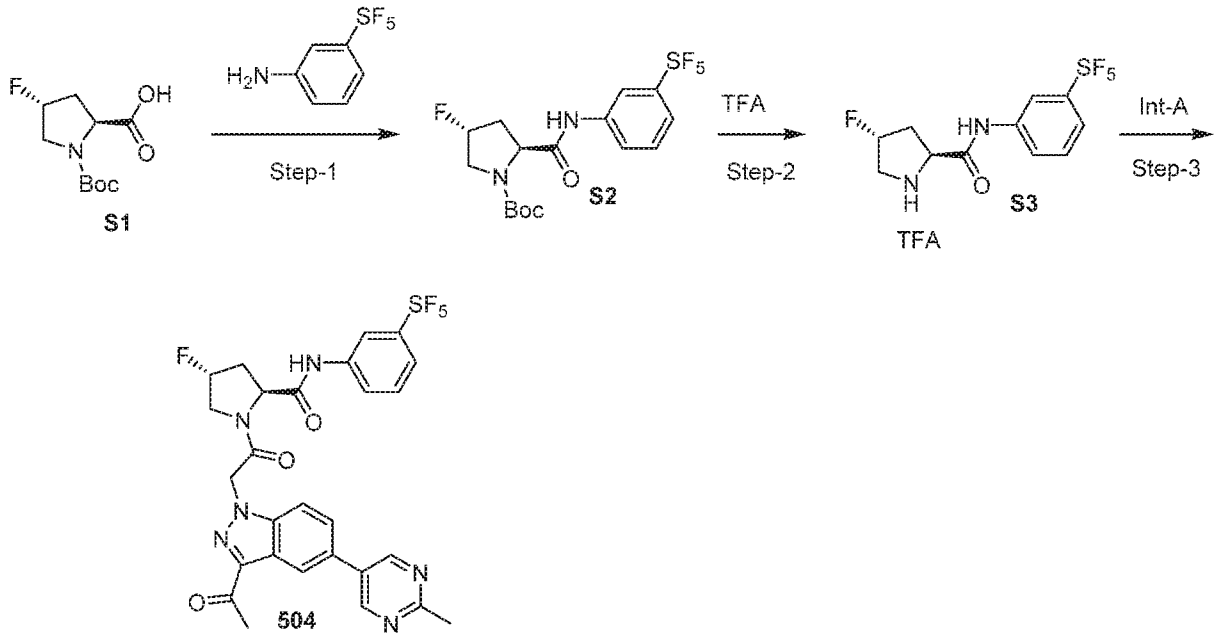
[0797] 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (Scheme 9-4, compound **S6,** 310 mg) was dissolved in DMF (10 mL) and DIPEA (0.412 mL) was added. This was followed by the addition of (2S,4R)-2-((3-(7-chloro-l-((2,2,2-trichloroethoxy)carbonyl)-lH-benzo[d]imidazol-6-yl)-2-fluorophenyl)carbamoyl)-4-fluoropyrrolidin-l-ium 2,2,2-trifluoroacetate (TFA salt, 315 mg) at 5 °C. HATU (380 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then added to water (25 mL + 5 g solid NaCl) and extracted with DCM (2 x 15 mL). The

organic layer was washed successively with an aqueous solution of NaHCCb (10 mL), water (10 mL), and brine (10 mL), dried over $Na_2SC"4$ and concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound.

Step-7: (2*S*, 4*R*)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-l *H*-indazol-l-yl)acetyl *)-N*-(3-(7-chloro-l *H*-benzo[</|imidazol-6-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide (S8)

[0798] 2,2,2-Trichloroethyl 6-(3-((2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)-2-fluorophenyl)-7-chloro-lH-benzo[d]imidazole-l-carboxylate (scheme 9-5 compound **S7,** 160 mg) was dissolved in THF (5 mL) and treated with TBAF (1 M in THF, 0.285 mL). The resulting solution was stirred at room temperature for 1 h. Then the reaction mixture was concentrated under reduced pressure, the remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound. lHNMR(400MHz, *OMSO-de):* (major rotamer) δ 2.14-2.31 (m, 1H), 2.54-2.2.59 (m, 1H), 2.64 (s, 3H), 2.69 (s, 3H), 3.97-4.08 (m, 1H), 4.21-4.30 (m, 1H),4.79 (t, J = 8.4 Hz, 1H), 5.51-5.67 (m, 2H), 5.85 (d, J = 17.2 Hz, 1H), 7.07-7.1 1 (m, 1H), 7.16 (d, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.55-7.57 (m, 1 H), 7.85 (s, 2H), 7.97 (t, J = 7.2 Hz, 1H), 8.35 (s, 1H).), 8.43 (s, 1H), 9.02 (s, 2H), 9.97 (s, 1H), 12.83. (s, 1H). 19F NMR (376 MHz, CDC13): δ -126.72, -176.18. LC (method A): tR = 1.51 min. LC/MS (EI) *m/z: [M* + H]+ 669.

Scheme 9-6



Step-1: *tert*-Butyl (2*S*,4*R*)-4-fluoro-2-((3-(pentafluoro-X ^{6}-sulfanyl)phenyl)carbamoyl)pyrrolidine-l-carboxylate (S2)

[0799] To an ice-cold solution of (2S, 4R)-l -(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 9-6 compound **SI,** 329 mg, 1.4 mmol) in DCM, (6 mL), l-chloro-N,N,2-trimethylprop-1 -en- 1-amine (0.19 mL, 1.1 equiv) was added dropwise with stirring. The stirring was continued for 3 h at the same temperature. Then 3-(pentafluoro-X6-sulfanyl)aniline (338 mg, 1.1 equiv) was added, followed by DIPEA (0.73 mL, 3 equiv). The cooling bath was removed and the reaction mixture was stirred at rt overnight. The solvent was co-evaporated with 5 mL of methanol, and the residue was purified by column chromatography (silica gel, ethyl acetate in hexane, gradient) to obtain the title compound as a white solid (592 mg).

Step-2: (2*S*,4*R*)-4-Fluoro-*N*-(3-(pentafluoro- λ^6-sulfanyl)phenyl)pyrrolidine-2-carboxamide (S3)

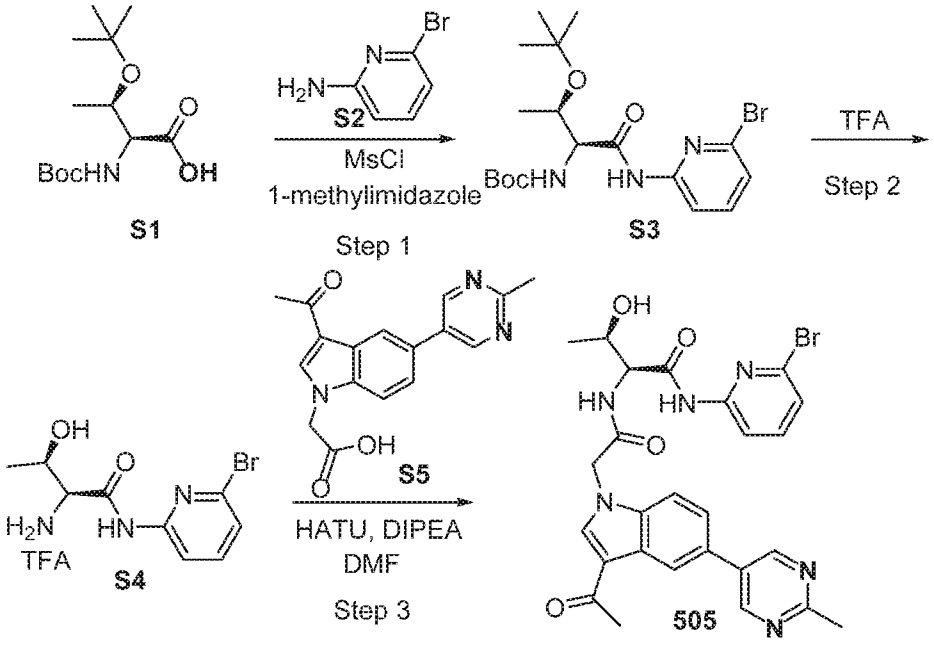
[0800] *tert*-Butyl (2S,4R)-4-fluoro-2-((3-(pentafluoro-X6 sulfanyl)phenyl)carbamoyl)pyrrolidine-l-carboxylate (scheme 9-6 compound **S2,** 592 mg) was dissolved in DCM (8 mL) and treated with TFA (8 mL). The resulting solution was stirred at room

temperature for 2 h. Then the reaction mixture was concentrated under reduced pressure and a portion of the remaining residue was used directly in the next synthetic step.

Step-3: (2*S*,4*R*)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoro-N-(3-(pentafluoro-X^6-sulfanyl)phenyl)pyrrolidine-2-carboxamide (504)

[0801] To a stirred solution of (2S,4R)-4-fluoro-N-(3-(pentafluoro-X6-sulfanyl)phenyl)pyrrolidine-2-carboxamide (scheme 9-6 compound **S3,** TFA salt, 121 mg) in DMF (5 mL) was added Int-A (from Scheme 4) (92 mg), HATU (154 mg, 1.1 equiv), and DIPEA (0.14 mL, 3 equiv). The reaction mixture was stirred at room temperature for 2 h and then diluted with EtOAc (15 mL) and water (10 mL). The organic layer was washed with brine (3 x 15 mL), dried over Na_2S04, and concentrated under reduced pressure. The resulting oil was purified by column chromatography (silica gel, 10% MeOH in DCM, gradient) to yield 92 mg (54%) of compound **504.** 1H NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.12-2.39 (m, 2H), 2.52-2.2.64 (m, 1H), 2.65 (s, 3H), 2.69 (s, 3H), 3.96-4.1 1 (m, 1H), 4.21-4.31 (m, 1H), 4.55 (t, 1H), 5.52-5.89 (m, 3H), 7.51-7.58 (m, 2H), 7.70 (d, 1H), 7.83-7.89 (m,, 2H), 8.27(s, 1H), 8.43 (s, 1H), 9.04 (s, 2H), 10.55 (s, 1H); 19F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -175.9. LC (method A): tR = 2.13 min. LC/MS (EI) *mlz*: [M + H]+ 627.

Scheme 9-7



Step 1: *tert*-Butyl (2S,3R)-l-(6-bromopyridin-2-ylamino)-3-ieri-butoxy-l-oxobutan-2-yl carbamate (S3)

[0802] To an ice-water cooled solution of scheme 9-7 compound **SI** (0.5 g, 1.82 mmol) in DCM (10 mL) was added 1-methylimidazole (0.23 g, 2.0 mmol) under nitrogen protection. The reaction was stirred at this temperature for 30 min followed by the addition of MeSChCl (0. 15 mL, 2.0 mmol). After stirring at 0 °C for 15 min, compound 2 (0.35 g, 2.0 mmol) was added. The mixture was stirred at room temperature overnight and then quenched with aqeuous NaHCCb. The resulting mixture was extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous $Na_2SC"4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1 to 2:1) to afford scheme 9-7 compound **S3** (0.25 g, yield 32%) as a yellow solid.

Step 2: (2S,3R)-2-Amino-N-(6-bromopyridin-2-yl)-3-hydroxybutanamide (S4)

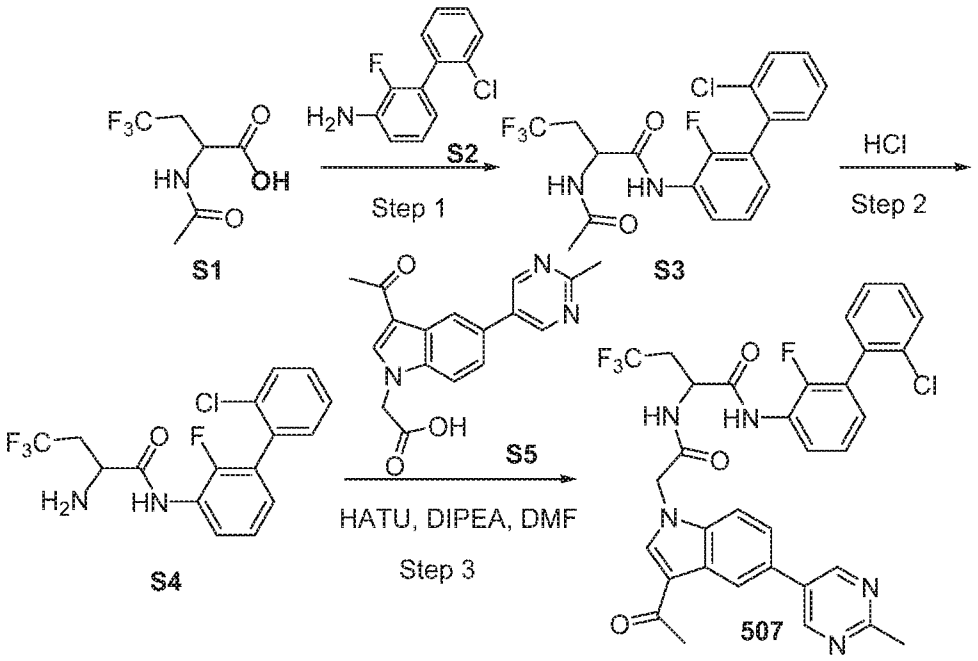
[0803] To a solution of scheme 9-7 compound **S3** (50 mg, 0.12 mmol) in DCM (2 mL) was dropwise added TFA (0.05 mL, 0.58 mmol). The resulting solution was stirred at room

temperature for 4 h and then concentrated to afford crude scheme 9-7 compound **S4** (35 mg), which was used in the next step without further purification. LC-MS: *mlz* 274 (M+H)+.

Step 3: (2S,3R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indol-l-yl)acetamido)-N-(6-bromopyridin-2-yl)-3-hydroxybutanamide (505)

[0804] To a solution of scheme 9-7 compound **S5** (43.6 mg, 0.1 mmol), scheme 9-7 compound **S4** (31 mg, 0.1 mmol), and DIPEA (25.8 mg, 0.2 mmol) in DMF (2 mL) was added HATU (57 mg, 0.15 mmol). The resulting solution was stirred at room temperature overnight and concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford the desired product **505** as a white solid (39 mg, yield 22%). LC-MS: *mlz* 565 (M+H)+. 1H-NMR: δ 10.8 (s, 1H), 8.98 (s, 2H), 8.57 (d, 1H), 8.42-8.45 (m, 2H), 8.08 (d, 1H), 7.73 (t, 1H), 7.62-7.65 (m, 2H), 7.35 (d, 1H), 5.18-5.22 (m, 3H), 4.47 (d, 1H), 4.16 (m, 1H), 2.68 (s, 3H), 2.45 (s, 3H), 1.12 (d, 3H).

Scheme 9-8



Step 1: 2-Acetamido-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4,4,4-trifluorobutanamide (S3)

[0805] To the solution of scheme 9-8 compound **SI** (0.15 g, 0.75 mmol) in DCM (10 mL) was added oxalyl dichloride (1 mL) under nitrogen protection. After being stirred at room temperature for 2 h, the reaction mixture was concentrated under high vacuum. The residue was

dissolved with DCM (10 mL) and scheme 9-8 compound **S2** (0.22 g, 1 mmol) was added, followed by the addition of TEA (0.15 g, 1.5 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with aqeuous NaHCCb. The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over Na_2S04, filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 100:1 to 2:1) to afford scheme 9-8 compound **S3** (0.15 g, yield 50%) as a yellow solid.

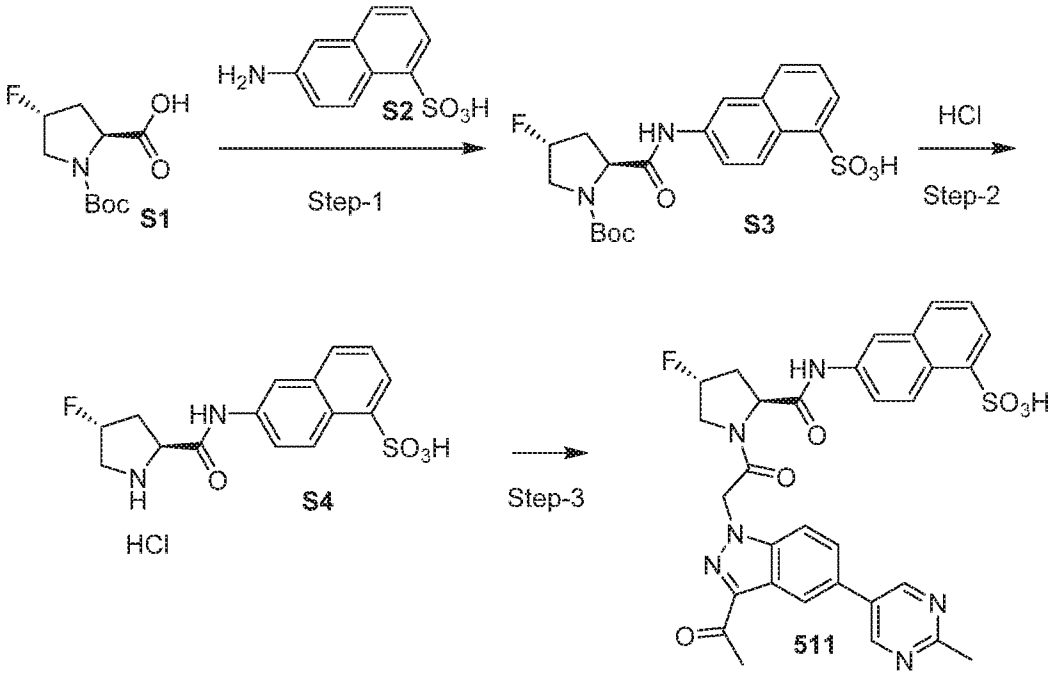
Step 2: 2-Amino-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4,4,4-trifluorobutanamide (S4)

[0806] To a mixture of scheme 9-8 compound **S3** (0.15 g, 0.38 mmol) in MeOH (5 mL) was added concentrated HC1 (1 mL). The resulting solution is stirred at 80 oC overnight and then concentrated to afford crude scheme 9-8 compound **S4** (0.1 g), which is used in the next step without further purification. LC-MS: *mlz* 274 (M+H)+.

Step 3: 2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indol-l-yl)acetamido)-N-(2'-chloro-2-fluoro biphenyl-3-yl)-4,4,4-trifluorobutanamide (507)

[0807] To a solution of scheme 9-8 compound **S4** (36 mg, 0.1 mmol), scheme 9-8 compound **S5** (31 mg, 0.1 mmol), and DIPEA (25.8 mg, 0.2 mmol) in DMF (2 mL) is added HATU (57 mg, 0.15 mmol). The resulting mixture is stirred at room temperature overnight and concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H20 as eluent) to afford the desired product **507** as a white solid (30 mg, yield 54%). LC-MS: *mlz* 652 (M+H)+. 1H-NMR: δ 8.84 (s, 2H), 8.45 (s, 1H), 8.17 (s, 1H), 7.81 (t, 1H), 7.43-7.40 (m, 3H), 7.29-7.21 (m, 3H), 7.22 (t, 1H), 7.03-7.01 (m, 1H), 5.01 (s, 2H), 4.97-4.94 (m, 1H), 2.89-2.82 (m, 2H), 2.68 (s, 3H), 2.44 (s, 3H).

Scheme 9-9



Step-1: 6-((2*S*,4*R*)-l-(ieri-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxamido)naphthalene-l-sulfonic acid (S3)

[0808] To an ice-cold solution of (2S,4R)-l -(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 9-9 compound **SI,** 233 mg) in DCM (20 mL) was added l-chloro-N,N,2-trimethyl-l-propenylamine (146 mg, 1.1 equiv) dropwise with stirring. Stirring was continued for 3 h at this temperature, and then solid 6-aminonaphthalene-l -sulfonic acid (256 mg, 1.1 equiv) was added, followed by DIPEA (0.49 mL, 3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then added to water (10 mL) and extracted with DCM (2 x 10 mL). The organic layer was washed successively with an aqueous solution of NaHCCb (10 mL), water (10 mL), and brine (10 mL), dried over $Na_2SC"4$ and concentrated under reduced pressure. The remaining material was used directly in the next synthetic step.

Step-2: 6-((2*S*,4*R*)-4-Fluoropyrrolidine-2-carboxamido)naphthalene-l-sulfonic acid hydrochloride (S4)

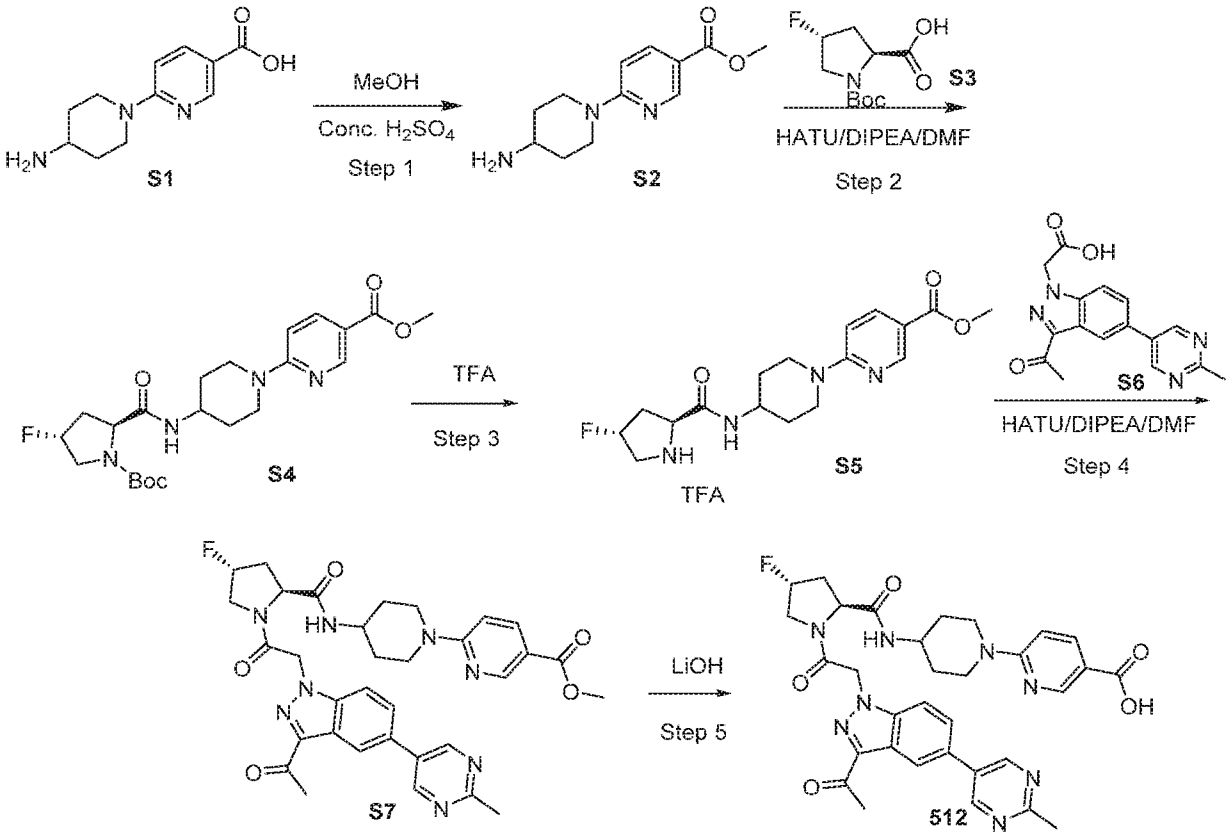
[0809] 6-((2S,4R)-l-(ter *t*-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxamido)naphthalene-l -sulfonic acid (scheme 9-9 compound **S3,** 438 mg) was stirred in 4 N

HC1 in dioxane (4 mL) for 5 h at room temperature. The volatiles were then removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step-3: 6-((2*S*,4*R*)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)naphthalene-l-sulfonic acid (511)

[0810] 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (310 mg) was dissolved in DMF (30 mL) and DIPEA (0.6 mL) was added. This was followed by the addition of 6-((2S,4R)-4-fluoropyrrolidine-2-carboxamido)naphthalene-l-sulfonic acid hydrochloride (scheme 9-9 compound **S4,** 375 mg) at 5 °C. HATU (400 mg) was added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 x 20 mL). The organic layer was washed successively with an aqueous solution of NaHCCb (20 mL), water (20 mL), and brine (20mL), dried over Na_2S04 and concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound **511.** 1H NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.07-2.37 (m, 2H), 2.54-2.75 (m, 7H), 3.95-4.36 (m, 2H), 4.57-4.68 (m, 1H), 5.41-5.90 (m, 3H), 7.32-7.56 (m, 2H), 7.61-7.97 (m, 5H), 8.24(s, 1H), 8.45 (s, 1H), 8.70 (m, 1H), 9.10 (s, 1H), 10.30 (s, 1H);). 19F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -175.9. LC (method A): tR = 0.98 min. LC/MS (EI) *mlz*: [M + H]+ 631.

Scheme 9-10



Step 1: Methyl 6-(4-aminopiperidin-l-yl)nicotinate (S2)

[081 1] To an ice-water cooled solution of scheme 9-10 compound **SI** (0.25 g, 1.1 mmol) in MeOH (10 mL) was added cone. H2SO4 (0.5 mL). The reaction mixture was stirred at 80 °C overnight and then quenched with aqeuous NaHCCb. The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous Na_2S04 and then concentrated to afford scheme 9-10 compound **S2** (0.2 g, yield 32%) as a black solid. The compound was carried forward without further purification.

Step 2: Methyl 6-(4-((2S,4R)-l-(ieri-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxamido) piperidin-l-yl)nicotinate (S4)

[0812] To a solution of scheme 9-10 compound **S2** (150 mg, 0.64 mmol), scheme 9-10 compound **S3** (298 mg, 1.28 mmol), andDIPEA (165 mg, 1.28 mmol) inDMF (10 mL) was added HATU (300 mg, 1.28 mmol). The resulting solution was stirred at room temperature overnight and then concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford scheme 9-10 compound **S4** (200 mg, yield 70%) as a white solid.

Step 3: Methyl 6-(4-((2S,4R)-4-fluoropyrrolidine-2-carboxamido)piperidin-l-yl)nicotinate (S5)

[0813] To a solution of scheme 9-10 compound **S4** (200 mg, 0.44 mmol) in DCM (5 mL), TFA (1 mL mmol) was added dropwise over 10 min. The resulting mixture was stirred at room temperature for 2 h and then concentrated to afford crude scheme 9-10 compound **S5** (200 mg), which was used in the next step without further purification. LC-MS: *mlz* 351 (M+H)+.

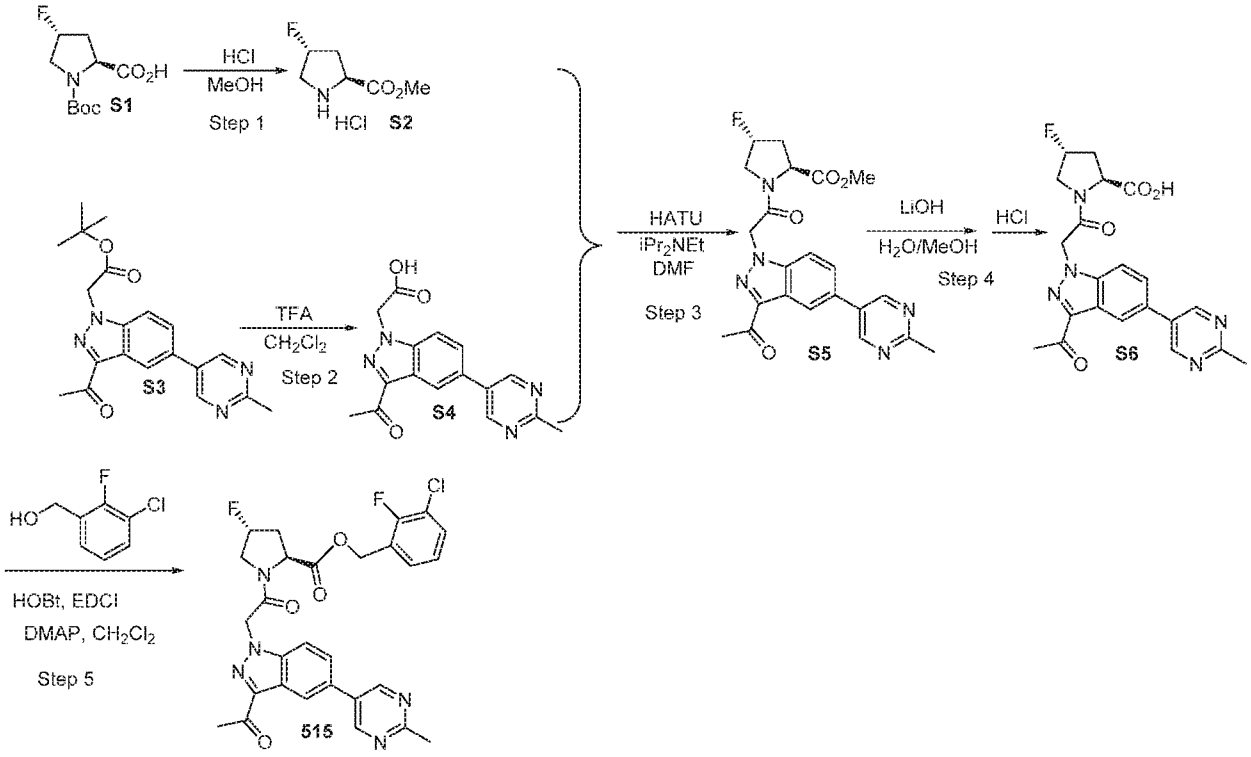
Step 4: Methyl 6-(4-((2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)
-4-fluoropyrrolidine-2-carboxamido)piperidin-l-yl)nicotinate (S7)

[0814] To a solution of scheme 9-10 compound **S5** (200 mg, 0.45 mmol), scheme 9-10 compound **S6** (280 mg, 0.9 mmol), and DIPEA (116 mg, 0.9 mmol) in DMF (5 mL) was added HATU (340 mg, 0.9 mmol). The resulting solution was stirred at room temperature overnight and then concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford the desired product scheme 9-10 compound **S7** as a white solid (90 mg, yield 32%).

Step 5: 6-(4-((2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)piperidin-l-yl)nicotinic acid (512)

[0815] To a solution of scheme 9-10 compound **S7** (40 mg, 0.06 mmol) in THF (2 mL)/water (1 mL) is added **LiOH·$H_2$0** (25 mg, 0.6 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated under high vacuum. The residue was purified by preparative HPLC (acidic condition, using CH3CN/H2O as eluent) to afford the desired product **512** as a white solid (10 mg, yield 25%). LC-MS: *mlz* 629 (M+H)+. 1H-NMR: δ 12.46 (s, 1H), 9.05 (d, 2H), 8.60 (dd, 1H), 8.44 (s, 1H), 7.73-7.99 (m, 4H), 6.85 (d, 1H), 5.79 (d, 1H), 5.58 (d, 1H), 5.43 (s, 1H), 4.10-4.43 (m, 4H), 3.86-4.03 (m, 1H), 3.81 (d, 1H), 3.07 (t, 2H), 2.59-2.76 (m, 6H), 2.37 (dd, 1H), 1.97-2.13 (m, 1H), 1.72 (d, 2H), 1.29 (d, 2H).

Scheme 9-11



Step 1: Methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate hydrochloride (S2)

[0816] (2S,4R)-l -(*tert*-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 9-11 compound **SI,** 233 mg) was treated with saturated HC1 in MeOH (20 mL) and stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the remaining crude title product was used directly in the next synthetic step.

Step 2: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (S4)

[0817] *tert*-Butyl 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetate (scheme 9-1 1 compound **S3,** 366 mg) was treated with TFA (2 mL) in CH2CI2 (2 mL) and stirred for 5 h at room termperature. The solvent was removed under reduced pressure and the remaining crude title product was used directly in the next synthetic step.

Step 3: Methyl (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate (S5)

[0818] To a mixture of methyl (2S,4R)-4-fluoropyrrolidine-2-carboxylate hydrochloride scheme 9-1 1 compound **S2),** 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 9-1 1 compound **S4,** 310 mg, 1 equiv), DMF (9 mL), and N-ethyl-N-isopropylpropan-2-amine (3 mL) was added HATU (380 mg). The reaction mixture was stirred for 10 min and concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound (400 mg).

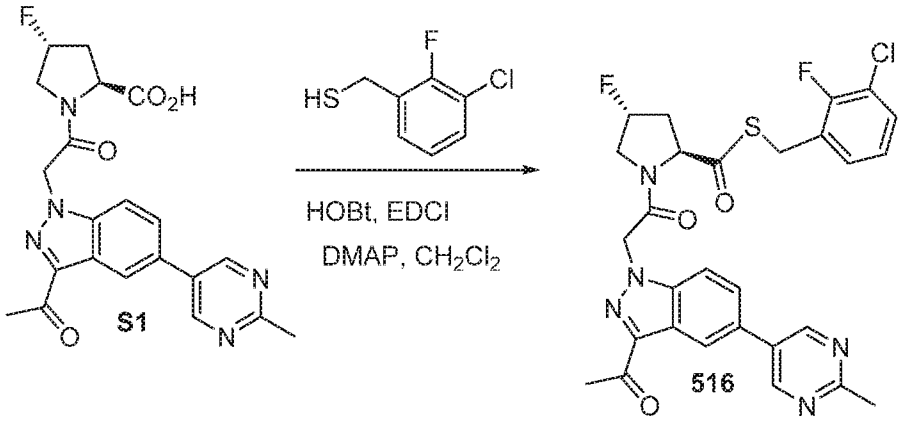
Step 4: (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (S6)

[0819] Methyl (2S,4R)- 1-(2-(3 -acetyl-5-(2-methylpyrimidin-5-yl)- lH-indazol- 1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate (scheme 9-1 1 compound **S5,** 439 mg) was treated with 2 N aqeuous LiOH (10 mL) and stirred for 5 h at rt. The reaction mixture was treated with HC1 (pH adjusted to ~1) and was then concentrated under reduced pressure. The remaining crude title product was used directly in the next synthetic step.

Step 5: 3-Chloro-2-fluorobenzyl (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluor opyrrolidine-2-carboxylate (515)

[0820] (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 9-1 1 compound **S6,** 425 mg) from the previous step was dissolved in CH2CI2 (20 mL) and HOBt (145 mg) was added. This was followed by the addition of EDCI (192 mg), DMAP (10 mg) and (3-chloro-2-fluorophenyl)methanol (g) (161 mg) at 5 °C. HATU (400 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 18 h at rt. The reaction mixture was concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title product **515.** 1H NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.07-2.67 (m, 1H), 2.65 (s, 3H), 2.70 (s, 3H), 3.91-3.96 (m, 1H), 3.99-4.08 (m, 1H), 4.18-4.30 (m, 1H), 4.46-4.53 (m, 1H), 5.1 1-5.25 (m, 1H), 5.27-5.87 (m, 2H), 7.13-7.19 (m, 1H), 7.36-7.42 (m, 1H), 7.53-7.58 (m, 1H), 7.77-7.88 (m, 2H), 8.45(s, 1H), 9.06 (s, 2H);). 19F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -120.5, -176.1 LC (method A): tR = 2.09 min. LC/MS (EI) *mlz*: [M + H]+ 568.

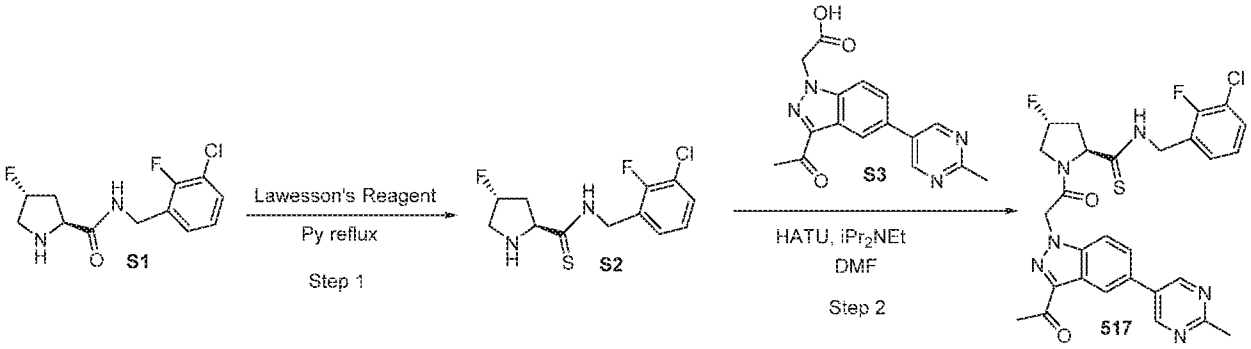
Scheme 9-12



S-(3-Chloro-2-fluorobenzyl) (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidine-2-carbothioate (516)

[0821] (2S,4R)- 1-(2-(3 -Acetyl-5-(2-methylpyrimidin-5-yl)- lH-indazol- 1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (scheme 9-12 compound **SI,** 425 mg) was dissolved in CH2CI2 (20 mL) and HOBt (145 mg) was added, which was followed by the addition of EDCI (192 mg), DMAP (10 mg) and (3-chloro-2-fluorophenyl)methanethiol (177 mg) at 5 °C. The reaction mixture was stirred for 18 h at room termperature and then concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound **516.** 1H NMR (400 MHz, DMSO-d_6): (major rotamer) δ 1.99-2.20 (m, 1H), 2.64 (s, 3H), 2.71 (s, 3H), 3.87-4.36 (m, 4H), 4.69 (m, 1H), 5.44 (m, 1H), 5.58 (m, 1H), 5.67-5.76 (m, 1H), 5.83-5.89 (m, 1H), 7.07-7.13 (m, 1H), 7.30-7.352 (m, 1H), 7.43-7.49 (m, 1H), 7.79-7.83 (m, 2H), 8.45(s, 1H), 9.06 (s, 2H);). 19F NMR (376 MHz, DMSO-i¾): (major rotamer) δ -119.3, -176.0 LC (method A): tR = 2.23 min. LC/MS (EI) *mlz*: [M + H]+ 584.

Scheme 9-13



Step 1: (2S,4R)-N-(3-Chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carbothioamide (S2)

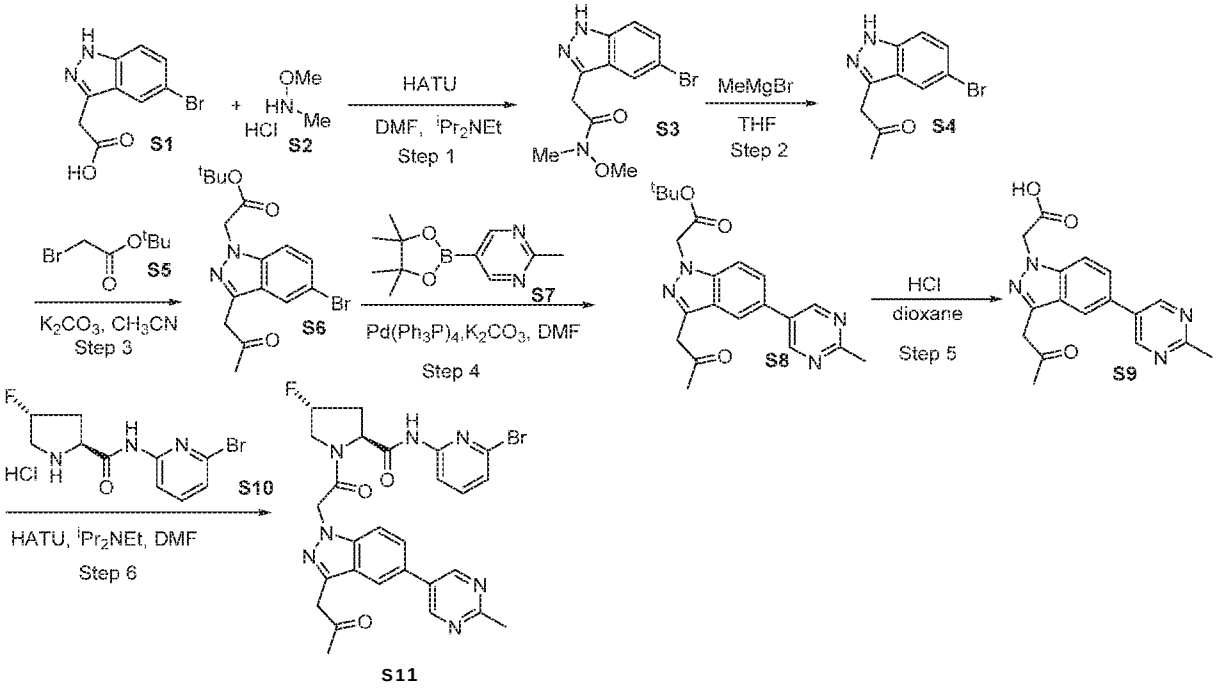
[0822] A mixture of (2S,4R)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (scheme 9-13 compound **SI,** 275 mg), Lawesson's Reagent (607 mg), and pyridine (20 mL) was refluxed for 18 h. The reaction mixture was then concentrated under reduced pressure and the remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound.

Step 2: (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carbothioamide (517)

[0823] (2S,4R)-N-(3-Chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carbothioamide (scheme 9-13 compound **S2,** 291 mg) from the previous step was dissolved in DMF (30 mL) and DIEA (0.6 mL) was added, which was followed by the addition of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (scheme 9-13 compound **S3,** 310 mg) at 5 °C. HATU (400 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 **x** 20 mL). The organic layer was washed successively with an aqueous solution of $NaHC0_3$ (20 mL), water (20 mL), and brine (20 mL), dried over Na_2S0_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, DCM/MeOH) to afford the title compound. IH NMR (400 MHz, *OMSO-de):* (major rotamer) δ 2.12-2.32 (m, IH), 2.65 (s, 3H), 2.70 (s, 3H), 3.95-4.42 (m, 2H), 4.69-5.04 (m, 3H), 5.21-5.89 (m, 4H), 6.89-6.99 (m, IH), 7.11-7.23 (m, IH), 7.39-7.54 (m, IH), 7.72-7.94 (m, 2H), 8.44(s, IH), 9.05 (s, 2H), 10.28-10.23 (m, IH);). 19FNMR(376 MHz, DMSO-

de): (major rotamer) δ -121.0, -175.5 LC (method A): tR = 2.12 min. LC/MS (EI) *mlz:* [M + H]+ 583.

Scheme 9-14



Step 1: 2-(5-Bromo-lH-indazol-3-yl)-N-methoxy-N-methylacetamide (S3).

[0824] To a solution of scheme 9-14 compound **SI** (255 mg, 1 mmol), scheme 9-14 compound **S2** (293 mg, 3 mmol), and DIPEA (646 mg, 5 mmol) in DMF (10 mL) at room temperature was added HATU (418 mg, 1.05 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by column chromatography on silica gel (eluted with CH2C12/MeOH) to afford compound 3 (260 mg, yield 87%) as a white solid. LC-MS: *mlz* 298 (M + H)+.

Step 2: l-(5-Bromo-lH-indazol-3-yl)propan-2-one (S4).

[0825] To a solution of scheme 9-14 compound **S3** (298 mg, 1 mmol) in THF (10 mL) at room temperature was added 3 N methylmagnesiumbromide in Et20 (2 mL, 6 mmol) at 5 °C. The reaction mixture was stirred at room temperature for 1 h and then quenched with 2 N HCl solution (20 mL). The resulting mixture was extracted with DCM (20 mL). The organic layer was separated,

dried over anhydrous Na_2SO_4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel to afford scheme 9-14 compound **S4** (220 mg, 87% yield). LC-MS: *mlz* 253 (M + H)+.

Step 3: *tert*-Butyl 2-(5-bromo-3-(2-oxopropyl)-lH-indazol-l-yl)acetate (S6).

[0826] To a mixture of scheme 9-14 compound **S4** (253 mg, 1 mmol) and K_2CO_3 (415 mg, 3 mmol) in MeCN (5 mL) was added scheme 9-14 compound **S5** (215 mg, 1.1 mmol). The resulting mixture was stirred at 60 °C for 4 h. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluted with hexanes/ethyl acetate = 1:1) to afford scheme 9-14 compound **S6** (355 mg, yield 97%). LC-MS: *mlz* 367 (M + H)+.

Step 4: *tert*-Butyl 2-(5-(2-methylpyrimidin-5-yl)-3-(2-oxopropyl)-lH-indazol-l-yl)acetate (S8).

[0827] A solution of scheme 9-14 compound **S6** (367 mg, 1 mmol), $Pd(Ph_3P)_4$ (231 mg, 0.2 mmol), K_2CO_3 (415 mg, 3 mmol), and scheme 9-14 compound **S7** (220 mg, 1 mmol) in DMF (20 mL) under nitrogen was stirred at 90 °C for 3 h and then concentrated. The residue was purified by column chromatography on silica gel to afford scheme 9-14 compound **S8** (360 mg, 95% yield). LC-MS: *m/z 381* (M + H)+.

Step 5: 2-(5-(2-Methylpyrimidin-5-yl)-3-(2-oxopropyl)-lH-indazol-l-yl)acetic acid (S9).

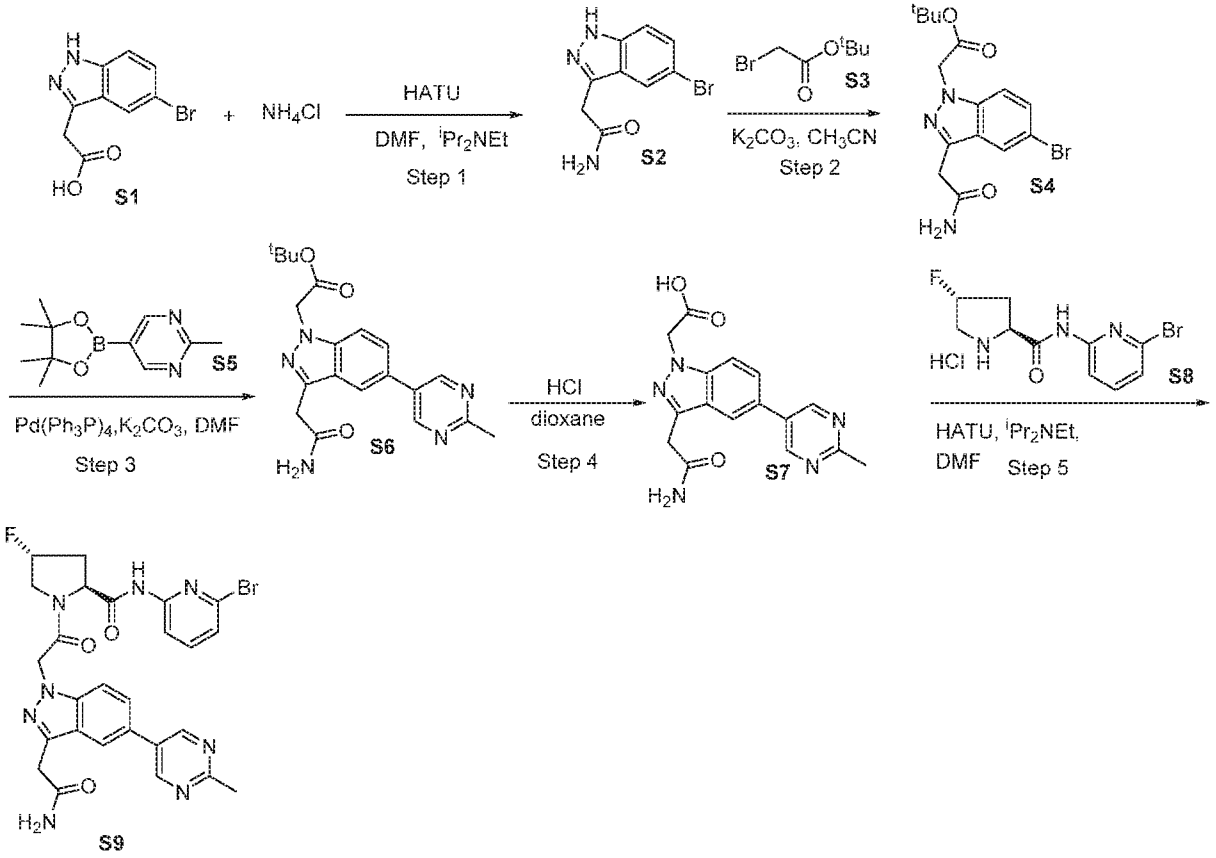
[0828] Scheme 9-14 compound **S8** (380 mg, 1 mmol) was treated with 4 N HC1 in dioxane (3 mL) at room temperature and stirred for 6 h. The reaction mixture was concentrated and the remaining material (scheme 9-14 compound **S9)** was used directly in the next synthetic step. LC-MS: *mlz* 325 (M + H)+.

Step 6: (2S,4R)-N-(6-Bromopyridin-2-yl)-4-fluoro-l-(2-(5-(2-methylpyrimidin-5-yl)-3-(2-oxopropyl)-lH-indazol-l-yl)acetyl)pyrrolidine-2-carboxamide (Sll)

[0829] To a solution of scheme 9-14 compound **S9** (324 mg, 1 mmol), scheme 9-14 compound **S10** (325 mg, 1 mmol), and DIPEA (646 mg, 5 mmol) in DMF (10 mL) at room temperature was added HATU (418 mg, 1.05 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by column chromatography

on silica gel (eluted with CHiCh/MeOH) to afford scheme 9-14 compound **Sll** (550 mg, yield 93%) as a white solid. 1H-NMR: 10.95 (s, 1H), 9.04 (s, 2H), 8.00-8.13 (m, 2H), 7.64-7.83 (m, 3H), 7.29-7.42 (m, 1H), 5.34-5.61 (m, 3H), 4.65 (m, 1H), 3.87-4.24(m, 3H), 3.38(m, 1H), 3.30 (s, 3H), 2.67 (s, 3H), 1.10 (m, 1H), 0.96 (m, 1H). LC-MS: *mlz* 594 (M + H)+.

Scheme 9-15



Step 1: 2-(5-Bromo-lH-indazol-3-yl)acetamide (S2).

[0830] To a solution of scheme 9-15 compound **SI** (255 mg, 1 mmol), ammonium chloride (160 mg, 3 mmol), and DIPEA (646 mg, 5 mmol) in DMF (10 mL) at room temperature was added HATU (418 mg, 1.05 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by column chromatography on silica gel (eluted with CH2C12/MeOH) to afford scheme 9-15 compound **S2** (229 mg, yield 90 %) as a white solid. LC-MS: *mlz* 254 (M + H)+.

Step 2: *tert*-Butyl 2-(3-(2-amino-2-oxoethyl)-5-bromo-lH-indazol-l-yl)acetate (S4).

[083 1] To a mixture of scheme 9-15 compound **S2** (254 mg, 1 mmol) and K2CO3 (415 mg, 3 mmol) in MeCN (5 mL) was added scheme 9-15 compound **S3** (215 mg, 1.1 mmol). The resulting mixture was stirred at 60 °C for 4 h. After filtration, the filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluted with hexanes/ethyl acetate = 1:1) to afford scheme 9-15 compound **S4** (355 mg, yield 96%). LC-MS: *mlz* 368 (M + H)+.

Step 3: *tert*-Butyl 2-(3-(2-amino-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetate (S6).

[0832] A solution of scheme 9-15 compound **S4** (368 mg, 1 mmol), $Pd(Ph_3P)_4$, (231 mg, 0.2 mmol), K2CO3 (415 mg, 3 mmol), and scheme 9-15 compound **S5** (220 mg, 1 mmol) in DMF (20 mL) under nitrogen was stirred at 90 °C for 3 h and then concentrated. The residue was purified by column chromatography on silica gel to afford scheme 9-15 compound **S6** (350 mg, 92% yield). LC-MS: *mlz* 382 (M + H)+.

Step 4: 2-(3-(2-Amino-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (S7).

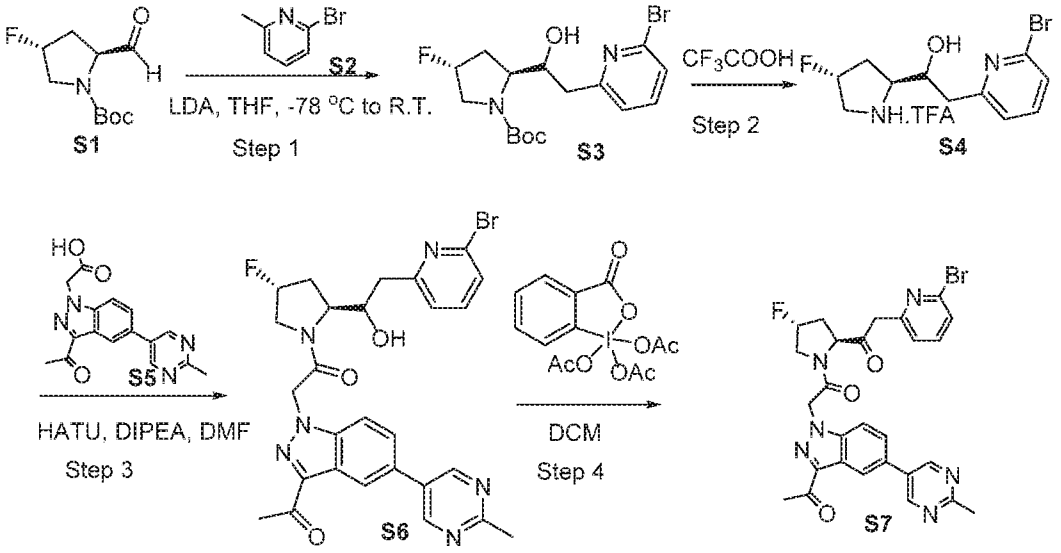
[0833] Scheme 9-15 compound **S6** (381 mg, 1 mmol) was treated with 4 N HC1 in dioxane (3 mL) at room temperature and stirred for 6 h. The reaction mixture was concentrated and the remaining material (scheme 9-15 compound **S7)** was used directly in the next synthetic step. LC-MS: *mlz* 326 (M + H)+.

Step 5: (2S,4R)-l-(2-(3-(2-Amino-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (S9)

[0834] To a solution of scheme 9-15 compound **S7** (325 mg, 1 mmol), scheme 9-15 compound **S8** (325 mg, 1 mmol), and DIPEA (646 mg, 5 mmol) in DMF (10 mL) at room temperature was added HATU (418 mg, 1.05 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by column chromatography on silica gel (eluted with CH_2Cl_2/MeOH) to afford scheme 9-15 compound **S9** (550 mg, yield 93 %) as a white solid. 1H-NMR: 10.96 (s, 1H), 9.03 (s, 2H), 8.18 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.79-7.63 (m, 3H), 7.54 (m, 1H), 7.33(d, J = 7.8 Hz, 1H), 7.00 (m, 1H), 5.32-5.61 (m, 3H), 4.65

(m, 1H), 4.18(m, 1H), 3.88-4.04 (m, 1H), 3.80 (m, 2H), 3.31 (s, 3H), 1.25 (m, 1H), 0.86 (m, 1H). LC-MS: *mlz* 595 (M + H)+.

Scheme 9-16



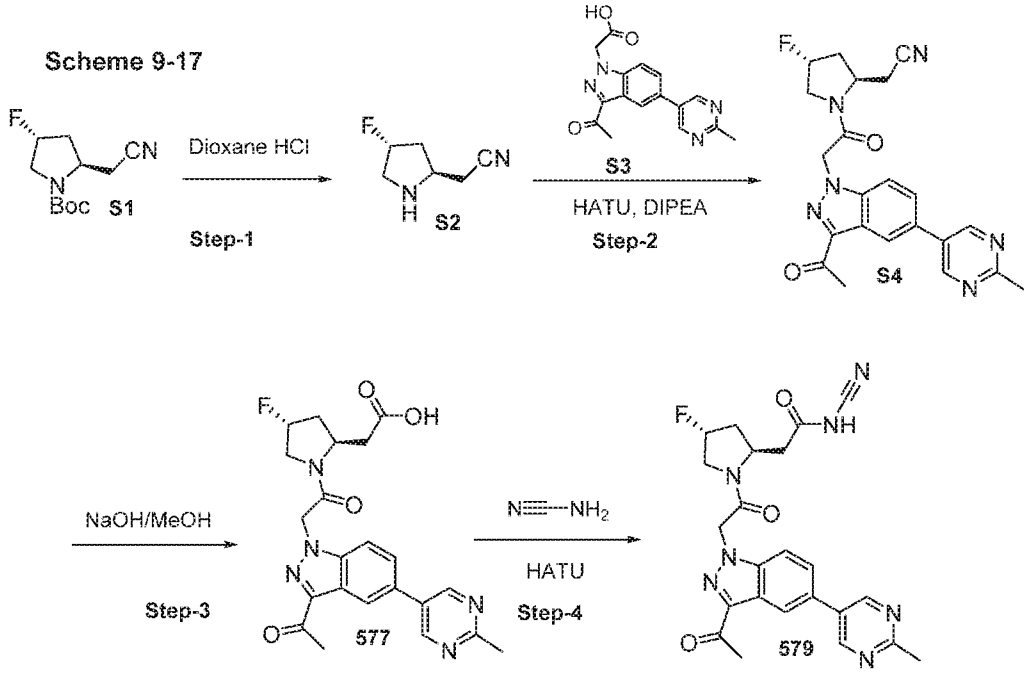
Step 1: (2S,4R)-tert-Butyl 2-((R)-2-(6-bromopyridin-2-yl)-l-hydroxyethyl)-4-fluoropyrrolidine-l-carboxylate (S3)

[0835] To a dry-ice/ethanol cooled solution of scheme 9-16 compound **S2** (80 mg, 0.46 mmol) in THF (2 mL) was added LDA (0.5 mL, 0.5 mmol). After addition, the reaction mixture was stirred at room temperature for 30 min and cooled to -70 °C followed by the addition of scheme 9-16 compound **SI** (100 mg, 0.46 mmol). After stirring at this temperature for 30 min, the reaction mixture was quenched with aqeuous NaHCCb (10 mL). The reaction mixture was extracted with ethyl acetate (20 mL). The organic phase was washed with brine, dried over anhydrous $Na_2SC"4$, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate =100:1 to 4:1) to afford scheme 9-16 compound **S3** (60 mg, yield 35%) as a yellow oil.

Step 2: (R)-2-(6-Bromopyridin-2-yl)-l-((2S,4R)-4-fluoropyrrolidin-2-yl)ethanol (S4)

[0836] To a solution of scheme 9-16 compound **S3** (60 mg, 0.15 mmol) in dry DCM (1 mL) was added TFA (1 mL) in portions. After stirring at room temperature for 1 h, the reaction

mixture was concentrated to afford crude scheme 9-16 compound **S4** (50 mg, yield 95%) as a yellow oil. This material was used in the next synthetic step without purification.



Step 1: 2-((2R,4R)-4-Fluoropyrrolidin-2-yl)acetonitrile (S2)

[0837] To a solution of *tert*-hutyl (2R,4R)-2-(cyanomethyl)-4-fluoropyrrolidine-l-carboxylate (9-17 compound **SI,** 1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCI in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h. The reaction mixture was concentrated to afford scheme 9-17 compound S2.

Step 2: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)acetonitrile (S4)

[0838] To a solution of scheme 9-17 compound **S2** (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added scheme 9-17 compound **S3** (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford scheme 9-17 compound **S4.**

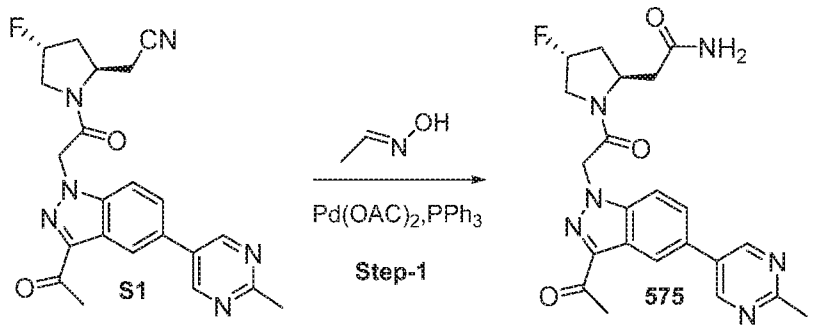
Step 3: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)acetic acid (577)

[0839] To a solution of scheme 9-17 compound **S4** (1 equiv) in MeOH (30 vol) at 0 °C was added 30 % aqueous NaOH solution (4 vol). The reaction mixture was stirred at 100 °C for 16 h and then concentrated. The resulting mixture was acidified with 1.5 N HC1 and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound 577. ¾ NMR (400 MHz, CD_3OD) δ 9.02 (s, 2H), 8.55 (s, 1H), 7.82 - 7.73 (m, 2H), 5.62 - 5.58 (m, 1H), 5.48 - 5.30 (m, 2H), 4.45 - 4.42 (m, 1H), 4.21 - 4.13 (m, 1H), 3.92 - 3.79 (m, 1H), 3.03 - 2.99 (m, 1H), 2.68 (s, 3H), 2.66 (s, 3H), 2.55 - 2.53 (m, 2H), 2.12 - 2.10 (m, 1H).

Step 4: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-cyanoacetamide (579)

[0840] To a solution of scheme 9-17 compound 577 (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added cyanamide (1.2 equiv), HATU (1.5 equiv) and TEA (3 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound 579. ¾ NMR (400 MHz, CD_3OD) δ 9.05 (s, 2H), 8.54 (s, 1H), 7.81 - 7.71 (m, 2H), 5.61 - 5.49 (m, 1H), 5.45 - 5.31 (m, 2H), 4.44 - 4.42 (m, 1H), 4.20 - 4.12 (m, 1H), 3.94 - 3.81 (m, 1H), 3.01 - 2.86 (m, 2H), 2.77 (s, 3H), 2.70 (s, 3H), 2.59 - 2.50 (m, 1H), 2.28 - 2.00 (m, 1H).

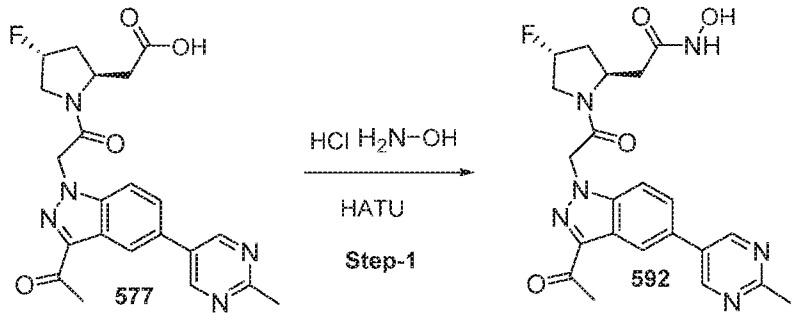
Scheme 9-18



Step-1: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)acetamide (575)

[0841] To a solution of 2-((2R,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyriOlidin--2-yl)acetonitrile (scheme 9-18 compound SI, 1 equiv) in IbO/EtOH (1:4, 10 vol) at 0 °**C** under nitrogen atmosphere was added acetaldoxime (2 equiv), Pd(GAc)?. (0.05 equiv) and PPł13 (0.1 equiv). The reaction mixture was stirred at 90 °**C** for 3 h. After completion of the reaction, the reaction mixture was filtered through celite and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound 575. ¾ NMR (400 MHz, DMSO-d) δ 9.07 (s, 2H), 8.45 (s, 1H), 7.87 - 7.84 (m, 2H), 7.32 (s, 1H), 6.83 (s, 1H), 5.77 - 5.72 (m, 1H), 5.54 - 5.36 (m, 2H), 4.24 - 4.22 (m, 1H), 4.14 - 4.06 (m, 1H), 3.87 - 3.75 (m, 1H), 2.89 - 2.86 (s, 1H), 2.69 (s, 3H), 2.65 (s, 3H), 2.36 - 2.33 (m, 1H), 2.25 - 1.98 (m, 2H).

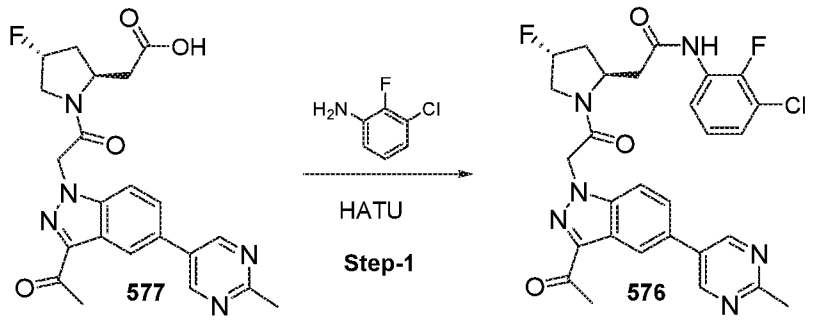
Scheme 9-19



Step-1: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl); acetyl)-4-fluoropyrrolidin-2-yl)-N-hydroxyacetamide (592)

[0842] To a solution of compound 577 (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added hydroxylamine hydrochloride (1.5 equiv), HATU (1.5 equiv) and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound 592. ¾ NMR (400 MHz, DMSO-d) δ 10.42 (s, 1H), 9.06 (s, 2H), 8.44 (s, 1H), 7.86 (d, J = 8.9 Hz, 2H), 5.77 - 5.73 (m, 1H), 5.56 - 5.49 (m, 1H), 5.38 - 5.34 (m, 1H), 4.25 - 4.12 (m, 2H), 4.10 - 4.07 (m, 1H), 2.68 (s, 3H), 2.65 (s, 3H), 2.36 - 2.30 (m, 2H), 2.14 - 2.08 (m, 2H).

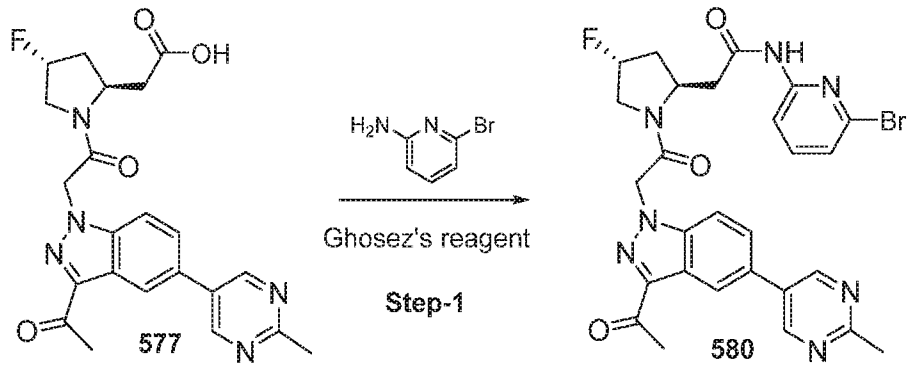
Scheme 9-20



Step-1: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-(3-chloro-2-fluorophenyl)acetamide (576)

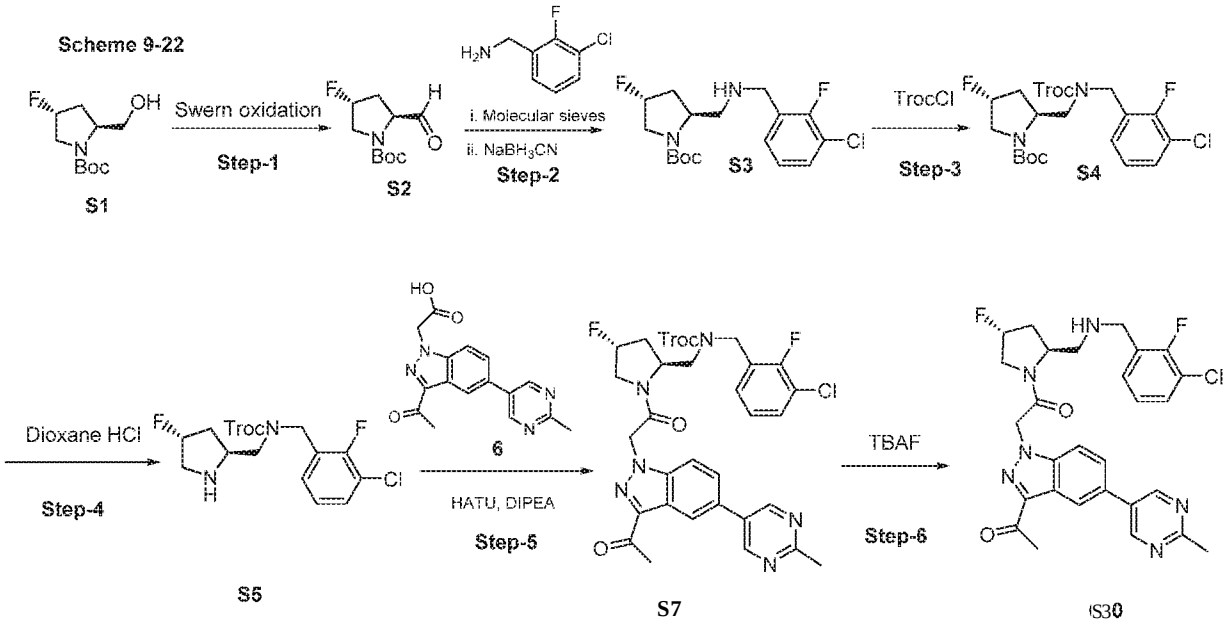
[0843] To a solution of compound 577 (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 3-chloro-2-fluoroaniline (1.5 equiv), HATU (1.5 equiv) and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound 576. ¾ NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.05 (s, 2H), 8.43 (m, 1H), 7.85 - 7.72 (m, 3H), 7.33 - 7.13 (m, 2H), 5.79 - 5.75 (m, 1H), 5.57 - 5.40 (m, 2H), 4.35 - 4.32 (m, 1H), 4.18 - 4.10 (m, 1H), 3.91 - 3.79 (m, 1H), 3.10 (dd, J = 18.4 Hz, 3.4 Hz, 1H), 2.69 (s, 3H), 2.64 (s, 3H), 2.25 - 2.00 (m, 1H), 1.27 - 1.24 (m, 2H).

Scheme 9-21



Step-1: 2-((2R,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-(6-bromopyridin-2-yl)acetamide (580)

[0844] To a solution of compound 577 (1 equiv) in DCM (10 vol) at 0 °**C** under nitrogen atmosphere was added Ghosez's reagent. The reaction mixture was stirred at same temperature for 3 h and then 6-bromopyridin-2-amine (1 equiv), DIPEA (3 equiv) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using **DCM/MeOH** to afford compound 580. ¾ NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 9.04 (s, 2H), 8.43 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.88 - 7.67 (m, 3H), 7.29 (d, J = 7.6 Hz, 1H), 5.76 - 5.71 (m, 1H), 5.52 - 5.38 (m, 2H), 4.34 - 4.32 (m, 1H), 4.13 - 4.07 (m, 1H), 3.80 - 3.78 (m, 1H), 3.08 - 3.03 (m, 1H), 2.70 (s, 3H), 2.08 - 2.66 (m, 1H), 2.63 (s, 3H), 2.61 - 2.59 (m, 1H), 2.18 - 2.00 (m, 1H).



Step-1: *tert*-Butyl (2S,4R)-4-fluoro-2-formylpyrrolidine-l-carboxylate (S2)

[0845] To a solution of oxalyl chloride (1.3 equiv) in DCM (20 vol) at -78 °C under nitrogen atmosphere was added DMSO (1.4 equiv). The reaction mixture was stirred at the same temperature for 30 min and then (2S,4R)-4-fluoiO-2-(hydiOxymethyl)pyrrolidine-l-carboxylate (scheme 9-22 compound **SI,** 1 equiv) was added to the reaction mixture and stirred at -78 °C for 2 h. The reaction mixture was cooled to 0 °C. TEA (4 equiv) was added to the reaction mixture and stirred at 0 °C for 1 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with 1.5 N HCi, 10% NaHCCb and brine, dried over anhydrous Na?.S04, filtered and then concentrated to afford scheme 9-22 compound **S2.**

Step-2: *tert-Butyl* (2S,4R)-2-(((3-chloro-2-fluorobenzyl)amino)methyl)-4-fluoropyrrolidine-1-carboxylate (S3)

[0846] (3-chloro-2-fluorophenyl)methanamine (1.2 equiv), molecular sieves (5%, w/w) and acetic acid (catalytic amount) were added to a solution of scheme 9-22 compound **S2** (1 equiv) in MeOH (10 vol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h. Sodium cyanoborohydride (1.5 equiv) was added to the reaction mixture and stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was

filtered through celite and then concentrated. The residue was purified by column chromatography on silica gel using Hexane/EtOAc to afford scheme 9-22 compound **S3**.

Step-3: *tert-Butyl* (2S,4R)-2-(((3-chloro-2-fluorobenzyl)((2,2,2-trichloroethoxy)carbonyl)amino)methyl)-4-fluoropyrrolidine-l-carboxylate (S4)

[0847] To a solution of scheme 9-22 compound **S3** (1 equiv) in DCM (20 vol) was added 2,2,2-trichlorethoxycarbonyl chloride (1.5 equiv) and potassium carbonate (1.5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was filtered through celite and then concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to afford scheme 9-22 compound **S4.**

Step 4: 2,2,2-Trichloroethyl (3-chloro-2-fluorobenzyl)(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)carbamate (S5)

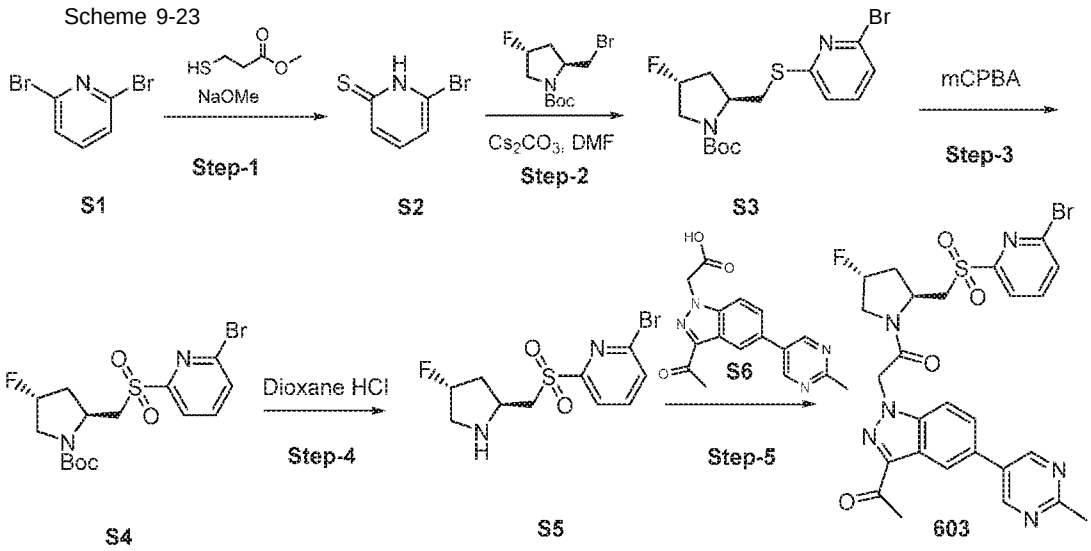
[0848] To a solution of scheme 9-22 compound S4 (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCl in 1,4-dioxane (10 vol). The reaction was stirred at room temperature for 3 h and then concentrated. The residue was taken in MTBE and stirred for 30 min. The resultant solid was filtered and dried to afford scheme 9-22 compound **S5.**

Step-5: 2,2,2-Trichloroethyl (((2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-4-fluoropyrrolidin-2-yl)methyl)(3-chloro-2-fluorobenzyl)carbamate (S7)

[0849] To a solution of scheme 9-22 compound **S5** (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added scheme 9-22 compound **S6** (1.5 equiv), HATU (1.5 equiv) and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford scheme 9-22 compound **S7.**

Step-6: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(((3-chloro-2-fluorobenzyl)amino)methyl)-4-fluoropyrrolidin-l-yl)ethan-l-one (630)

[0850] To a solution of scheme 9-22 compound **S7** (1 equiv) in THF (10 vol) at 0 °C was added TBAF (1.5 equiv). The reaction mixture was stirred at room temperature for 12 h and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound **630.** ¾ NMR (400 MHz, CD_3OD) δ 9.03 (s, 2H), 8.57 - 8.55 (m, 1H), 7.84 - 7.78 (m, 2H), 7.53 - 7.50 (m, 1H), 7.34 - 7.30 (m, 1H), 7.14 - 7.10 (m, 1H), 5.77 - 5.73 (m, 1H), 5.55 - 5.35 (m, 2H), 4.49 - 4.47 (m, 1H), 4.35 - 4.25 (m, 3H), 4.03 - 3.91 (m, 1H), 3.42 - 3.36 (m, 2H), 2.78 (s, 3H), 2.70 (s, 3H), 2.64 - 2.62 (m, 1H), 2.18 - 2.03 (m, 1H).



Step-1: 6-Bromopyridine-2(lH)-thione (S2)

[085 1] To a solution of 2,6-dibromopyridine (scheme 9-23 compound **SI,** 1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added sodium methoxide (2 equiv) and methyl 3-mercaptopropanoate (2 equiv). The reaction mixture was stirred at 70 °C for 2 h and then concentrated. The resulting mixture was dissolved in MeOH (10 vol) and then sodium methoxide (2 equiv) was added to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h. After completion of the reaction, the reaction mixture was concentrated and extracted with ether. The aqueous layer was acidified with acetic acid and filtered the solid and dried to afford scheme 9-23 compound **S2.**

Step-2: *tert-Butyl* (2S,4R)-2-(((6-bromopyridin-2-yl)thio)methyl)-4-fluoropyrrolidine-l-carboxylate (S3)

[0852] To a solution of scheme 9-23 compound **S2** (1 equiv) in DMF (10 vol) was added cesium carbonate (2 equiv) and *tert*-butyl (2S,4R)-2-(bromomethyl)-4-fluoropyrrolidine-l-carboxylate (1 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was filtered through ceiite and then concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to afford scheme 9-23 compound **S3.**

Step-3: *tert-Butyl* (2S,4R)-2-(((6-bromopyridin-2-yl)sulfonyl)methyl)-4-fluoropyrrolidine-l-carboxylate (S4)

[0853] To a solution of scheme 9-23 compound **S3** (1 equiv) in DCM (20 vol) was added mCPBA (0.7 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to afford scheme 9-23 compound **S4.**

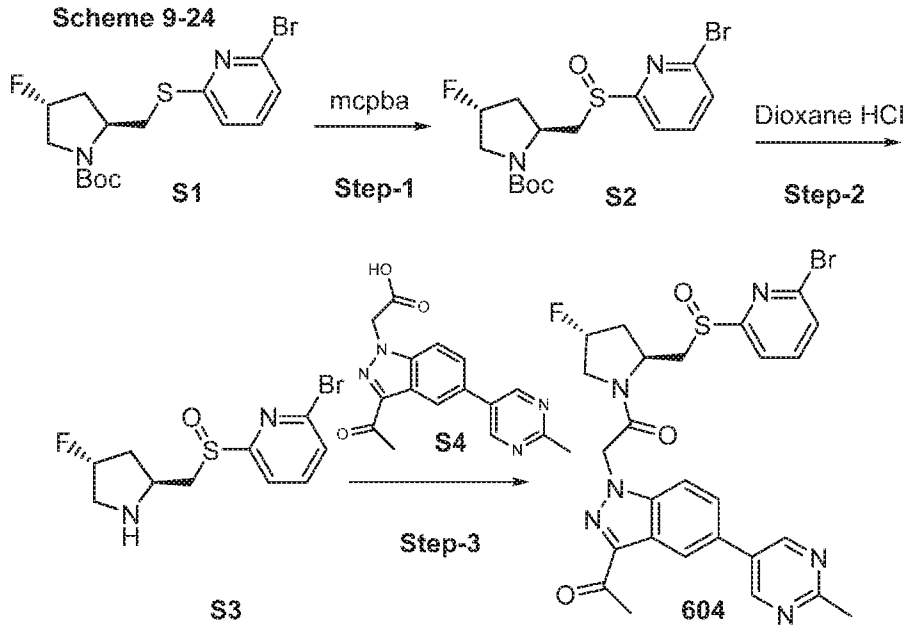
Step 4: 2-Bromo-6-((((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)sulfonyl)pyridine (S5)

[0854] To a solution of scheme 9-23 compound **S4** (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCi in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h and then concentrated. The residue was taken up in MTBE and stirred for 30 min. The resultant solid was filtered and dried to afford 9-23 compound **S5.**

Step-5: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(((6-bromopyridin-2-yl)sulfonyl)methyl)-4-fluoropyrrolidin-l-yl)ethan-l-one (603)

[0855] To a solution of scheme 9-23 compound **S5** (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added scheme 9-23 compound **S6** (1.5 equiv), HATU (1.5 equiv) and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound **603.** ¾ NMR (400 MHz, DMSO-d) δ 9.05 (s, 2H), 8.41

(s, 1H), 8.10 - 8.01(m, 3H), 7.89 - 7.83 (m, 2H), 5.79 - 5.74 (m, 1H), 5.54 - 5.41 (m, 2H), 4.39 - 4.37 (m, 1H), 4.19 - 4.07 (m, 2H), 3.86 - 3.69 (m, 2H), 2.69 (s, 3H), 2.64 (s, 3H), 2.48 - 2.47 (m, 2H).



Step-1: *tert-Butyl* (2S,4R)-2-(((6-bromopyridin-2-yl)sulfinyl)methyl)-4-fluoropyrrolidine-l-carboxylate (S2)

[0856] To a solution of *tert*-butyl (2S,4R)-2-(((6-bromopyridin-2-yl)thio)methyl)-4-fluoropyrrolidine-l-carboxylate (9-24 compound **SI,** lequiv) in DCM (20 vol) was added mCPBA (0.7 equiv). The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to afford scheme 9-24 compound **S2.**

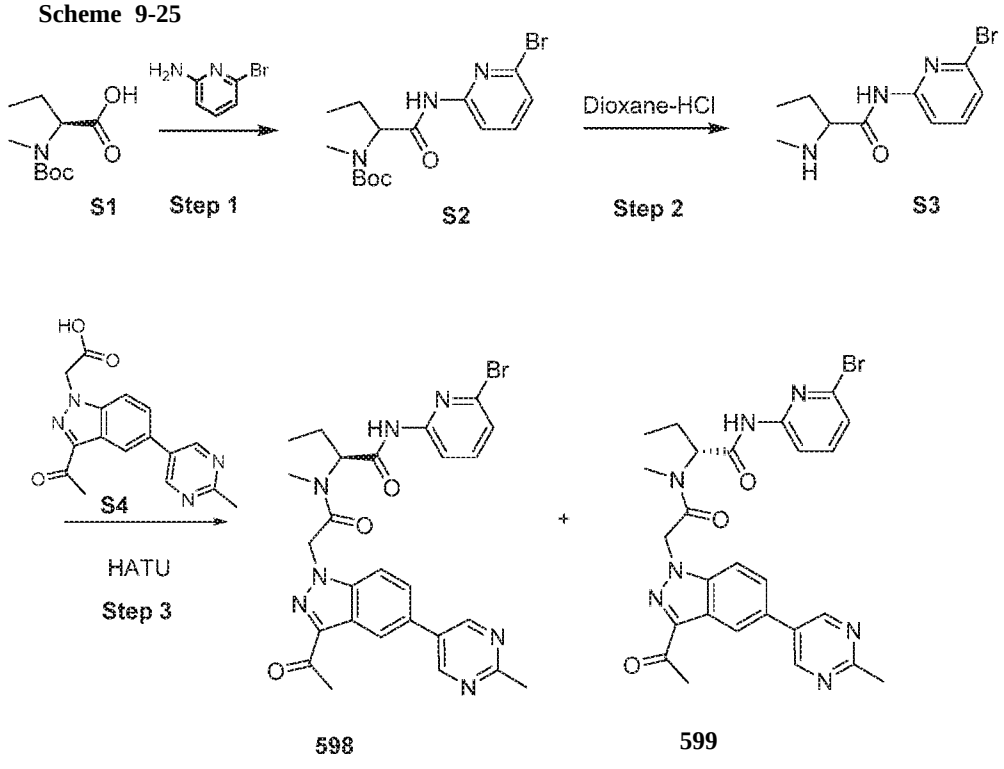
Step 2: 2-Bromo-6-((((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)sulfinyl)pyridine (S3)

[0857] To a solution of scheme 9-24 compound S2 (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCl in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h and then concentrated. The residue was taken in MTBE and stirred for 30 min. The resultant solid was filtered and dried to afford scheme 9-24 compound **S3.**

Step-3: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(((6-bromopyridin-2-yl)sulfinyl)methyl)-4-fluoropyrrolidin-l-yl)ethan-l-one (604)

[0858] To a solution of scheme 9-24 compound **S4** (1 equiv) in **DMF** (10 vol) at 0 **°C** under nitrogen atmosphere was added scheme 9-24 compound **S3** (1.5 equiv), HATU (1.5 equiv) and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with **DCM.** The organic layer was washed with brine, dried over anhydrous Na2S04, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford compound **604.** ¾ NMR (400 MHz, CD_3OD) δ 9.04 - 9.02 (m, 2H), 8.55 (s, 1H), 7.94 - 7.92 (m, 2H), 7.79 - 7.78 (m, 2H), 7.73 - 7.68 (m, 1H), 5.61 - 5.37 (m, 3H), 4.30 - 4.22 (m, 1H), 3.98 - 3.86 (m, 1H), 3.66 - 3.63 (m, 1H), 3.51 - 3.49 (m, 2H), 2.77 (s, 3H), 2.71 (s, 3H), 2.69 - 2.58 (m, 1H), 2.41 - 2.38 (m, 1H).

Scheme 9-25



Step-1 : *tert*-Butyl (l-((6-bromopyridin-2-yl)amino)-l-oxobutan-2-yl)(methyl)carbamate (S2)

[0859] To a solution of (S)-2 -((*tert*-butoxycarbonyl)(methyl)amino)butanoic acid (scheme 9-25 compound **SI,** 1 equiv) in 1,2-dichloroethane (10 vol) at 0 °C under nitrogen atmosphere was added 6-bromopyridin-2-amine (1.2 equiv), EEDQ (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated and the residue was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using Hexane/EtOAc to afford scheme 9-25 compound **S2.**

Step 2 : N-(6-Bromopyridin-2-yl)-2-(methylamino)butanamide hydrochloride (S3)

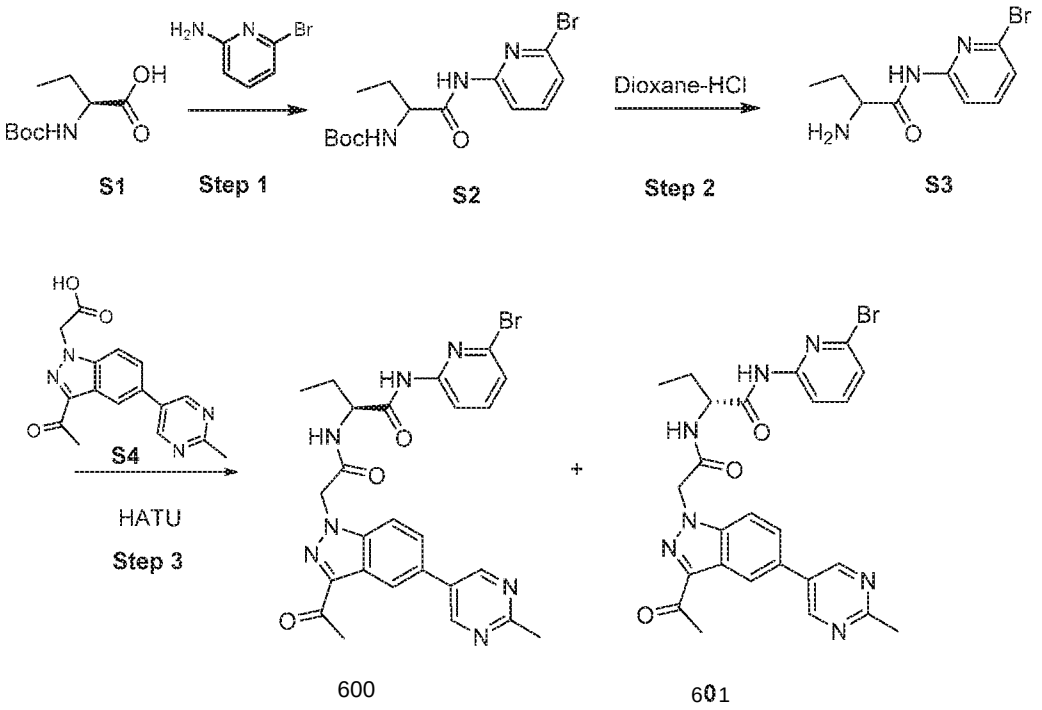
[0860] To a solution of scheme 9-25 compound S2 (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCl in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h. The reaction mixture was concentrated to afford scheme 9-25 compound S3.

Step-3: (S)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-N-methylacetamido)-N-(6-bromopyridin-2-yl)butanamide (598) & (R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-N-methylacetamido)-N-(6-bromopyridin-2-yl)butanamide (599)

[0861] To a solution of scheme 9-25 compound **S3** (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added scheme 9-25 compound **S4** (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford racemic product. This racemic product was purified by SFC to afford compound 598 as one isomer and compound 599 was another isomer. **598:** ¾ NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 9.05 (s, 2H), 8.44 (s, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.91 - 7.72 (m, 3H), 7.35 (d, J = 7.6 Hz, 1H), 5.82 - 5.81 (m, 2H), 4.98 - 4.89 (m, 1H), 3.21 (s, 3H), 2.69 (s, 3H), 2.65 (s, 3H), 1.91 - 1.72 (m, 2H), 0.92 (t, **J** = 7.3 Hz, 3H). **599:** ¾ NMR (400

MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.04 (s, 2H), 8.43 (s, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.87 - 7.71 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 5.79 - 5.78 (m, 2H), 4.97 - 4.93 (m, 1H), 3.20 (s, 3H), 2.68 (s, 3H), 2.64 (s, 3H), 1.97 - 1.77 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

Scheme 9-26



Step-1: *tert*-Butyl (l-((6-bromopyridin-2-yl)amino)-l-oxobutan-2-yl)carbamate (S2)

[0862] To a solution of (S)-2-((*tert*-butoxycarbonyl)amino)butanoic acid (scheme 9-26 compound **SI,** 1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 6-bromopyridin-2-amine (1.2 equiv), EEDQ (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated and the residue was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to afford scheme 9-26 compound **S2.**

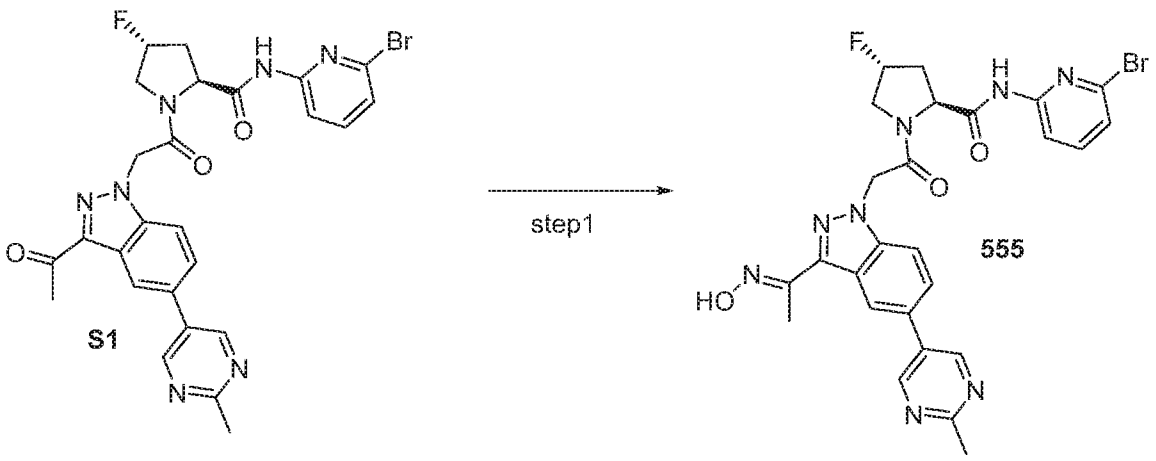
Step 2: 2-amino-N-(6-bromopyridin-2-yl)butanamide hydrochloride (S3)

[0863] To a solution of scheme 9-26 compound S2 (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HCl in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h. The reaction mixture was concentrated to afford scheme 9-26 compound S3.

Step-3: (S)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetamido)-N-(6-bromopyridin-2-yl)butanamide (600) & (R)-2-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetamido)-N-(6-bromopyridin-2-yl)butanamide (601)

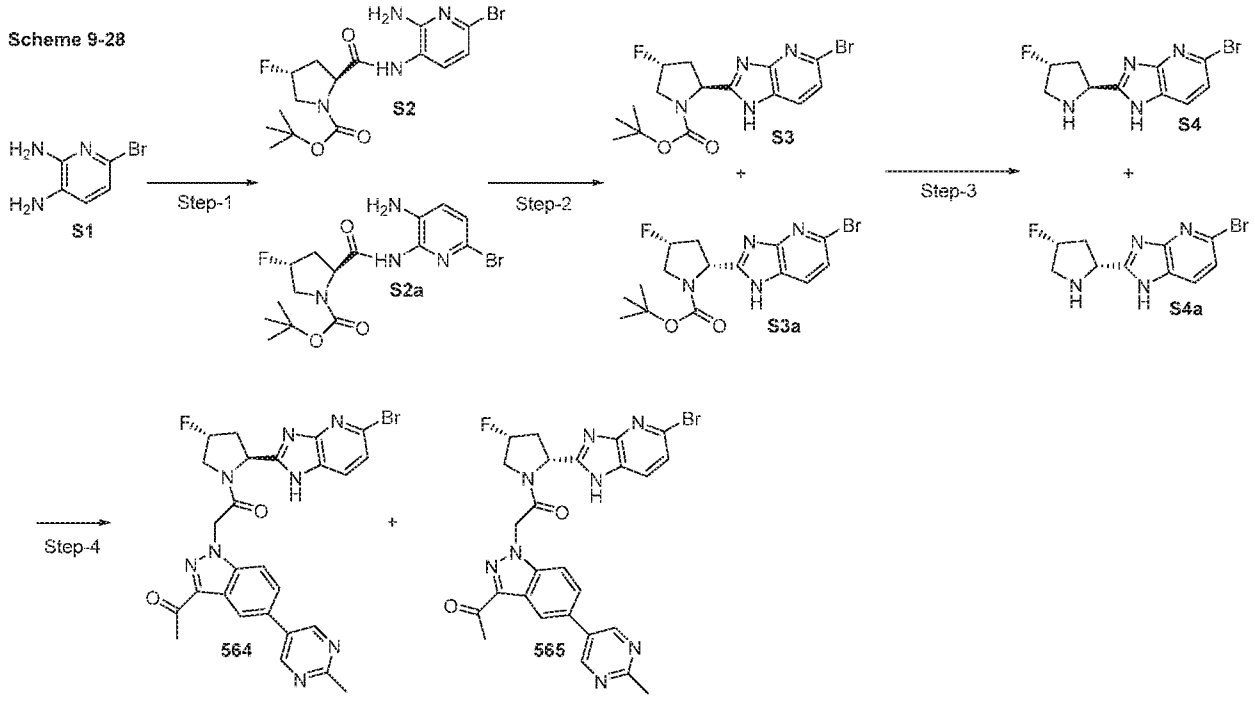
[0864] To a solution of scheme 9-26 compound **S3** (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added scheme 9-26 compound **S4** (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford racemic product. This racemic product was purified by SFC to afford compound 600 as one isomer and compound 601 was another isomer. **600:** ¾ NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.05 (s, 2H), 8.77 (d, J = 7.4 Hz, 1H), 8.43 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.92 - 7.86 (m, 2H), 7.17 - 7.73 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 5.48 - 5.38 (m, 2H), 4.52 - 4.47 (m, 1H), 2.69 (s, 3H), 2.65 (s, 3H), 1.81 - 1.72 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). **601:** ¾ NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.04 (s, 2H), 8.72 (S, 1H), 8.43 (d, J = 2.4 Hz, 1H), 8.09 - 8.07 (m, 1H), 7.88 - 7.87 (m, 2H), 7.76 - 7.71 (m, 1H), 7.35 - 7.33 (m, 1H), 5.46 - 5.40 (m, 2H), 4.48 - 4.47 (m, 1H), 2.68 (s, 3H), 2.63 (s, 3H), 1.17 - 1.69 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H).

Scheme 9-27



Step l : (2S,4R)-N-(6-Bromopyridin-2-yl)-4-fluoro-l-(2-(3-((E)-l-(hydroxyimino)ethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)pyrrolidine-2-carboxamide (555)

[0865] The solution of (2S,4R)-l-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (scheme 9-27 compound **SI,** 50 mg, 0.086mmol) and hydroxylamine hydrochloride (90 mg, 1.3mmol) in the co-solvent of ethanol-H_2**0** (2.0mL-0.5mL) was heated at 90°C for 30 min with microwave reactor. The mixture was purified by preparative HPLC to afford 29.2 mg of title product **555.** ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) δ: 2.02-2. 17(m, 1H), 2.19 (s, 3H), 2.47-2.54 (m, 1H), 2.60 (s, 3H), 3.86-3.90 (m, 1H), 3.97-4.19 (m, 1H),4.59 (t, J=8.4Hz, 1H), 5.39-5. 53(m, 3H), 7.24 (d, J=7.6Hz, 1H), 7.63-7.73 (m, 3H), 7.95 (d, J=8.0Hz, 1H), 8.32(s, 1H), 8.90 (s, 2H), 10.90 (s, 1H), 11.32(s, 1H) ppm; ^{19}F NMR (376 MHz, *OMSO-de):* (major rotamer) δ -175.66; LC (method A): t_R = 1.62min. LC/MS (EI) *mlz:* $[M + H]^+$ 597.06.



Step 1: *tert*-Butyl (2S,4R)-2-((2-amino-6-bromopyridin-3-yl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S2) and *tert*-butyl (2S,4R)-2-((3-amino-6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (S2a)

[0866] To the solution of (2S,4R)-l -(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (456 mg, 1.95mmol), 6-bromopyridine-2,3 -diamine (scheme 9-28 compound **SI,** 405 mg, 2.15mmol) and EDCI (412 mg, 2.15mmol) in CH_3CN (15mL), DIEA (775 mg, 6.0mmol) was added dropwise at 0°C. After completion of addition, the mixture was warmed to room temperature and stirred for additional 2 h. The volatiles were evaporated and the residue was mixed with water (25mL), the resulting solid was collected, washed with water and dried. The compounds scheme 9-28 **S2a** and **S2** were carried forward without further purification.

Step 2: *tert*-Butyl (2S,4R)-2-(5-bromo-lH-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidine-1-carboxylate (S3) and *tert*-butyl (2R,4R)-2-(5-bromo-lH-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidine-l-carboxylate (S3a)

[0867] Scheme 9-28 compounds **S2a** and **S2** were suspended in toluene (20ml) followed by addition of acetic acid (4mL). The mixture was heated at 130°C overnight. The reaction was cooled to room temperature and the volatiles were evaporated. The resulting residue was

neutralized with ammonium hydroxide. The precipitation was dissolved in ethyl acetate, washed with water and dried over MgS04. The solution was filtered and concentrated. The resulting title compounds were used in the next step without further purification.

Step 3: 5-Bromo-2-((2S,4R)-4-fluoropyrrolidin-2-yl)-lH-imidazo[4,5-b]pyridine hydrochloride (S4) and 5-bromo-2-((2R,4R)-4-fluoropyrrolidin-2-yl)-lH-imidazo[4,5-b]pyridine (S4a)

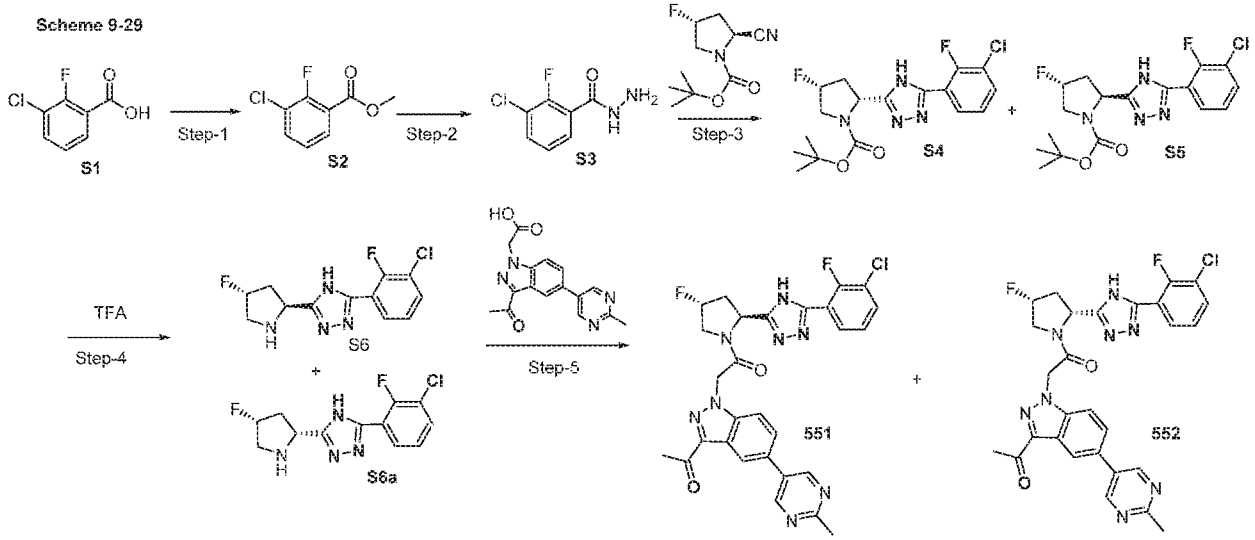
[0868] Scheme 9-28 compounds **S3a** and **S3** were taken in 4N HC1 dioxane (3.0 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, which was monitored by HPLC, the solvent was removed under reduced pressure and the compound mixture was carried forward without further purification.

Step 4: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(5-bromo-lH-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidin-l-yl)ethan-l-one (564) and 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2R,4R)-2-(5-bromo-lH-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidin-l-yl)ethan-l-one (565)

[0869] To the solution of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (106 mg, 0.34mmol), scheme 9-28 compounds **S4a** and **S4** (101 mg, 0.31mmol) in DMF (3.0 mL), HATU (178 mg, 0.47mmol) was added, followed by dropwise addition of DIEA (0.55mL) at room temperature. The mixture was stirred for 1 h at room temperature and the solution was purified by preparative HPLC. The fractions were combined and lyophilized to afford 16.9 mg of compound **564** and 14.4 mg of **565.**

[0870] **564:** ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.42-2.55 (m, 1H), 2.66 (s, 3H), 2.69 (s, 3H), 2.74-2.82 (m, 1H), 4.20-4.29 (m, 2H), 5.38-5.92 (m, 4H), 7.38 (d, J=8.0Hz, 1H), 7.89-8.01 (m, 3H), 8.43 (s, 1H), 9.09 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major) δ -172.56ppm. LC (method A): t_R = 1.29 min. LC/MS (EI) *mlz:* $[M + H]^+$ 577.1 1.

[0871] **565:** ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.37-2.45 (m, 1H), 2.62 (s, 3H), 2.68 (s, 3H), 2.75-2.82 (m, 1H), 4.10-4.40 (m, 2H), 5.23 (t, J=8.40Hz, 1H), 5.58-5.89 (m, 3H), 7.38 (d, J=8.0Hz, 1H), 7.89-8.01 (m, 3H), 8.43 (s, 1H), 9.09 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-d_6): (major) δ -176.95ppm. LC (method A): t_R = 1.32 min. LC/MS (EI) *mlz:* $[M + H]^+$ 577.09.



Step-1: Methyl 3-chloro-2-fluorobenzoate (S2)

[0872] To the solution of 3-chloro-2-fluorobenzoic acid (Scheme 9-29 compound **SI** 9.56g, 54.8mmol) in lOOmL of anhydrous methanol, concentrated H2SO4 (0.8mL) was added carefully. The mixture was refluxed for 24 h and then cooled to room temperature. The volatiles were evaporated. The residue was dissolved in ethyl acetate (80mL) and quenched carefully with saturated aqueous NaHCCb to PH=7. The organic layer was washed with water, brine, and then dried over MgS04. The solid was filtered off and the filtrate was concentrated. The resulting oil (10.7g) was carried forward without further purification.

Step-2: 3-Chloro-2-fluorobenzohydrazide (S3)

[0873] To the solution of methyl 3-chloro-2-fluorobenzoate (Scheme 9-29 compound **S2,** 4.74g, 25mmol) in methanol (60mL), hydrazine monohydrate (3.77g, 3.65mL, 75mmol) was added dropwise at room temperature. Following overnight stirring, the volatiles were evaporated. The residue was suspended in hexane (lOOmL), filtered and washed with hexanes. The solid was carried forward without further purification to afford the title compound. ^{1}H NMR (400 MHz, CDCh): δ 4.17 (s, br, 2H), 7.21-7.27 (m, 1H), 7.56 (t, J=7.6Hz, 1H), 7.87 (s, br, 1H), 7.98 (t, J=7.6Hz, 1H) ppm; LC (method A): t_R =0.53 min. LC/MS (EI) *m/z: [M* + H]$^+$ 189.08, 191.04.

Step-3: *tert*-Butyl (2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-l,2,4-triazol-3-yl)-4-fluoropyrrolidine-l-carboxylate (S5) and *tert-butyl* (2R,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-l,2,4-triazol-3-yl)-4-fluoropyrrolidine-l-carboxylate (S4)

[0874] To the solution of 3-chloro-2-fluorobenzohydrazide (Scheme 9-29 compound **S3,** 377 mg, 2.0mmol) and *tert*-butyl (2S,4R)-2-cyano-4-fluoropyrrolidine-l-carboxylate (428 mg, 2.0mmol) in butanol (lOmL), solid potassium carbonate (65 mg) was added. The mixture was heated in an oil bath at 110°C for 6 h. The reaction mixture was cooled to rt, and the volatiles were evaporated. The residue was purified to afford 508 mg of desired product Scheme 9-28 compound **S5,** and racemized product Scheme 9-29 compound **S4** (ratio 70:30).

Step-4: 3-(3-Chloro-2-fluorophenyl)-5-((2S,4R)-4-fluoropyrrolidin-2-yl)-4H-l,2,4-triazole (S6) and 3-(3-Chloro-2-fluorophenyl)-5-((2R,4R)-4-fluoropyrrolidin-2-yl)-4H-l,2,4-triazole (S6a)

[0875] Scheme 9-29 compounds **S5 and S4** were dissolved in DCM (4mL) and treated with TFA (2mL) at room temperature. The mixture was stirred overnight. The volatiles were evaporated and the resulting residue was co-evaporated with toluene (lOmL) twice. The residue was further dried via vacuum and carried forward without further purification.

Step-5: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-l,2,4-triazol-3-yl)-4-fluoropyrrolidin-l-yl)ethan-l-one (551) and 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2R,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-l,2,4-triazol-3-yl)-4-fluoropyrrolidin-l-yl)ethan-l-one (552)

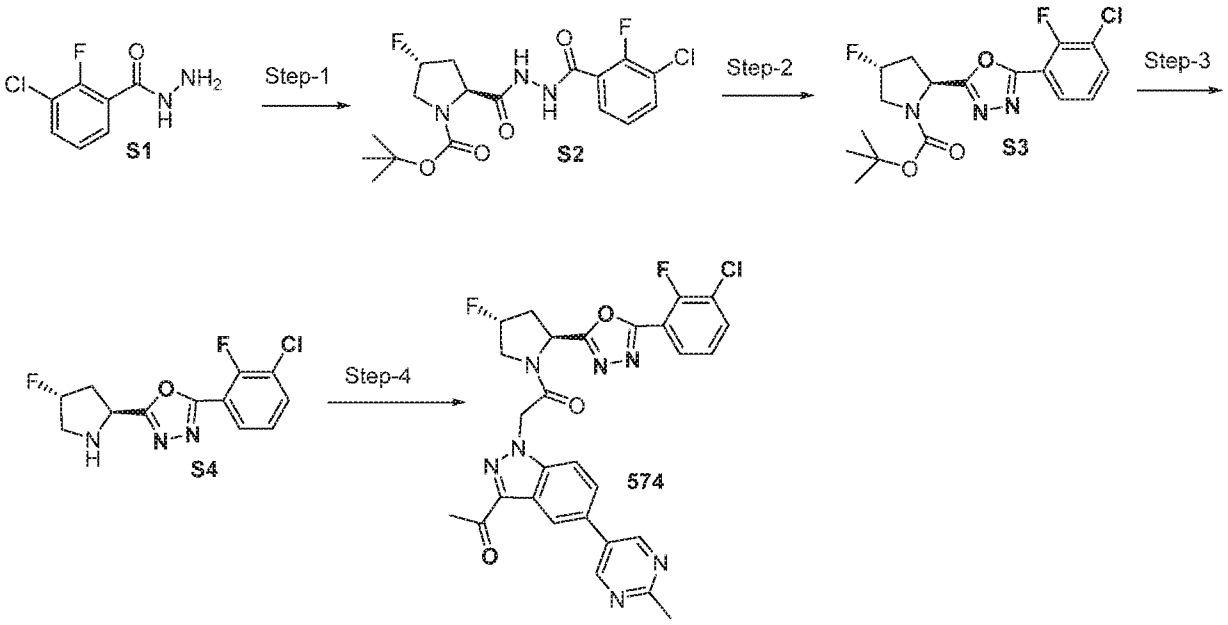
[0876] To the solution of 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (170 mg, 0.55mmol), Scheme 9-29 compounds **S4** and **S5** (250 mg, 0.65mmol) in DMF (3.0 mL), HATU (272 mg, 0.72mmol) and DIEA (0.55mL) were added successively at room temperature. The mixture was stirred for 1 h at room temperature and the solution was purified by preparative FIPLC. The fractions were combined and lyophilized to afford 119.8 mg of compound **551** and 62.2 mg of compound **552.**

[0877] **551:** ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.25-2.41(m,lH), 2.55 (s, 3H), 2.61(s, 3H), 2.62-2.71(m, 1H), 4.22-4.30 (m, 2H), 5.18 (t, J=8.0Hz, 1H), 5.49-5.84 (m, 3H), 7.26 (t, J=8.0Hz, 1H), 7.58 (t, J=6.8Hz, 1H), 7.66-7.64 (m, 2H), 7.84 (t, J=6.8Hz, 1H), 8.34 (s,

1H), 8.94 (s, 2H)ppm. ^{19}F NMR (376 MHz, *OMSO-de):* (major) δ -115.28, -177.12ppm. LC (method A): t_R = 1.63 min. LC/MS (EI) *m/z: [M* + H]$^+$ 577.11.

[0878] **552:** ^{1}H NMR (400 MHz, DMSO-i¾): (major rotamer) δ 2.30-2.5 l(m,lH), 2.57 (s, 3H), 2.61(s, 3H), 2.62-2.78(m, 1H), 4.08-4.25 (m, 2H), 5.30-5.36(m, 1H), 5.44-5.84 (m, 3H), 7.24 (t, J=8.0Hz, 1H), 7.56 (t, J=6.8Hz, 1H), 7.80-7.92 (m, 2H), 7.94-7.98 (m, 1H), 8.36 (s, 1H), 8.97 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major) δ -115.24, -172.60ppm. LC (method A): t_R = 1.60 min. LC/MS (EI) *m/z: [M* + H]$^+$ 577.11.

Scheme 9-30



Step 1: *tert-Butyl* (2S,4R)-2-(2-(3-chloro-2-fluorobenzoyl)hydrazine-l-carbonyl)-4-fluoropyrrolidine-l-carboxylate (S2)

[0879] To the solution of (2S,4R)-l-(ter *t*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (466 mg, 2.0mmol), 3-chloro-2-fluorobenzohydrazide (Scheme 9-30 compound **SI,** 380 mg, 2.0mmol), EDCI (1.2eq) in CH3CN (lOmL), DIEA (3.0eq) was added dropwise, and the mixture was stirred for 2 h at room temperature. The volatiles were evaporated and the resulting residue was dissolved in 30 mL of ethyl acetate. The solution was quenched with saturated aqueous NaHCCb (lOmL), extracted with ethyl acetate (30mL), washed with water and brine and dried.

The solution was filtered and concentrated to afford 702 mg of desired product. The compound was carried forward without further purification.

Step 2: *tert-Butyl* (2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-l,3,4-oxadiazol-2-yl)-4-fluoropyrrolidine-l-carboxylate (S3)

[0880] The solution of *tert*-butyl (2S,4R)-2-(2-(3-chloro-2-fluorobenzoyl)hydrazine-l-carbonyl)-4-fluoropyrrolidine-l-carboxylate (Scheme 9-30 compound **S2,** 702 mg, 1.74mmol) and Burgess' reagent (1.2eq) in THF (15mL) was refluxed for 2 h under Ar. The solution was cooled to room temperature and further concentrated. The resulting residue was purified to afford 615 mg of desire product. ¾ NMR (400 MHz, CChD): (major rotamer) 61.30 (s, 9H), 2.43-2.53 (m, 1H), 2.73-2.83 (m, 1H), 3.69-3.82 (m, 1H), 3.97-4.13 (m, 1H), 5.27-5.40 (m, 2H), 7.22-7.30 (m, 1H), 7.58-7.61 (m, 1H), 7.96 (t, J=7.2Hz, 1H) ppm

Step 3: 2-(3-Chloro-2-fluorophenyl)-5-((2S,4R)-4-fluoropyrrolidin-2-yl)-l,3,4-oxadiazole hydrochloride (S4)

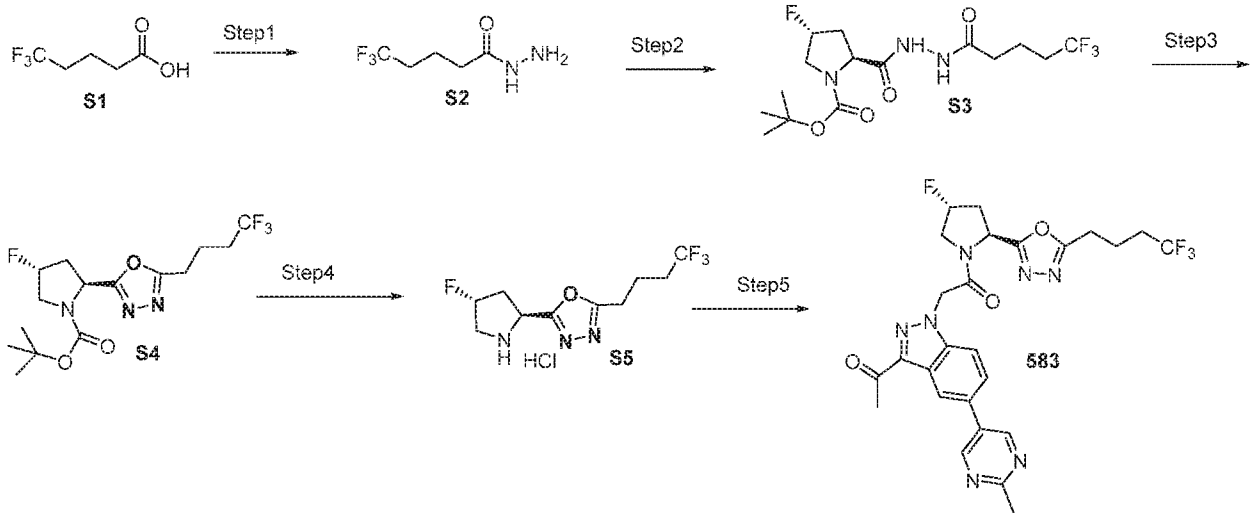
[0881] ter*t*-Butyl (2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-l,3,4-oxadiazol-2-yl)-4-fluoropyrrolidine-l-carboxylate (Scheme 9-30 compound **S3,** 615 mg) was taken in 4N HC1 dioxane (3.0 mL) and the resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction, which was monitored by HPLC, the solvent was removed under reduced pressure. The residue was used carried forward without further purification.

Step 4: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-l,3,4-oxadiazol-2-yl)-4-fluoropyrrolidin-l-yl)ethan-l-one (574)

[0882] To the solution of 2-(3-chloro-2-fluorophenyl)-5-((2S,4R)-4-fluoropyrrolidin-2-yl)-l,3,4-oxadiazole hydrochloride (Scheme 9-30 compound **S4,** 180 mg, 0.56mmol), 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (173 mg, 0.56mmol) in DMF (2.5 mL), HATU (277 mg, 0.73mmol) was added followed by dropwise addition of DIEA (4.0eq) at room temperature. The mixture was stirred for 1 h at room temperature and the volatiles were evaporated. The residue was diluted with 50 mL of 10% sodium carbonate and extracted with ethyl acetate. The combined organic solution was successively washed with water, brine and dried over $MgSO_4$. The solution was filtered and the solvent was removed. The

residue was purified to afford 152.4 mg of the title compound. ¾ NMR (400 MHz, DMSO-de): (major rotamer) δ 2.37-2.47(m,lH), 2.53 (s, 3H), 2.60(s, 3H), 2.67-2.78(m, 1H), 4.05-4.31 (m, 2H), 5.33 (t, J=8.0Hz, 1H), 5.47-5.80 (m, 3H), 7.37 (t, J=8.0Hz, 1H), 7.65 (d, J=8.8Hz, 1H), 7.73 (d, J=8.8Hz, 1H), 7.80 (t, J=8.0Hz, 1H), 7.87 (t, J=8.0Hz, 1H), 8.31 (s, 1H), 8.90 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-d_6): (major) δ -112.74, -176.79ppm. LC (method A): t_R = 1.77 min. LC/MS (EI) *mlz:* $[M + H]^+$ 578. 16.

Scheme 3-31



Stepl: 5,5,5-Trifluoropentanehydrazide (S2)

[0883] To the solution of 5,5,5-trifluoropentanoic acid (Scheme 9-31 compound **SI,** 1.05g, 6.72mmol) in methanol (30mL), concentrated H2SO4 (0.2mL) was added. The mixture was refluxed for 6 h and then cooled to room temperature. Hydrazine monohydrate (1.69g, 1.64mL, 33.6mmol) was added dropwise at room temperature and the mixture was allowed to stir for 72 h. Following evaporation of the volatiles, the white solid residue was mixed with a minimal volume of water and filtered. The title compound (925 mg) was carried forward without further purification.

Step 2: *tert-Butyl* (2S,4R)-4-fluoro-2-(2-(5,5,5-trifluoropentanoyl)hydrazine-l-carbonyl)pyrrolidine-l-carboxylate (S3)

[0884] To the solution of (2S,4R)-l-(ter *t*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (Scheme 9-31 compound **S2,** 1.1 5g, 4.93 mmol), 5,5,5-trifluoropentanehydrazide (840 mg, 4.93mmol), EDCI (**1.2eq)** in CH3CN (15mL), DIEA **(3.0eq)** was added dropwise and the mixture was stirred for 2 h at room temperature. The volatiles were evaporated and the resulting residue was dissolved in 50 mL of ethyl acetate. The solution was quenched with saturated aqueous NaHCCb (15mL) and the upper layer of the solution was collected. The aqueous phase was extracted with ethyl acetate (50mL). The combined organic phase was washed with water and brine and dried. The solution was filtered and concentrated to afford 1.65g of desired product. The compound was carried forward without further purification.

Step 3: *tert-Butyl* (2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazol-2-yl)pyrrolidine-l-carboxylate (S4)

[0885] The solution of *ter t*-butyl (2S,4R)-4-fluoro-2-(2-(5,5,5-trifluoropentanoyl)hydrazine-l-carbonyl)pyrrolidine-l-carboxylate (Scheme 9-31 compound **S3,** l.lg, 2.88 mmol) and Burgess' reagent (2.4eq, 1.64g) in THF (15mL) was refluxed for 24 h under Ar. The solution was cooled to room temperature and further concentrated. The resulting residue was purified to afford 873 mg of the title compound.

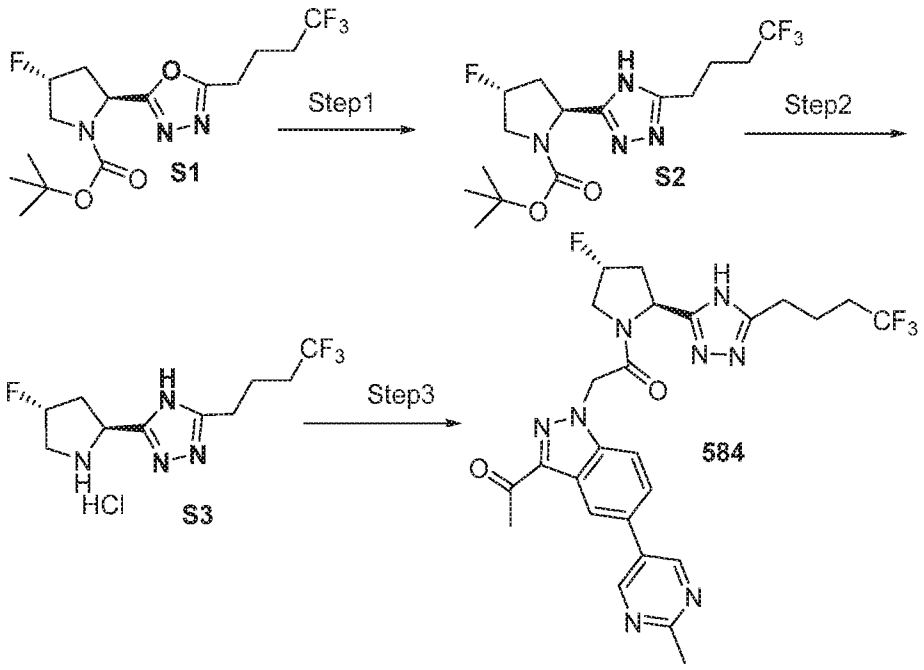
Step 4: 2-((2S,4R)-4-Fluoropyrrolidin-2-yl)-5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazole hydrochloride (S5)

[0886] ter *t*-Butyl (2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazol-2-yl)pyrrolidine-l-carboxylate (Scheme 9-3 1 compound **S4,** 315 mg, 0.85mmol) was taken up in 4N HC1 dioxane (3.0 mL) and the resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction, which was monitored by HPLC, the solvent was removed under reduced pressure. The remaining residue was used directly without further purification.

Step 5: 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazol-2-yl)pyrrolidin-l-yl)ethan-l-one (583)

[0887] To the solution of 2-((2S,4R)-4-fluoropyrrolidin-2-yl)-5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazole hydrochloride (Scheme 9-31 compound **S5,** 0.85mmol), 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (267 mg, 0.85mmol) in DMF (3.0 mL), HATU (485 mg, 1.23mmol) was added followed by dropwise addition of DIEA (4.0eq) at room temperature. The mixture was stirred for 1 h at rt and the volatiles were evaporated. The residue was diluted with 50 mL of 10% sodium carbonate and extracted with ethyl acetate. The combined organic solution was successively washed with water, brine and dried over $MgSO_4$. The solution was filtered and the solvent was removed. The residue was purified to afford 83.6 mg of the title compound **583.** ¾ NMR (400 MHz, **DMSO-de):** (major rotamer) 61.76-1.84 (m, 2H), 2.20-2.28 (m, 2H), 2.37-2.42(m,lH), 2.56 (s, 3H), 2.62(s, 3H), 2.60-2.63 (m, 1H), 2.84(t, J=7.6Hz, 1H), 3.97-4.10 (m, 1H), 4.18-4.27 (m, 1H), 5.19 (t, J=8.4Hz, 1H), 5.47-5.94 (m, 3H), 7.72 (t, J=8.8Hz, 2H), 8.36 (s, 1H), 8.97 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major) δ -64.93, -176.91ppm. LC (method A): t_R = 1.63 min. LC/MS (EI) *mlz:* $[M + H]^+$ 560.10.

Scheme 9-32



Step 1: *tert-Butyl* (2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-4H-l,2,4-triazol-3-yl)pyrrolidine-l-carboxylate (S2)

[0888] To the solution of *tert*-Butyl (2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-l,3,4-oxadiazol-2-yl)pyrrolidine-l-carboxylate (Scheme 9-32 compound **SI,** 70 mg) in o-xylene, ammonium acetate (150 mg) was added. The mixture was refluxed for 72 h while three additional batches of ammonium acetate (150 mg) were added periodically. Following consumption of the starting material, the remaining residue was dissolved in 50 mL of ethyl acetate. The solution was quenched carefully with saturated aqueous NaHCCb (15mL), extracted into EtOAc, washed with water and brine, dried, and filtered. The title compound was carried forward without additional purification.

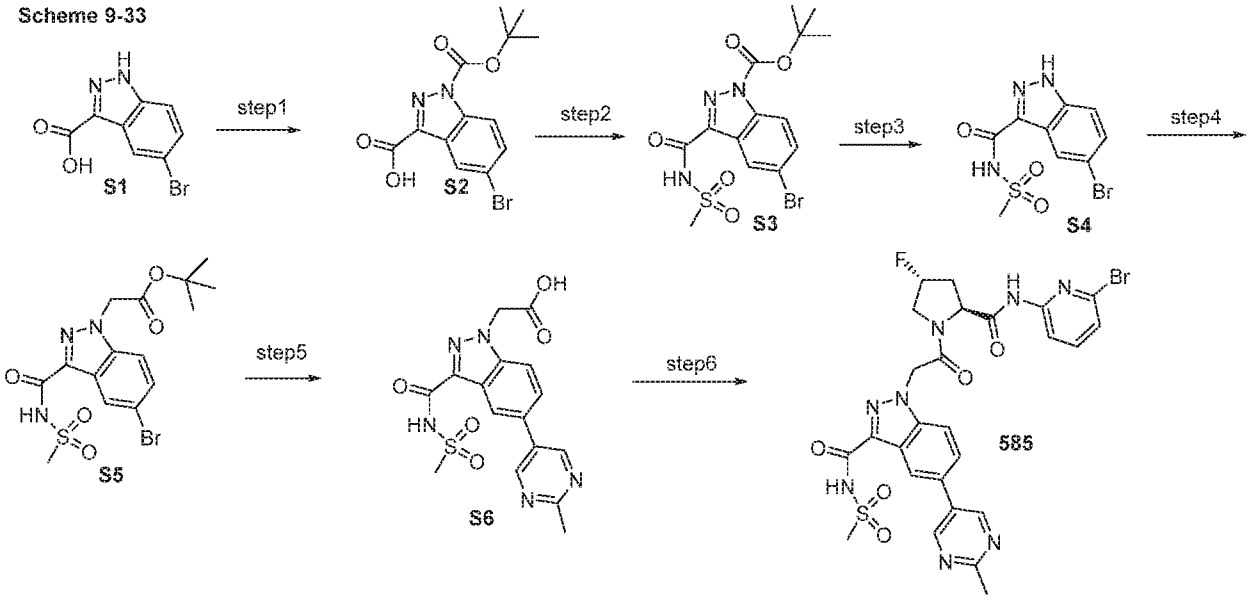
Step 2: 3-((2S,4R)-4-Fluoropyrrolidin-2-yl)-5-(4,4,4-trifluorobutyl)-4H-l,2,4-triazole hydrochloride (S3)

[0889] *tert*-Butyl (2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-4H-l,2,4-triazol-3-yl)pyrrolidine-l-carboxylate (Scheme 9-32 compound **S2)** was taken up in 4N HC1 dioxane (3.0 mL) and the resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction, which was monitored by HPLC, the solvent was removed under reduced pressure. The remaining residue was used directly without further purification.

Step: 3 2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)-l-((2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-4H-l,2,4-triazol-3-yl)pyrrolidin-l-yl)ethan-l-one (584)

[0890] To the solution of 3-((2S,4R)-4-fluoropyrrolidin-2-yl)-5-(4,4,4-trifluorobutyl)-4H-l,2,4-triazole hydrochloride (Scheme 9-32 compound **S3,** 0.13mmol), 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid (0.13mmol) in DMF (3.0 mL), HATU (1.3eq) was added followed by dropwise addition of DIEA (4.0eq) at room temperature. The mixture was stirred for 1 h at rt and the volatiles were evaporated. The residue was diluted with 50 mL of 10% sodium carbonate and extracted with ethyl acetate. The combined organic solution was successively washed with water and brine and dried over $MgSO_4$. The solution was filtered and the solvent was removed. The residue was purified to afford 41.1 mg of the title compound. ¾ NMR (400 MHz, DMSO-i¾): (major rotamer) 61.84-1.98 (m, 2H), 2.24-2.40 (m,3H), 2.58-2.66 (m, 1H), 2.63 (s, 3H), 2.69(s, 3H), 2.75(t, J=7.6Hz, 1H), 2.86-2.90 (m, 1H),

4.01-4.12 (m, 1H), 4.24-4.33 (m, 1H), 5.15 (t, J=8.4Hz, 1H), 5.27-5.65 (m, 2H), 5.84 (t, J=16.8Hz, 1H), 7.82 (t, J=8.8Hz, 2H), 8.43 (s, 1H), 9.04 (s, 2H)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major) δ -64.76, -177.07ppm. LC (method A): t_R = 1.43 min. LC/MS (EI) *mlz:* $[M + H]^+$ 559.26.



Stepl 5-Bromo-l-(ieri-butoxycarbonyl)-lH-indazole-3-carboxylic acid (S2)

[0891] To the solution of 5-bromo-lH-indazole-3-carboxylic acid (Scheme 9-33 compound **SI,** 1.69g, 7.0mmmol) in THF (20mL), IN NaOH (20mmol, 20mL) was added in one portion followed by addition of B0C2O (2.18g, lOmmol) at room temperature. The mixture was stirred for 2 h at room temperature and the volatiles were evaporated. The residue was acidified with aqueous citric acid (10%, 15mL), and the resulting solid was collected, washed with water, and dried. The compound was carried forward without further purification.

Step 2: *tert*-Butyl 5-bromo-3-((methylsulfonyl)carbamoyl)-lH-indazole-l-carboxylate (S3)

[0892] To the solution of 5-bromo-l-(ter *t*-butoxycarbonyl)-lH-indazole-3-carboxylic acid (Scheme 9-33 compound **S2,** 994 mg, 3.0mmol), methanesulfonamide (566 mg, 6.0mmol) in DMF (15.0 mL), HATU (2.30g, 6.0mmol) was added followed by dropwise addition of DIEA (4.0eq) at room temperature. The mixture was stirred for 1 h at rt and the volatiles were evaporated. The residue was diluted with 50 mL of saturated aqueous sodium bicarbonate, and the

resulting solid was collected, washed with water and dried for next step use without further purification.

Step 3: 5-Bromo-N-(methylsulfonyl)-lH-indazole-3-carboxamide hydrochloride (S4)

[0893] *tert*-butyl 5-bromo-3-((methylsulfonyl)carbamoyl)-lH-indazole-l-carboxylate (Scheme 9-33 compound **S3,** 465 mg, l.l lmmol) was taken up in 4N HC1 dioxane (3.0 mL) and stirred overnight at rt. After completion of the reaction, which was monitored by HPLC, the solvent was removed under reduced pressure. The remaining residue was used directly without further purification.

Step4 *tert-Butyl* 2-(5-bromo-3-((methylsulfonyl)carbamoyl)-lH-indazol-l-yl)acetate (S5)

[0894] 5-bromo-N-(methylsulfonyl)-lH-indazole-3-carboxamide hydrochloride (Scheme 9-33 compound **S4)** was mixed with *tert*-butyl 2-bromoacetate (1.5eq) and solid potassium carbonate (3.0eq) in CH3CN (15mL) and the mixture was refluxed overnight. The reaction was cooled to rt and filtered. The solid residue was acidified with citric acid (10%, 50mL) and the resulting aqueous phase was extracted with ethyl acetate three times (3x50mL). The combined organic phases were washed with water and brine and dried. The solution was filtered, concentrated, and purified to afford 400 mg of title product. LC (method A): t_R = 2.16 min. LC/MS (EI) *mlz:* $[M + H]^+$ 431.99, 434.09.

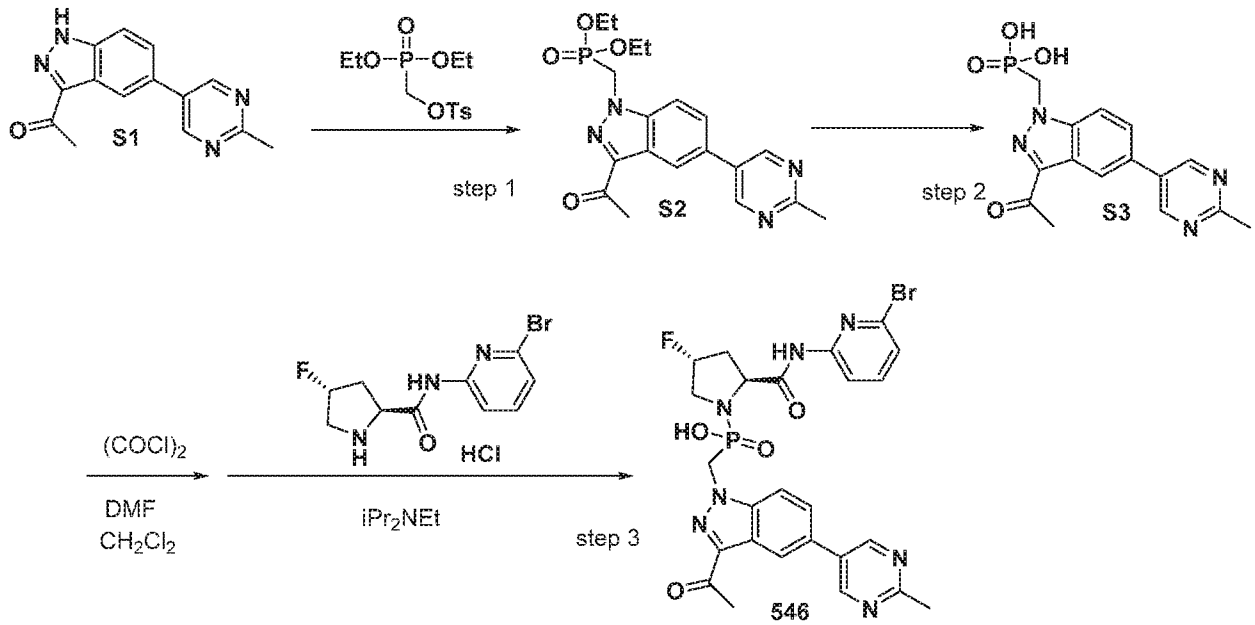
Step 5: 2-(5-(2-Methylpyrimidin-5-yl)-3-((methylsulfonyl)carbamoyl)-lH-indazol-l-yl)acetic acid (S6)

[0895] A mixture of *tert*-butyl 2-(5-bromo-3-((methylsulfonyl)carbamoyl)-l H-indazol-l-yl)acetate (Scheme 9-33 compound **S5,** 400 mg), 2-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidine (220 mg), K3PO4 (675 mg) and Pd(dppf)2Cl2 (124 mg) in solvent (dioxane 12mL, H20 3.0mL) was purged with argon in a pressure vessel for 5 min and stirred for 15 h at 95°C. The volatiles were removed under reduced pressure and the residue was washed with ethyl acetate twice. The remaining solid was then quenched with citric acid (10%) and the resulting precipitate was collected and dried for next step use without further purification. LC (method A): t_R = 0.65 min. LC/MS (EI) *mlz:* $[M + H]^+$ 390. 13.

Step 6: l-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-N-(methylsulfonyl)-lH-indazole-3-carboxamide (585)

[0896] To the solution of (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (0.24mmol), 2-(5-(2-methylpyrimidin-5-yl)-3-((methylsulfonyl)carbamoyl)-lH-indazol-l-yl)acetic acid (Scheme 9-33 compound **S6,** 94 mg, 0.24mmol) in DMF (3.0 mL), HATU **(1.3eq)** was added followed by dropwise addition of DIEA (4.0eq) at room temperature. The mixture was stirred for 1 h at rt and the solution was purified by preparative HPLC to afford 87.9 mg of the title compound. ¾ NMR (400 MHz, **DMSO-de):** (major rotamer) 62.01-2.24 (m, 1H), 2.51-2.61 (m,lH), 2.69(s, 3H), 3.39 (s, 3H), 3.86-4.09 (m, 1H), 4.20-4.29 (m, 1H), 4.67 (t, J=8.4Hz, 1H), 5.45-5.82 (m, 3H), 7.32 (d, J=7.6Hz, 1H), 7.71 (t, J=7.6Hz, 1H), 7.90 (s, 2H), 8.01 (d, J=8.4Hz, 1H), 8.39 (s, 1H), 9.06 (s, 2H), 11.01 (s, 1H), 12.00 (br, s, lH)ppm. ^{19}F NMR (376 MHz, DMSO-i¾): (major) δ -175.68ppm. LC (method A): t_R = 1.51 min. LC/MS (EI) *mlz:* $[M + H]^+$ 658.88, 661.05.

Scheme 9-34



Step 1: Diethyl ((3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)methyl)phosphonate (S2)

[0897] A mixture of l-(5-(2-methylpyrimidin-5-yl)-lH-indazol-3-yl)ethan-l-one (scheme 9-34 compound **SI,** 500 mg), (diethoxyphosphoryl)methyl 4-methylbenzenesulfonate (770 mg)

and potassium carbonate (820 mg) in CH3CN (20 mL) was stirred for 16 h at 90 °C. Volatiles were removed in vacuoo and the residue was purified by silic agel chromatography to afford 790 mg of the title compound.

Step 2: ((3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)methyl)phosphonic acid (S3)

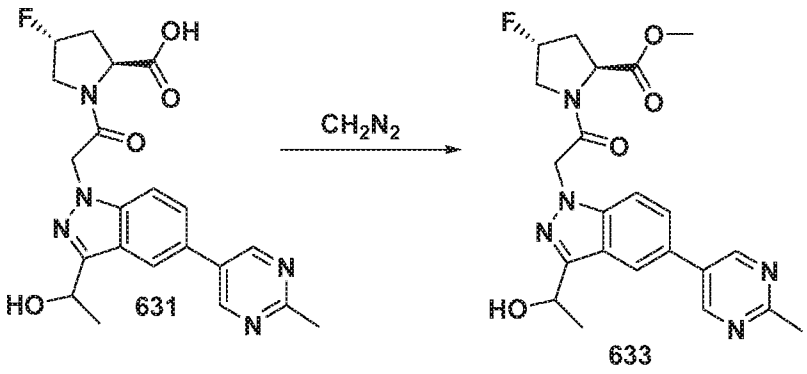
[0898] diethyl ((3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)methyl)phosphonate (scheme 9-34 compound **S2**,402 mg) was dissolved in DCM (5 mL) and TMS-Br (1 mL) was added. The reaction mixture was stirred overnight at rt and then the solvent was removed under reduced pressure. The remaining material was used directly in the next step.

Step 3 (2S,4R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (546)

[0899] To a solution of ((3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)methyl)phosphonic acid (scheme 9-34 compound **S3)** in DCM (5 mL) was added oxalyl chloride (1 mL) followed by DMF. The reaction was refluxed. Following removal of solvent, the residue was added to DCM (10 mL). (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride and DIEA (0.5 mL) were added successively and the reaction was stirred for 16 h at room temperature. Excess solvent was removed in vacuoo and the residue was purified by HPLC to afford the title compound.

[0900] ¾ NMR (400 MHz, DMSO) δ 1.91 - 2.04 (m, 1H), 2.01 - 2.21 (m, 1H), 2.52 (d, *J* = 5.4 Hz, 1H), 2.53 - 2.64 (m, 2H), 2.97 - 3.12 (m, 2H), 3.15 (s, 1H), 3.25 (m, 1H), 3.46 - 3.54 (m, 1H), 4.17 (t, *J* = 8.7 Hz, 1H), 4.55 (t, *J* = 10.2 Hz, 1H), 4.62 - 4.74 (m, 1H), 5.17 - 5.27 (m, 0.5H), 5.31 - 5.42 (m, 0.5H), 7.22 - 7.36 (m, 1H), 7.62 - 7.76 (m, 2H), 7.87 (d, *J* = 11.2 Hz, 1H), 7.88 - 8.04 (m, 2H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.82 (d, *J* = 11.4 Hz, 1H), 8.93 (d, *J* = 14.4 Hz, 1H), 10.77 (s, 1H).; ^{19}F NMR (376 MHz, DMSO) (major rotamer) δ -174.64. ^{31}P NMR (162 MHz, DMSO) δ 9.50. LC (method A): t_R = 1.10 min. LC/MS (EI) *m/z*: $[M + H]^+$ 616.

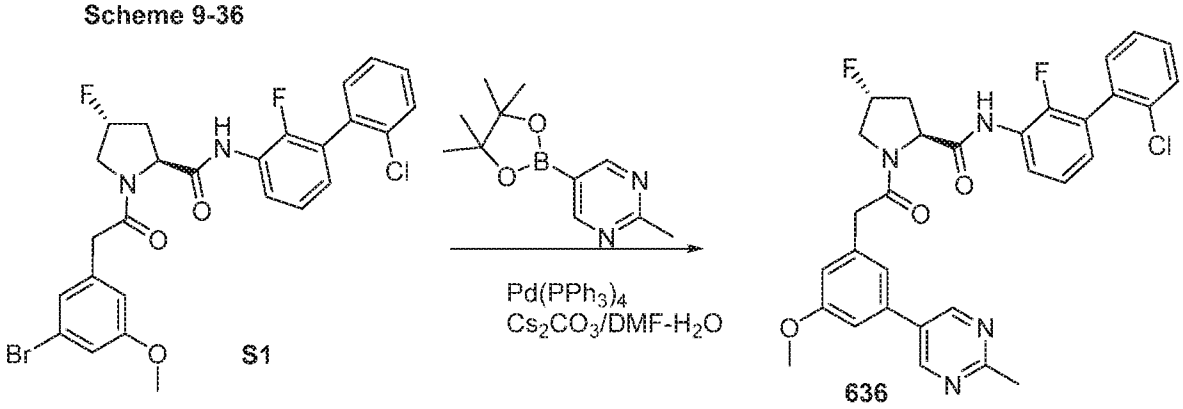
Scheme 3-35



Methyl (2S,4R)-4-fluoro-l-(2-(3-(l-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)pyrrolidine-2-carboxylate (633)

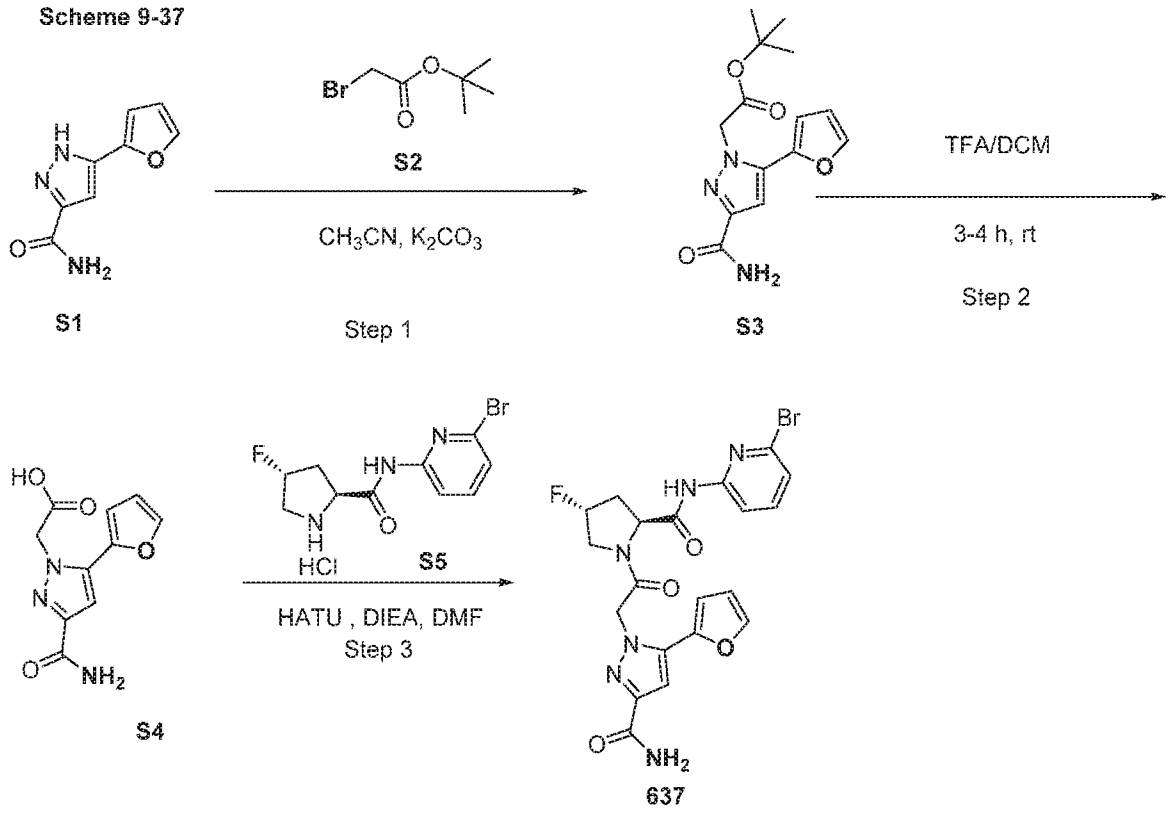
[0901] To a solution of (2S,4R)-4-fluoro-l-(2-(3-(l-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)pyrrolidine-2-carboxylic acid (scheme 9-35 compound **631**,**427** mg) in Et_20 (5 mL) was added diazomethane Et_20 solution dropwise. The reaction was stirred for 3 h. The reaction mixture was then added AcOH and removed all solvent. The remaining residue was purified by HPLC to afford the title compound **633.** ¾ NMR (400 MHz, DMSO) δ 1.59 (m, 2H), 2.01 - 2.23 (m, 1H), 2.68 (s, 3H), 3.01 (s, 0.5H), 3.61 (s, 3H), 3.77 - 3.89 (m, 1H), 3.95 (d, *J* = 12.5 Hz, 0.5H), 4.18 (dd, *J* = 12.6, 21.9 Hz, 1H), 4.39 (m, 1H), 5.12 - 5.20 (m, 1H), 5.26 - 5.58 (m, 3H), 5.57 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 0.5H), 7.46 - 7.68 (m, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 8.04 (s, 0.5H), 8.28 (s, 1H), 9.05 (s, 2H).; ^{19}F NMR (376 MHz, DMSO-i¾): (major rotamer) 5 - 176.06. LC (method A): t_R = 0.95 min. LC/MS (EI) *mlz*: $[M + H]^+$ 442.

Scheme 9-36



[0902] **(2S,4R)-N-(2'-chloro-2-fluoro-[l,l'-biphenyl]-3-yl)-4-fluoro-l-(2-(3-methoxy-5-(2-methylpyrimidin-5-yl)phenyl)acetyl)pyrrolidine-2-carboxamide (636):** Pd(PPh3)4 (3.7 mg, 0.0032 mmol) was added into a mixture of (2S,4R)-l-(2-(3-bromo-5-methoxyphenyl)acetyl)-N-(2'-chloro-2-fluoro-[l ,r-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (scheme 9-36 compound **SI,** 36 mg, 0.064 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidine (17 mg, 0.077 mmol), and CS2CO3 (42 mg, 0.128 mmol) in DMF-water (1-0.1 mL) The mixture was heated at 80 °C under Ar for 6 h and then cooled to rt. Water was added and the mixture was extracted with AcOEt. After washing with brine and drying over anhydrous Na_2S04, solvent was removed by evaporation. The residue was purified on silica gel column chromatography with EtOAc in hexane (50-100%) as the eluent to afford (2S,4R)-N-(2'-chloro-2-fluoro-[l ,r-biphenyl]-3-yl)-4-fluoro-l-(2-(3-methoxy-5-(2-methylpyrimidin-5-yl)phenyl)acetyl)pyrrolidine-2-carboxamide (scheme 9-36 compound **636,** 24.3 mg).

[0903] ¾ NMR (400 MHz, CDCh) δ 9.34 (d, J = 2.9 Hz, 1H), 8.78 (s, 2H), 8.26 (ddd, J = 1.7, 7.3, 8.7 Hz, 1H), 7.46 (ddt, J = 1.6, 3.2, 6.4 Hz, 1H), 7.36 - 7.25 (m, 3H), 7.16 (td, J = 1.1, 8.0 Hz, 1H), 7.06 - 6.97 (m, 2H), 6.94 (dd, J = 1.6, 2.4 Hz, 1H), 6.85 (dd, J = 1.5, 2.4 Hz, 1H), 5.43 - 5.22 (m, 1H), 5.00 (dd, J = 7.0, 8.4 Hz, 1H), 3.99 (ddt, J = 1.7, 12.5, 19.7 Hz, 1H), 3.87 - 3.75 (m, 2H), 3.73 (s, 3H), 3.64 (ddd, J = 3.5, 12.4, 32.8 Hz, 1H), 2.96 - 2.80 (m, 1H), 2.54 - 2.37 (m, 1H). LC (method A): t_R = 2.18 min. LC/MS (EI) *m/z*: $[M + H]^+$ 577.



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(furan-2-yl)-lH-pyrazol-l-yl)acetate (S3)

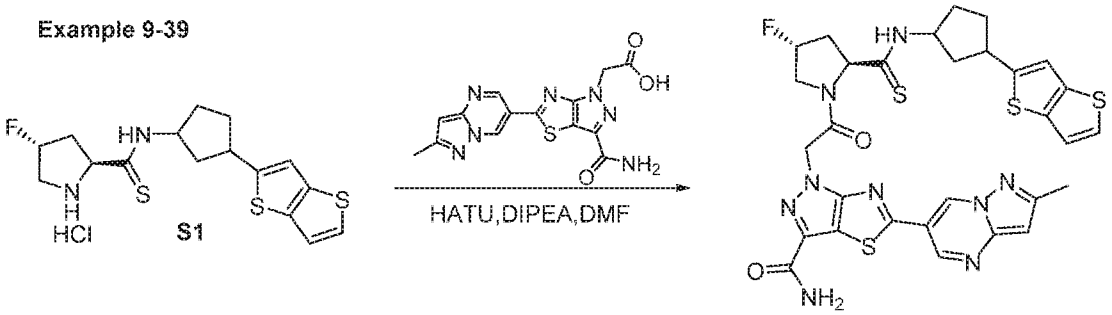
[0904] To a solution of 5-(furan-2-yl)-lH-pyrazole-3-carboxamide (scheme 9-37 compound **SI,** 1 equiv) in CH3CN (10 vol) was added ter*t*-butyl 2-bromoacetate (scheme 9-37 compound **S2,** 1.1 equiv) and potassium carbonate (1.1 equiv). The mixture was refluxed overnight under an atmosphere of argon. After cooling the reaction mixture to room temperature, the mixture was filtered through Celite and washed with CH3CN . The filtrate was concentrated under high vacuum and the residue was purified by column chromatography on silica gel (EtOAc/DCM) to afford scheme 9-37 compound **S3.**

Step 2: 2-(3-Carbamoyl-5-(furan-2-yl)-lH-pyrazol-l-yl)acetic acid (S4)

[0905] To a solution of scheme 9-37 compound **S3** (1 equiv) in DCM (10 vol) at 0 °C under an atmosphere of nitrogen was added TFA (5 vol). The reaction mixture was stirred at room temperature for 3 h and then concentrated. The remaining material was carried forward without further purification.

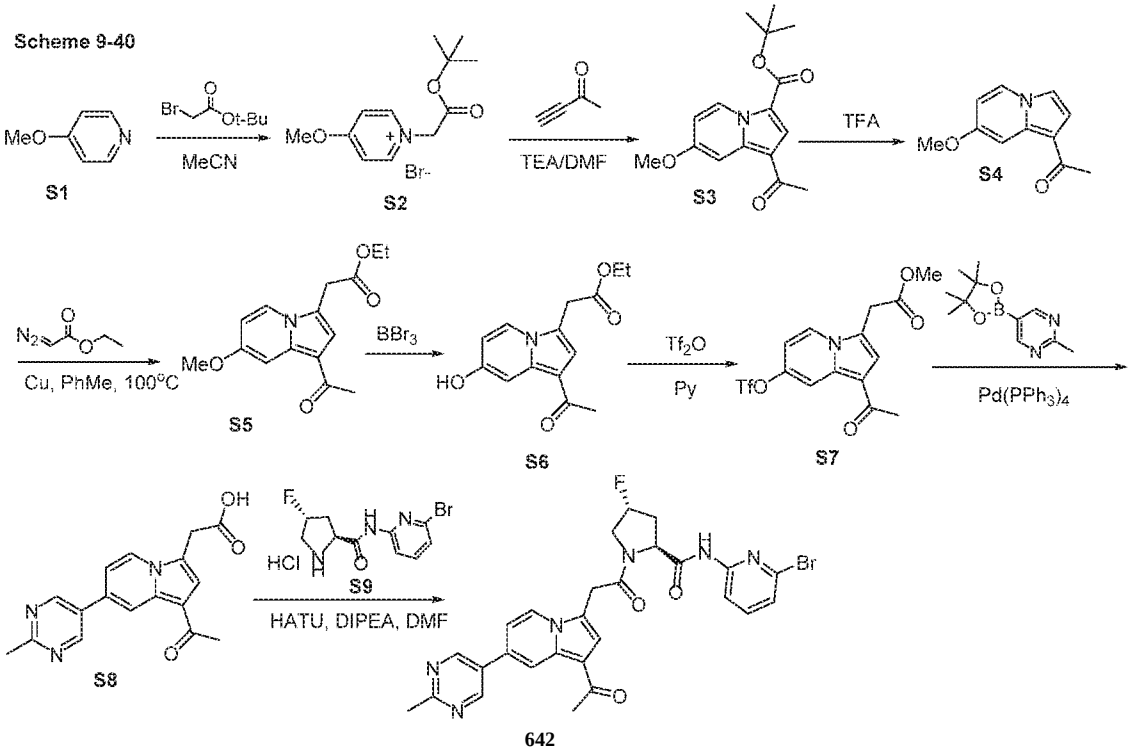
Step 3: l-(2-((2S,4R)-2-((6-Bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-5-(furan-2-yl)-lH-pyrazole-3-carboxamide (637)

[0906] To a solution of scheme 9-37 compound **S4** (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (1 equiv), HATU (2.1 equiv), and DIPEA (5 equiv). The reaction mixture was stirred at room temperature for 3 h and then quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2S04, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to afford compound **637.** ¾ NMR (400 MHz, DMSO-d_6) δ 2.04 - 2.27 (m, 1H), 2.53 - 2.63 (m, 1H), 3.82 - 4.01 (m, 1H), 4.12 - 4.29 (m, 1H), 4.68 (t, J = 8.5 Hz, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.43 - 5.61 (m, 2H), 6.64 (dd, J = 1.8, 3.5 Hz, 1H), 6.77 (d, J = 3.5 Hz, 1H), 6.94 (s, 1H), 7.25 - 7.39 (m, 2H), 7.53 (s, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.78 (s, 1H), 8.03 (d, J = 8.2 Hz, 1H), 11.02 (s, 1H). ^{19}F NMR (376 MHz, DMSO-i¾): δ -175.15. LC (method A): t_R = 1.39 min. LC/MS (EI) *mlz:* $[M + H]^+$ 505.



[0907] **l-(2-((2S,4R)-4-fluoro-2-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)pyrrolidin-l-yl)-2-oxoethyl)-5-(2-methylpyrazolo[l,5-a]pyrimidin-6-yl)-lH-pyrazolo[3,4-d]thiazole-3-carboxamide (641):** The titled compound was prepared according to the procedure from Scheme 38 from appropriate starting materials. ¾ NMR (400 MHz, DMSO-d_6) δ: 10.03 (d, *J* =6 Hz, 1H), 9.67 (s, 1H), 9.01 (s, 1H), 8.45 (s, 1H), 7.87-7.90 (m, 1H), 7.53-7.63 (m, 2H), 7.09-7.34 (m, 2H), 6.69 (s, 1H), 5.30-5.68 (m, 3H), 4.53-4.89 (m, 2H), 4.01-4.24 (m, 2H), 2.46 (s, 3H), 1.99-2.07 (m, 2H),1.74-1.79 (m, 2H), 1.63-1.69 (m, 2H). LC/MS (ESI) *mlz:* 694 (M+H).

(2S,4R)-l-(2-(l-Acetyl -7-(2-methylpyrimidin-5-yl)indolizin-3-yl) acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (642)



Step 1: l-(2-(tert-Butoxy)-2-oxoethyl)-4-methoxypyridin-l-ium bromide (S2)

[0908] To a solution of 4-methoxypyridine (5.0 g, 45.9 mmol) in MeCN (100 mL) was added tert-butyl 2-bromoacetate (8.9 g, 45.9 mmol) and the reaction mixture was stirred at 50 °C for 2 hrs. The mixture was evaporated under reduced pressure and the residue was re-crystallized from Et_20 to give the title compound (12.6 g, 90.6% yield) as white solid.

Step 2: tert-Butyl l-acetyl -7-methoxyindolizine-3-carboxylate (S3)

[0909] To a solution of l-(2-(tert-butoxy)-2-oxoethyl)-4-methoxypyridin-l-ium bromide (8.0 g, 26.4 mmol) in DMF (120 mL) was added but-3-yn-2-one (1.8 g, 26.4 mmol) and TEA (11 mL, 79.2 mmol) and the reaction mixture was stirred at 60 °C for 3 hrs. The mixture was poured into ice water (250 mL) and extracted with EtOAc 9(2 x 50 mL). The combined organic layers are washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (PE: EtOAc =20: 1 to 10: 1) to give the title compound (6.6 g, 86.8% yield) as yellow solid.

Step 3: l-(7-Methoxyindolizin-l-yl)ethanone (S4)

[0910] To a solution of tert-butyl l-acetyl-7-methoxyindolizine-3-carboxylate (2.0 g, 6.9 mmol) in DCM (150 mL) was added TFA (5.1 mL, 69.2 mmol) at 0 °C and the reaction was stirred at room temperature overnight. The mixture was poured into ice-cooled aq.NaHCCb solution (250 mL) and extracted with DCM (2 x 50 mL). The combined organic layers are washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (PE: EtOAc= 6: 1 to 4: 1) to give the title compound (530 mg, 40.8% yield) as yellow solid.

Step 4: Ethyl 2-(l-acetyl-7-methoxyindolizin-3-yl)acetate (S5)

[091 1] To a mixture of l-(7-methoxyindolizin-l-yl)ethanone (1.0 g, 5.3 mmol) and Cu powder (371 mg, 5.8 mmol) in toluene (25 mL) at 100 °C was added a solution of ethyl 2-diazoacetate (661.2 mg, 5.8 mmol) in toluene (4 mL) dropwise. The reaction was stirred at this temperature for 4 hrs. The mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (PE: EtOAc= 6: 1 to 4: 1) to give the title compound (500 mg, 34.4% yield) as a brown solid.

Step 5: Ethyl 2-(l-acetyl-7-hydroxyindolizin-3-yl)acetate (S6)

[0912] To a solution of ethyl 2-(l-acetyl-7-methoxyindolizin-3-yl)acetate (430 mg, 1.6 mmol) in DCM (20 mL) was added dropwise a solution of BBr_3 (3.9 g, 16.0 mmol) in DCM (5 mL) at -78 °C and the reaction mixture was stirred at room temperature overnight. The mixture was quenched by addition MeOH (10 mL) at -78 °C then allowed to stir at room temperature for 1 hr. The mixture was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (DCM: MeOH=40: 1 to 20: 1) to give the title compound (230 mg, crude) as a green solid.

Step 6: Methyl 2-(l-acetyl-7-(((trifluoromethyl)sulfonyl)oxy)indolizin-3-yl)acetate (S7)

[0913] To a solution of ethyl 2-(l-acetyl-7-hydroxyindolizin-3-yl)acetate (230 mg, 0.93 mmol) in pyridine (3 mL) was added dropwise Tf_20 (288 mg, 1.02 mol) at 0 °C for 30 min. The reaction was stirred at room temperature for 1 hr. The mixture was diluted with DCM and washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure.

The residue was purified by chromatography on silica gel (PE: EtOAc = 4: 1 to 2: 1) to give the title compound (30 mg, 8.5% yield) as green oil.

Step 7 and Step 8: 2-(l-Acetyl-7-(2-methylpyrimidin-5-yl)indolizin-3-yl)acetic acid (S8)

[0914] A mixture of methyl 2-(l-acetyl-7-(((trifluoromethyl)sulfonyl)oxy)indolizin-3-yl) acetate (20 mg, 0.058 mmol), (2-methylpyrimidin-5-yl)boronic acid (11 mg, 0.08 mmol), Na_2C0_3 (22 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was degassed and stirred at 90 °C under N_2 atmosphere overnight. The mixture was diluted with EtOAc and washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by prep-TLC (PE: EtOAc = 1: 2) to afford the desired product (12 mg, 68.9% yield) as yellow solid.

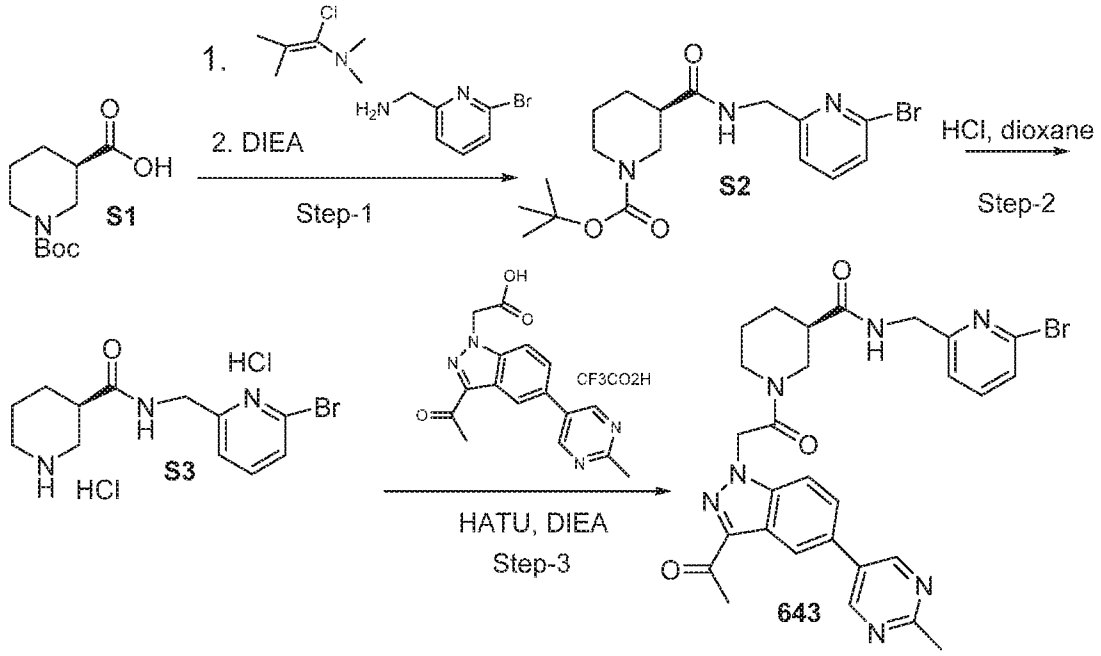
[0915] To a solution of 2-(l-acetyl-7-(2-methylpyrimidin-5-yl)indolizin-3-yl)acetic acid (12 mg, 0.04 mmol) in THF (1 mL) was added a solution of LiOH (3 mg, 0.11 mmol) in water (0.5 mL) at 0 °C. Then the reaction mixture was stirred at room temperature for 1 hr. The mixture was washed with diethyl ether and acidified by adding 1 N aq. HCl. The mixture was extracted with DCM and the organic layer dried over anhydrous sodium sulfate, and concentrated to give the title compound (11 mg, 100% yield) as yellow solid.

Step 9: (2S,4R)-l-(2-(l-Acetyl-7-(2-methylpyrimidin-5-yl)indolizin-3-yl)acetyl)-N- (6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (642)

[0916] A mixture of 2-(l-acetyl-7-(2-methylpyrimidin-5-yl)indolizin-3-yl)acetic acid (10 mg, 0.03 mmol), **S9** (13 mg, 0.04 mmol), HATU (17 mg, 0.05 mmol) and DIPEA (12 mg, 0.09 mmol) in DMF (2 mL) was stirred at room temperature overnight. The mixture was partitioned with EtOAc and water. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by prep-HPLC to afford the desired product (1.2 mg, 6.9% yield) as white solid. ¾ NMR (400 MHz, CDCh) δ: 9.04 (s, 1H), 8.94 (s, 2H), 8.74 (d, J = 1.1 Hz, 1H), 8.21 (d, J = 7.3 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.51 (t, J = 5.0 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.14 (s, 1H), 7.07 (dd, J = 7.3, 2.0 Hz, 1H), 5.44 (s, 1H), 5.31 (s, 1H), 4.87 (t, 1H), 4.07 (s, 3H), 3.76 (dd, J = 12.3, 3.2 Hz, 1H), 3.68 (dd, J = 12.4, 3.4 Hz, 1H), 2.81 (s, 3H), 2.54 (s, 3H). LC/MS (ESI) m/z: 579 $(M+H)^+$

(R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-((6-bromopyridin-2-yl)methyl)piperidine-3-carboxamide (643)

Scheme 9-41



Step-1: tert-Butyl (R)-3-(((6-bromopyridin-2-yl)methyl)carbamoyl)piperidine-l-carboxylate (S2)

[0917] To an ice-cold solution of (R)-l-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (1.09g, 4.75mmol) in 50 mL of CH_2Cl_2, l-chloro-N,N,2-trimethyl-l-propenylamine (0.69mL, 5.3mmol) was added dropwise with stirring. The stirring was continued for 2 h at this temperature, then (6-bromopyridin-2-yl)methanamine (750mg, 4.0mmol) was added, followed by 1.6 mL of iPn NEt . The cooling bath was removed and the reaction mixture was stirred overnight at rt. After completion of the reaction monitored by HPLC, the reaction mixture was added to water (120 mL) and extracted with DCM (2 x 120 mL). The organic layer was washed successively with an aqueous solution of NaHCCb (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2S04 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (ISCO eluted with Hexanes/EtOAC) to give 1.1 Og of desire title compound.

Step-2: (R)-N-((6-Bromopyridin-2-yl)methyl)piperidine-3-carboxamide dihydrochloride (S3)

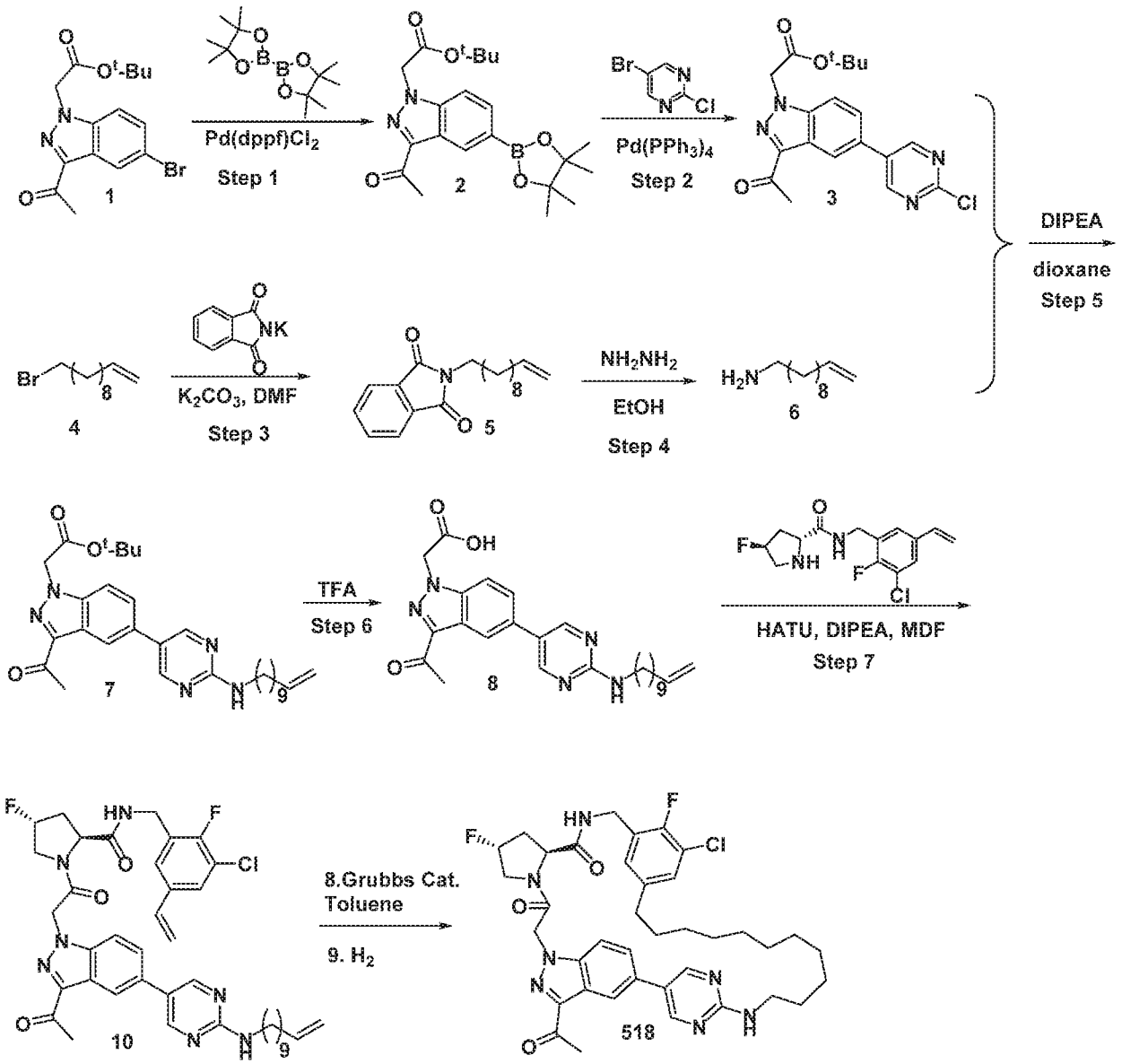
[0918] Tert-butyl (R)-3-(((6-bromopyridin-2-yl)methyl)carbamoyl)piperidine-l-carboxylate (1.10g) was taken in 4N HC1 dioxane (10 mL) and the resulting reaction mixture was stirred at room temperature for 2 h. After completion of the reaction monitored by HPLC, the solvent was removed under reduced pressure. The remaining residue was used directly without further purification.

Step-3: (R)-l-(2-(3-Acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetyl)-N-((6-bromopyridin-2-yl)methyl)piperidine-3-carboxamide (643)

[0919] 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-lH-indazol-l-yl)acetic acid TFA salt (502 mg, 1.14mmol),(R)-N-((6-bromopyridin-2-yl)methyl)piperidine-3-carboxamide dihydrochloride (400mg, 1.31mmol) are dissolved in DMF (10 mL) and HATU (548 mg, 1.44mmol) was added, followed by addition of DIEA (5 equiv). The reaction mixture was stirred overnight at rt. The volatiles are evaporated under reduced pressure. The remaining material was treated with saturated NaHCCb. The resulting solid was collected and dried. The solid was dissolved in minimum co-solvent MeOH-DCM (15%) and loaded on silica gel for chromatography. The purification affords title compound (14.4mg). ¾ NMR (400 MHz, DMSO-de): (major rotamer) δ: 1.32-1.37 (m, 1H), 1.54-1.77 (m, 2H), 1.79-1.92 (m, 1H), 2.23-2.35 (m, 1H), 2.57 (s, 3H), 2.62 (s, 3H), 2.78-2.84 (m, 1H), 3.27-3.38 (m, 1H), 3.86-3.9 (m, 2H), 4.24-4.40 (m, 2H), 5.58-5.75(m, 2H), 7.18-7.31 (m, 1H),7.41-7.46 (m, 1H), 7.59-7.78 (m, 3H), 8.37(s, 1H), 8.51-8.59 (m, 1H), 8.97 (s, 2H) ppm; LC (method A): t_R = 1.48min. LC/MS (EI) *mlz:* $[M + H]^+$ 590.34, 592.30

EXAMPLE 10. SYNTHESIS OF ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I'

Scheme 10-1



[0920] Scheme 10-1 : In Step 1 the appropriately substituted aryl bromide is converted to a boronic acid as known in the art. In Step 2 the appropriately substituted boronic acid is subjected to an aryl bromide as known in the art to afford a biaryl species. In Step 3 the appropriately substituted bromide is subjected to a phthalimide to afford a protected alkene species. In Step 4 the appropriately substituted phthalimide-protected amine is subjected to hydrazine as known in the art to afford a free amine. In Step 5 the two appropriately substituted species previously

prepared react as known in the art to afford an alkene species. In Step 6 the appropriately substituted ester is treated with TFA to afford a carboxylic acid. In Step 7 the appropriately substituted carboxylic acid is converted to an amide as known in the art. In Step 8 the di-alkene species is cyclized as known in the art to form a macrocyclic species. In Step 9 the appropriately substituted macrocyclic-alkene species is reduced with hydrogen to afford a macrocyclic-alkyl species.

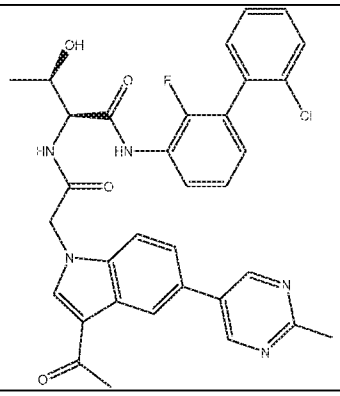
EXAMPLE 11. NON-LIMITING EXAMPLES OF ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I

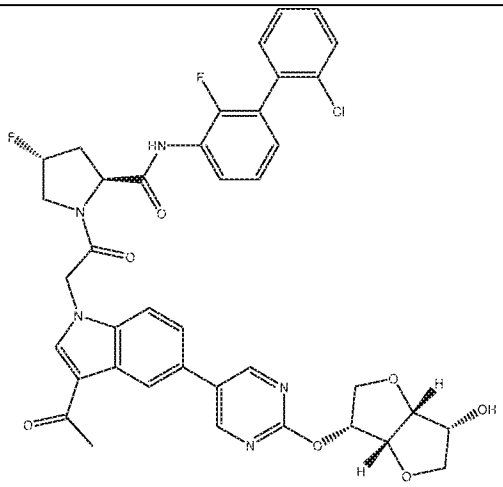
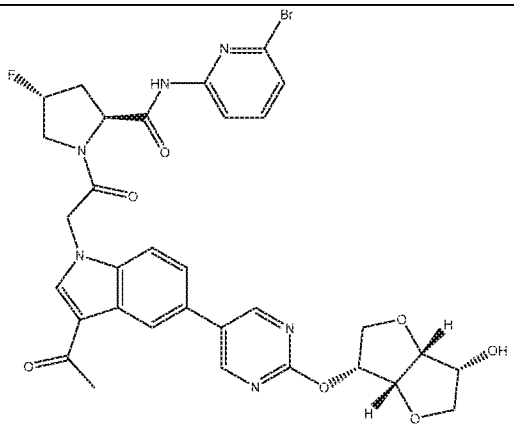
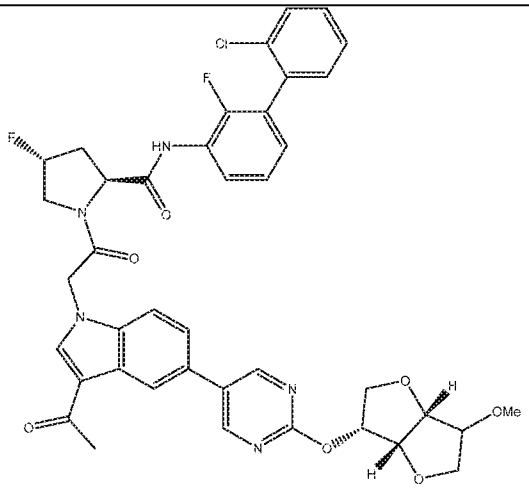
[0921] In the illustrative compounds of Figure 17, and elsewhere herein, R^{32} is depicted as Z^{32}, which are intended to be the same moieties.

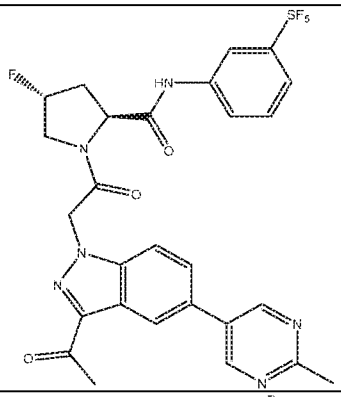
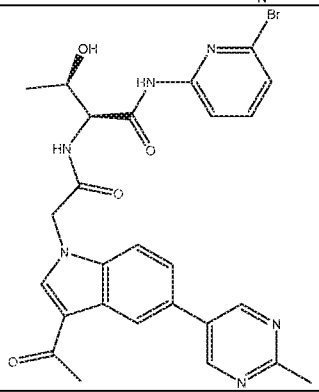
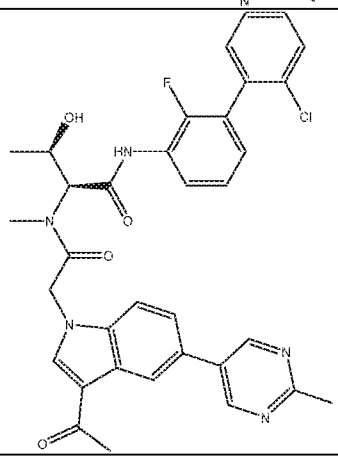
EXAMPLE 12. NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I, FORMULA I' AND FORMULA I"

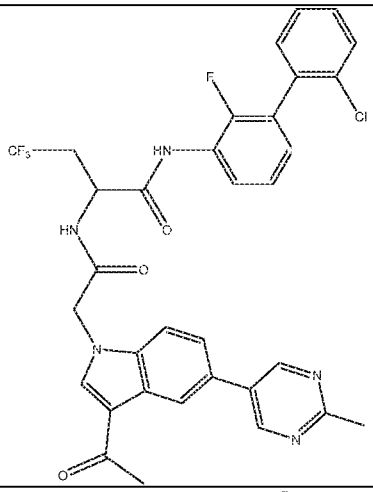
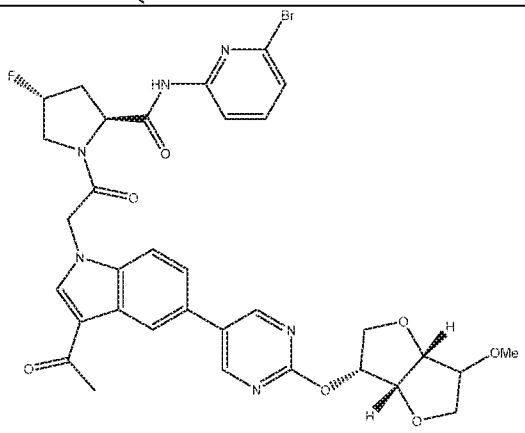
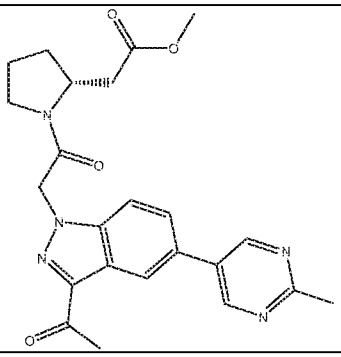
[0922] Table 3 shows illustrative Factor D inhibitors with characaterizing data. The assay of Example 13 was used to determine the ICso's of the compounds. Other standard factor D inhibition assays are also available. Three ***s are used to denote compounds with an IC50 less than 1 micromolar; two **s indicate compound with an IC50 between 1 micromolar and 10 micromolar, and one * denotes compounds with an IC50 greater than 10 micromolar.

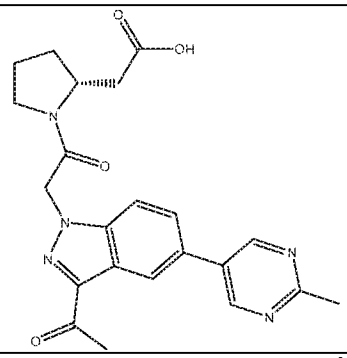
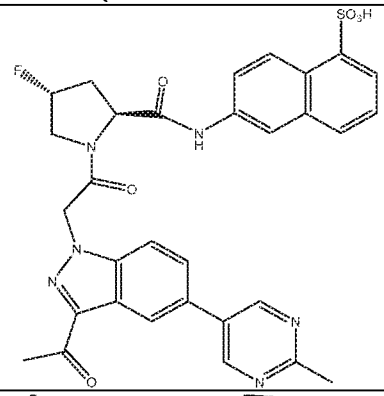
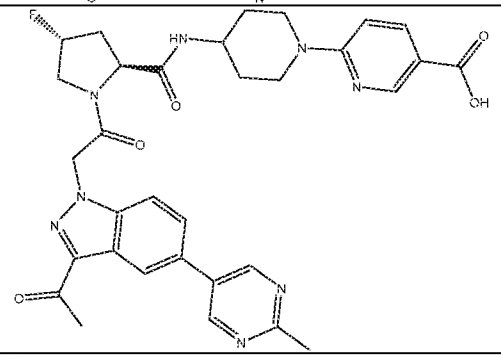
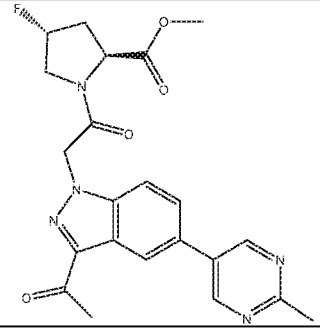
Table 3. Non-limiting Examples of Compounds of Formula I, Formula Γ and Formula I"

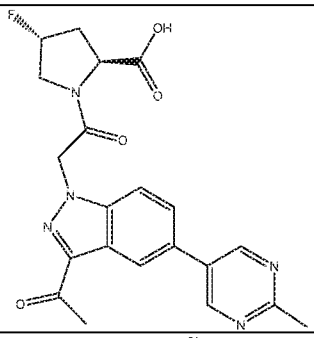
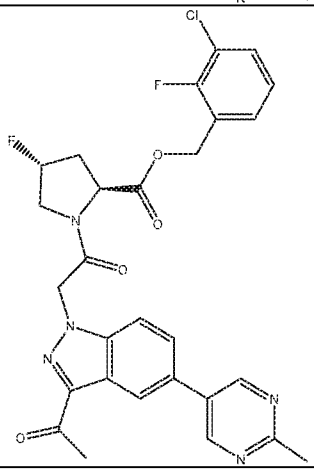
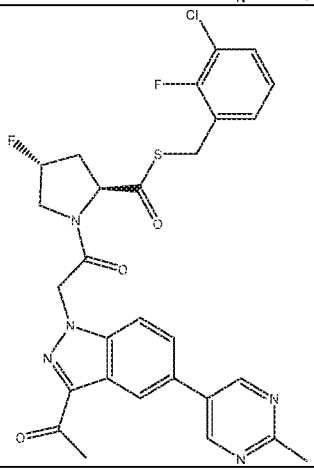
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
500		(2S,3R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetamido)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-3-hydroxybutanamide	***	3.58 (B)	614

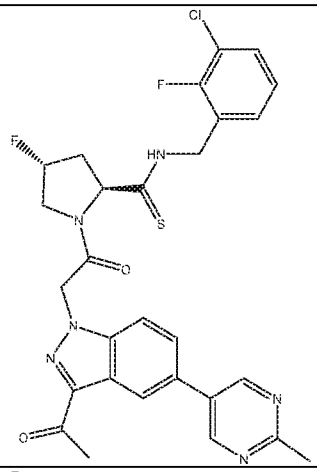
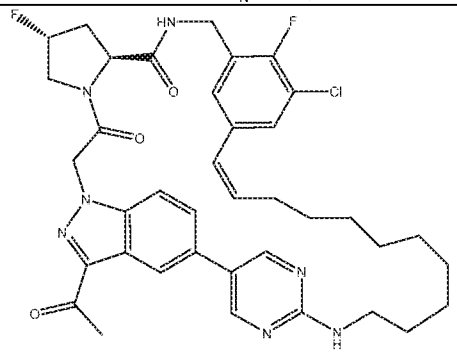
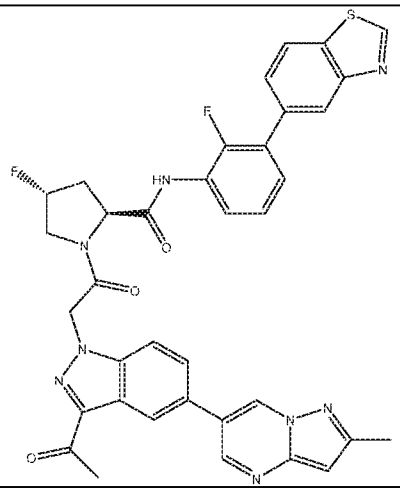
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
501		(2S,4R)-1-(2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.42 (B)	758
502		(2S,4R)-1-(2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.94 (B)	709
503		(2S,4R)-1-(2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.63 (B)	772

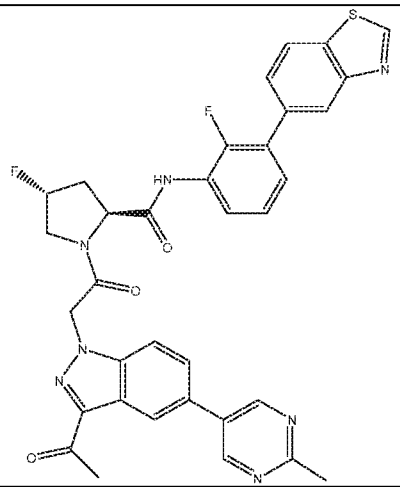
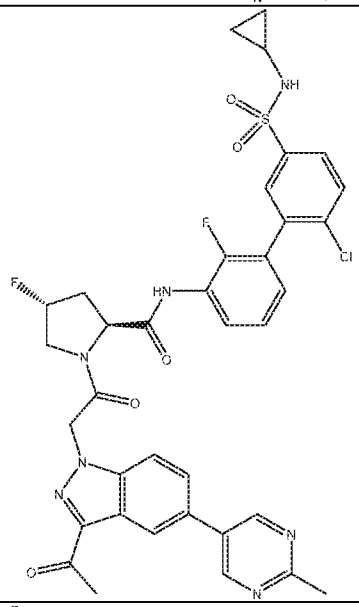
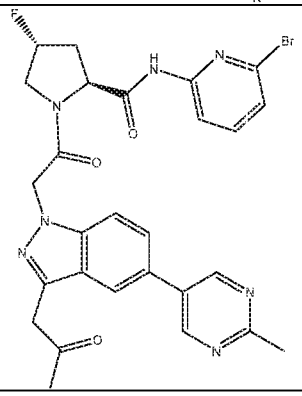
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
504		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoro-N-(3-(pentafluoro-□^{6}-sulfanyl)phenyl)pyrrolidine-2-carboxamide	***	2.13 (A)	627
505		(2S,3R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetamido)-N-(6-bromopyridin-2-yl)-3-hydroxybutanamide	***	2.85 (B)	565
506		(2S,3R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)-N-methylacetamido)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-3-hydroxybutanamide	**	4.07 (B)	628

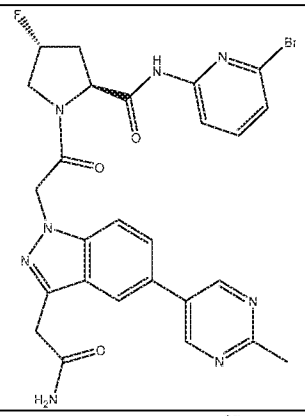
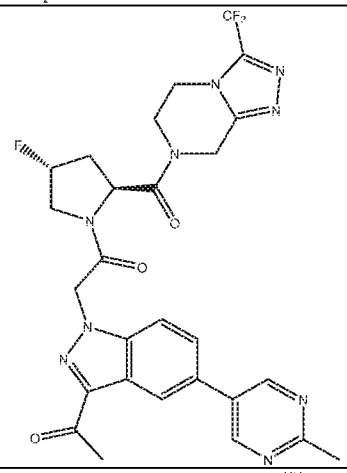
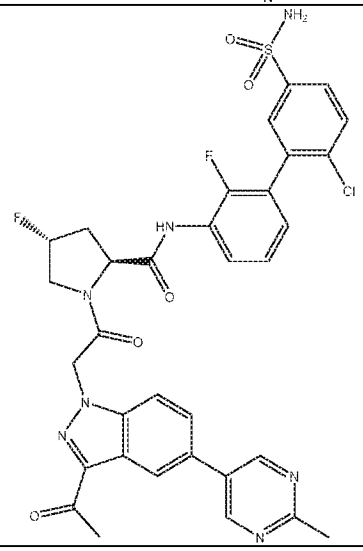
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
507		2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetamido)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4,4,4-trifluorobutanamide	*	4.02 (B)	652
508		(2S,4R)-1-(2-(3-acetyl-5-(2-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.14 (B)	723
509		(R)-methyl 2-(1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidin-2-yl)acetate	*	2.35 (A)	436

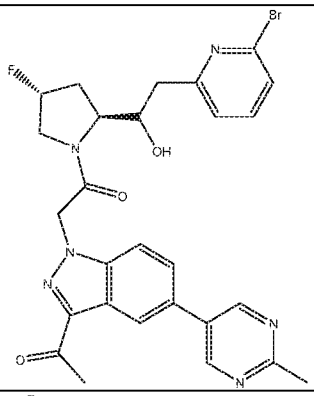
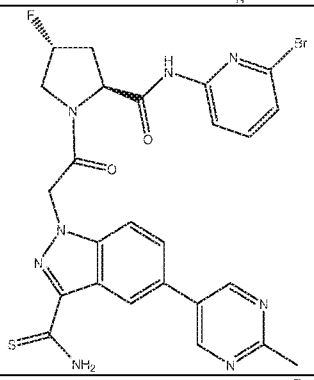
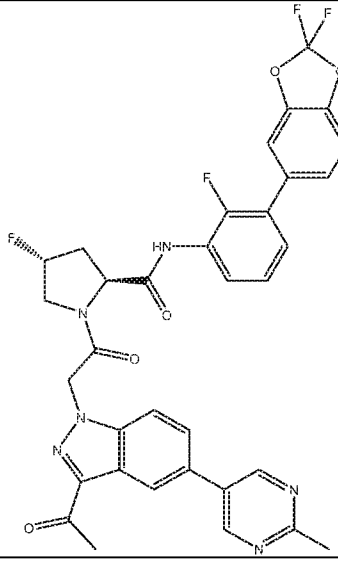
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
510		(R)-2-(1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidin-2-yl)acetic acid	*	2.33 (A)	422
511		6-((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)naphthalene-1-sulfonic acid	**	0.98 (A)	631
512		6-(4-((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)piperidin-1-yl)nicotinic acid	**	2.17 (B)	629
513		(2S,4R)-methyl 1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate	*	1.21 (A)	440

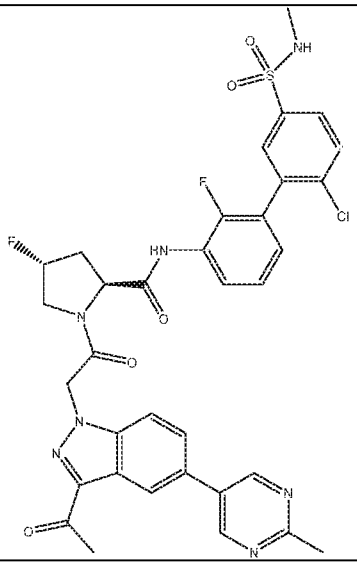
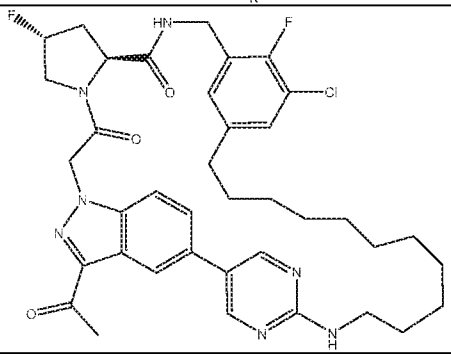
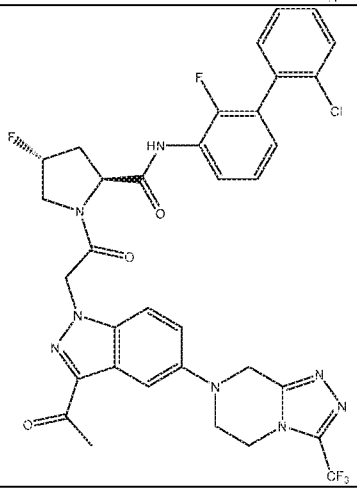
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
514		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid	*	0.88 (A)	311
515		(2S,4R)-3-chloro-2-fluorobenzyl 1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate	**	2.09 (A)	568
516		(2S,4R)-S-3-chloro-2-fluorobenzyl 1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carbothioate	**	2.23 (A)	584

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
517		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carbothioamide	***	2.12 (A)	583
518		(5^2S,5^4R,Z)-2^3-acetyl-9^5-chloro-5^4,9^6-difluoro-2^1H-7,21-diaza-2(5,1)-indazola-1(5,2)-pyrimidina-5(1,2)-pyrrolidina-9(1,3)-benzenacyclohenicosaphan-10-ene-4,6-dione	***	4.60 (B)	718
519		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1H-indazol-1-yl)acetyl)-N-(3-(benzo[d]thiazol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	2.10 (A)	691

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
520		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3-(benzo[d]thiazol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	1.87 (A)	652
521		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-5'-(N-cyclopropylsulfamoyl)-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***		
522		(2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoro-1-(2-(5-(2-methylpyrimidin-5-yl)-3-(2-oxopropyl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxamide	***	1.53 (A)	594

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
523		(2S,4R)-1-(2-(3-(2-amino-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	**	1.25 (A)	595
524		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-4-fluoro-2-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine-7-carbonyl)pyrrolidin-1-yl)ethanone	*	1.23 (A)	600
525		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-5'-sulfamoylbiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.68 (A)	708

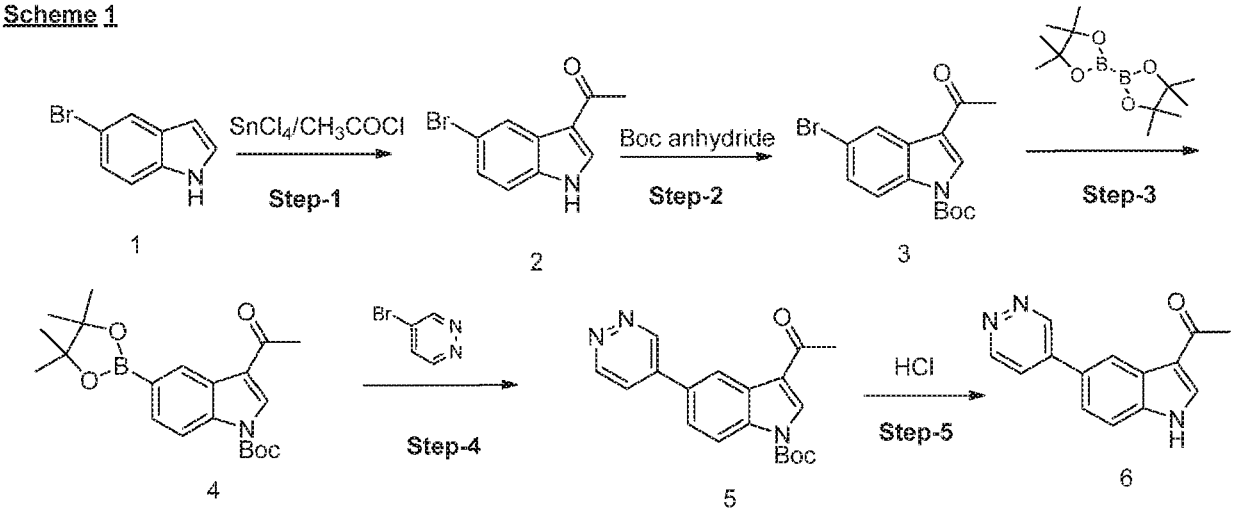
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
526		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-((S)-2-(6-bromopyridin-2-yl)-1-hydroxyethyl)-4-fluoropyrrolidin-1-yl)ethanone	**		
527		(2S,4R)-N-(6-bromopyridin-2-yl)-1-(2-(3-carbamothioyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide	***	1.58 (A)	597
528		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	2.36 (A)	675

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
529		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-5'-(N-methylsulfamoyl)biphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.86 (A)	722
530		(5^2S,5^4R)-2^3-acetyl-9^5-chloro-5^4,9^6-difluoro-2^1H-7,21-diaza-2(5,1)-indazola-1(5,2)-pyrimidina-5(1,2)-pyrrolidina-9(1,3)-benzenacyclohenicosaphane-4,6-dione			
531		(2S,4R)-1-(2-(3-acetyl-5-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***		

EXAMPLE 13. NON-LIMITING SYNTHETIC EXAMPLES OF ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I

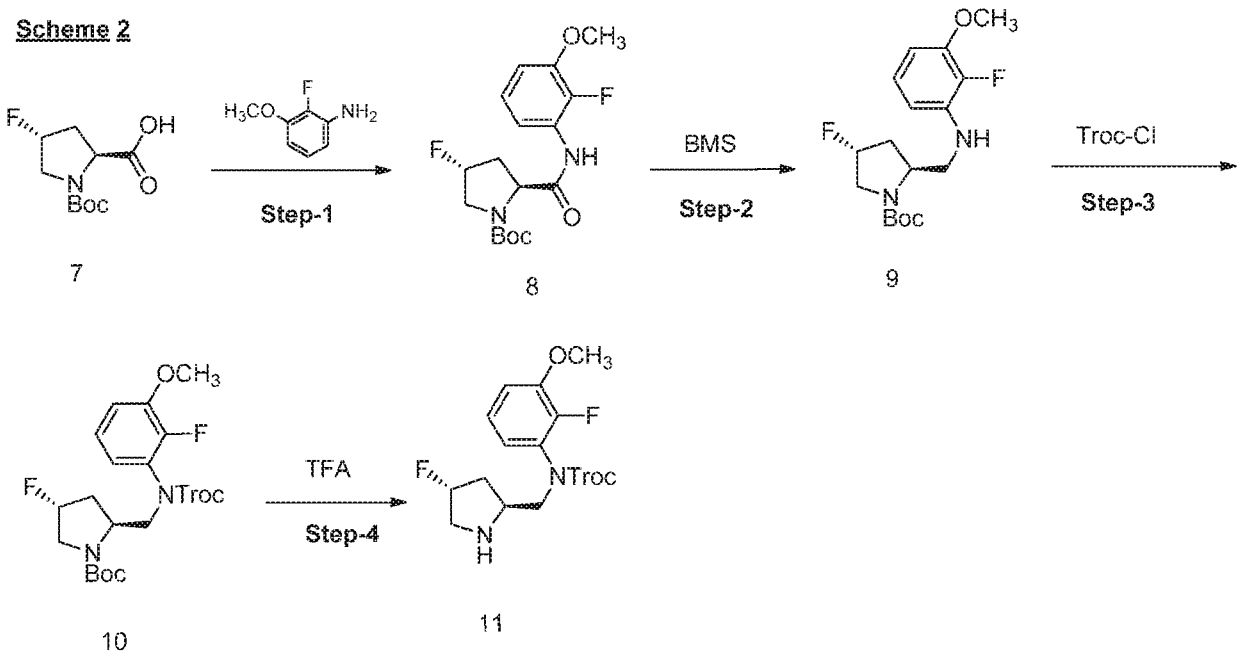
Synthesis of l-(l-((3-((2S,4R)-4-fluoro-2-(((2-fluoro-3-methoxyphenyl)amino)methyl)pyrrolidin-l-yl)oxetan-3-yl)methyl)-5-(pyridazin-4-yl)-lH-indol-3-yl)ethan-l-one

Scheme 1



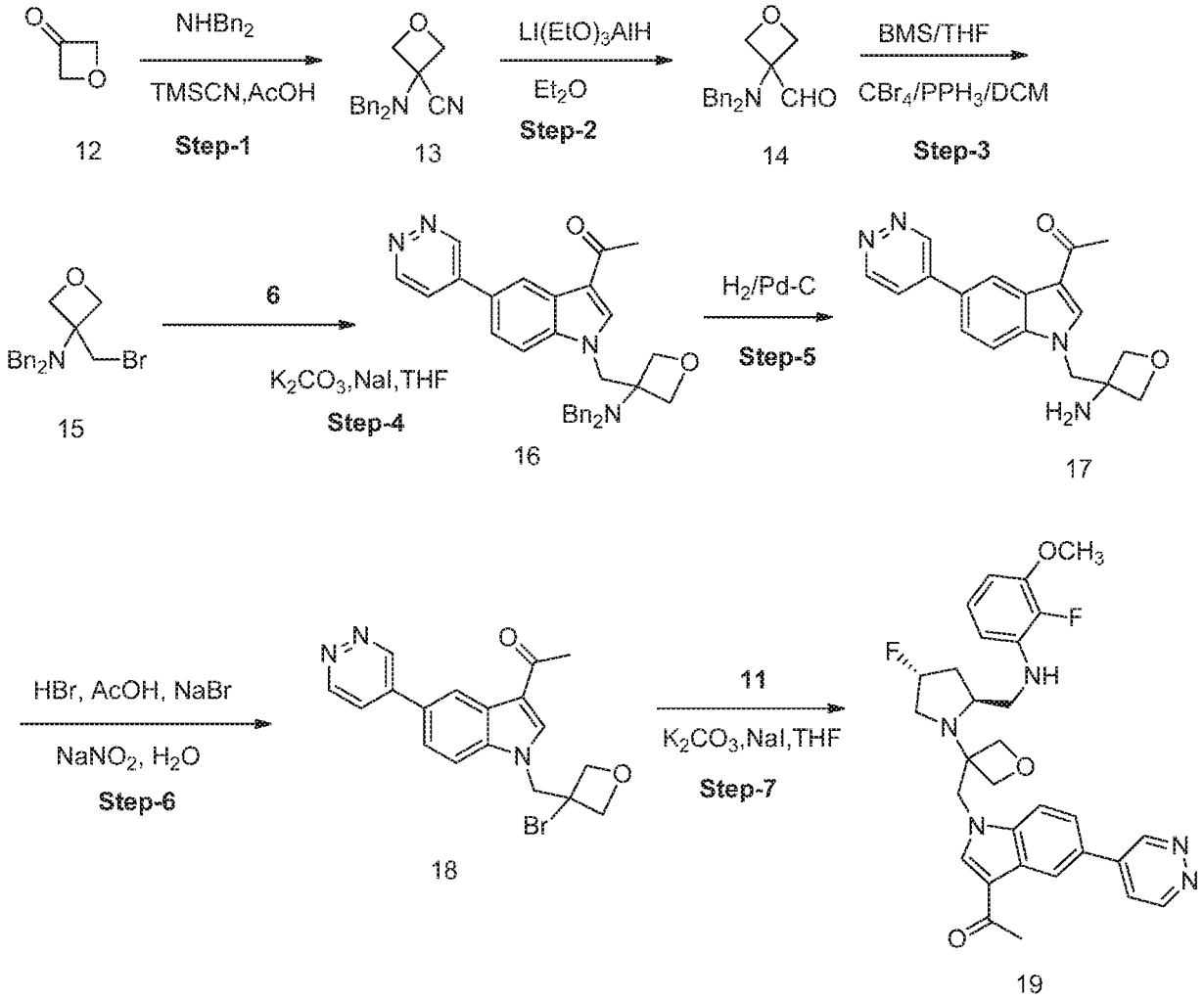
1 2 3 4 5 6

Scheme 2



7 8 9 10 11

Scheme 3



Scheme 1

Step 1: l-(5-bromo-lH-indol-3-yl)ethan-l-one (2)

[0923] To a solution of compound 1 (1 equiv) in toluene (10 vol) at 0 °C is added acetyl chloride (2 equiv) and SnC14 in toluene (2 equiv) drop wise. The reaction mixture is stirred at room temperature for 3 h and then quenched with 10 % NaHC03. The resulting mixture is extracted with ethyl acetate, washed with water. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated to afford compound 2.

Step 2: *tert-butyl* 3-acetyl-5-bromo-lH-indole-l-carboxylate (3)

[0924] To a solution of compound 2 (1 equiv) in DCM (10 vol) is added Boc anhydride (1.2 equiv) and DMAP (0.1 equiv). The reaction mixture is stirred at room temperature for 12 h and then quenched with water. The resulting mixture is extracted with DCM. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated to afford compound 3.

Step 3: *tert-butyl* 3-acetyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-indole-l-carboxylate (4)

[0925] To a mixture of compound 3 (1 equiv) and Bis(pinacolato)diboron (1.1 equiv) in DMF (10 vol) is added Pd(PPh3)2C12 (0.1 equiv) and potassium acetate (2 equiv). After degassing with nitrogen, the resulting mixture is stirred at 100 °C for 24 h and then cooled to room temperature. Water is added to the reaction mixture and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 4.

Step 4: *tert-butyl* 3-acetyl-5-(pyridazin-4-yl)-lH-indole-l-carboxylate (5)

[0926] To a mixture of compound 4 (1.5 equiv) and 4-bromopyridazine (1 equiv) in DMF/water (10:1) is added cesium carbonate (1.4 equiv) and Pd(PPh3)4 (0.1 equiv). After degassing with nitrogen, the resulting mixture is stirred at 100 °C for 12 h and then cooled to room temperature. Water is added to the reaction mixture and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 5.

Step 5: l-(5-(pyridazin-4-yl)-lH-indol-3-yl)ethan-l-one (6)

[0927] To a solution of compound 5 (1 equiv) in 1,4-dioxane (2 vol) at 0 °C is added 4 N HC1 in dioxane (10 vol). The reaction mixture is stirred at room temperature for 6 h and then concentrated. The residue is taken in MTBE and stirred for 30 min. The resultant solid is filtered and dried to afford compound 6.

Scheme 2

Step 1: *tert-butyl* (2S,4R)-4-fluoro-2-((2-fluoro-3-methoxyphenyl)carbamoyl)pyrrolidine-l-carboxylate (8)

[0928] To a solution of 2-fluoro-3-methoxy aniline (1.2 equiv) and compound 7 (lequiv) in DMF (10 vol) is added DIPEA (2equiv) and HATU (1.2 equiv). The reaction mixture is stirred at room temperature for 12 h then quenched with water. The resulting mixture is extracted with EtOAc. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 8.

Step 2: *tert-butyl* (2S,4R)-4-fluoro-2-(((2-fluoro-3-methoxyphenyl)amino)methyl)pyrrolidine-l-carboxylate (9)

[0929] To a solution of compound 8 (1 equiv) in THF (2 vol) at 0 oC is added Borane dimethyl sulphide complex (5 equiv). The reaction mixture is stirred at 50 oC for 12 h then quenched with methanol. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 9.

Step 3: *tert-butyl* (2S,4R)-4-fluoro-2-(((2-fluoro-3-methoxyphenyl)((2,2,2-trichloroethoxy)carbonyl)amino)methyl)pyrrolidine-l-carboxylate (10)

[0930] To a solution of compound 9 (1 equiv) and potassium carbonate (2 equiv) in DCM (10 vol) at 0 °C is added Troc-Cl (1.1 equiv). The reaction mixture is stirred at room temperature for 12 h and then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 10.

Step 4: (2,2,2-trichloroethyl (2-fluoro-3-methoxyphenyl)(((2S,4R)-4-fluoropyrrolidin-2-yl)methyl)carbamate (11)

[0931] To a solution of compound 10 (1 equiv) in DCM (10 vol) at 0 °C is added TFA (5 vol). The reaction mixture is stirred at 50 °C for 3 h and then concentrated. The residue is re-crystallized from MTBE to afford compound 11.

Scheme 3

Step 1: 3-(dibenzylamino)oxetane-3-carbonitrile (13)

[0932] To a solution of dibenzylamine (2 equiv) in acetic acid (10 vol) is added compound 12 (2 equiv) and trimethylsilyl cyanide (2 equiv). The reaction mixture is stirred at room temperature for 16 h and then concentrated. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 13.

Step 2: 3-(dibenzylamino)oxetane-3-carbaldehyde (14)

[0933] To a solution of compound 13 (1 equiv) in toluene (10 vol) at -78 oC under nitrogen atmosphere is added DIBAL-H (1.2 equiv). The resulting mixture is stirred at -78 oC for 1 h and then quenched with 10 % sodium bicarbonate and stirred at room temperature for 1 h. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 14.

Step 3: N,N-dibenzyl-3-(bromomethyl)oxetan-3-amine (15)

[0934] To a solution of compound 14 (1 equiv) in THF (2 vol) at 0 oC is added Boranedimethyl sulphide complex (5 equiv). The reaction mixture is stirred at 50 oC for 12 h then quenched with methanol. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford hydroxy compound.

[0935] To a solution of hydroxy compound (1 equiv) and triphenylphosphine (1.2 equiv) in DCM (10 vol) at 0 oC under nitrogen atmosphere, is added carbon tetrabromide (1.5 equiv). The reaction mixture is stirred at 0 oC for 1 h then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 15.

Step 4: l-(l~((3-(dibenzy!amino)oxetan-3-y!)methyi)-5-(pyridazin-4-yl)-1H-indol-3-yI)ethan-l-oiie (16)

[0936] To a solution of compound 6 (1 equiv) in THF (10 vol) is added compound 6 (1.2 equiv), K2C03 (2 equiv) and Nal (cat). The reaction mixture is stirred at room temperature for 16 h and then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 16.

Step 5: l-(l-((3-aminooxetaii-3-y!)methy!)-5-(pyridazisi-4-yI)-lH-i!idol-3-yl)ethaii-l-osie **(17)**

[0937] To a solution of compound 16 (1 equiv) in methanol (10 vol) is added Pd/C (10 % w/w). The reaction mixture is degassed and stirred at room temperature for 9 h under an atmosphere of hydrogen gas (50 psi). After completion of the reaction, the catalyst is removed by filtration through Celite. The filtrate is concentrated to afford compound 17.

Step 6: l-(l-((3-bromooxetan-3-yI)methyl)-5-(pyridaziii-4-yl)-lH-iiii!oS-3-yl)ethan-l-0!ie (18)

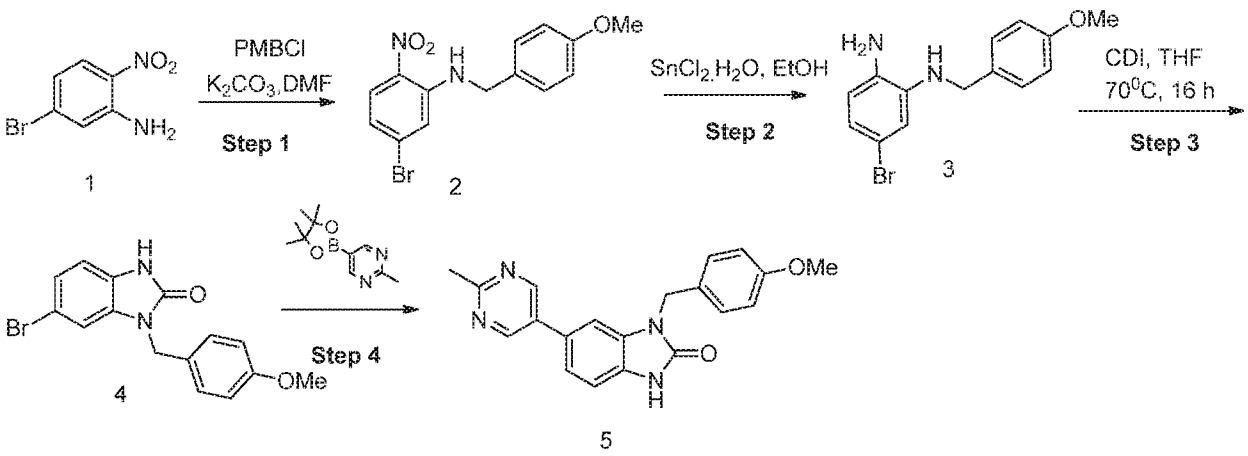
[0938] To a solution of compound 17 (1 equiv) in acetic acid at 0 oC is added potassium bromide (1 equiv) and hydrogen bromide in acetic acid (3 equiv) under nitrogen atmosphere. The resulting mixture is cooled to 0 °C and sodium nitrite (1.5 equiv) is added and stirred for 1 h and then quenched with water. The resulting mixture is extracted with DCM. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated to afford compound 18.

Step 7: l-(l-((3-((2S,4R)-4-fliioro-2-(((2-fluoro-3-iiiethoxypheny!)ami!io)siiethyI)pyrroiidi!i-l-yl)oxetan-3-yl)methy!)-5-(pyridazin-4-yI)-lH-indol-3-y!)ethan-l-one (19)

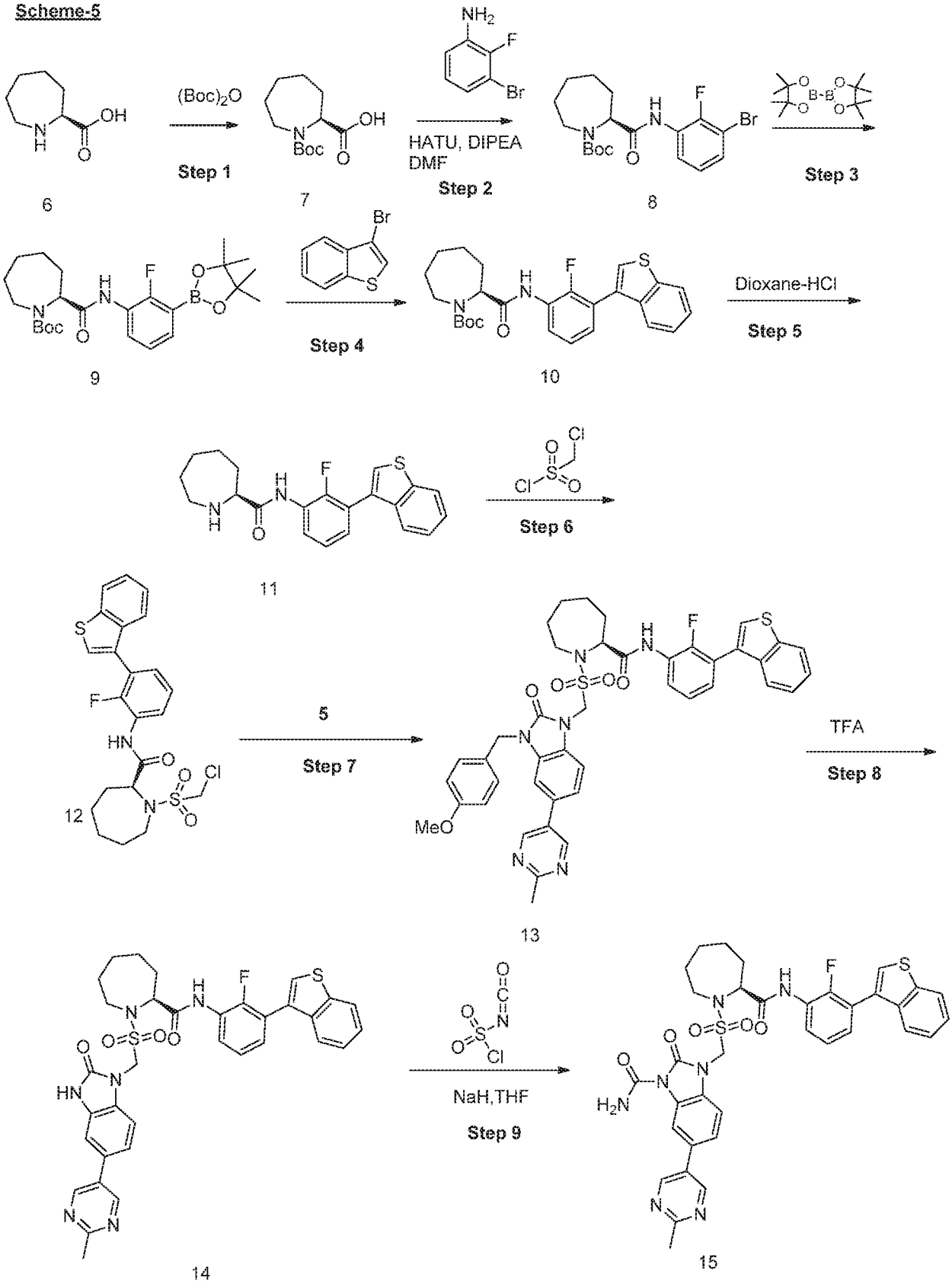
[0939] To a solution of compound 18 (1 equiv) in THF (10 vol) is added compound 11 (1.2 equiv), K2C03 (2 equiv) and Nal (cat). The reaction mixture is stirred at room temperature for 16 h. The resulting mixture is concentrated and quenched with water, extracted with ethyl acetate , washed with 10 % sodium bicarbonate. The organic layer is separated, dried over anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 19.

Synthesis of (S)-3-(((2-((3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)carbamoyl)azepan-l-yl)sulfonyl)methyl)-6-(2-methylpyrimidin-5-yl)-2-oxo-2,3-dihydro-lH-benzo[d]imidazole-l-carboxamide

Scheme-4


PMBCl
K2CO3,DMF
Step 1
SnCl2.H2O, EtOH
Step 2
CDI, THF
70°C, 16 h
Step 3
Step 4
1
2
3
4
5

Scheme-5



6 7 8 9 10 11 12 13 14 15

Scheme 4

Step 1: 5-bromo-N-(4-methoxybenzyl)-2-nitroaniline (2)

[0940] To a solution of compound 1 (1 equiv) and potassium carbonate (2 equiv) in DMF (20 vol) is added 4-methoxybenzylchloride (1.5 equiv). The reaction mixture is stirred at room temperature for 12 h and then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 2.

Step 2: 5-bromo-N ^{1}-(4-methoxybenzyl)benzene-l,2-diamine (3)

[0941] To a solution of compound 2 (1 equiv) in EtOH/water (10:2) at 0 °C is added stannous chloride (1.5 equiv). The reaction mixture is stirred at 50 °C for 4 h and then quenched with saturated NaHC03 solution. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 3.

Step 3: 6-bromo-l-(4-methoxybenzyl)-l,3-dihydro-2H-benzo[d]imidazol-2-one (4)

[0942] To a solution of compound 3 (1 equiv) in THF (10 vol) is added CDI (5 equiv). The reaction mixture is stirred at 65 °C for 16 h and then concentrated. The residue is taken in ethyl acetate and washed with water, dried over Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 4.

Step 4: l-(4-methoxybenzyl)-6-(2-methylpyrimidin-5-yl)-l,3-dihydro-2H-benzo[d]imidazol-2-one (5)

[0943] To a mixture of 2-methyl-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyrimidine (1.5 equiv) and compound 4 (1 equiv) in DMF/water (10:1) is added cesium carbonate (1.4 equiv) and Pd(PPh3)4. After degassing with nitrogen, the resulting mixture is stirred at 100 °C for 12 h and then cooled to room temperature. Water is added to the reaction mixture and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over

anhydrous Na2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 5.

Scheme 5

Step 1: (S)-l-(terf-butoxycarbonyl)azepane-2-carboxylic acid (7)

[0944] To a solution of compound 6 (1 equiv) and 2 M NaOH (2 equiv) in THF (10 vol) at 0 °C is added Boc anhydride (1.2 equiv). The reaction mixture is stirred at room temperature for 16 h and then quenched 1M HC1. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is re-crystallized from MTBE to afford compound 7.

Step 2: *tert-butyl* (S)-2-((3-bromo-2-fluorophenyl)carbamoyl)azepane-l-carboxylate (8)

[0945] To a solution of compound 7 (1 equiv) and 3-bromo-2-fluoroaniline (1.2 equiv) in DMF (10 vol) is added DIPEA (3 equiv) and HATU (1.2 equiv). The reaction mixture is stirred at room temperature for 16 h and then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 8.

Step 3: *tert-butyl* (S)-2-((2-fluoro-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)carbamoyl)azepane-l-carboxylate (9)

[0946] To a mixture of compound 8 (1 equiv) and Bis(pinacolato)diboron (1.1 equiv) in DMF (10 vol) is added $PdCl_2(PPh_3)_2$ (O.lequiv) and potassium acetate (2 equiv). After degassing with nitrogen, the resulting mixture is stirred at 100°C for 24 h and then cooled to room temperature. Water is added to the reaction mixture and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 9.

Step 4: *tert-butyl* (S)-2-((3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)carbamoyl)azepane-l-carboxylate (10)

[0947] To a mixture of 3-bromobenzo[b]thiophene (1.5 equiv) and compound 9 (1 equiv) in DMF/water (10:1) is added cesium carbonate (1.4 equiv) and Pd(PPh3)4. After degassing with nitrogen, the resulting mixture is stirred at 100 °C for 12 h and then cooled to room temperature. Water is added to the reaction mixture and the resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 10.

Step 5: (S)-N-(3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)azepane-2-carboxamide (11)

[0948] To a solution of compound 10 (1 equiv) in 1,4-dioxane (2 vol) at 0 °C is added 4 N HC1 in dioxane (10 vol). The reaction mixture is stirred at room temperature for 6 h and then concentrated. The residue is taken in MTBE and stirred for 30 min. The resultant solid is filtered and dried to afford compound 11.

Step 6: (S)-N-(3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)-l-((chloromethyl)sulfonyl)azepane-2-carboxamide (12)

[0949] To a solution of compound 11 (1 equiv) in DCM (2 vol) at 0 °C is added chloromethanesulfonylchloride (1.2 equiv). The reaction mixture is stirred at room temperature for 3 h and then quenched with water. The resulting mixture is extracted with DCM. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated to afford compound 12.

Step 7: (S)-N-(3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)-l-(((3-(4-methoxybenzyl)-5-(2-methylpyrimidin-5-yl)-2-oxo-2,3-dihydro-lH-benzo[d]imidazol-l-yl)methyl)sulfonyl)azepane-2-carboxamide (13)

[0950] To a solution of compound 12 (1 equiv) and compound 5 (1.2 equiv) in DMF (10 vol) is added potassium carbonate (3 equiv). The reaction mixture is stirred at 80 °C for 2 h and then quenched with water. The resulting mixture is extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S0_4, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 13.

Step 8: (S)-N-(3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)-l-(((5-(2-methylpyrimidin-5-yl)-2-oxo-2,3-dihydro-lH-benzo[d]imidazol-l-yl)methyl)sulfonyl)azepane-2-carboxamide (14)

[0951] To a solution of compound 13 (1 equiv) in DCM (10 vol) at 0 °C is added TFA (5 vol). The reaction mixture is stirred at 50 °C for 3 h and then concentrated. The residue is re-crystallized from MTBE to afford compound 14.

Step 9: (S)-3-(((2-((3-(benzo[b]thiophen-3-yl)-2-fluorophenyl)carbamoyl)azepan-l-yl)sulfonyl)methyl)-6-(2-methylpyrimidin-5-yl)-2-oxo-2,3-dihydro-lH-benzo[d]imidazole-l-carboxamide (15)

[0952] To a solution of NaH (1.5 equiv) in THF (20 vol) at 0 °C is added compound 14 (1 equiv). The reaction mixture is stirred at 0 °C for 30 min then chlorosulfonyl isocyanate (2 equiv) is added. The reaction mixture is stirred at room temperature for 4 h, acetic acid (10 vol) is added and stirred for 1 h. The resulting mixture is quenched with ice-water, extracted with ethyl acetate. The organic layer is separated, dried over anhydrous Na_2S04, filtered and then concentrated. The residue is purified by column chromatography on silica gel to afford compound 15.

EXAMPLE 14. HUMAN FACTOR D ASSAY

[0953] Human Factor D (purified from human serum, Complement Technology, Inc.) at 80 nM final concentration is incubated with test compound at various concentrations for 5 min at room temperature in 50 mM Tris, 1M NaCl, pH 7.5. A synthetic substrate Z-L-Lys-SBzl and DTNB (Ellman's reagent) are added to final concentrations of 100 μM each. Absorbance at 405 nm (A405) is recorded at 30 second intervals for 30 min using a microplate spectrophotometer. IC50 values are calculated by nonlinear regression of complement Factor D reaction rates as a function of test compound concentration.

EXAMPLE 15. HEMOLYSIS ASSAY

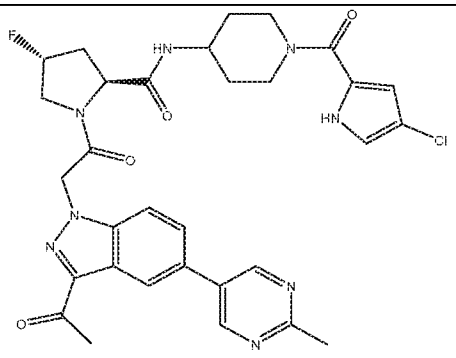
[0954] The hemolysis assay was previously described by G. Ruiz-Gomez, et al., J. Med. Chem. (2009) 52: 6042-6052. Prior to the assay, the optimum concentration of Normal Human Serum (NHS) needed to achieve 100% lysis of rabbit erythrocytes (RE) is determined by titration. In the assay, NHS (Complement Technology) is diluted in GVB° Buffer (0.1 % gelatin, 5 mM

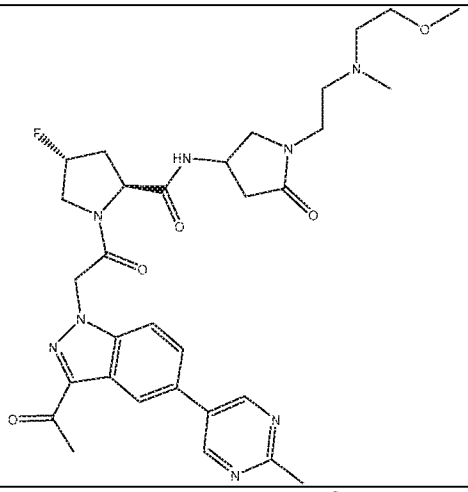
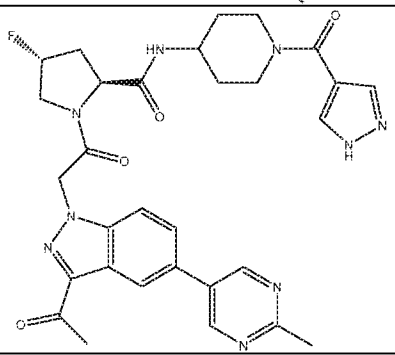
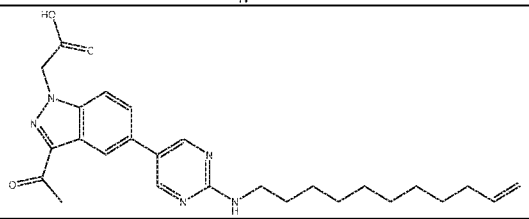
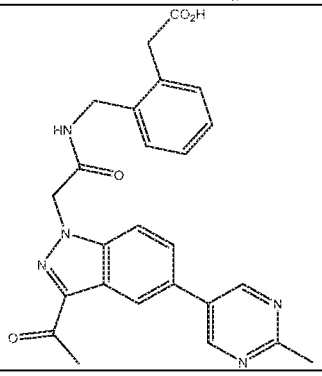
Veronal, 145 mMNaCl, 0.025 % NaN_3, pH 7.3, Complement Technology) plus 10 mM Mg-EGT A and incubated with test compound at various concentrations for 15 min at 37°C. RE (Complement Technology) freshly suspended in GVB° plus 10 mM Mg-EGTA are added to a final concentration of 1 x 10^8 cells/mL and reactions are incubated for 30 min at 37°C. Positive control reactions (100% lysis) consist of GVB° plus 10 mM Mg-EGTA with NHS and RE but without test compound; negative control reactions (0% lysis) consist of GVB° plus 10 mM Mg-EGTA with RE only. Samples are centrifuged at 2000g for 3 min and supernatants collected. Absorbance at 405 nm (A405) is recorded using a microplate spectrophotometer. IC50 values are calculated by nonlinear regression from the percentage of hemolysis as a function of test compound concentration.

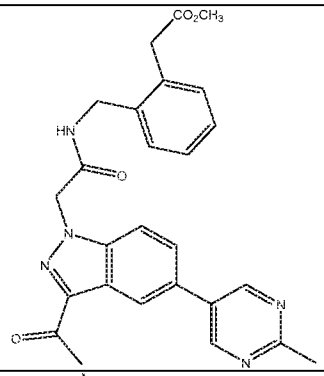
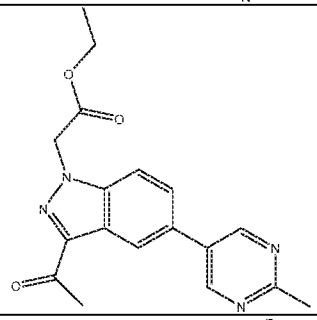
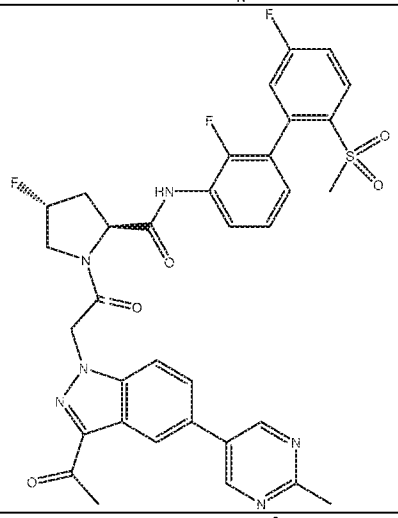
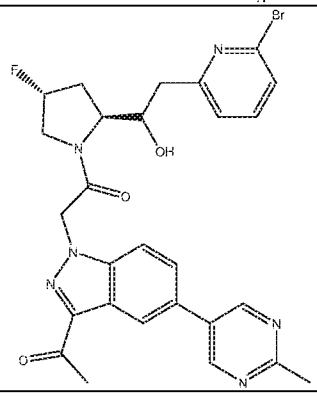
EXAMPLE 16. ADDITIONAL NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I, FORMULA I' AND FORMULA I"

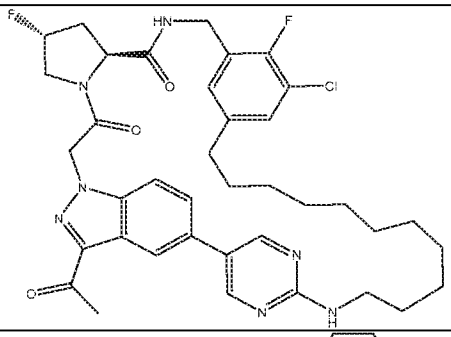
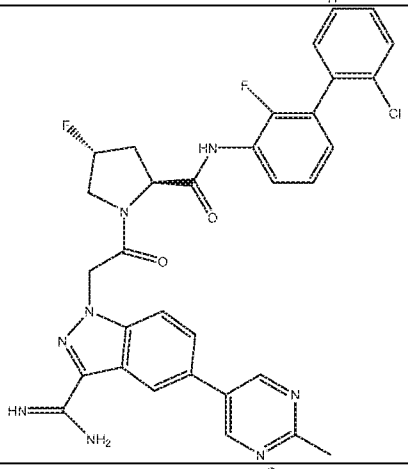
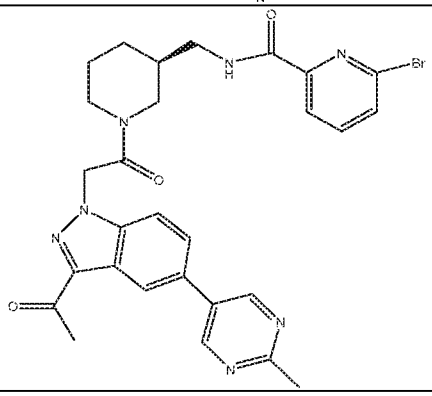
[0955] Table 4 shows illustrative Factor D inhibitors with characaterizing data. The assay of Example 14 was used to determine the ICso's of the compounds. Other standard factor D inhibition assays are also available. Three ***s are used to denote compounds with an IC50 less than 1 micromolar; two **s indicate compound with an IC50 between 1 micromolar and 10 micromolar, and one * denotes compounds with an IC50 greater than 10 micromolar.

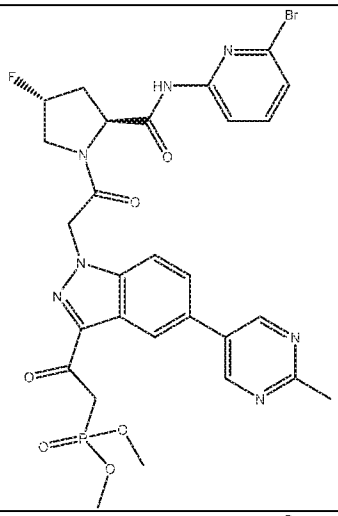
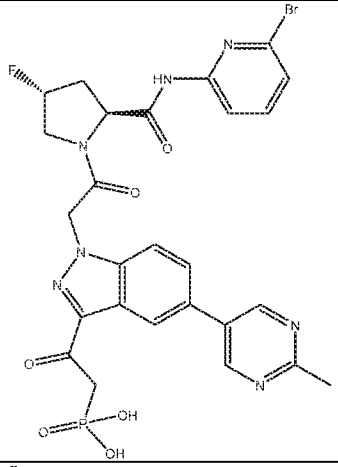
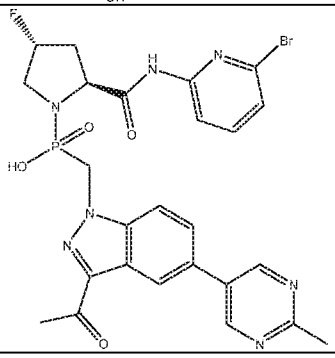
Table 4. Non-limiting Examples of Compounds of Formula I, Formula Γ and Formula I"

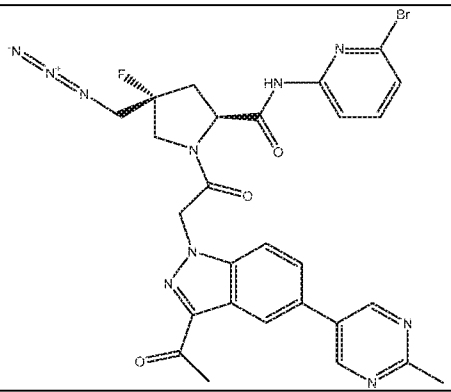
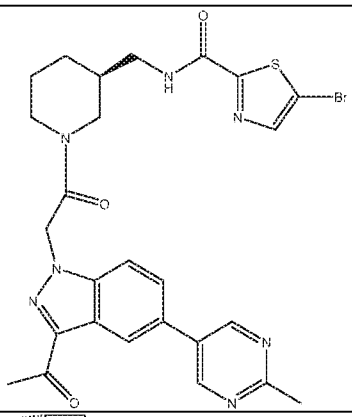
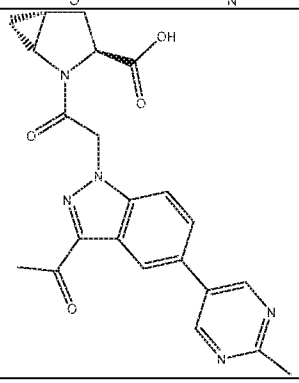
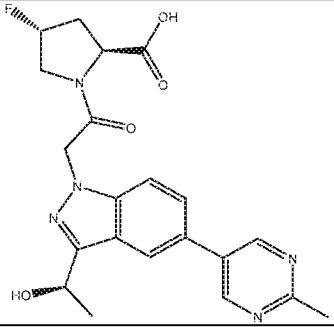
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
532		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(1-(4-chloro-1H-pyrrole-2-carbonyl)piperidin-4-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.16 (B)	635

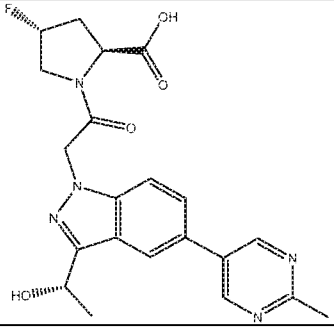
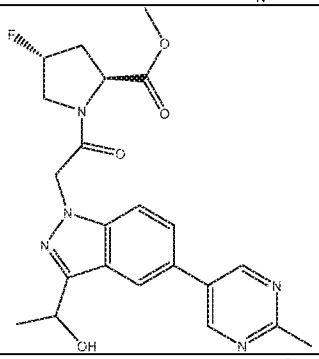
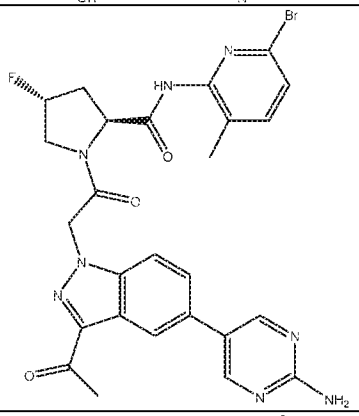
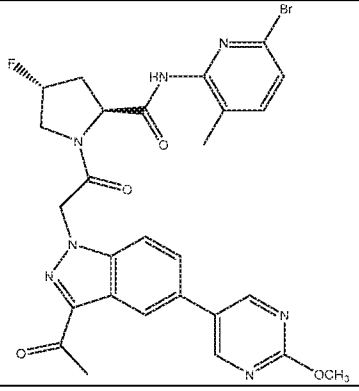
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
533		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoro-N-(1-(2-((2-methoxyethyl)(methyl)amino)ethyl)-5-oxopyrrolidin-3-yl)pyrrolidine-2-carboxamide	*	2.63 (B)	623
534		6-(4-((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)piperidin-1-yl)nicotinic acid	**	2.54 (B)	602
535		2-(3-acetyl-5-(2-(undec-10-en-1-ylamino)pyrimidin-5-yl)-1H-indazol-1-yl)acetic acid	*	4.77 (B)	464
536		2-(2-((2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetamido)methyl)phenyl)acetic acid	*	1.29 (A)	458

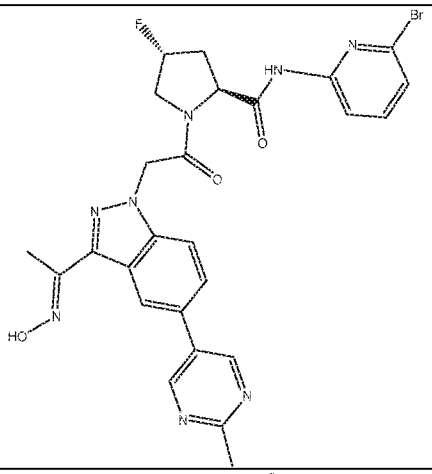
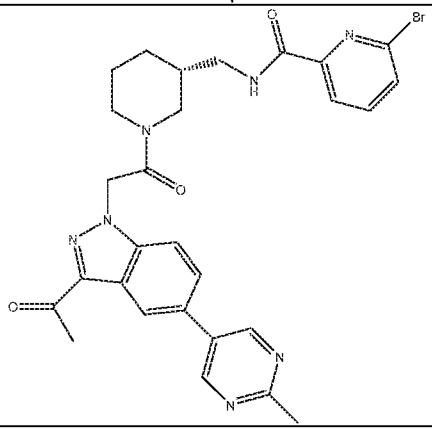
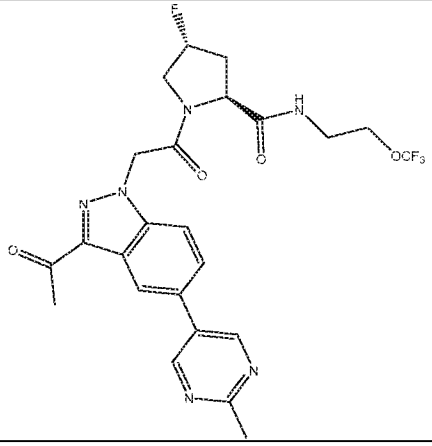
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
537		methyl 2-(2-((2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetamido)methyl)phenyl)acetate	*	1.56 (A)	472
538		ethyl 2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetate			
539		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2,5'-difluoro-2'-(methylsulfonyl)-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.74 (A)	691
540		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-((S)-2-(6-bromopyridin-2-yl)-1-hydroxyethyl)-4-fluoropyrrolidin-1-yl)ethan-l-one	**	3.60 (B)	581

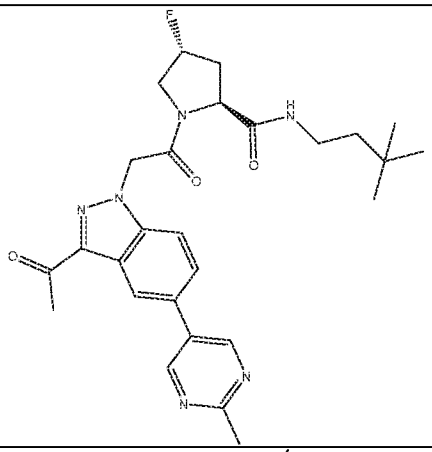
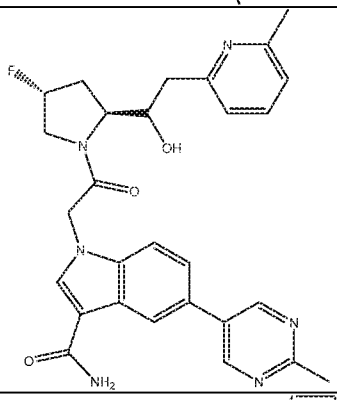
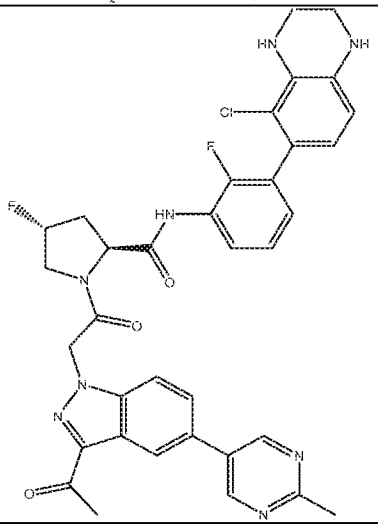
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
541			*	2.30 (B)	720
542		(2S,4R)-1-(2-(3-carbamimidoyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.64 (A)	629
543		(S)-N-((1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)piperidin-3-yl)methyl)-6-bromopicolinamide	*	1.72 (A)	592

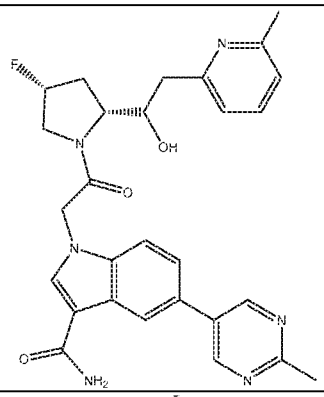
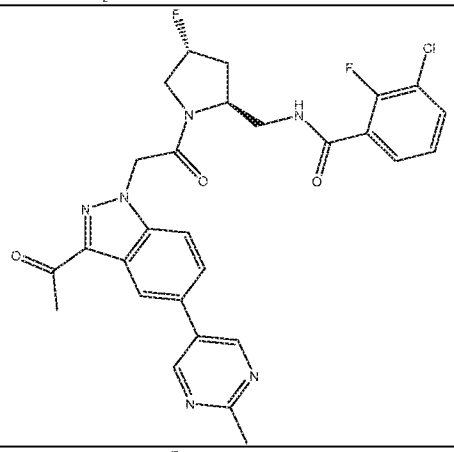
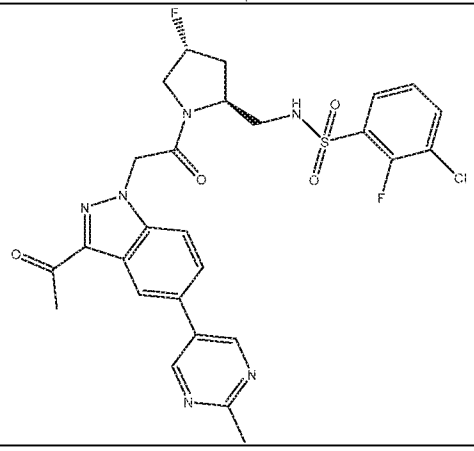
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
544		dimethyl (2-(1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-3-yl)-2-oxoethyl)phosphonate	*	1.49 (A)	690
545		(2-(1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-3-yl)-2-oxoethyl)phosphonic acid	*	1.02 (A)	662
546		((3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)methyl)((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)phosphinic acid	*	1.10 (A)	616

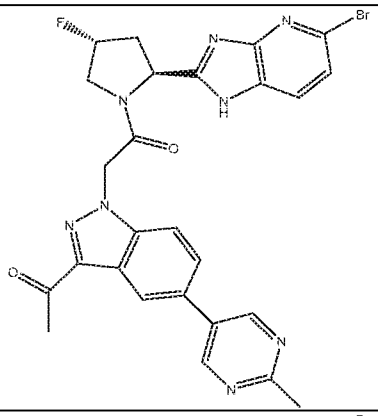
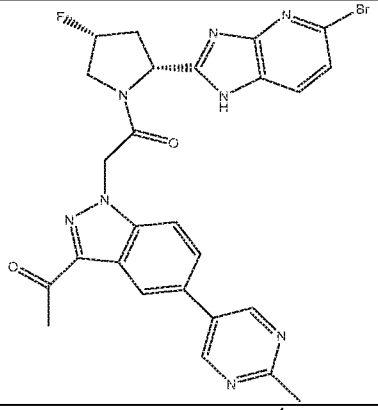
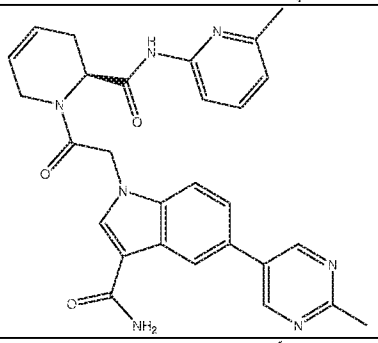
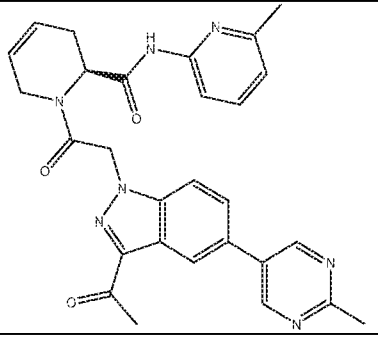
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
547		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-(azidomethyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.66 (B)	635
548		(S)-N-((1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)piperidin-3-yl)methyl)-5-bromothiazole-2-carboxamide	*	1.78 (A)	598
549		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid	*	1.11 (A)	420
550		(2S,4R)-4-fluoro-1-(2-(3-((R)-1-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxylic acid	*		

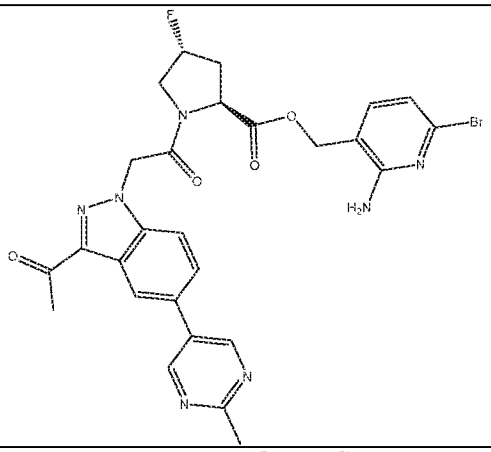
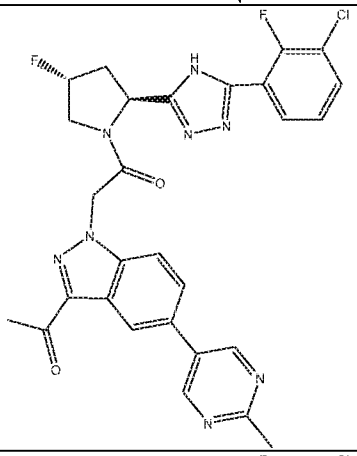
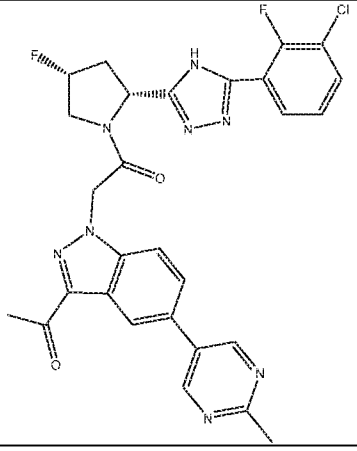
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
551		(2S,4R)-4-fluoro-1-(2-(3-((S)-1-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxylic acid	*		
552		(2S,4R)-methyl 4-fluoro-1-(2-(3-(1-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxylate	*	0.95 (A)	442
553		(2S,4R)-1-(2-(3-acetyl-5-(2-aminopyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.28 (A)	595
554		(2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.67 (A)	610

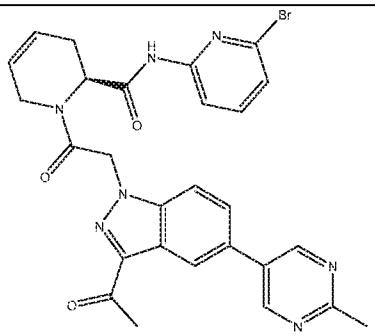
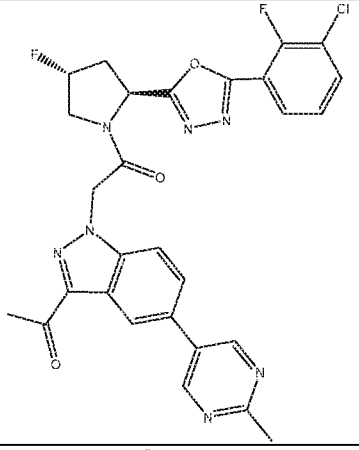
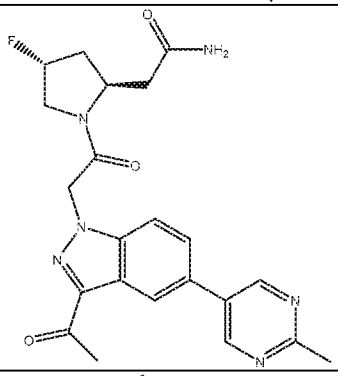
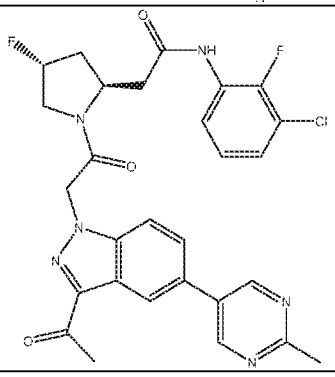
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
555		(2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoro-1-(2-(3-((E)-1-(hydroxyimino)ethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxamide	***	1.62 (A)	597
556		(R)-N-((1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)piperidin-3-yl)methyl)-6-bromopicolinamide	*	1.72 (A)	592
557		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoro-N-(2-(trifluoromethoxy)ethyl)pyrrolidine-2-carboxamide	***	1.42 (A)	536

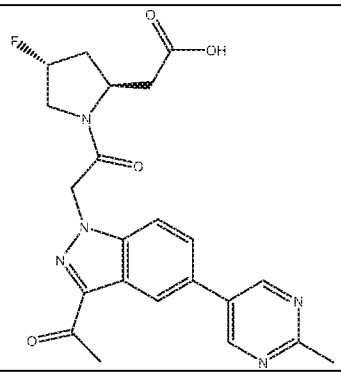
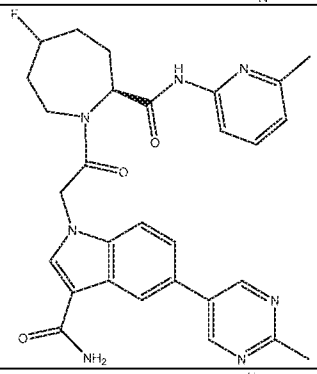
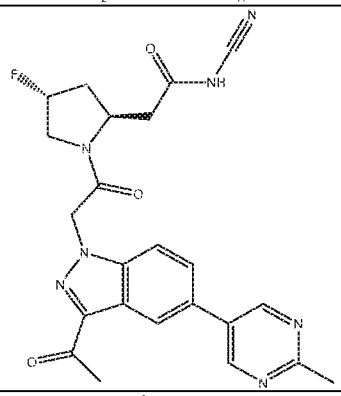
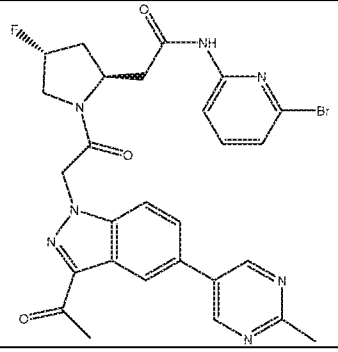
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
558		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3,3-dimethylbutyl)-4-fluoropyrrolidine-2-carboxamide	***	1.69 (A)	508
559		1-(2-((2S,4R)-4-fluoro-2-((S)-1-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indole-3-carboxamide	*	1.33 (B)	517
560		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3-(5-chloro-1,2,3,4-tetrahydroquinoxalin-6-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	1.77 (A)	685

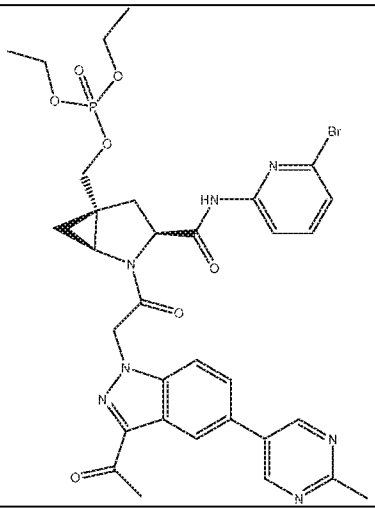
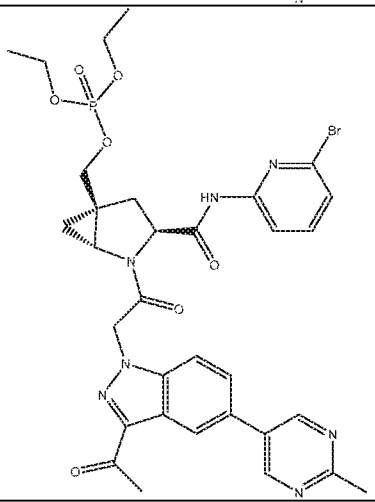
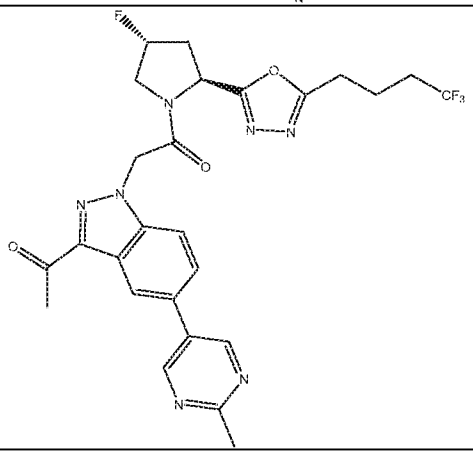
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
561		1-(2-((2R,4R)-4-fluoro-2-((R)-1-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indole-3-carboxamide	*		
562		N-(((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)methyl)-3-chloro-2-fluorobenzamide	*	1.68 (A)	567
563		N-(((2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)methyl)-3-chloro-2-fluorobenzenesulfonamide	***	1.82 (A)	603

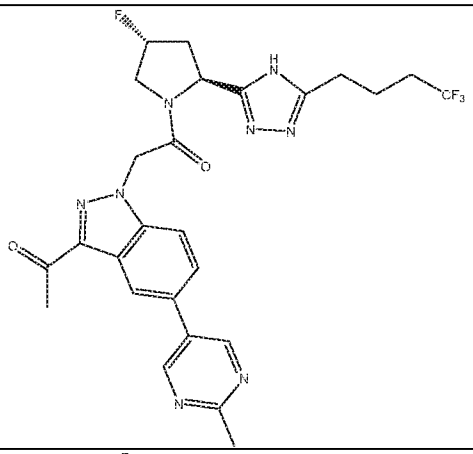
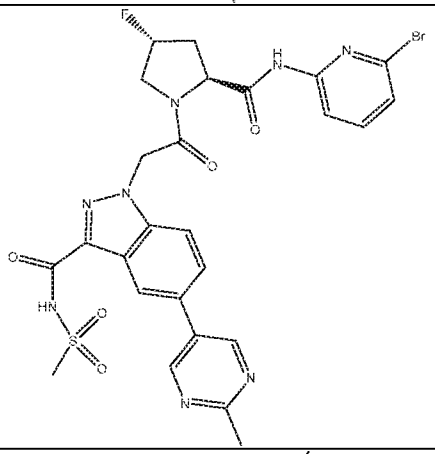
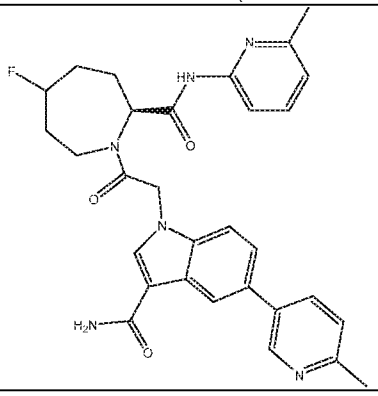
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
564		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(5-bromo-1H-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidin-1-yl)ethan-1-one	*	1.29 (A)	577
565		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2R,4R)-2-(5-bromo-1H-imidazo[4,5-b]pyridin-2-yl)-4-fluoropyrrolidin-1-yl)ethan-1-one	*	1.32 (A)	579
566		(S)-1-(2-(6-((6-methylpyridin-2-yl)carbamoyl)-5,6-dihydropyridin-1(2H)-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indole-3-carboxamide	*	1.75 (B)	510
569		(S)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-methylpyridin-2-yl)-1,2,3,6-tetrahydropyridine-2-carboxamide	*	2.79 (B)	510

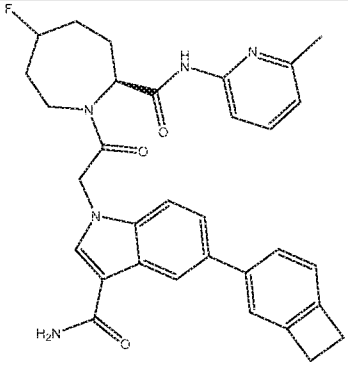
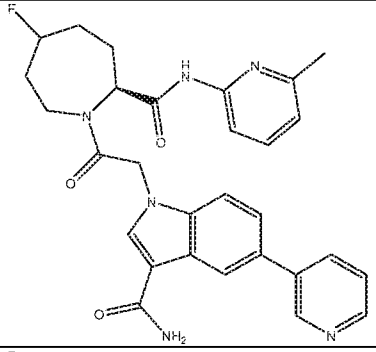
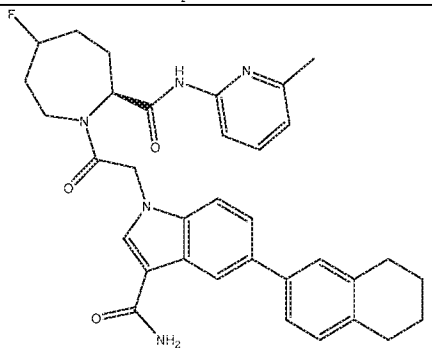
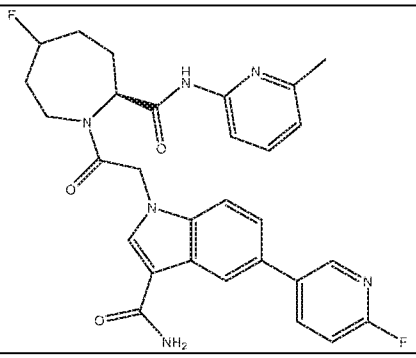
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
570		(2S,4R)-(2-amino-6-bromopyridin-3-yl)methyl 1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate	*	1.65 (A)	610
571		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4-fluoropyrrolidin-1-yl)ethan-1-one	*	1.63 (A)	577
572		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2R,4R)-2-(5-(3-chloro-2-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4-fluoropyrrolidin-1-yl)ethan-1-one	*	1.60 (A)	577

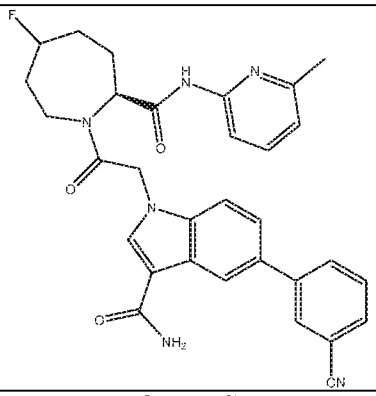
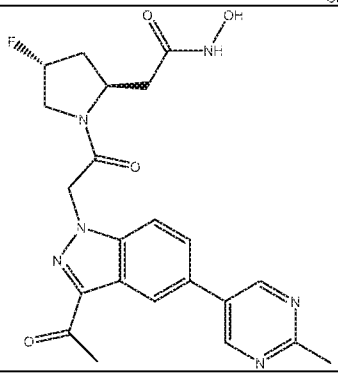
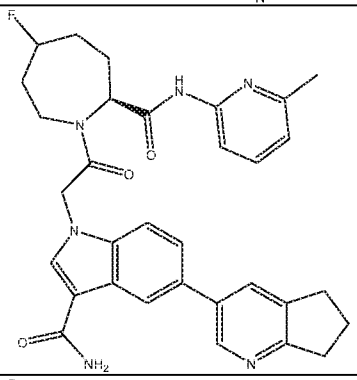
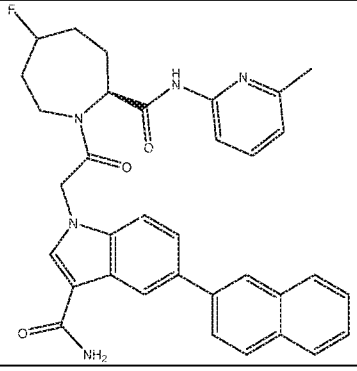
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
573		(S)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-1,2,3,6-tetrahydropyridine-2-carboxamide	***	3.41 (B)	574
574		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(5-(3-chloro-2-fluorophenyl)-1,3,4-oxadiazol-2-yl)-4-fluoropyrrolidin-1-yl)ethan-1-one	**	1.77 (A)	578
575		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)acetamide	*	7.39 (D)	439
576		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-(3-chloro-2-fluorophenyl)acetamide	*	11.03 (D)	567

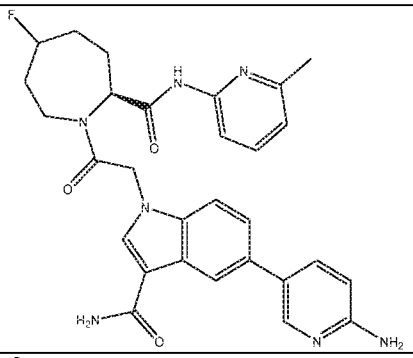
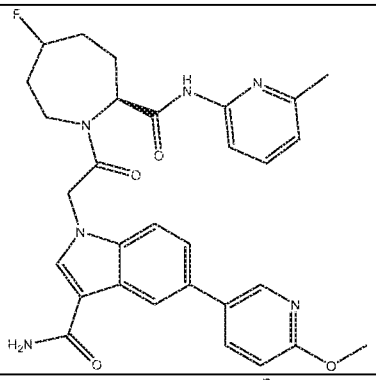
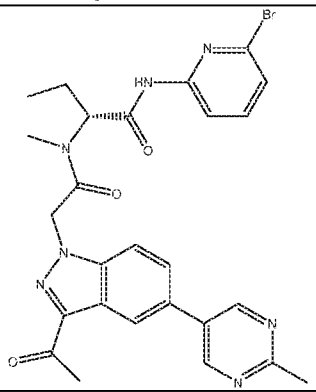
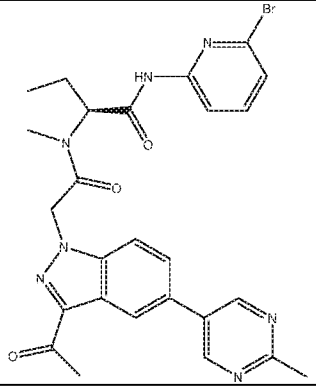
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
577		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)acetic acid	*	6.46 (D)	440
578		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indole-3-carboxamide	*	3.39 (B)	544
579		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-cyanoacetamide	*	6.79 (D)	464
580		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-(6-bromopyridin-2-yl)acetamide	*	10.68 (D)	596 (M+2)

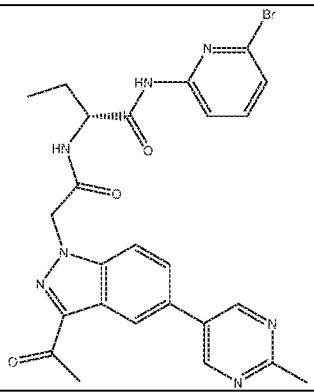
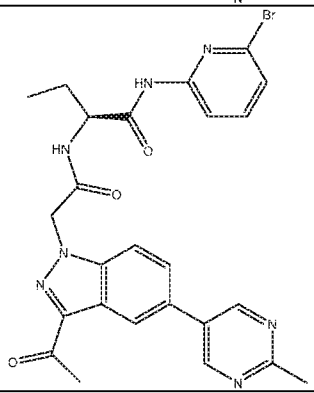
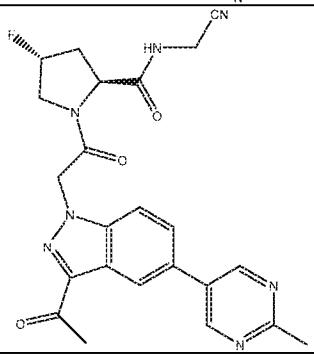
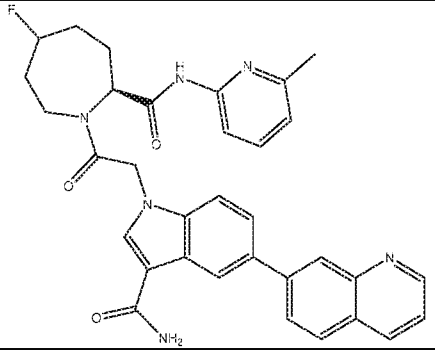
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
581		((1S,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate	**	3.66 (B)	740
582		((1R,3S,5S)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate	***	3.50 (B)	740
583		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl)ethan-1-one	**	1.63 (A)	560

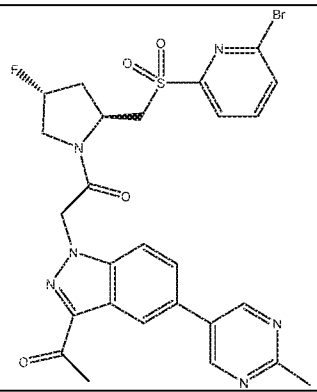
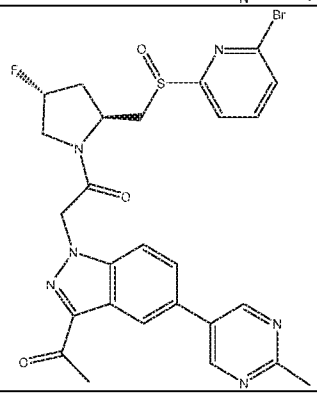
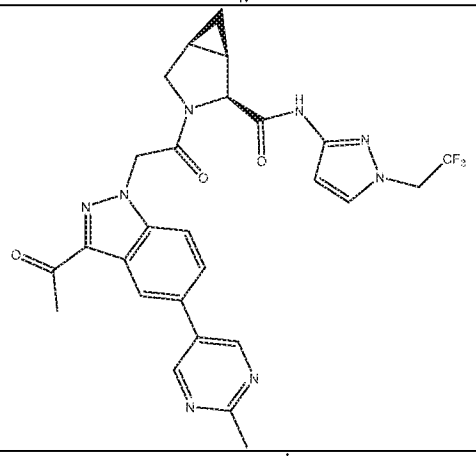
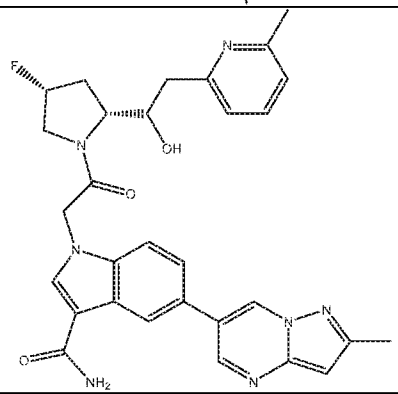
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
584		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-4-fluoro-2-(5-(4,4,4-trifluorobutyl)-4H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)ethan-1-one	**	1.43 (A)	559
585		1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-N-(methylsulfonyl)-1H-indazole-3-carboxamide	*	1.51 (A)	659
586		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(6-methylpyridin-3-yl)-1H-indole-3-carboxamide	*	3.30 (B)	543

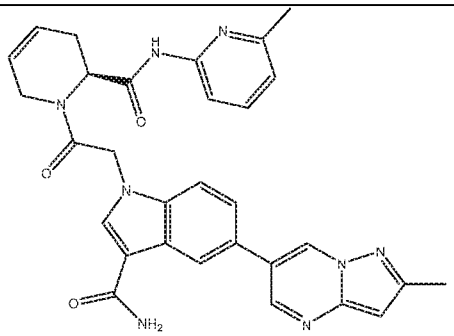
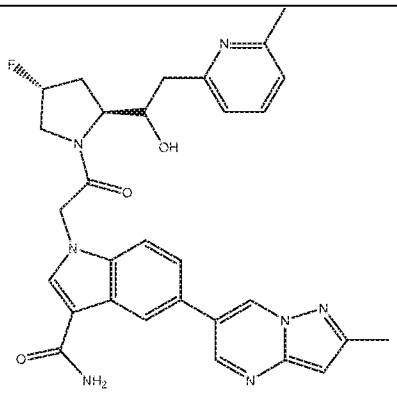
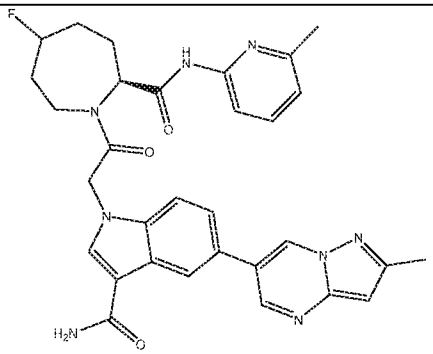
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
587		5-(bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)-1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	3.38 (B)	554
588		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(pyridin-3-yl)-1H-indole-3-carboxamide	*	3.27 (B)	529
589		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-indole-3-carboxamide	*	3.98 (B)	582
590		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(6-fluoropyridin-3-yl)-1H-indole-3-carboxamide	*	2.33 (B)	547

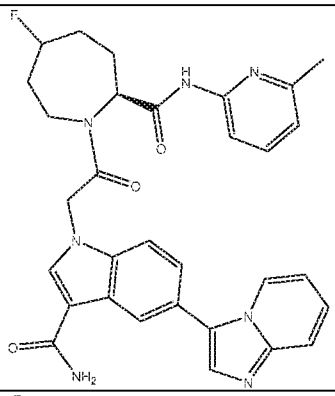
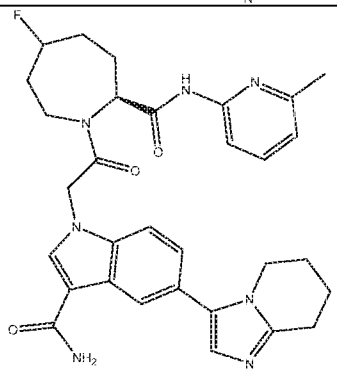
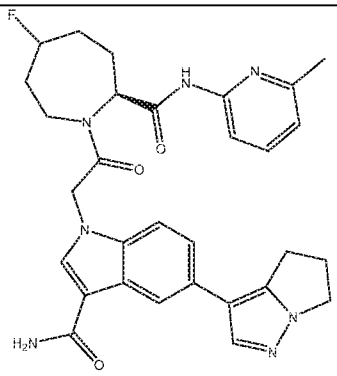
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
591		5-(3-cyanophenyl)-1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	2.82 (B)	553
592		2-((2R,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-4-fluoropyrrolidin-2-yl)-N-hydroxyacetamide	*	5.53 (C)	455
593		5-(6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)-1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	3.86 (B)	569
594		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(naphthalen-2-yl)-1H-indole-3-carboxamide	*	4.02 (B)	578

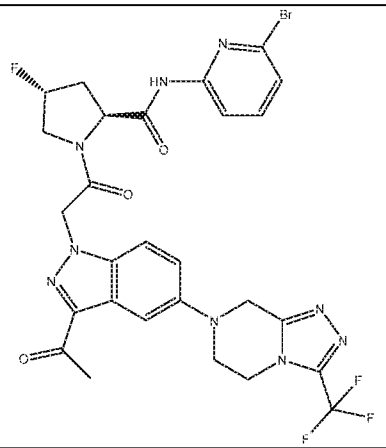
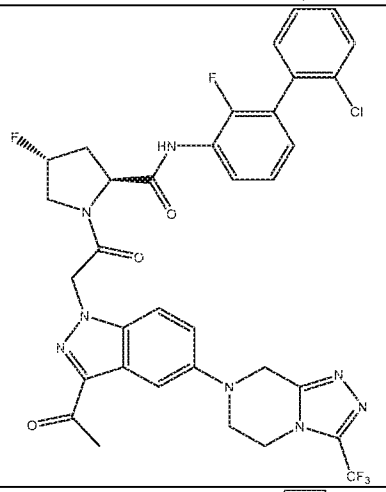
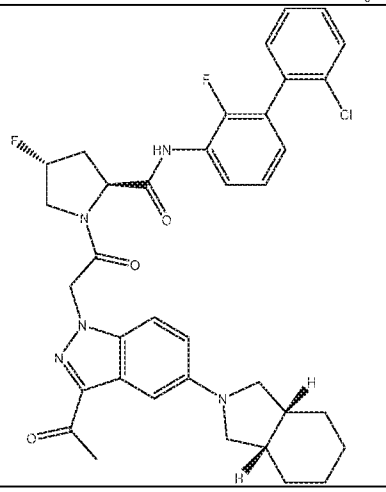
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
595		5-(6-aminopyridin-3-yl)-1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	3.25 (B)	544
596		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(6-methoxypyridin-3-yl)-1H-indole-3-carboxamide	*	2.48 (B)	559
597		(R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-N-methylacetamido)-N-(6-bromopyridin-2-yl)butanamide	*	11.72 (D)	564
598		(S)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-N-methylacetamido)-N-(6-bromopyridin-2-yl)butanamide	**	11.72 (D)	564

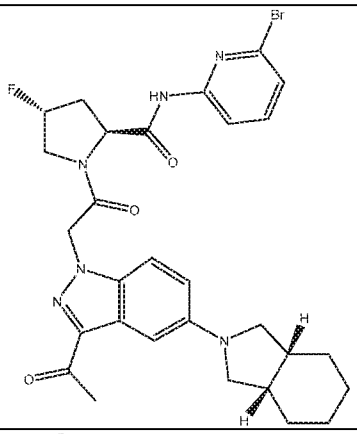
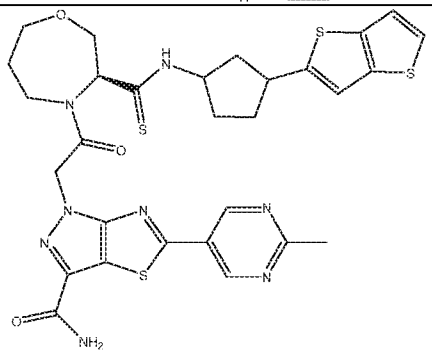
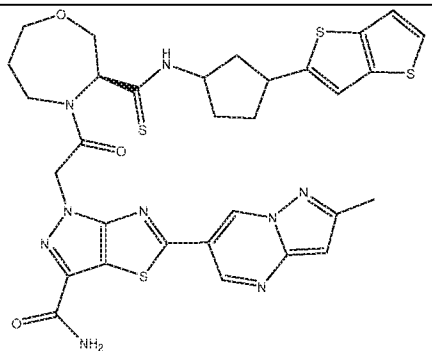
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
599		(R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetamido)-N-(6-bromopyridin-2-yl)butanamide	*	10.69 (D)	550
600		(S)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetamido)-N-(6-bromopyridin-2-yl)butanamide	***	10.67 (D)	552 (M+2)
601		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(cyanomethyl)-4-fluoropyrrolidine-2-carboxamide	***	1.91 (B)	464
602		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(quinolin-7-yl)-1H-indole-3-carboxamide	*	2.99 (B)	579

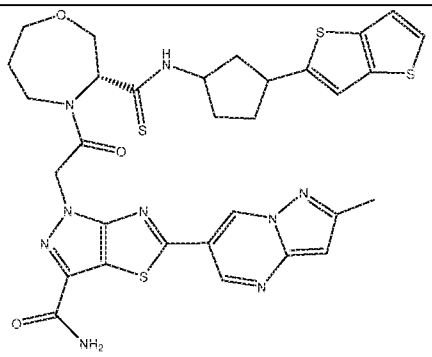
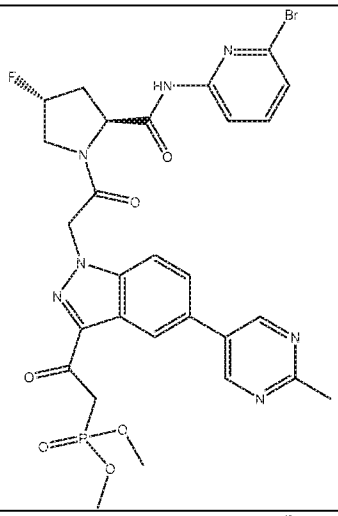
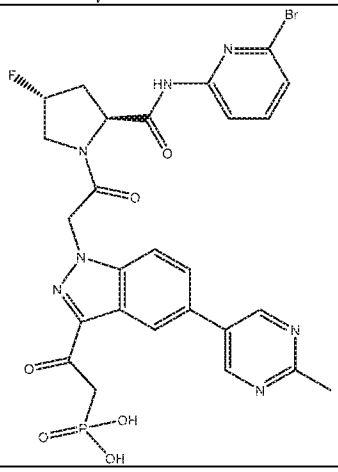
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
603		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(((6-bromopyridin-2-yl)sulfonyl)methyl)-4-fluoropyrrolidin-1-yl)ethan-1-one	*	10.54 (D)	615
604		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(((6-bromopyridin-2-yl)sulfinyl)methyl)-4-fluoropyrrolidin-1-yl)ethan-1-one	**	9.74 (D)	599
606		(1R,2S,5S)-3-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide	***	1.49 (A)	567
611		1-(2-((2R,4R)-4-fluoro-2-((R)-1-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-	*	3.80 (B)	556

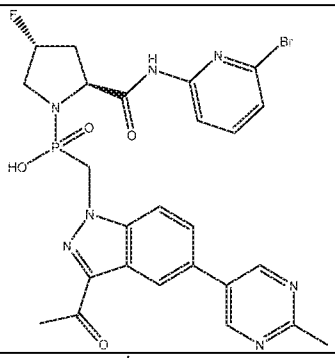
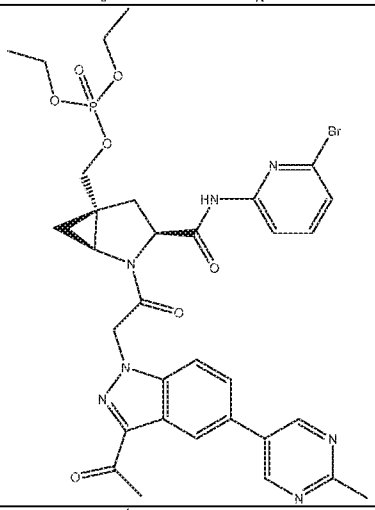
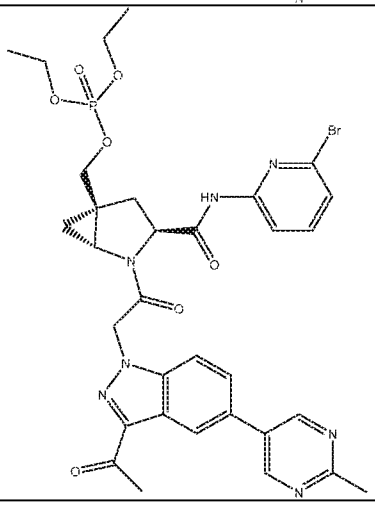
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
		1H-indole-3-carboxamide			
612		(S)-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1-(2-(6-((6-methylpyridin-2-yl)carbamoyl)-5,6-dihydropyridin-1(2H)-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	2.45 (B)	549
613		1-(2-((2S,4R)-4-fluoro-2-((S)-1-hydroxy-2-(6-methylpyridin-2-yl)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1H-indole-3-carboxamide	*	3.63 (B)	557
614		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1H-indole-3-carboxamide	*	2.42 (B)	583

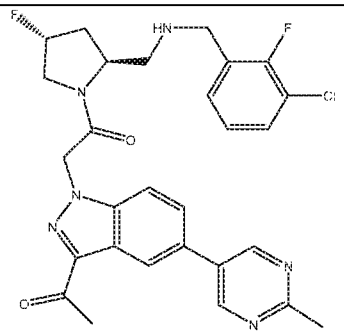
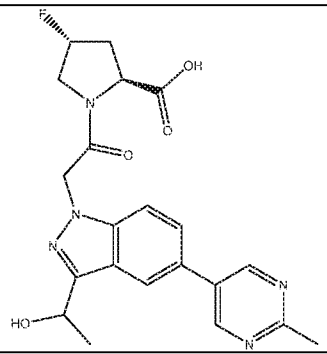
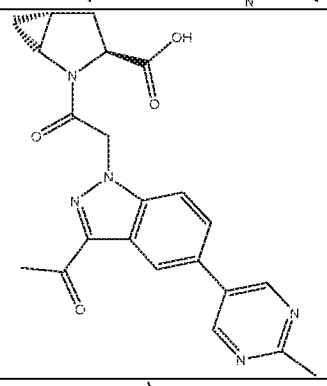
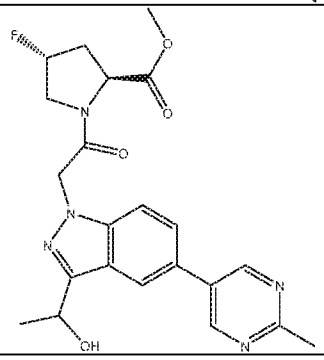
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
615		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(imidazo[1,2-a]pyridin-3-yl)-1H-indole-3-carboxamide	*	2.52 (B)	569
616		1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)-1H-indole-3-carboxamide	*	2.86 (B)	572
617		5-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-1-(2-((2S)-5-fluoro-2-((6-methylpyridin-2-yl)carbamoyl)azepan-1-yl)-2-oxoethyl)-1H-indole-3-carboxamide	*	1.92 (B)	558

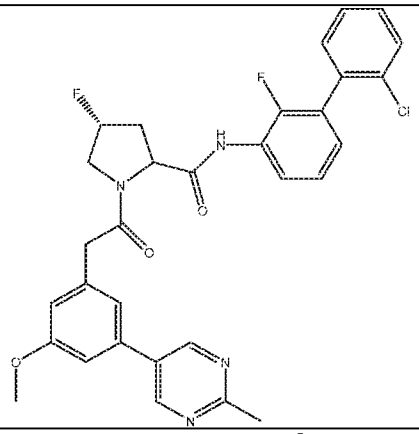
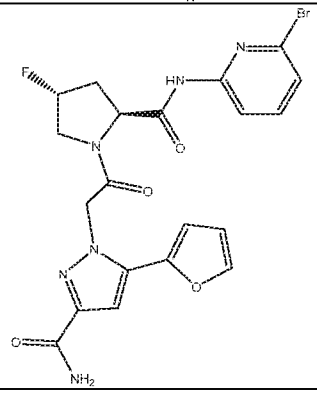
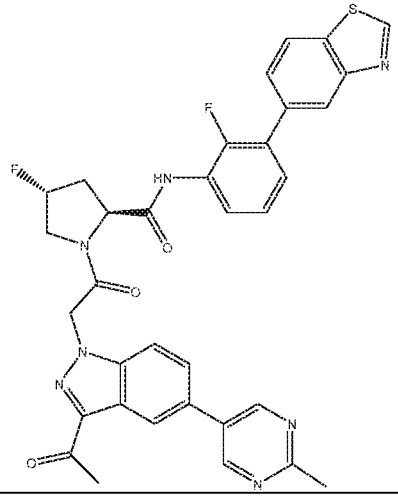
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
618		(2S,4R)-1-(2-(3-acetyl-5-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.35 (A)	678
619		(2S,4R)-1-(2-(3-acetyl-5-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide	***		
620		(2S,4R)-1-(2-(3-acetyl-5-((3aR,7aS)-hexahydro-1H-isoindol-2(3H)-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.12 (A)	661

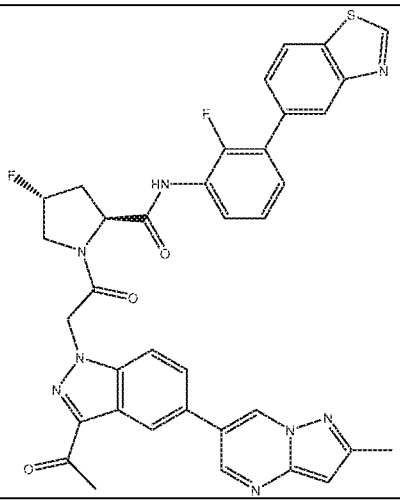
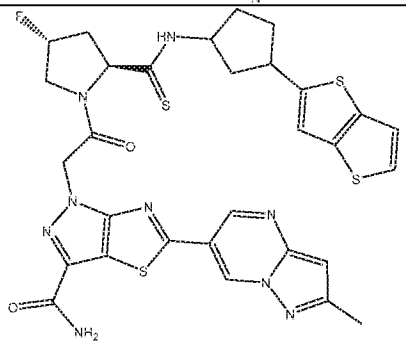
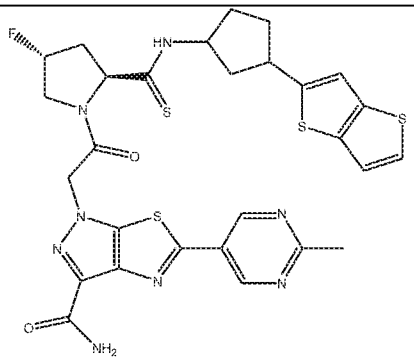
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
621		(2S,4R)-1-(2-(3-acetyl-5-((3aR,7aS)-hexahydro-1H-isoindol-2(3H)-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.79 (A)	611
622		5-(2-methylpyrimidin-5-yl)-1-(2-oxo-2-((3S)-3-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)-1,4-oxazepan-4-yl)ethyl)-1H-pyrazolo[3,4-d]thiazole-3-carboxamide		2.98 (B)	667
623		5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1-(2-oxo-2-((3S)-3-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)-1,4-oxazepan-4-yl)ethyl)-1H-pyrazolo[3,4-d]thiazole-3-carboxamide		4.00 (B)	706

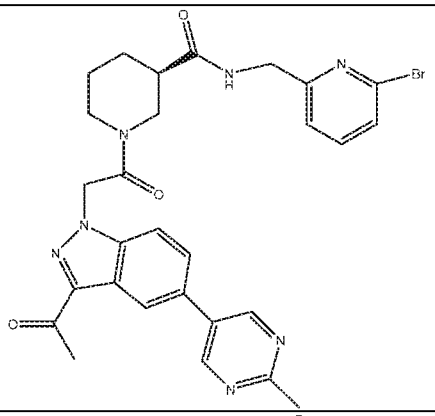
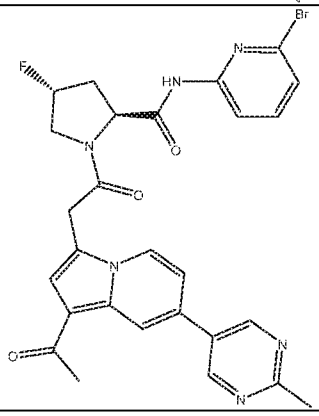
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
624		5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1-(2-oxo-2-((3R)-3-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)-1,4-oxazepan-4-yl)ethyl)-1H-pyrazolo[3,4-d]thiazole-3-carboxamide		4.16 (B)	706
625		dimethyl (2-(1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-3-yl)-2-oxoethyl)phosphonate	*	1.49 (A)	690
626		(2-(1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-3-yl)-2-oxoethyl)phosphonic acid	*	1.02 (A)	662

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
627		((3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)methyl)((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)phosphinic acid	*	1.10 (A)	616
628		((1S,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate	**	3.66 (B)	740
629		((1R,3S,5S)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-5-yl)methyl diethyl phosphate	***	3.50 (B)	740

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
630		2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)-1-((2S,4R)-2-(((3-chloro-2-fluorobenzyl)amino)methyl)-4-fluoropyrrolidin-1-yl)ethan-1-one	**	11.14 (D)	553
631		(2S,4R)-4-fluoro-1-(2-(3-(1-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxylic acid	*	0.72 (A)	428
632		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid	*	1.11 (A)	420
633		(2S,4R)-methyl 4-fluoro-1-(2-(3-(1-hydroxyethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)pyrrolidine-2-carboxylate	*	0.95 (A)	442

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
636		(4R)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoro-1-(2-(3-methoxy-5-(2-methylpyrimidin-5-yl)phenyl)acetyl)pyrrolidine-2-carboxamide	***	2.18 (A)	577
637		1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(furan-2-yl)-1H-pyrazole-3-carboxamide	***	1.39 (A)	504
638		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(3-(benzo[d]thiazol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	1.87 (A)	652

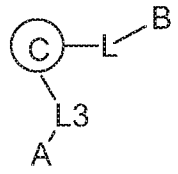
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
639		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1H-indazol-1-yl)acetyl)-N-(3-(benzo[d]thiazol-5-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	2.10 (A)	691
640		1-(2-((2S,4R)-4-fluoro-2-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazolo[3,4-d]thiazole-3-carboxamide	*	4.07 (B)	694
641		1-(2-((2S,4R)-4-fluoro-2-((3-(thieno[3,2-b]thiophen-2-yl)cyclopentyl)carbamothioyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-pyrazolo[4,3-d]thiazole-3-carboxamide	*	3.65 (B)	655

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
642		(R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-((6-bromopyridin-2-yl)methyl)piperidine-3-carboxamide	*	1.48 (A)	592
643		(2S,4R)-1-(2-(1-acetyl-7-(2-methylpyrimidin-5-yl)indolizin-3-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.61 (B)	579

[0956] This specification has been described with reference to embodiments of the invention. However, one of ordinary skill in the art appreciates that various modifications and changes can be made without departing from the scope of the invention as set forth in the claims below. Accordingly, the specification is to be regarded in an illustrative rather than a restrictive sense, and all such modifications are intended to be included within the scope of invention.

We claim:

1. A compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein

A is selected from Al, A1' and A2;

B is selected from Bl, Bl', B2, B3, and B4;

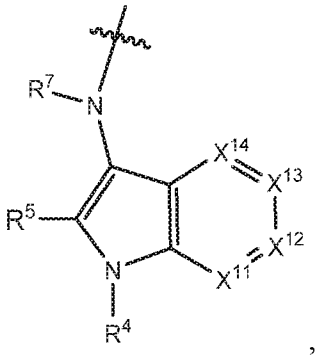
C is selected from CI, CI', C2, and C3;

L is selected from LI, LI', and L2;

L3 is selected from L4 and L5;

at least one of A, B, C, L, or L3 is selected from A2, B3, C3, L2, or L5;

A1 is selected from: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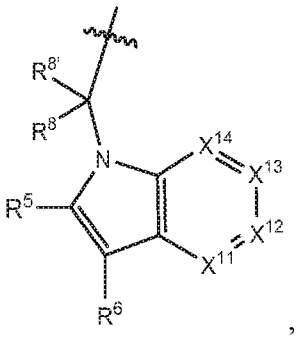
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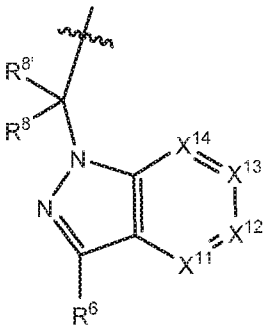
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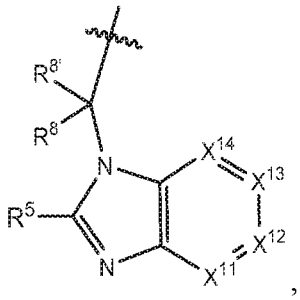
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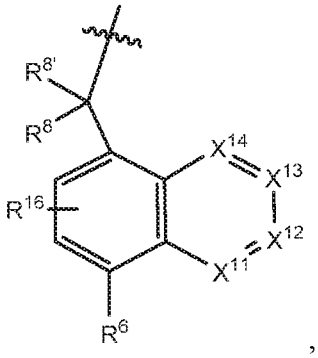
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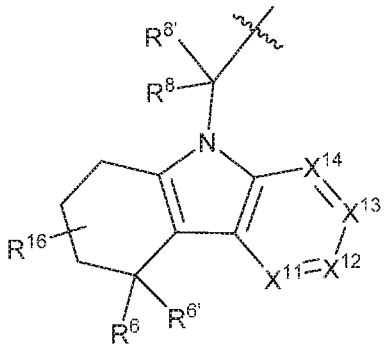
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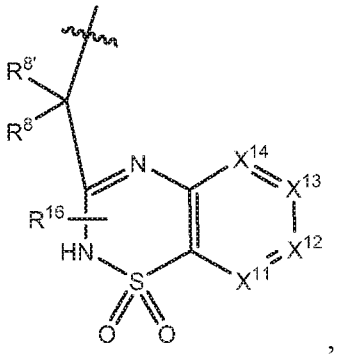
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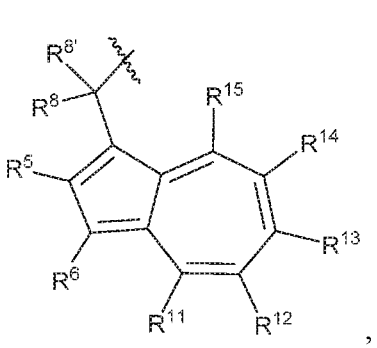
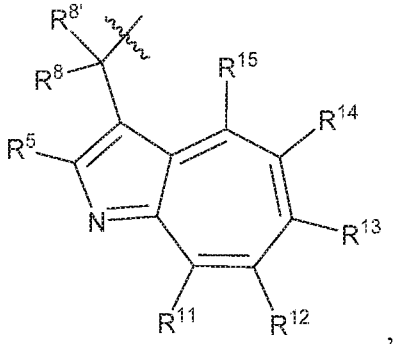
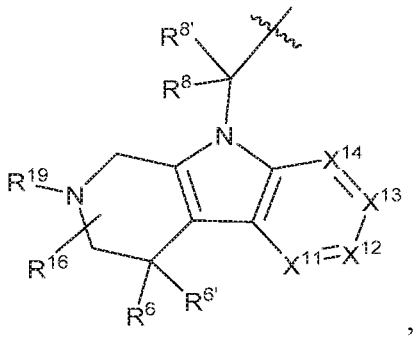
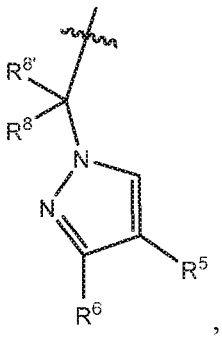
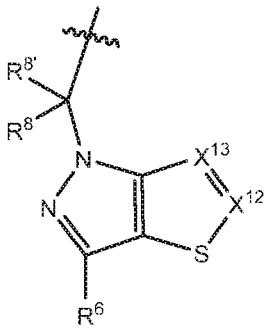
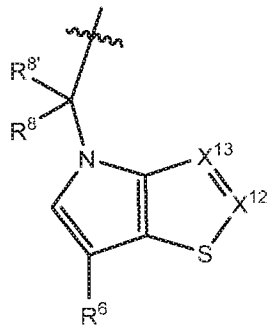
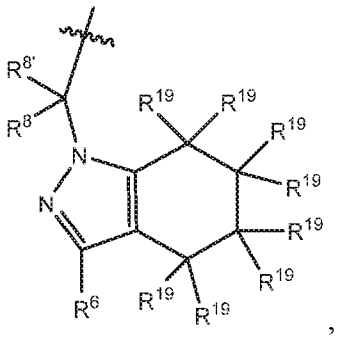
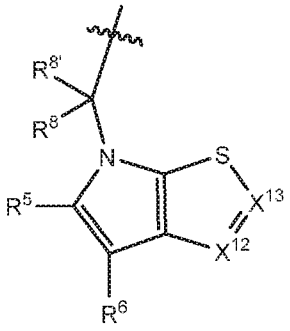
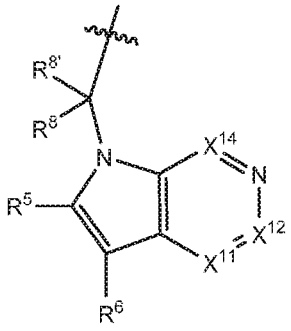
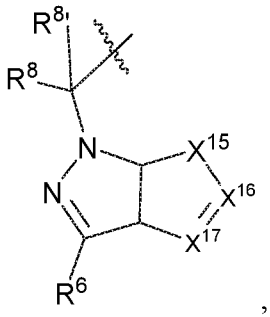










and ;

A1' is selected from the moieties in Fig. 6;

A2 is selected from: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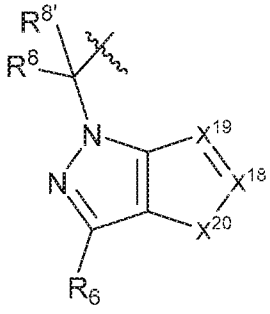
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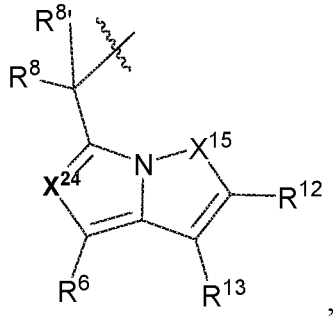
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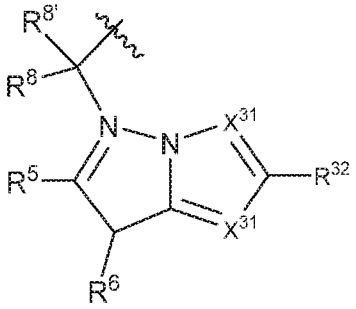
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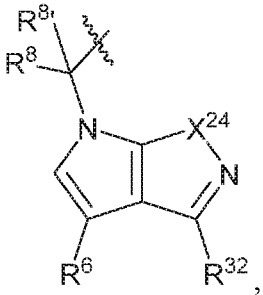
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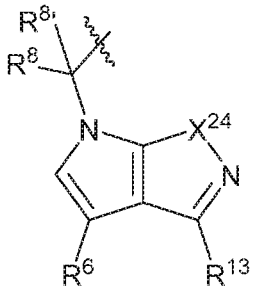
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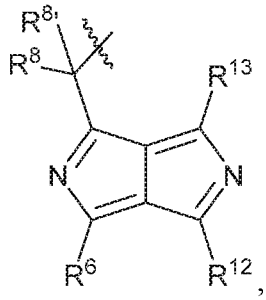
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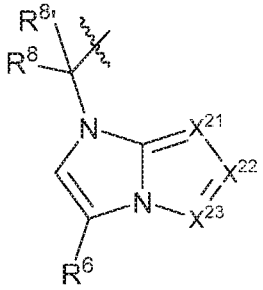
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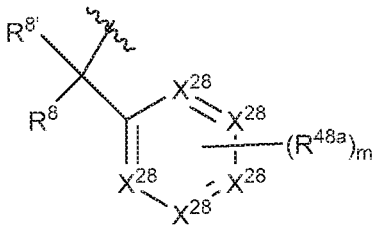
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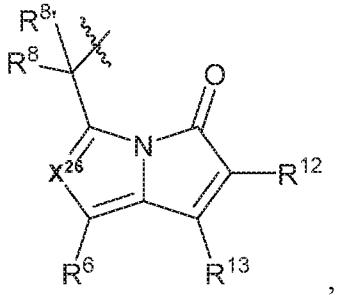
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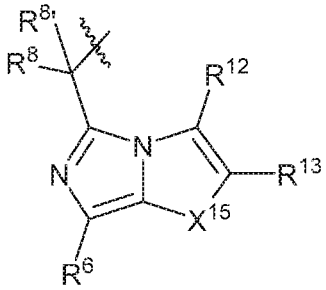
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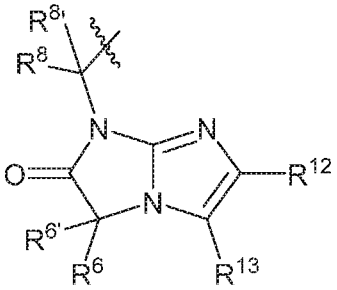
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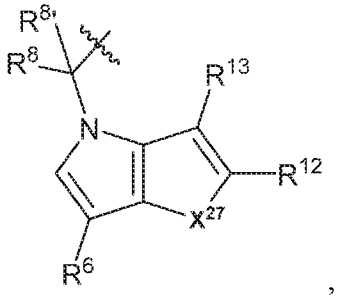
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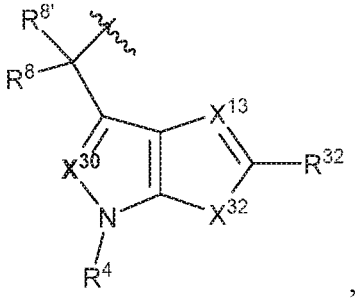
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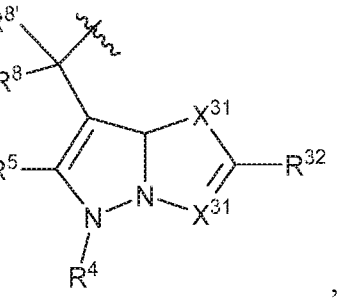
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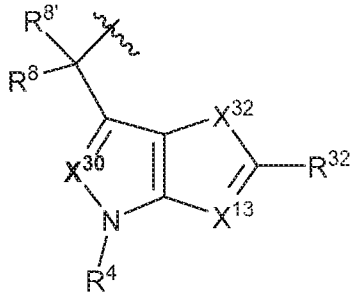
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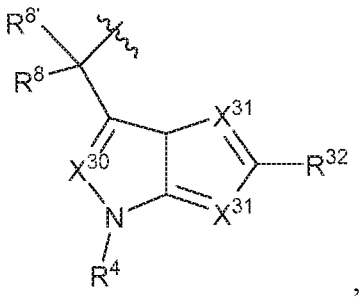
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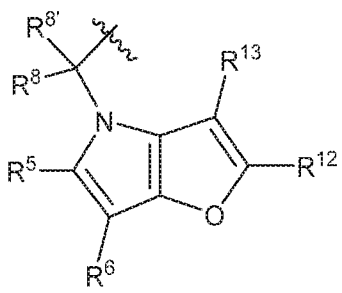
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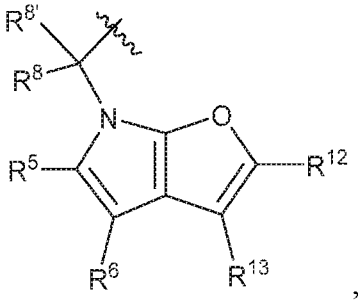
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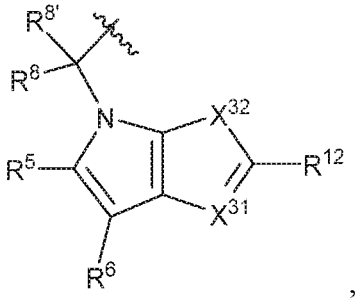
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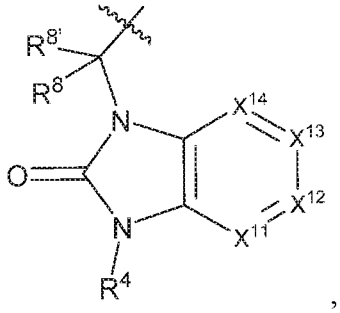
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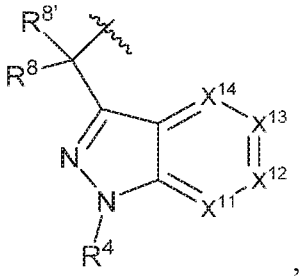
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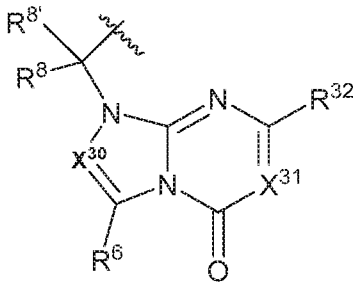
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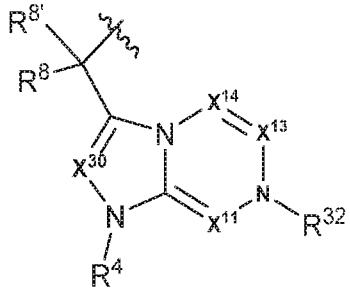
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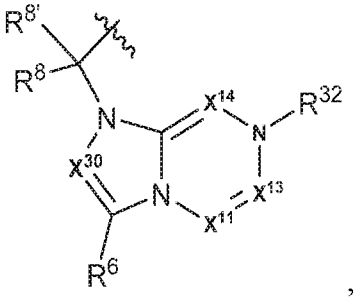
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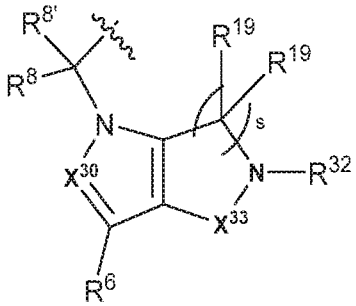
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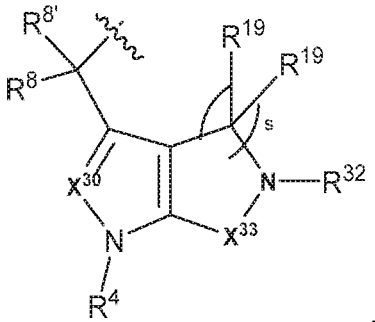
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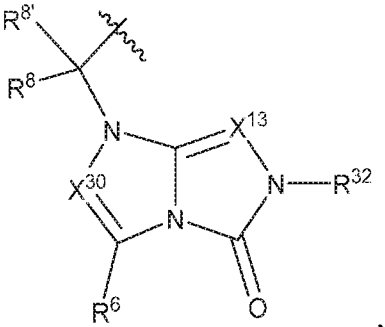
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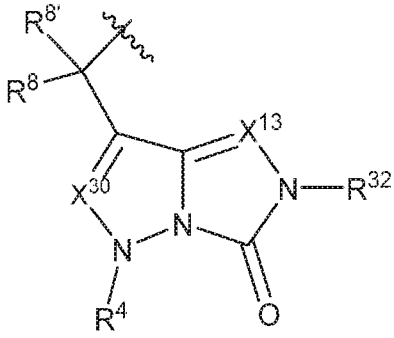
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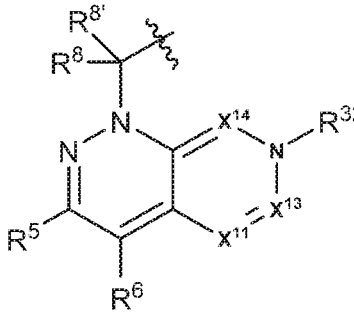
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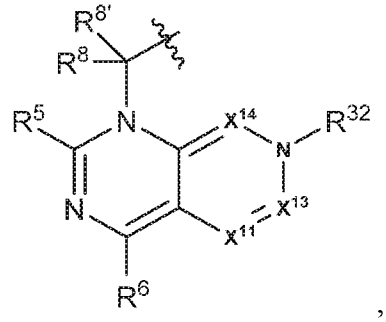
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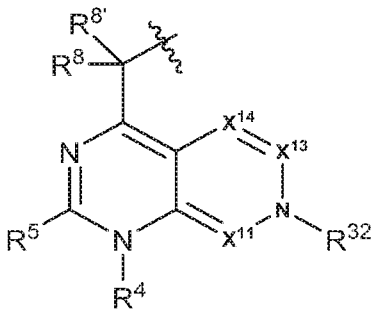
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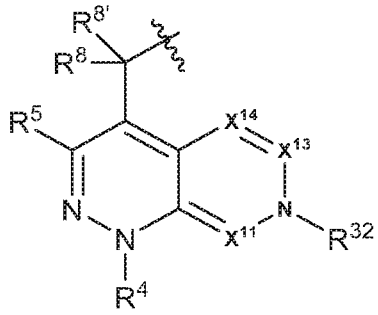
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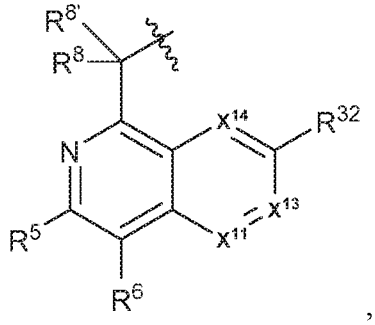
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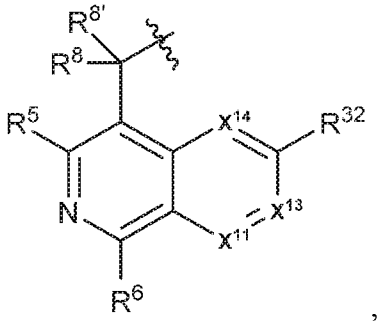
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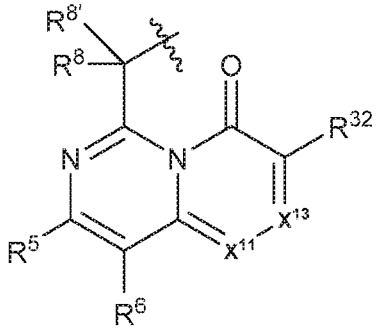
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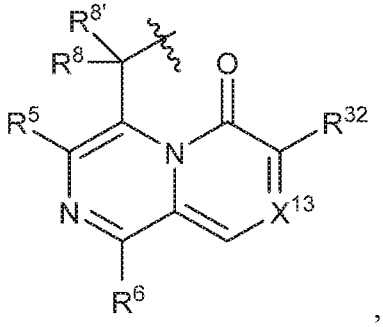
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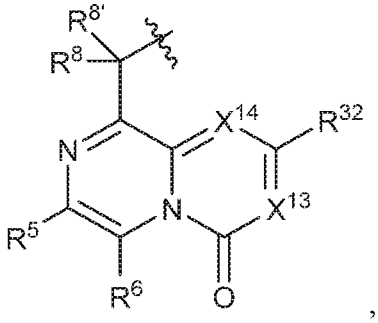
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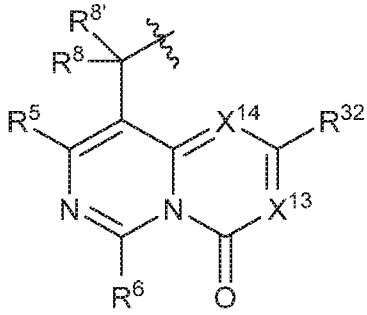
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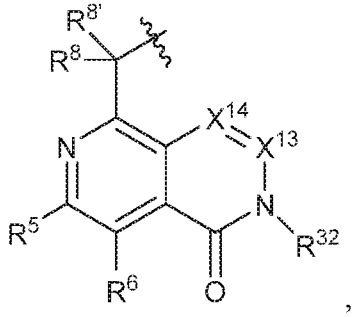
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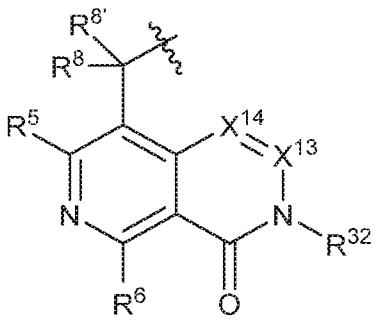
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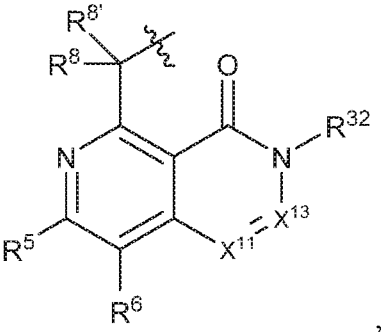
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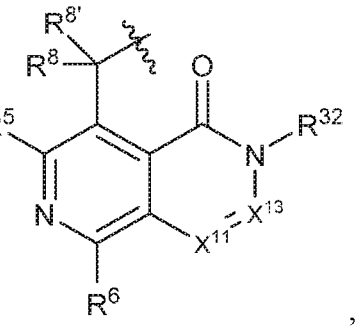
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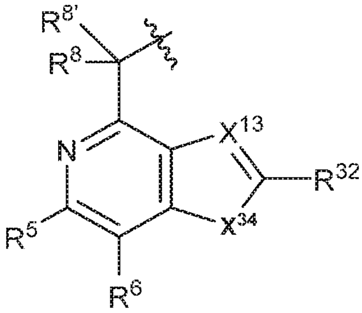
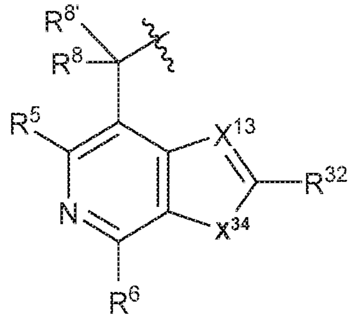
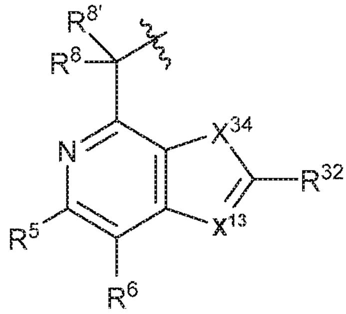
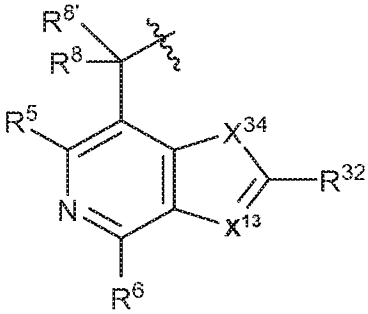
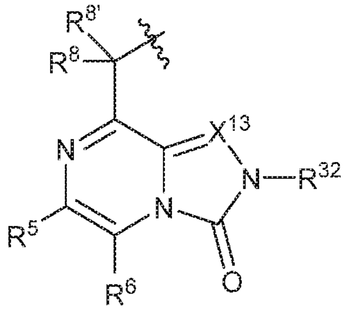
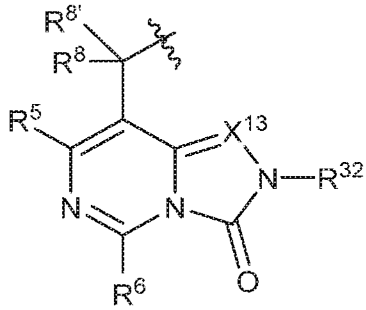
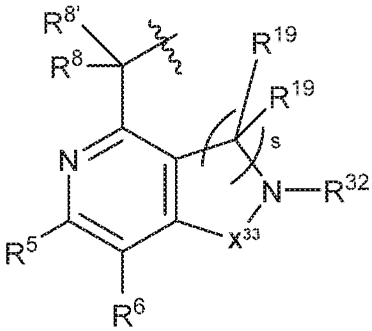
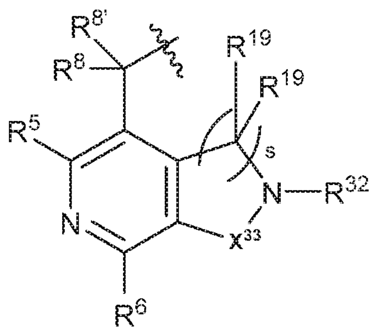
 ,
 ,
 ,
 ,
 ,
 ,
 , and
 ;

B1 is selected from a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C_2-C_6alkenyl; C2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl), each of which B1 is unsubstituted or substituted with one or more substituents independently chosen from R^{33} and R^{34}, and 0 or 1 substituents chosen from R^{35} and R^{36};

B1’ is selected from a moiety in Fig. 11A, 11B, 11C and 11D;

B2 is selected from a moiety of Fig. 12;

B3 is selected from:

(i) a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms

per ring; C2-C_6alkenyl; C2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl); each of which B3 is substituted with one or more of the following: S(0)=NR^{21}, SFs, and JC(R^9)=NR^{21};

(ii) a monocyclic, bicyclic, or tricyclic heterocyclic group that has at least one boron or silicon atom in the ring or a monocyclic, bicyclic, or tricyclic heteroaryl group that has at least one boron in the ring;

(iii) a 6-membered aryl group fused to a 5-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N and S wherein one of the CH_2 groups of the 5-membered cyclic group is optionally substituted by oxo, excluding dihydrobenzofuran;

(iv) (optionally substituted alkyl)-(optionally substituted cycloalkyl), (optionally substituted alkenyl)-(optionally substituted cycloalkyl), or (optionally substituted alkynyl)-(optionally substituted cycloalkyl);

wherein B3 can be further substituted one or more times with the substituents independently selected from R^{35}, R^{36} and R^{48};

B4 is selected from the following:

(i) a 4-membered carbocyclic fused to a 5- or 6- membered heteroaryl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S; wherein the 4-5 or 4-6 ring system can be optionally substituted;

(ii) a 4-membered carbocyclic fused to a 6-membered aryl ring wherein the 4-6 ring system can be optionally substituted;

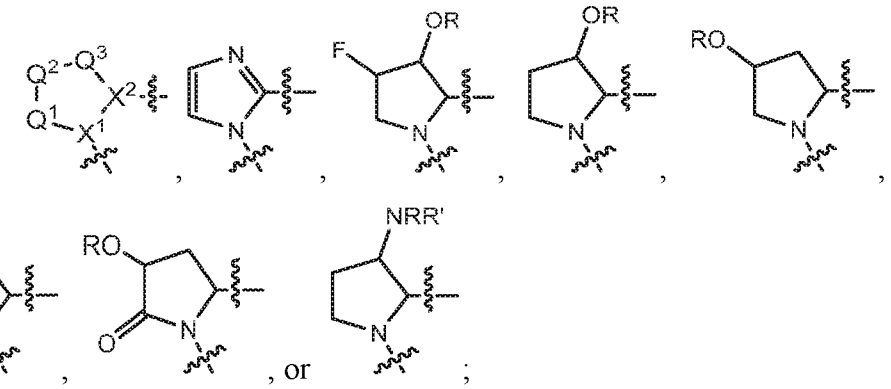
(iii) a monocyclic or bicyclic carbocyclic; a monocyclic or bicyclic carbocyclic-oxy group; a monocyclic, bicyclic, or tricyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C2-C_6alkenyl; C2-C_6alkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(biphenyl); each of which B3 is substituted one or more times with S(0) $_2$OR^{21};

(iv) (cycloalkyl)-(optionally substituted aryl), (cycloalkyl)-(optionally substituted heteroaryl), (cycloalkyl)-(optionally substituted heterocyclic), (alkyl)-alkenyl), cycloalkyl-alkenyl;

(v) alkyl, (alkyl)-(alkenyl), alkyl(alkynyl), cycloalkyl-alkenyl each of which can be optionally substituted;

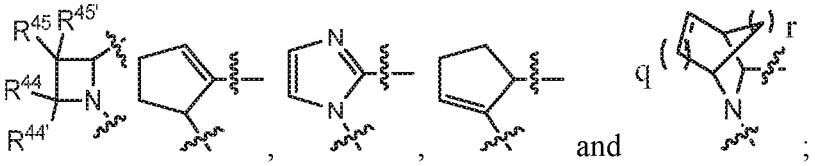
(vi) (optionally substituted alkyl)-(optionally substituted cycloalkyl), (alkenyl)-(optionally substituted cycloalkyl), (alkynyl)-(optionally substituted cycloalkyl), (optionally substituted cycloalkyl)-(optionally substituted cycloalkyl);

wherein B4 can be substituted 1, 2, 3 or 4 times or more with the substituents independently selected from R^{33}, R^{34}, R^{35} R^{36} and R^{48};

C1 is 

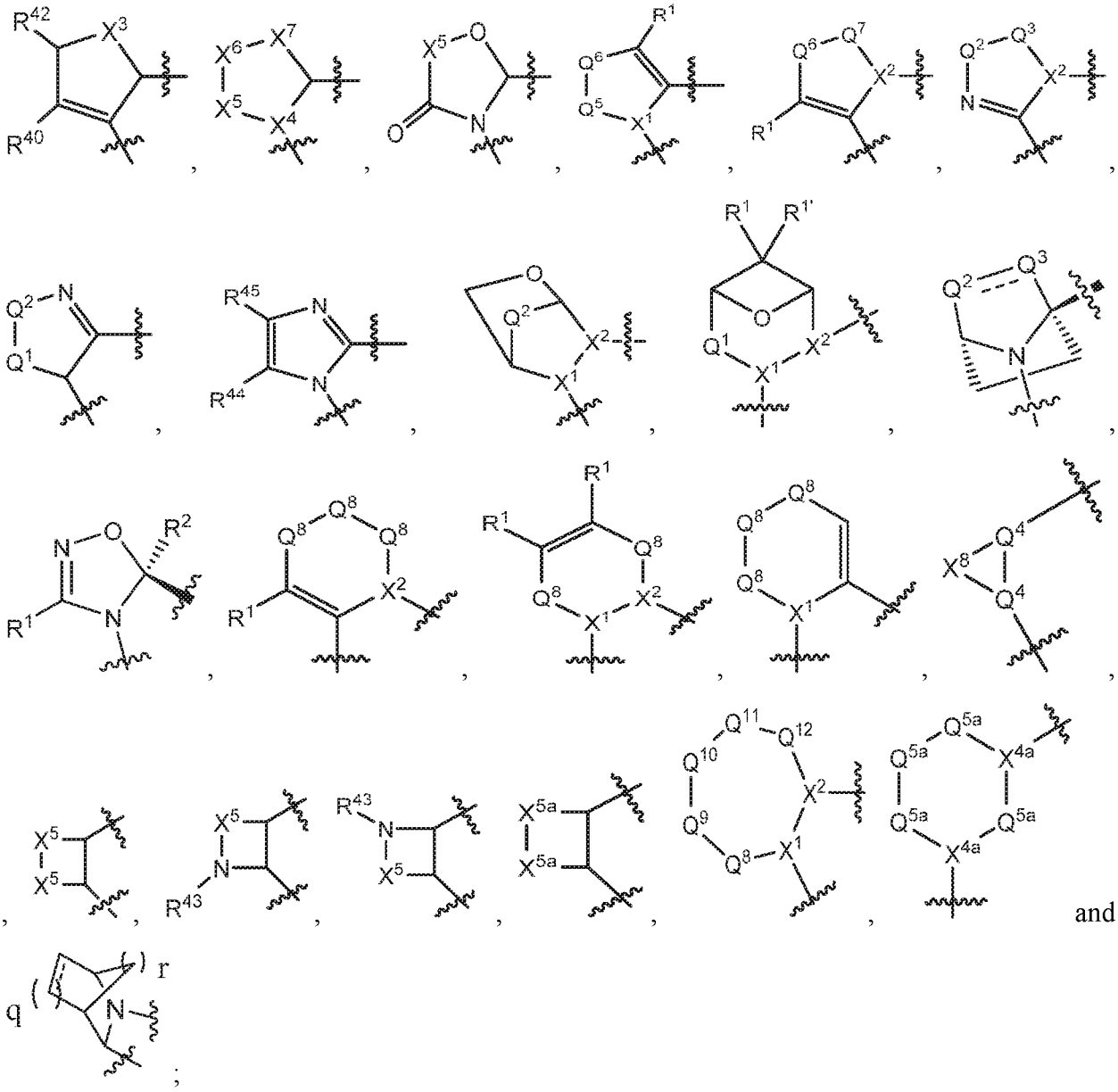
C1' is selected from a moiety in Fig 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 21, 2J, 2L and 2M;

C2 is selected from:



wherein q is 0, 1, 2 or 3 and r is 1, 2 or 3;

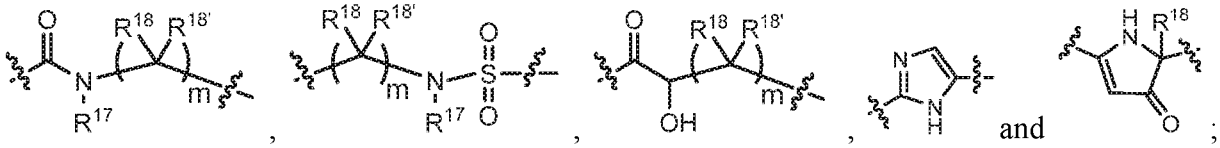
C3 is selected from:



and

;

L I is a bond or is chosen from the formulas

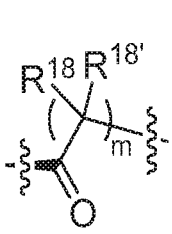


and

;

LI' is selected from a moiety of Figure 8, wherein a methyl group can optionally be replaced with another alkyl group;

L2 is selected from: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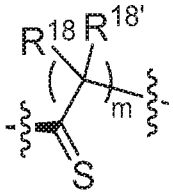
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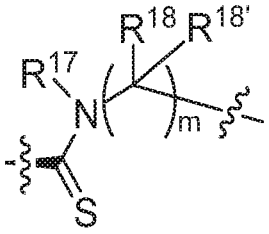
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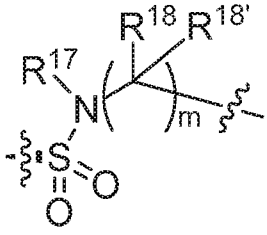
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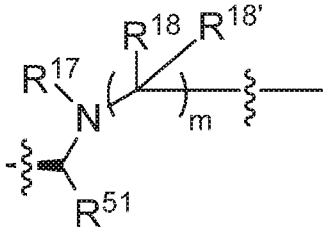
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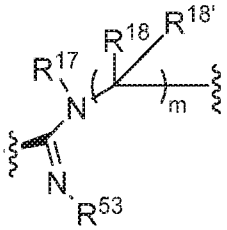
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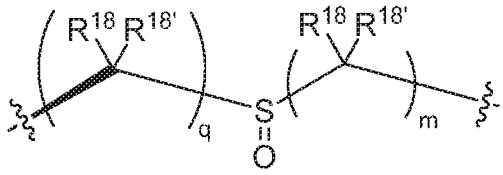
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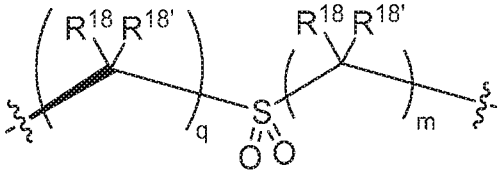
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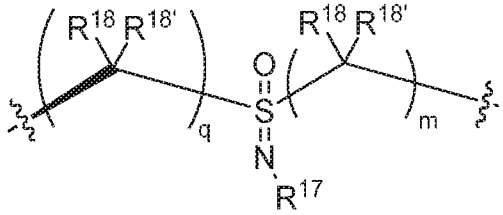
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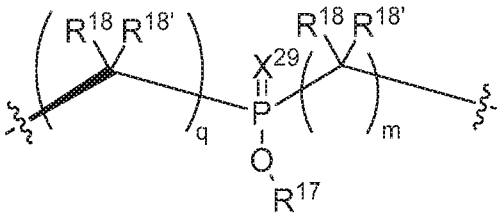
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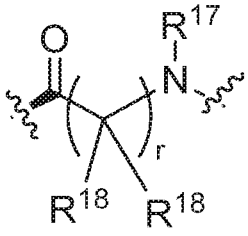
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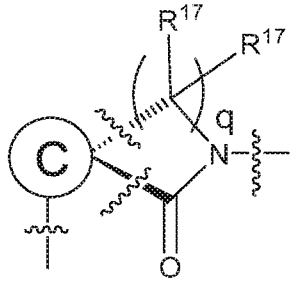
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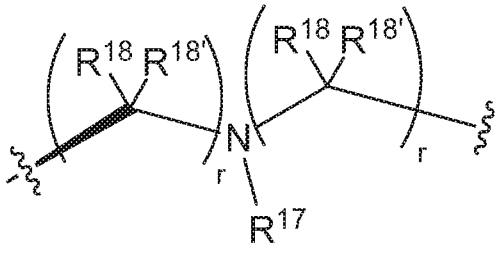

;

or an optionally substituted monocyclic or bicyclic carbocyclic; an optionally substituted monocyclic or bicyclic carbocyclic-oxy group; an optionally substituted monocyclic or bicyclic heterocyclic group having 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and from 4 to 7 ring atoms per ring, an optionally substituted -(Co-C4alkyl)(aryl); an optionally substituted -(Co-C4alkyl)(5-membered heteroaryl) selected from pyrrole, furan, thiophene, pyrazole, oxazole, isoxazole, thiazole and isothiazole or a substituted imidazole; an optionally

substituted -(Co-C4alkyl)(6-membered heteroaryl); an optionally substituted -(Co-C4alkyl)(8-membered heteroaryl); an optionally substituted -(Co-C4alkyl)(9-membered heteroaryl) selected from isoindole, indazole, purine, indolizine, benzothiophene, benzothiazole, benzoxazole, benzofuran, and furopyridine; and -(Co-C4alkyl)(10-membered heteroaryl); q is 1, 2 or 3;

L3 is selected from L4 or L5;

L4 is -C(O)-;

L5 is -C(S)-, -P(0)OH-, -S(O)-, -S(0)$_2$- or -C(R^{52})$_2$-;

Q^1 is N(R*) or C^R $^{1'}$);

Q^2 is C($R^2R^{2'}$), C($R^2R^{2'}$)-C($R^2R^{2'}$), S, 0 , N(R^2) or C($R^2R^{2'}$)0;

Q^3 is N(R^3), S, or C($R^3R^{3'}$);

Q^4 is N or CH;

Q^5 is N(R^{47}) or C($R^{46}R^{46'}$);

^{Q5a} is C($R^{47}R^{47}$), N(R^{47}), 0 , S, SO, or S0$_2$;

Q^6 is N(R^{47}), C($R^{46}R^{46'}$), S, or 0 ;

Q^7 is C($R^{46}R^{46'}$), S orN(R^{47});

Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} are each independently C($R^2R^{2'}$), S, SO, SO2, O, N(R^2), B(R^{50}), Si(R^{49})$_2$, however if X^1 is N and X^2 is CH then L and B taken together cannot be anisole substituted in the 4 position;

X^1 and X^2 are independently N, CH, or CZ, or X^1 and X^2 together are C=C;

Z is F, CI, NH2, CH3, CH2D, CHD$_2$, or CD$_3$;

X^3 is C($R^1R^{1'}$);

X^4 is N or CH;

X^{4a} is N, CH or CZ;

X^5 and X^6 are C^R $^{1'}$) or X^4 and X^5 or X^5 and X^6 together are C=C;

X^{5a} is *C($R^1R^{1'}$)* or O;

X^7 is SO or SO$_2$;

X^8 is C(R¾ $^{1'}$) or N(R^{43});

X^{11} is N or CR^{11};

X^{12} is N or CR^{12};

X^{13} is N or CR^{13};

X^{14} is N or CR^{14}, and wherein no more than 2 of X^{11}, X^{12}, X^{13}, and X^{14} are N;

X^{15} is NH, 0 , or S;

X^{16} is CR^{12};

X^{17} is N or CR^{13};

X^{18} is CR^{12};

X^{19} is N or CR^{13};

X^{20} is NH or 0 ;

X^{21} is N or CR^{14};

X^{22} is N or CR^{13};

X^{23} is CR^{12};

X^{24} is O or S;

X^{26} is N or CR^{41};

X^{27} is CR^{12}, NH or O;

X^{28} is N or CH;

X^{29} can be O or S;

X^{30} is N or CR^{5};

X^{31} is N, $C(R^{54})_2$ or CR^{54};

X^{32} is NH, $C(R^{54})_2$ or CR^{54};

X^{33} is -CO- or -SO- or - SO_2-;

X^{34} is CHR^{13}, NH, O, or S;

s is 1 or 2;

R and R' are independently chosen from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted;

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, amino, Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, Ci-C_6alkoxy, C_2-C_6alkynyl, C_2-C_6alkanoyl, Ci-C_6thioalkyl, hydroxyCi-Cealkyl, aminoCi-Cealkyl, -Co-C_4alkylNR^9R^{10}, -C(0)OR^9, -OC(0)R^9, -NR^9C(0)R^{10}, -C(0)NR^9R^{10}, -OC(0)NR^9R^{10}, -NR^9C(0)OR^{10}, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

or R^1 and R^2 are linked to form a 3- to 6-membered carbocyclic or aryl ring;

or R^2 and R^3 are linked to form a 3- to 6-membered carbocyclic ring;

or R^1 and $R^{1'}$, or R^2 and $R^{2'}$, or R^3 and $R^{3'}$ are linked to form a 3- to 6-membered carbocyclic spiro ring;

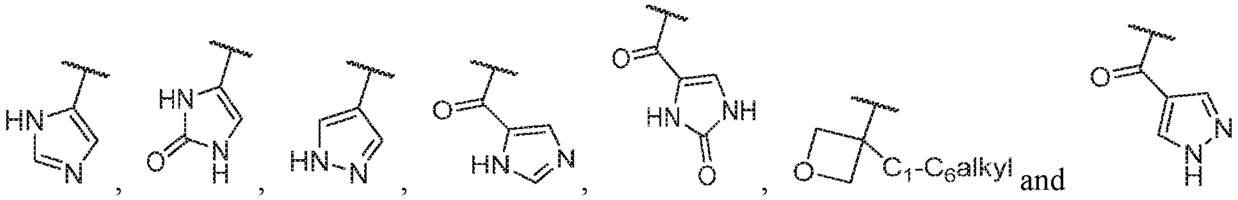
or R^1 and $R^{1'}$, R^2 and $R^{2'}$ or R^3 and $R^{3'}$ are linked to form a 3- to 6-membered heterocyclic spiro ring;

each of which ring is unsubstituted or substituted with 1 or more substituents independently chosen from halogen, hydroxyl, cyano, -COOH, Ci-C4alkyl, C_2-C4alkenyl, C_2-C4alkynyl, Ci-C4alkoxy, C_2-C4alkanoyl, hydroxyCi-C4alkyl, (mono- and di-Ci-C4alkylamino)Co-C_4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), -0-Co-C4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

or R^1 and $R^{1'}$ or R^2 and $R^{2'}$ are linked to form a carbonyl group;

or R^1 and R^2 or R^2 and R^3 can be taken together to form a carbon-carbon double bond;

R^4, R^5, and R^6 are selected from hydrogen, -JCHO, -JC(0)NH $_2$, -JC_2-C_6alkanoyl, -JC(0)NH(CH $_3$), -J-COOH, -JP(0)(OR ^{9})$_2$, -JOC(0)R ^{9}, -JC(0)OR ^{9}, -JC(0)N(CH $_2$CH$_2$R^9)(R^{10}), -JNR^{9}C(0)R ^{10}, -JSO2NH2, -JS(0)NH $_2$, -JC(CH$_2$)$_2$F, -JCH(CF$_3$)NH$_2$, -JC(0)Co-C $_2$alkyl(C$_3$-C_7cycloalkyl), -JNR^9(C_2-C_6alkanoyl), -JNR^{9}C(0)NR^{9}R^{10}, -JS0$_2$(Ci-C$_6$alkyl), -JS0$_2$(Ci-Cehaloalkyl), -JS0$_2$NR^{7}R^7, -JSO=NH(C_1-C_6alkyl), -J-nitro, -J-halogen, -J-hydroxyl, -J-phenyl, a 5- to 6-membered heteroaryl, -J-cyano, -J-cyanoimino, -J-amino, -J-imino, -Ci-C$_6$alkyl, -Co-C4alkyl(C_3-C7heterocycloalkyl), -Co-C4alkyl(C3-C7cycloalkyl),



, , , , , , and ;

each of which R^4, R^5 and R^6 other than hydrogen, nitro, halogen, cyano, cyanoimino, or -CHO, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, Ci-C$_2$alkyl, Ci-C$_2$alkoxy, -Co-C_2alkyl(mono- and di-Ci-C4alkylamino), Ci-C_2haloalkyl, and Ci-C$_2$haloalkoxy;

$R^{6'}$ is hydrogen, halogen, hydroxyl, Ci-C4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), or Ci-C4alkoxy; or R^6 and $R^{6'}$ may be taken together to form an oxo, vinyl, or imino group;

R^7 is hydrogen, Ci-C$_6$alkyl, or -Co-C4alkyl(C3-C7cycloalkyl);

R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, hydroxyl, Ci-C$_6$alkyl, -Co-C4alkyl(C3-C7cycloalkyl), Ci-C$_6$alkoxy, and (Ci-C4alkylamino)Co-C$_2$alkyl; or R^8 and $R^{8'}$ are taken

together to form an oxo group; or R^8 and $R^{8'}$ can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring;

R^9 and R^{10} are independently chosen at each occurrence from hydrogen, Ci-C_6alkyl, (C_3-C7cycloalkyl)Co-C_4alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), and -0-Co-C_4alkyl(C3-C7cycloalkyl);

R^{11}, R^{14}, and R^{15} are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -0(PO)(OR^9)$_2$, -(PO)(OR^9)$_2$, Ci-Cealkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C6alkenyl(aryl), C_2-C6alkenyl(cycloalkyl), C_2-C6alkenyl(heterocycle), C_2-C6alkenyl(heteroaryl), C_2-C_6alkynyl, C_2-C6alkynyl(aryl), C_2-C6alkynyl(cycloalkyl), C_2-C6alkynyl(heterocycle), C_2-C6alkynyl(heteroaryl), C_2-C_6alkanoyl, Ci-C_6alkoxy, Ci-C_6thioalkyl, -Co-C_4alkyl(mono- and di-C-i-C6alkylamino), -Co-C_4alkyl(C3-C7cycloalkyl), -Co-C_4alkoxy(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

one of R^{12} and R^{13} is chosen from R^{31} and the other of R^{12} and R^{13} is chosen from R^{32} or both R^{12} and R^{13} are each independently selected from an R^{32} moiety;

R^{16} is absent or selected from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, Ci-C_6alkoxy, -Co-C_4alkyl(mono- and di-Ci-C6alkylamino), -Co-C_4alkyl(C3-C7cycloalkyl), Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

R^{17} is hydrogen, Ci-C_6alkyl, or -Co-C_4alkyl(C3-C7cycloalkyl);

R^{18} and $R^{18'}$ are independently selected from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3;

R^{19} is hydrogen, Ci-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -S0$_2$Ci-C_6alkyl, (mono- and di-Ci-C6alkylamino)Ci-C_4alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), -Co-C_4alkyl(C3-C7heterocycloalkyl), -Co-C_4alkyl(aryl), Co-C_4alkyl(heteroaryl), and wherein R^{19} other than hydrogen is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, -COOH, and -C(0)OCi-C_4alkyl;

R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, Ci-C_6alkyl, Ci-C_6haloalkyl, Ci-C_6alkoxy, (C3-C7cycloalkyl)Co-C_4alkyl, (phenyl)Co-C_4alkyl, -Ci-C_4alkylOC(0)OCi-C_6alkyl, -Ci-C_4alkylOC(0)Ci-C_6alkyl, -Ci-C_4alkylC(0)OCi-C_6alkyl, (4- to 7-membered heterocycloalkyl)Co-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{21} and R^{22} can be optionally substituted;

R^{23} is independently chosen at each occurrence from Ci-C6alkyl, Ci-C_6haloalkyl, (aiyl)Co-C_4alkyl, (C3-C7cycloalkyl)Co-C4alkyl, (phenyl)Co-C_4alkyl, (4- to 7-membered heterocycloalkyl)Co-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{23} can be optionally substituted;

R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyl group, or a 6- to 10- membered bicyclic heterocyclic group having fused, spiro, or bridged rings, and each R^{24} and R^{25} can be optionally substituted;

R^{31} is chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, Ci-C2haloalkyl, Ci-C2haloalkoxy, Ci-C_6alkyl, -Co-C_4alkyl(C3-C7cycloalkyl), C2-C_6alkenyl, C_2-Cealkanoyl, Ci-Cealkoxy, C2-C_6alkenyloxy, -C(0)OR^9, Ci-Cethioalkyl, -Co-C_4alkylNR^9R^{10}, -C(0)NR^9R^{10}, -SO2R^9, -$S0_2NR^9R^{10}$, -OC(0)R^9, and -C(NR^9)NR^9R^{10}, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C2haloalkyl, and Ci-C2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ Ci-C2haloalkyl, and Ci-C2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent chosen from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, Ci-C_6alkyl, C2-C_6alkenyl, C2-C_6alkanoyl, Ci-C_6alkoxy, (mono- and di-Ci-C6alkylamino)Co-C_4alkyl, Ci-C6alkylester, -Co-C_4alkyl)(C3-C7cycloalkyl), Ci-C2haloalkyl, and Ci-C2haloalkoxy;

R^{32} is selected from aryl, heteroaryl; saturated or unsaturated heterocycle; wherein the aryl, heteroaryl, saturated or unsaturated heterocycle ring can be optionally substituted.

R^{33} is independently chosen from halogen, hydroxyl, -COOH, cyano, Ci-C_6alkyl, C2-Cealkanoyl, Ci-Cealkoxy, -Co-C_4alkylNR^9R^{10}, -SO2R^9, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

R^{34} is independently chosen from nitro, C2-C_6alkenyl, C2-C_6alkynyl, Ci-C_6thioalkyl, -JC3-Cvcycloalkyl, -$B(OH)_2$, -JC(0)NR^9R^{23}, -$JOS0_2OR^{21}$, -C(0)(CH_2)i-$_4$S(0)R^{21}, -0(CH_2)i-$_4$S(0)$NR^{21}R^{22}$, -JOP(0)(OR^{21})(OR^{22}), -JP(0)(OR^{21})(OR^{22}), -JOP(0)(OR^{21})R^{22}, -JP(0)(OR^{21})R^{22}, -JOP(0)$R^{21}R^{22}$, -JP(0)$R^{21}R^{22}$, -JSP(0)(OR^{21})(OR^{22}), -JSP(0)(OR^{21})(R^{22}), -JSP(0)(R^{21})(R^{22}), -JNR^9P(0)(NHR^{21})(NHR^{22}), -JNR^9P(0)(OR^{21})(NHR^{22}), -JNR^9P(0)(OR^{21})(OR^{22}), -JC(S)R^{21}, -JN$R^{21}$$S0_2R^{22}$, -JN$R^9$S(O)$NR^{10}R^{22}$, -JN$R^9SO_2NR^{10}R^{22}$,

-JS0 $_2$NR^{9}COR^{22}, -JS0 $_2$NR^{9}CONR^{21}R^{22}, -JNR^{21}S0 $_2$R^{22}, -JC(0)NR ^{21}S0 $_2$R^{22}, -JC(NH$_2$)=NR^{22}, -JCH(NH $_2$)NR^{9}S(0) $_2$R^{22}, -JOC(0)NR ^{21}R^{22}, -JNR^{21}C(0)OR ^{22}, -JNR^{21}OC(0)R ^{22}, -(CH$_2$)i-$_4$C(0)NR^{21}R^{22}, -JC(0)R ^{24}R^{25}, -JNR^{9}C(0)R ^{21}, -JC(0)R ^{21}, -JNR^{9}C(O)NR^{10}R^{22}, -CCR^{21}, -(CH$_2$)i-$_4$OC(0)R ^{21}, and -JC(0)OR ^{23}; each of which R^{34} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -CONH$_2$, -P(0)(OH) $_2$, Ci-Cealkyl, -Co-C$_4$alkyl(C$_3$-C7cycloalkyl), Ci-C$_6$alkoxy, -Co-C$_2$alkyl(mono- and di-Ci-C$_4$alkylamino), Ci-C6alkylester, Ci-C$_4$alkylamino, Ci-C$_4$hydroxylalkyl, Ci-C$_2$haloalkyl, and Ci-C$_2$haloalkoxy;

R^{35} is independently chosen from naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)Co-C$_4$alkyl containing 1 or 2 heteroatoms chosen from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R^{35} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, Ci-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkanoyl, Ci-C$_6$alkoxy, (mono- and di-Ci-C6alkylamino)Co-C$_4$alkyl, Ci-C$_6$alkylester, -Co-C$_4$alkyl(C$_3$-C7cycloalkyl), -S0 $_2$R^9, Ci-C$_2$haloalkyl, and Ci-C$_2$haloalkoxy;

R^{36} is independently chosen from tetrazolyl, (phenyl)Co-C$_2$alkyl, (phenyl)Ci-C $_2$alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently chosen from N, O, B, and S, each of which R^{36} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, Ci-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkanoyl, Ci-C$_6$alkoxy, (mono- and di-Ci-C6alkylamino)Co-C$_4$alkyl, Ci-C6alkylester, -Co-C$_4$alkyl(C$_3$-C$_7$cycloalkyl), -SOzR^9, -OSi(CH$_3$)$_2$C(CH$_3$)$_3$, -Si(CH $_3$)$_2$C(CH$_3$)$_3$, Ci-C$_2$haloalkyl, and Ci-C$_2$haloalkoxy;

R^{40} is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl wherein each group can be optionally substituted;

R^{41} is hydrogen, Ci-Cealkyl, or -(Co-C$_2$alkyl)(C$_3$-C$_5$cycloalkyl);

R^{42} is halo, hydroxy, Ci-C$_6$alkoxy, Ci-C$_6$haloalkoxy, -SH, or -S(Ci-C $_6$alkyl);

R^{43} is hydrogen, acyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted;

R^{44}, R$^{44'}$, R^{45}, R$^{45'}$ are independently hydrogen, hydroxyl, amino, cyano, halogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; wherein each group can be optionally substituted;

R^{46} and $R^{46'}$ are independently hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted and at least one of R^{46} or $R^{46'}$ is not hydrogen;

R^{47} is hydrogen, acyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted;

R^{48} is independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, Ci-C_6alkyl, Ci-C_6haloalkyl, C2-C_6alkenyl, C2-C_6alkynyl, Ci-C_6thioalkyl, Ci-C_6alkoxy, -JC3-Cvcycloalkyl, -B(OH)$_2$, -JC(0)NR^9R^{23},-JOS0_2OR^{21}, -C(0)(CH_2)i-$_4$S(0)R^{21}, -0(CH_2)i-$_4$S(0)$NR^{21}R^{22}$, -JOP(0)$(OR^{21})(OR^{22})$, -JP(0)$(OR^{21})(OR^{22})$, -JOP(0)$(OR^{21})R^{22}$, -JP(0)$(OR^{21})R^{22}$, -JOP(0)$R^{21}R^{22}$, -JP(0)$R^{21}R^{22}$, -JSP(0)$(OR^{21})(OR^{22})$, -JSP(0)$(OR^{21})(R^{22})$, -JSP(0)$(R^{21})(R^{22})$, -JNR^9P(0)$(NHR^{21})(NHR^{22})$, -JNR^9P(0)$(OR^{21})(NHR^{22})$, -JNR^9P(0)$(OR^{21})(OR^{22})$, -JC(S)R^{21}, -J$NR^{21}S0_2R^{22}$, -JNR^9S(O)$NR^{10}R^{22}$, -J$NR^9SO_2NR^{10}R^{22}$, -JS$0_2NR^9COR^{22}$, -JS$0_2NR^9CONR^{21}R^{22}$, -J$NR^{21}S0_2R^{22}$, -JC(0)$NR^{21}S0_2R^{22}$, -JC(NH_2)=NR^{22}, -JCH$(NH_2)NR^9S(0)_2R^{22}$, -JOC(0)$NR^{21}R^{22}$, -JNR^{21}C(0)OR^{22}, -JNR^{21}OC(0)R^{22}, -(CH_2)i-$_4$C(0)$NR^{21}R^{22}$, -JC(0)$R^{24}R^{25}$, -JNR^9C(0)R^{21}, -JC(0)R^{21}, -JNR^9C(O)$NR^{10}R^{22}$, -CCR^{21}, -(CH_2)i-$_4$OC(0)R^{21}, -JC(0)OR^{23}; SC$_1$-C_6alkyl(O)=NH; each of which R^{48} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)$_2$, -Si$(CH_3)_3$, -COOH, -CONH2, -P(0)$(OH)_2$, Ci-Cealkyl, -Co-C_4alkyl(C_3-C_7cycloalkyl), Ci-Cealkoxy, -Co-C_4alkyl(mono- and di-Ci-C_4alkylNR^9R^{10}), Ci-C_6alkylester, Ci-C_4alkylamino, Ci-C_4hydroxylalkyl, Ci-C_2haloalkyl, Ci-C_2haloalkoxy, -OC(0)R^9, -NR^9C(0)R^{10}, -C(0)NR^9R^{10}, -OC(0)NR^9R^{10}, -NR^9C(0)OR^{10}, Ci-C_2haloalkyl, and Ci-C_2haloalkoxy;

R^{48a} is R^{48}, S(0)=NR^{21}, SFs, or JC(R^9)=NR^{21} and SO2OR^{21};

R^{49} is halo, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl wherein each group can be optionally substituted or two R^{49} groups can be taken together to form a double bond that can be optionally substituted;

R^{50} is hydroxy or Ci-C_6alkyoxy;

R^{51} is CH_3, CH2F, CHF2 or CF_3;

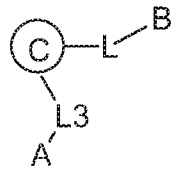
R^{52} is independently selected from halo, hydrogen, or optionally substituted Cl-C $_6$alkyl;

R^{53} is cyano, nitro, hydroxyl or Ci-C_6alkoxy;

R^{54} is hydrogen, Ci-C6alkyl, C2-C_6alkenyl, C2-C_6alkynyl, Ci-C_6alkoxy, C2-C_6alkynyl, C_2-C_6alkanoyl, Ci-C_6thioalkyl, hydroxyCi-Cealkyl, aminoCi-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), (phenyl)Co-C4alkyl-, (heterocycloalkyl)Co-C4alkyl and (heteroaryl)Co-C4alkyl- wherein the groups can be optionally substituted;

J is independently chosen at each occurrence from a covalent bond, Ci-C4alkylene, -OCi-C4alkylene, C2-C4alkenylene, and C2-C4alkynylene.

2. A compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein

A is selected from Al, A1' and A2;

B is selected from Bl, Bl', B2, B3, and B4;

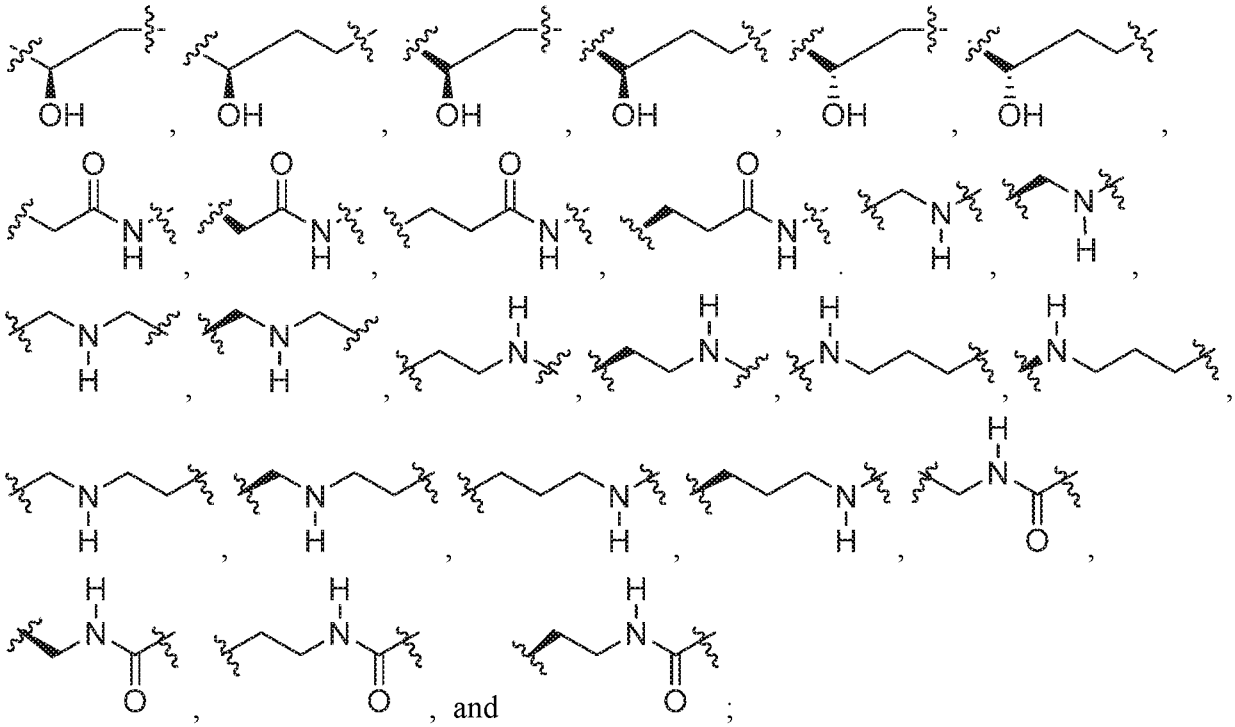
C is selected from CI, CI', C2, C3, and C4;

L is selected from LI, LI', L2, and L2';

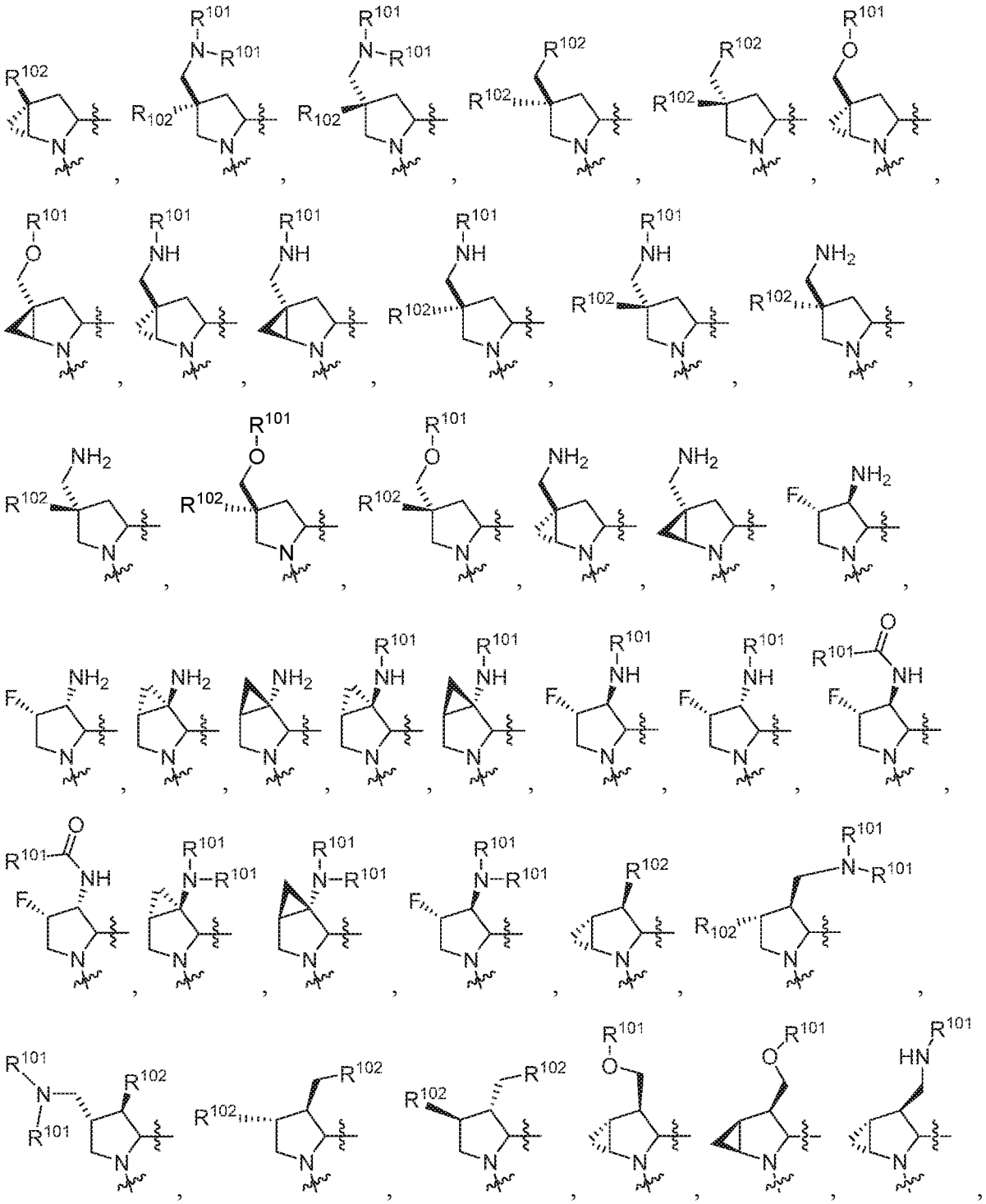
L3 is selected from L4 and L5;

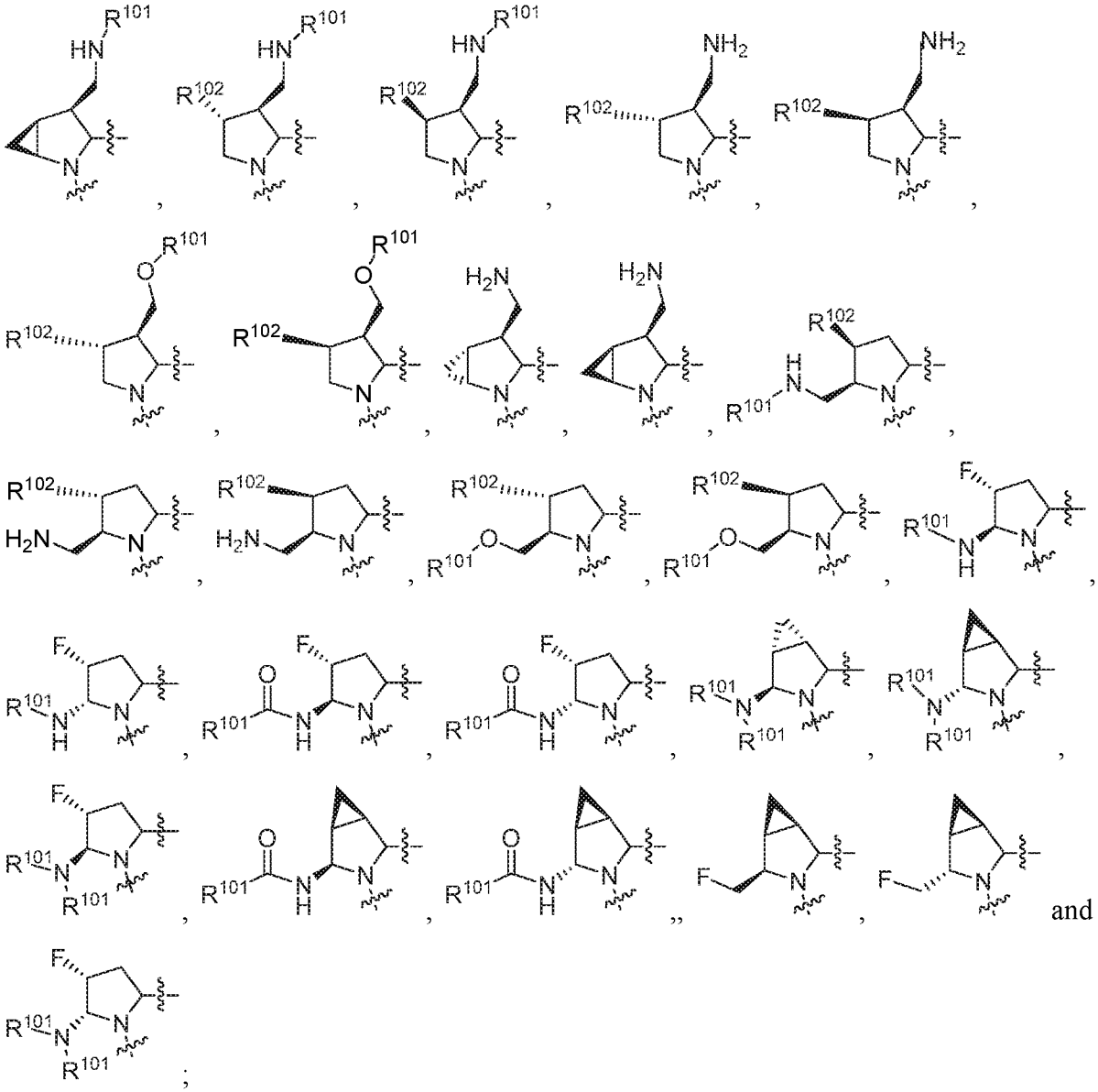
at least one of A, B, C, L, or L3 is selected from A2, B3, C3, (L2 or L2') or L5, and either C is C4 or L is L2';

L2' is selected from:



C4 is selected from





and

;

R^{101} is C1-C4 alkyl;

R^{102} is C1-C4 alkyl, Br, CI or F; and wherein

Al, Al', A2, Bl, Bl', B2, B3, B4, CI, CI', C2, C3, LI, LI', L2, L4, and L5 are as defined in claim 1.

3. A method for the treatment of a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, comprising administering an effective amount of a compound selected from claim 1 or claim 2.

4. A method for the treatment of a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound selected from claim 1 or claim 2.

5. A compound selected from claim 1 or claim 2 for use to treat of a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy.

6. A compound selected from claim 1 or claim 2 for use to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease.

7. Use of a compound of claim 1 or claim 2 in the manufacture of a medicament to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy.

8. Use of a compound of claim 1 or claim 2 in the manufacture of a medicament to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease.

9. A compound of claim 1 or claim 2 for use to treat of a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver

inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy.

10. A compound of claim 1 or claim 2 for use to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease.

11. The method of claim 3 or 4, wherein the disorder is NASH, and the host is a human.

12. The method of claim 3 or 4, wherein the disorder is fatty liver, and the host is a human.

13. The method of claim 3 or 4, wherein the disorder is cirrhosis, and the host is a human.

14. The method of claim 3 or 4, wherein the disorder is liver failure, and the host is a human.

15. The method of claim 3 or 4, wherein the disorder amyotrophic lateral sclerosis, and the host is a human.

16. The method of claim 3 or 4, wherein the disorder is cytokine or inflammatory reactions in response to a pharmaceutical or biotherapeutic, or an inflammatory reaction to CAR T-cell therapy, and the host is a human.

17. The compound of claim 5 or 6, wherein the disorder is NASH, and the host is a human.

18. The compound of claim 5 or 6, wherein the disorder is fatty liver, and the host is a human.

19. The compound of claim 5 or 6, wherein the disorder is cirrhosis, and the host is a human.

20. The compound of claim 5 or 6, wherein the disorder is liver failure, and the host is a human.

21. The compound of claim 5 or 6, wherein the disorder amyotrophic lateral sclerosis, and the host is a human.

22. The compound of claim 5 or 6, wherein the disorder is cytokine or inflammatory reactions in response to a pharmaceutical or biotherapeutic, or an inflammatory reaction to CAR T-cell therapy, and the host is a human.

23. The use of claim 7 or 8, wherein the disorder is NASH, and the host is a human.

24. The use of claim 7 or 8, wherein the disorder is fatty liver, and the host is a human.

25. The use of claim 7 or 8, wherein the disorder is cirrhosis, and the host is a human.

26. The compound of claim 7 or 8, wherein the disorder is liver failure, and the host is a human.

27. The compound of claim 7 or 8, wherein the disorder amyotrophic lateral sclerosis, and the host is a human.

28. The compound of claim 7 or 8, wherein the disorder is cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, and the host is a human.

FIG. 1

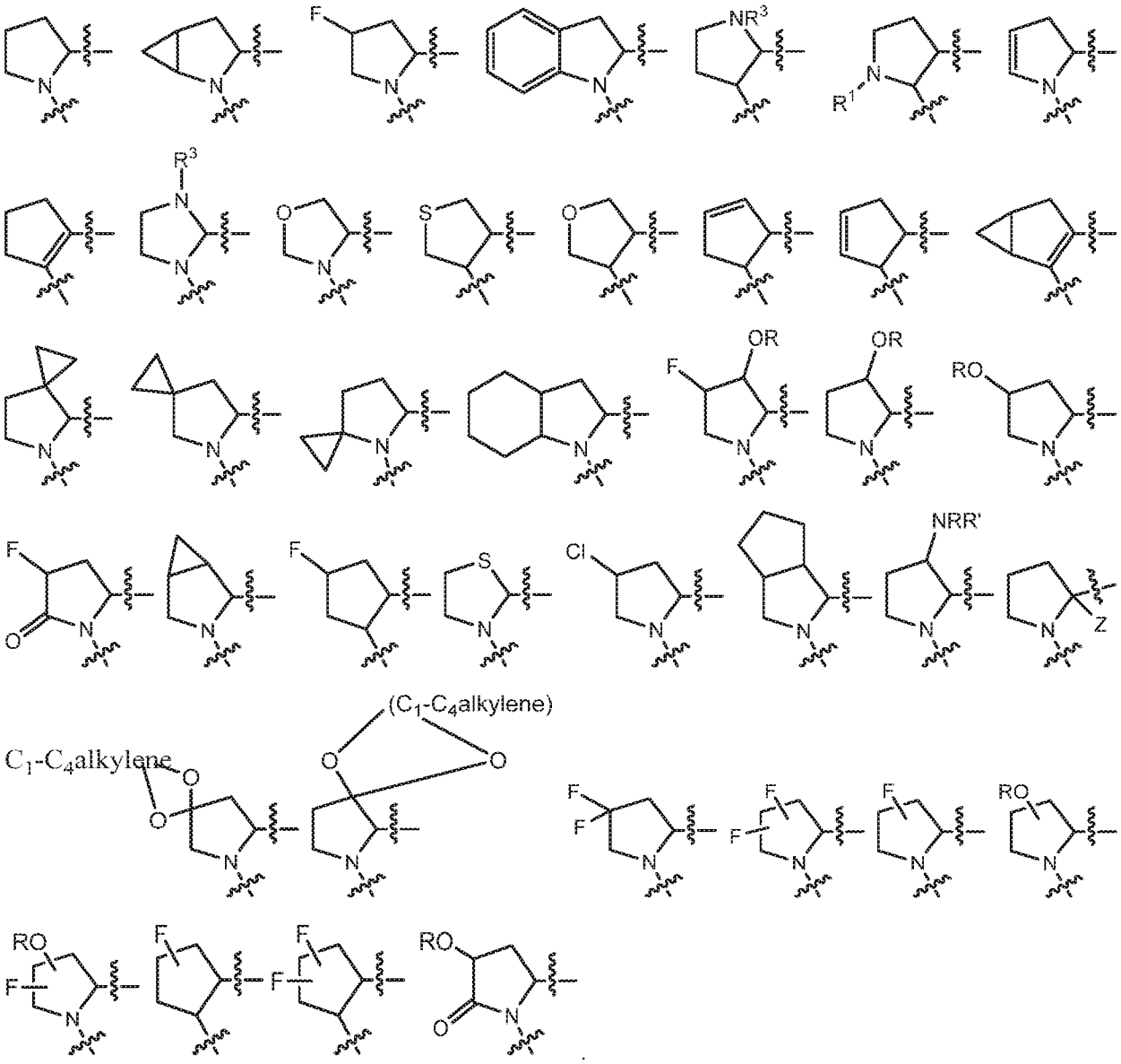

F
NR3
R1
R3
O
S
OR
OR
RO
F
O
F
S
Cl
NRR'
Z
(C1-C4alkylene)
C1-C4alkylene
O
O
O
O
F
F
F
F
F
RO
RO
F
F
F
O
N

FIG. 2A

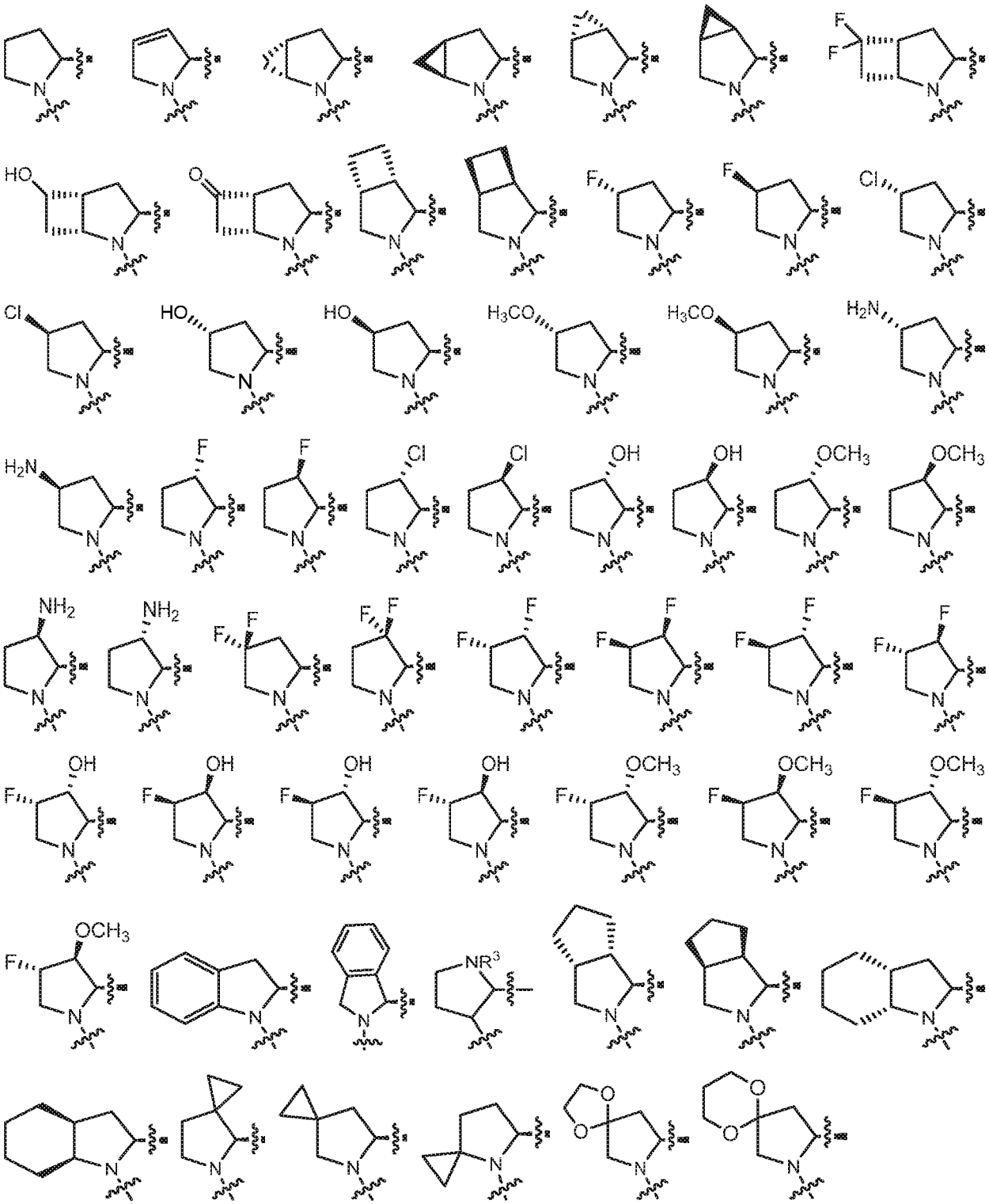

F
F
HO
O
F
F
Cl
Cl
HO
HO
H3CO
H3CO
H2N
H2N
F
F
Cl
Cl
OH
OH
OCH3
OCH3
NH2
NH2
F
F
F
F
F
F
F
F
F
F
OH
OH
OH
OH
OCH3
OCH3
OCH3
F
F
F
F
F
F
OCH3
NR3
O
O
O
O
N

FIG. 2B

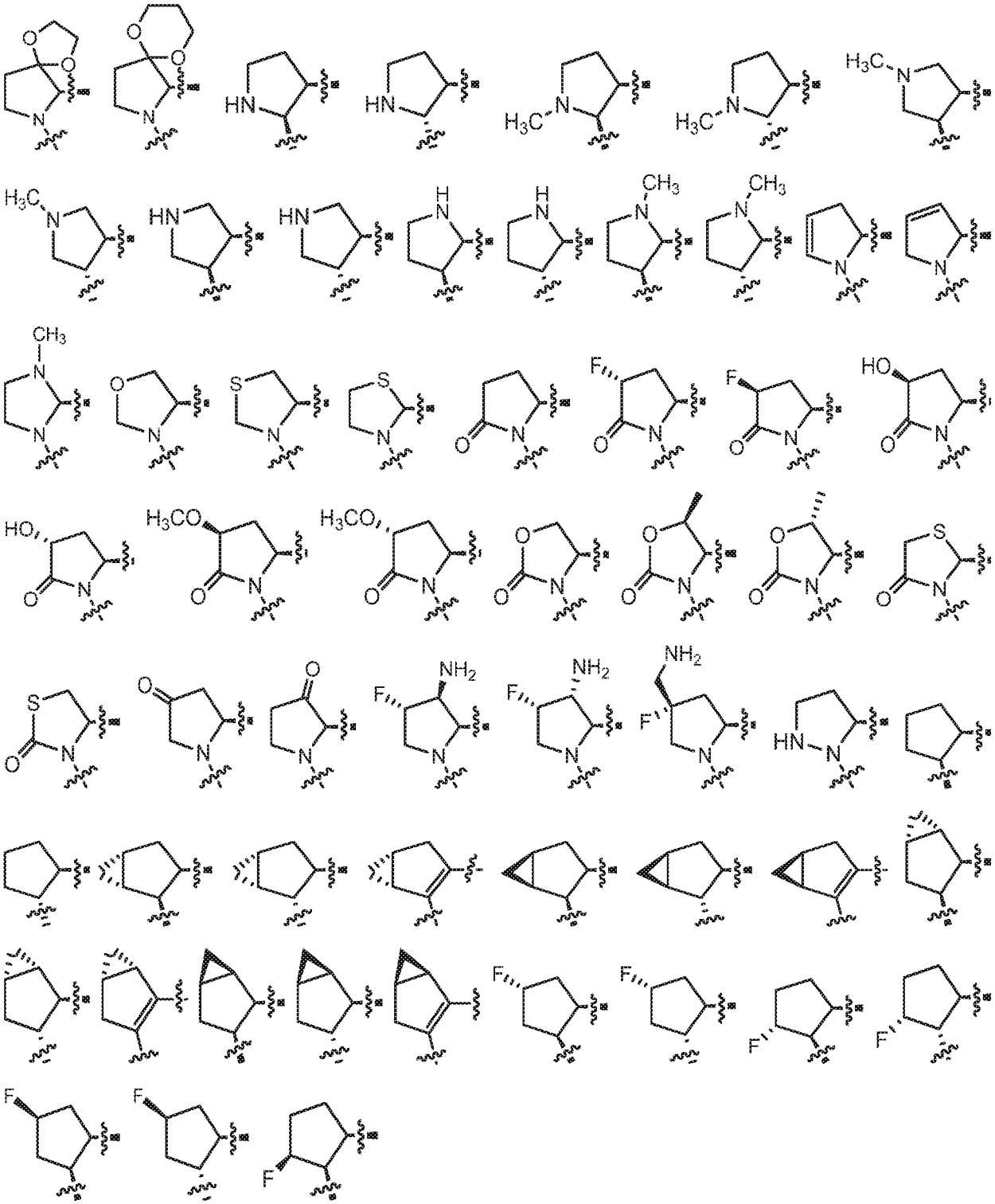


FIG. 2C

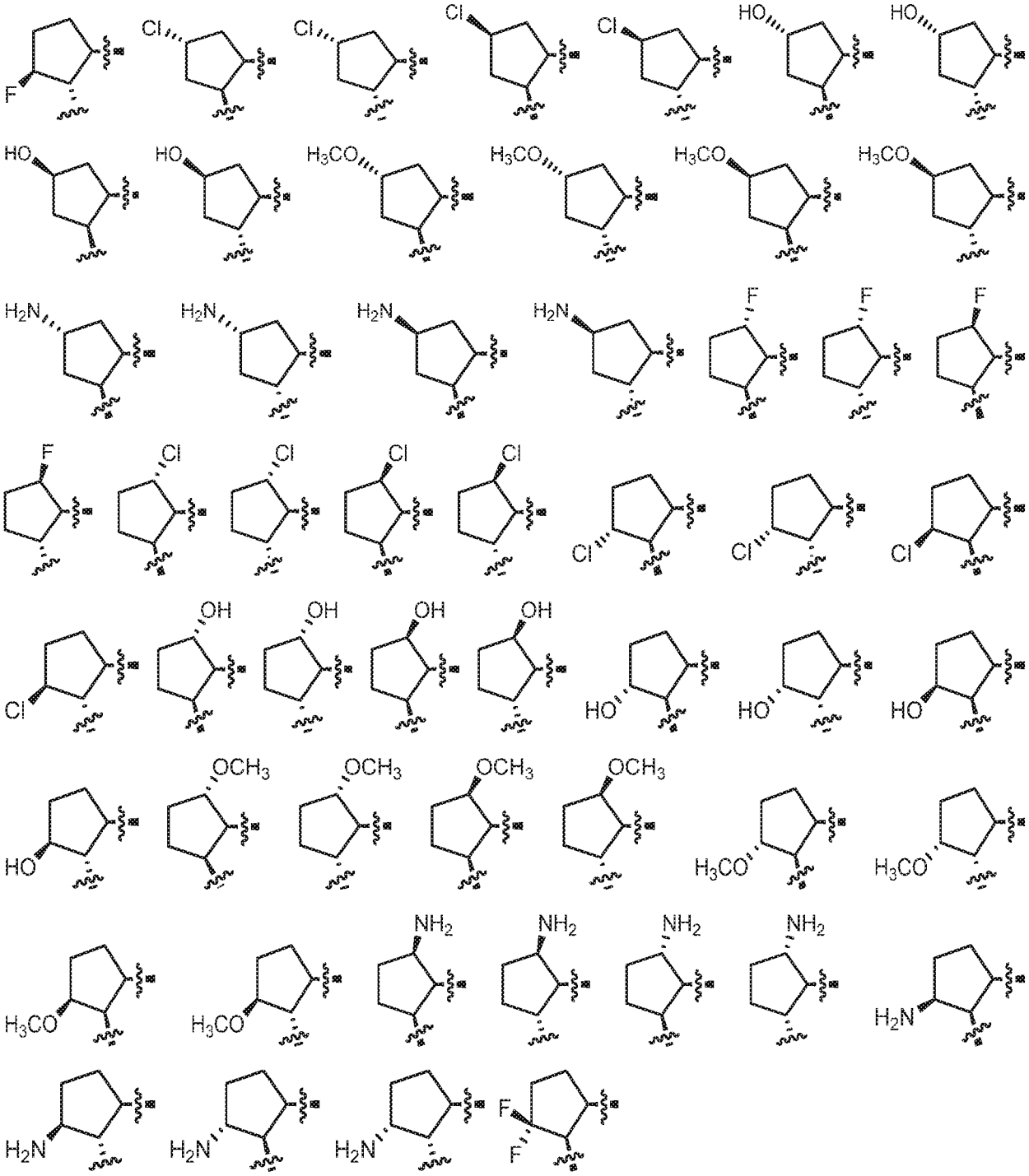

F
Cl
Cl
Cl
Cl
HO
HO
HO
HO
H3CO
H3CO
H3CO
H3CO
H2N
H2N
H2N
H2N
F
F
F
F
Cl
Cl
Cl
Cl
Cl
Cl
Cl
OH
OH
OH
OH
HO
HO
HO
OCH3
OCH3
OCH3
OCH3
H3CO
H3CO
NH2
NH2
NH2
NH2
H3CO
H3CO
H2N
H2N
H2N
H2N
F
F

FIG. 2D

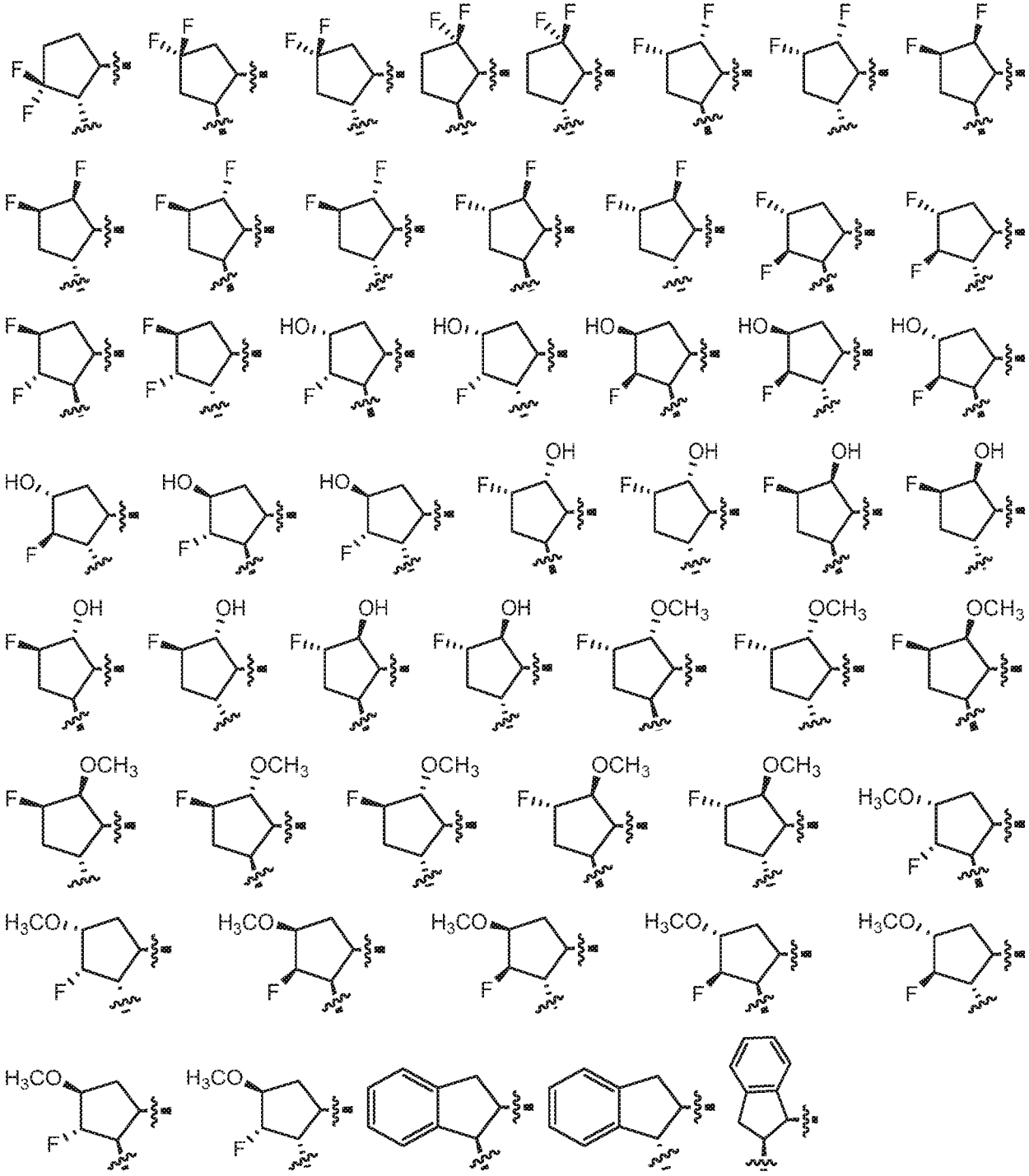


FIG. 2E

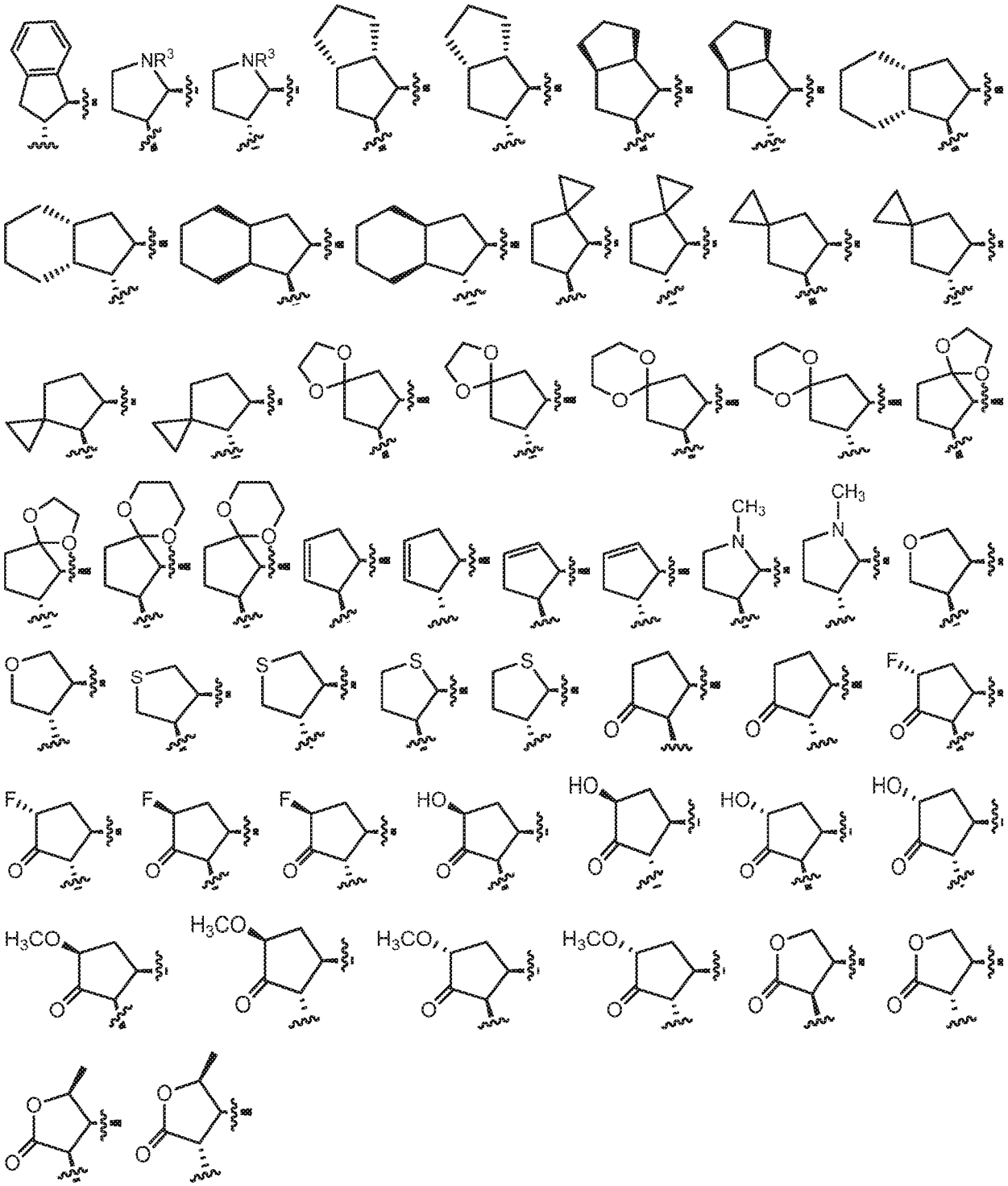


FIG. 2F

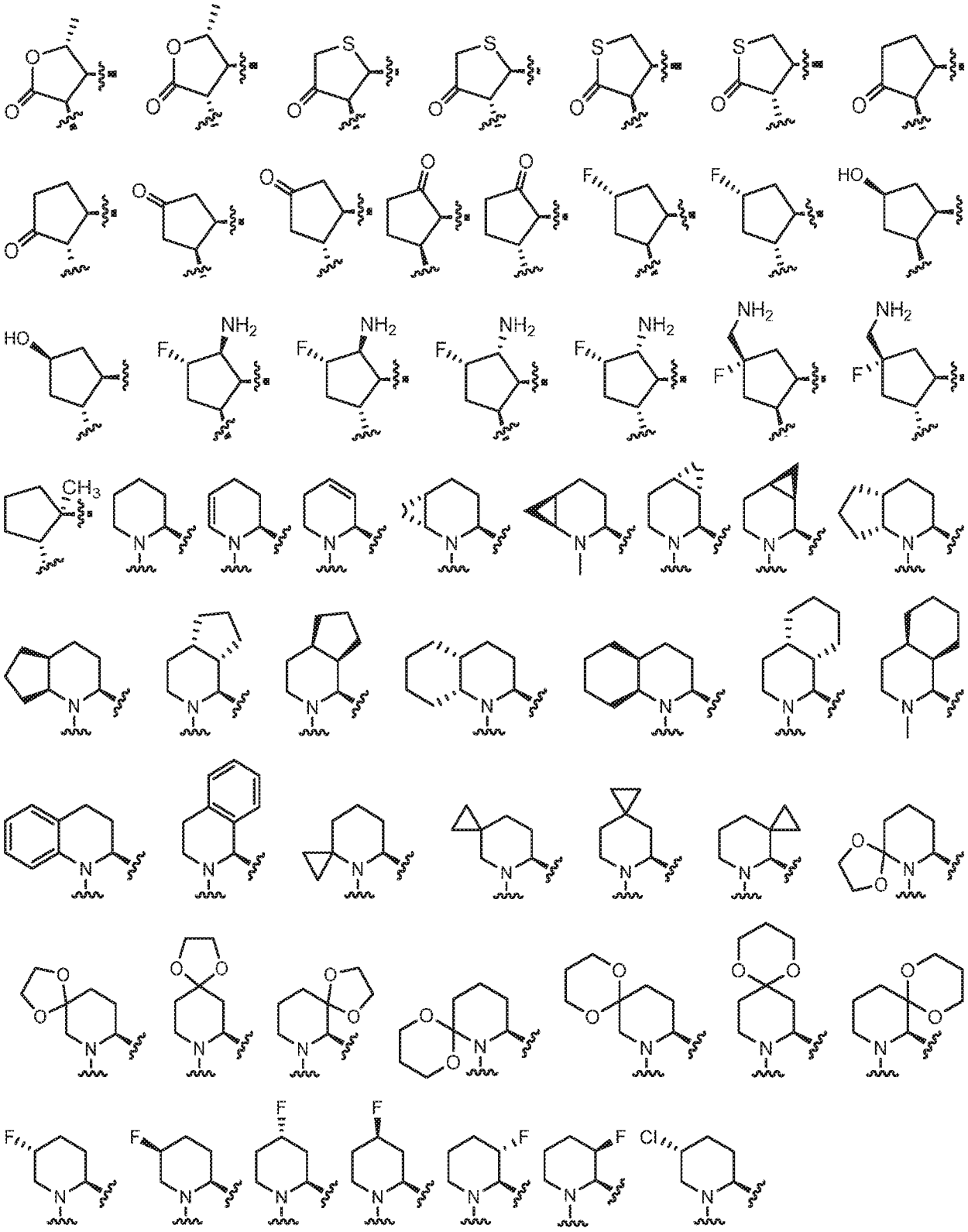


FIG. 2G

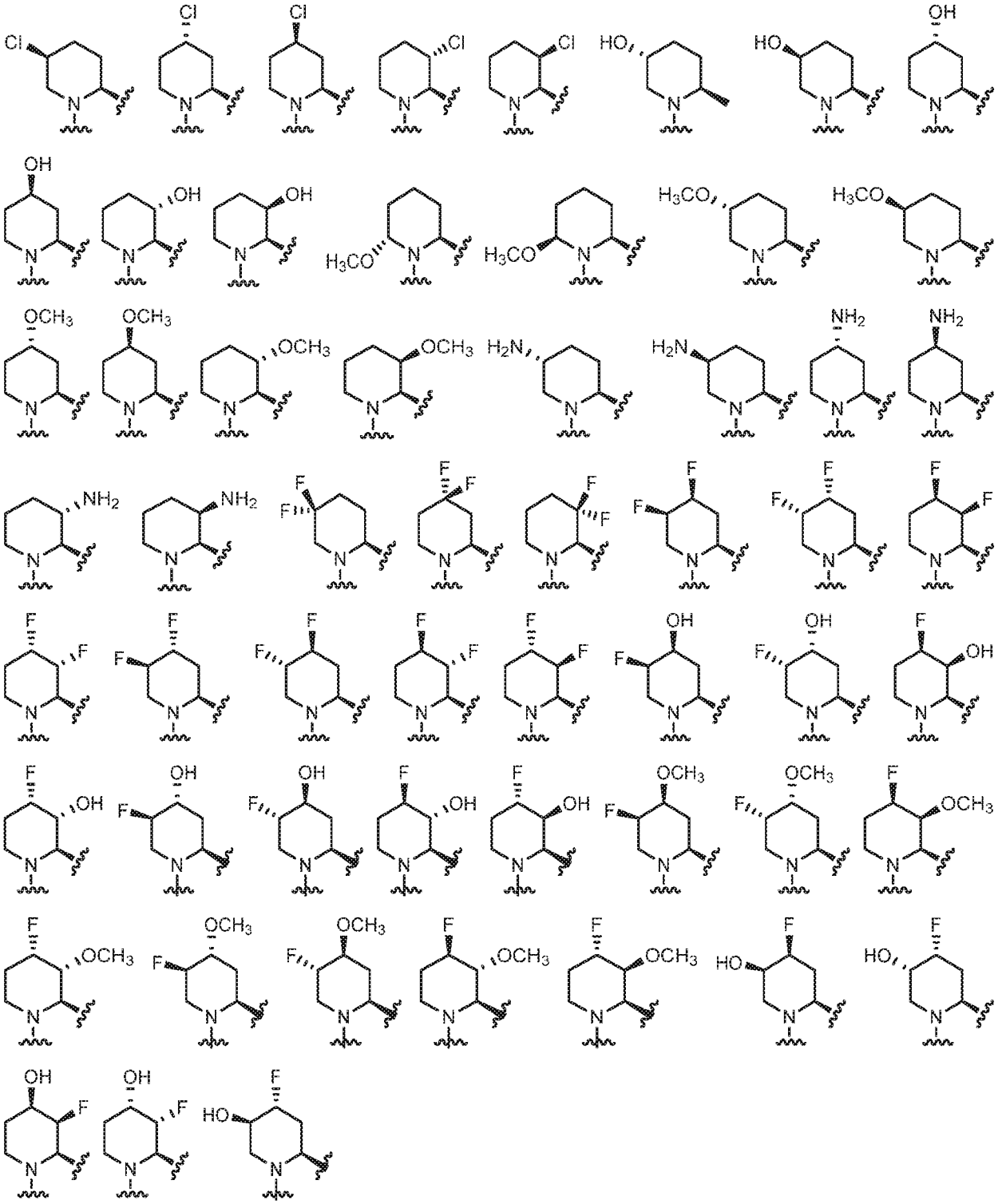


FIG. 2H

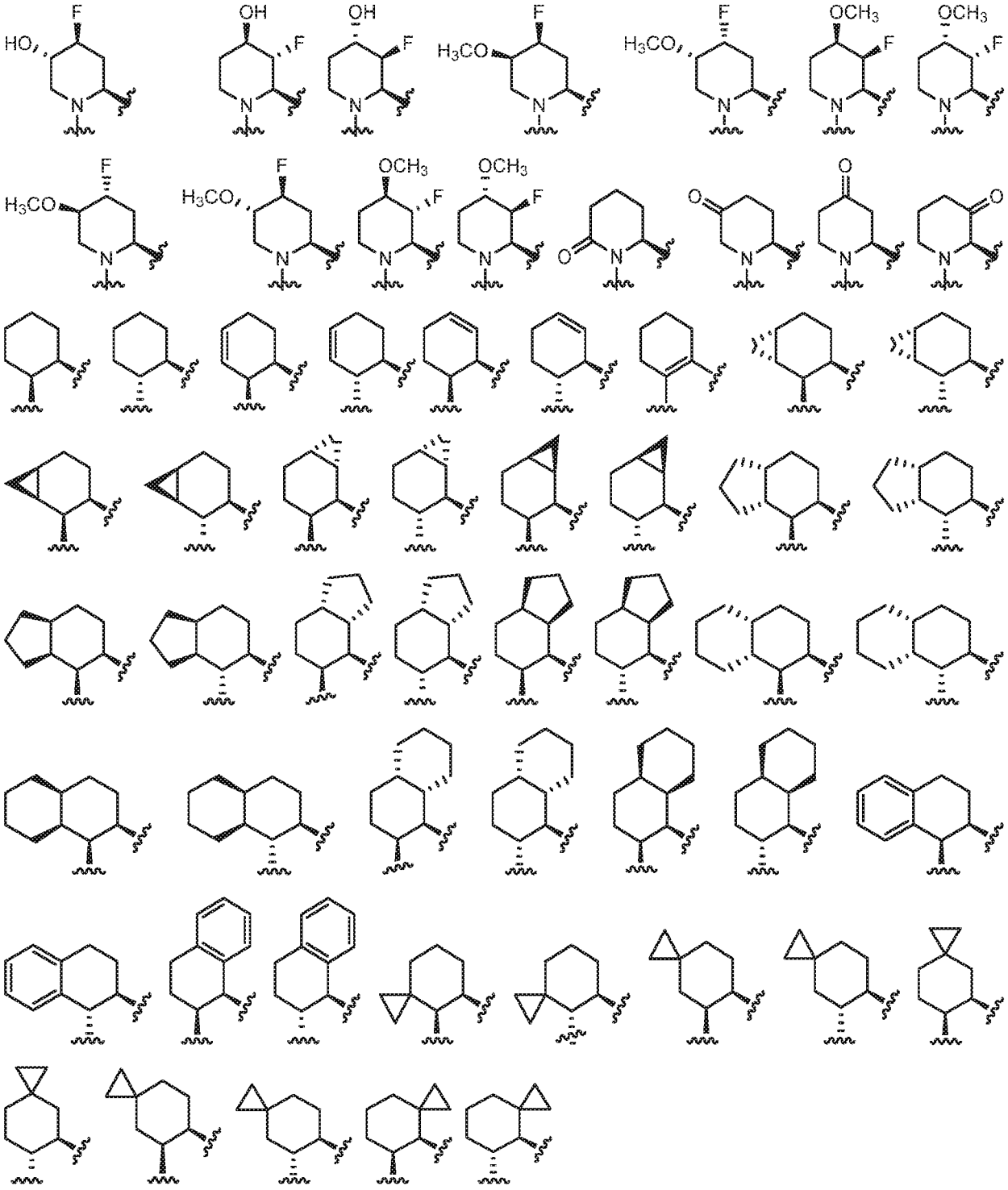


FIG. 2I

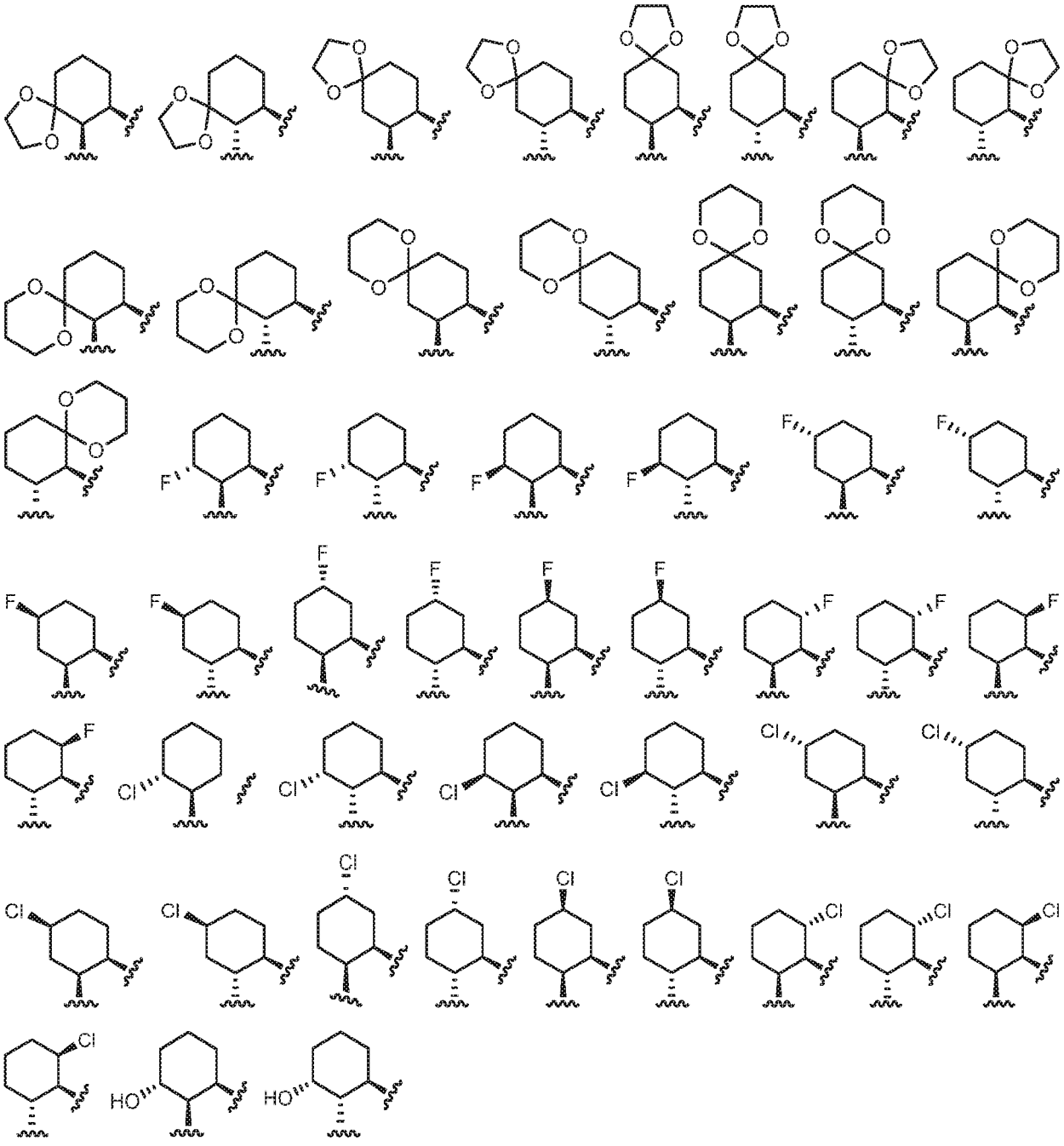


FIG. 2J

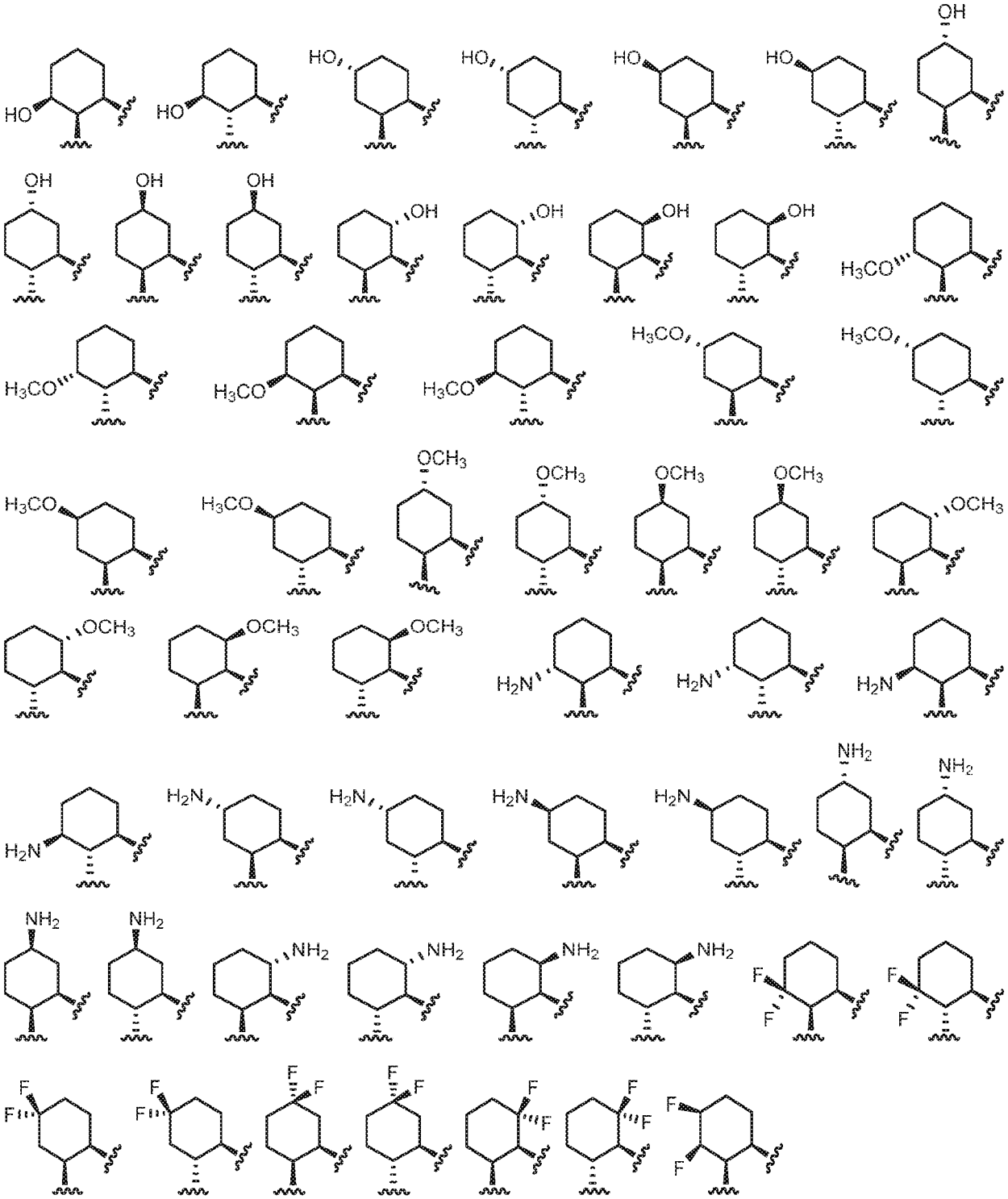


FIG. 2K

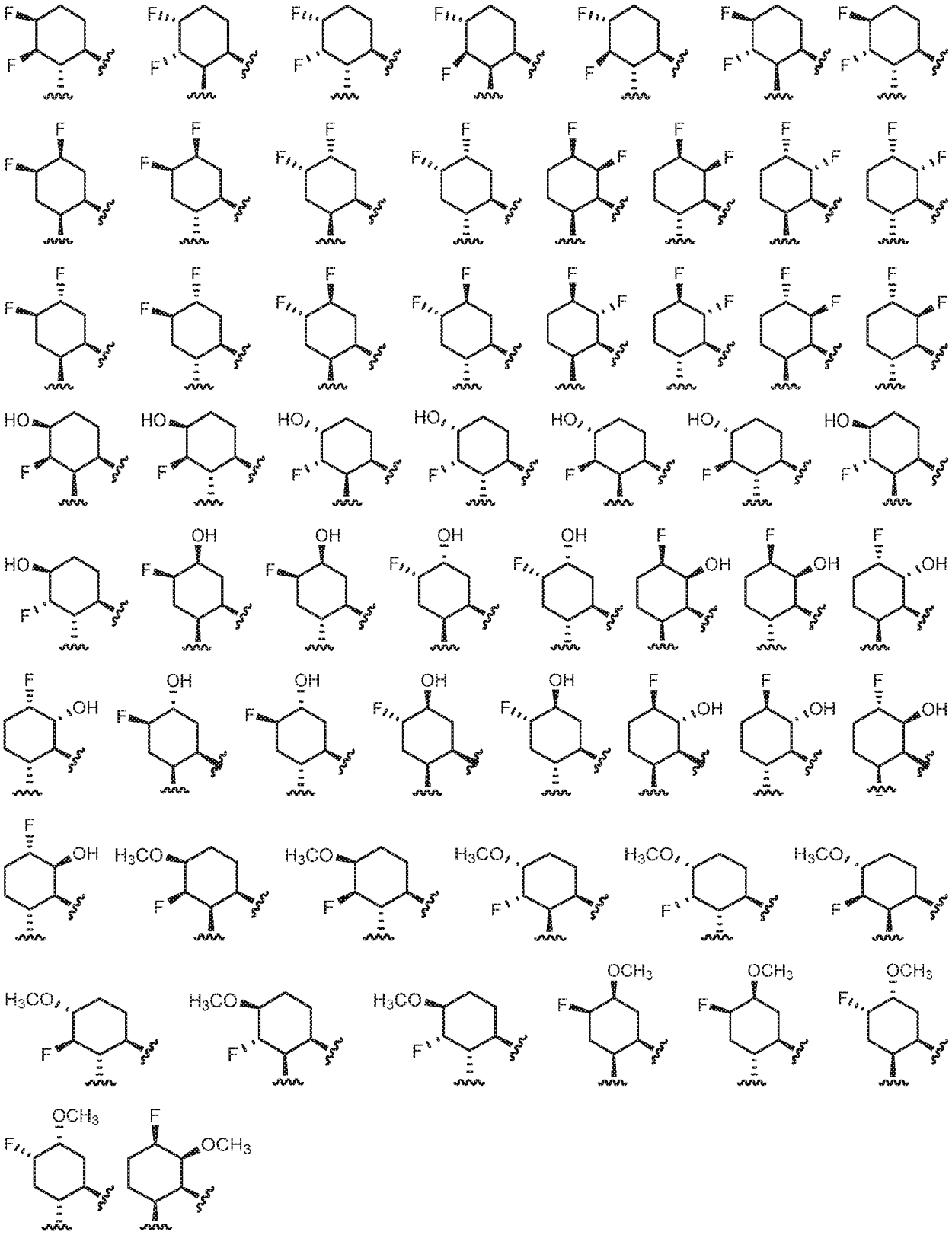


FIG. 2L

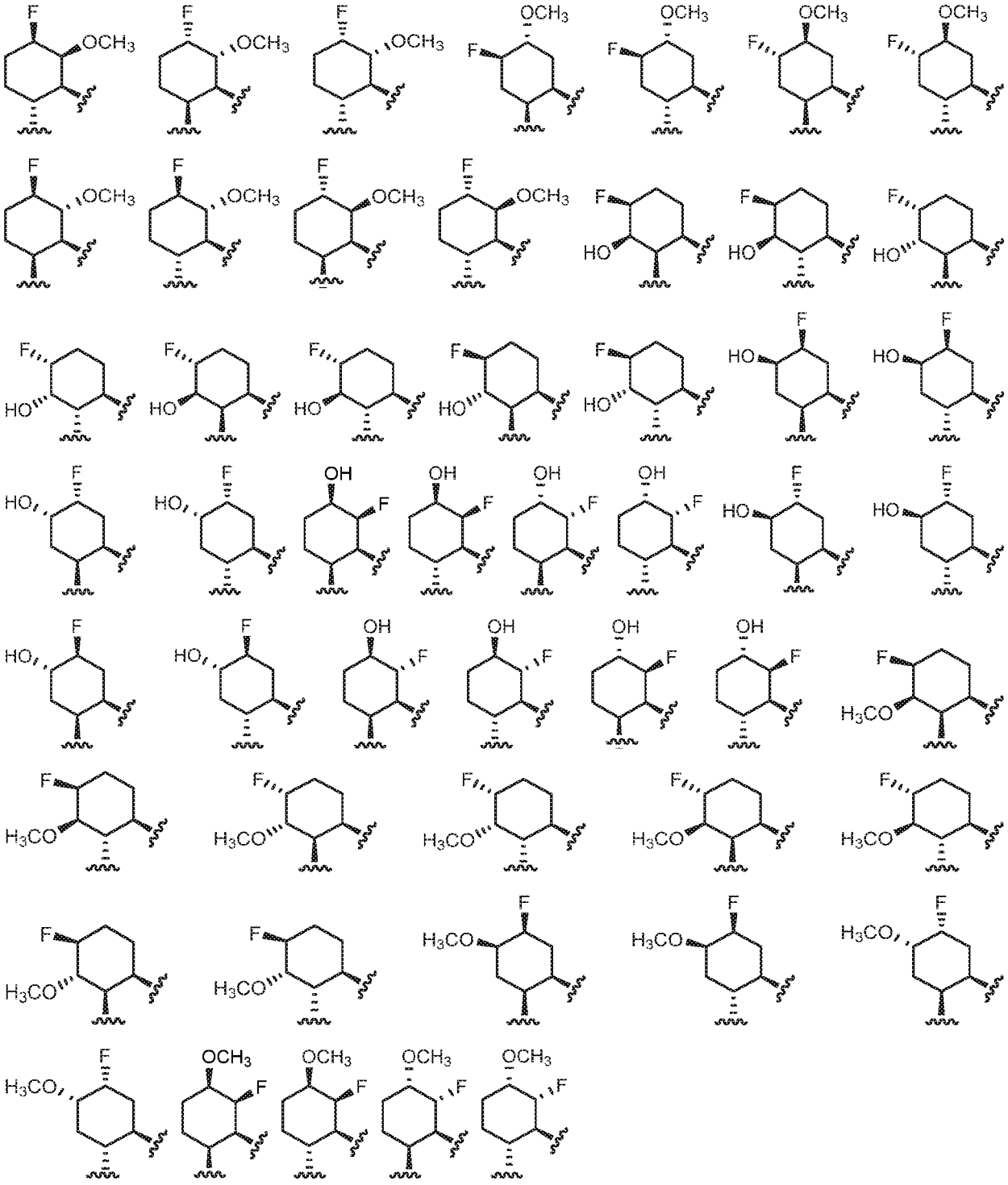


FIG. 2M

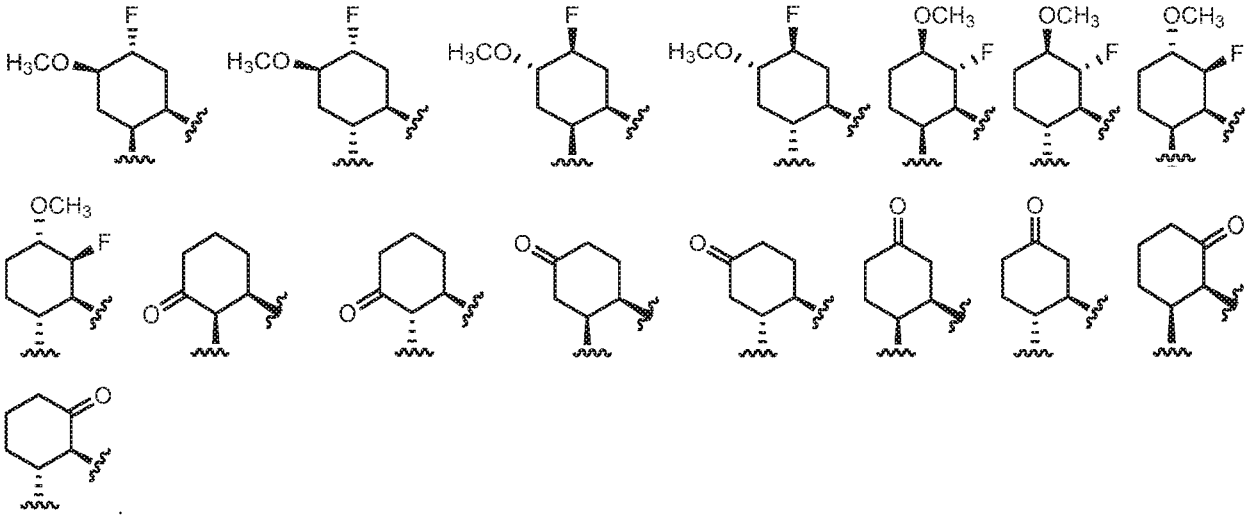


FIG. 3

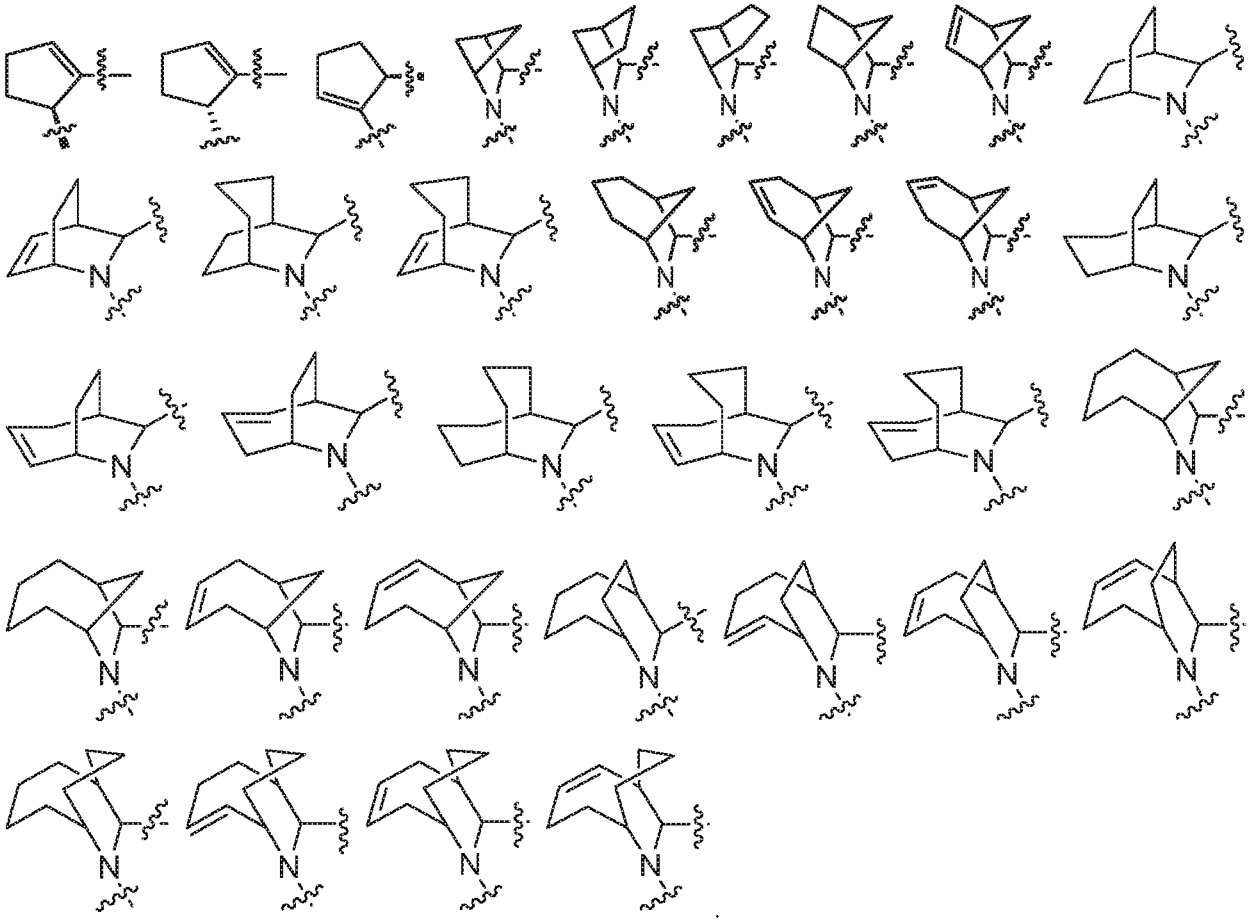


FIG. 4A

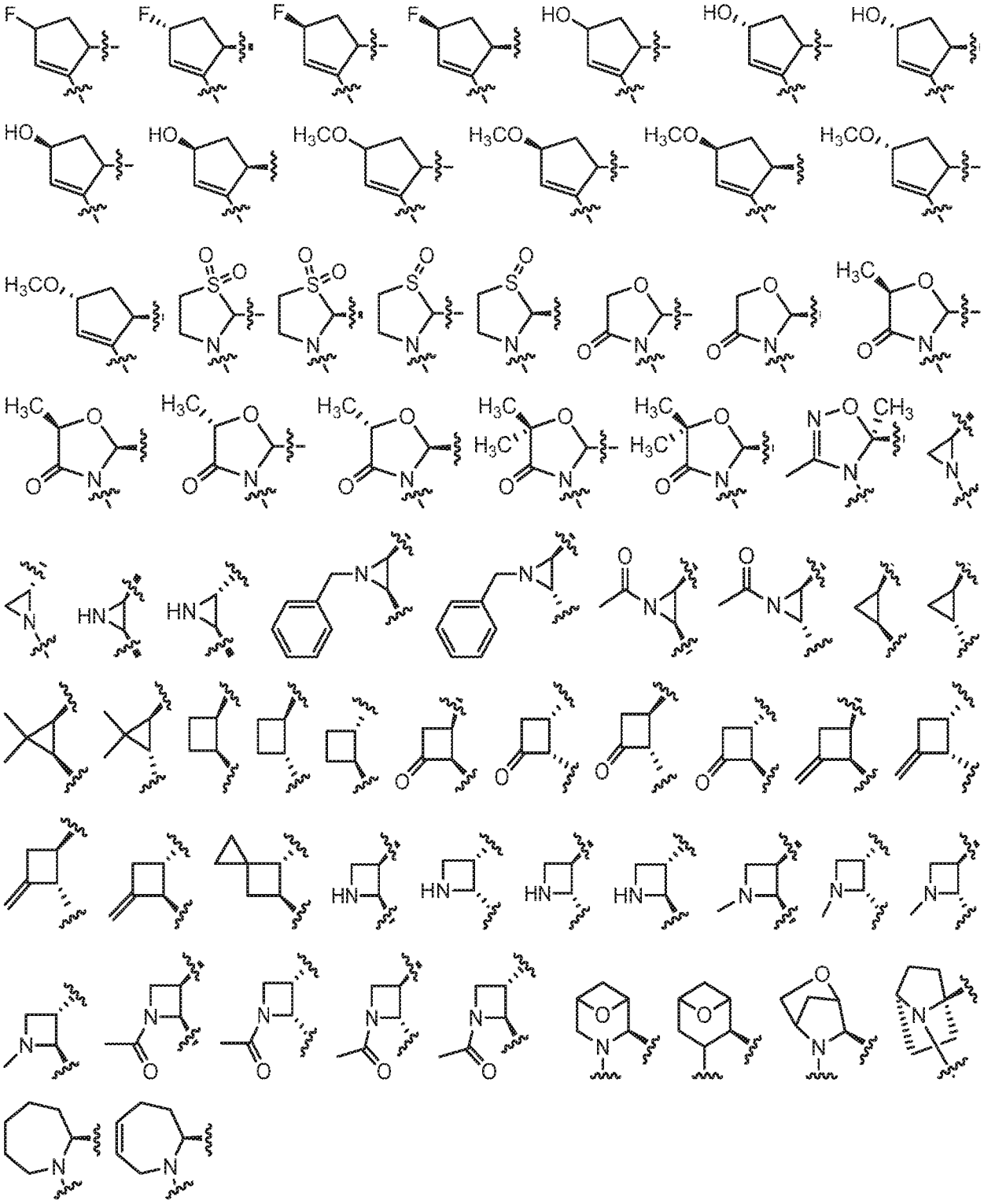


FIG. 4B

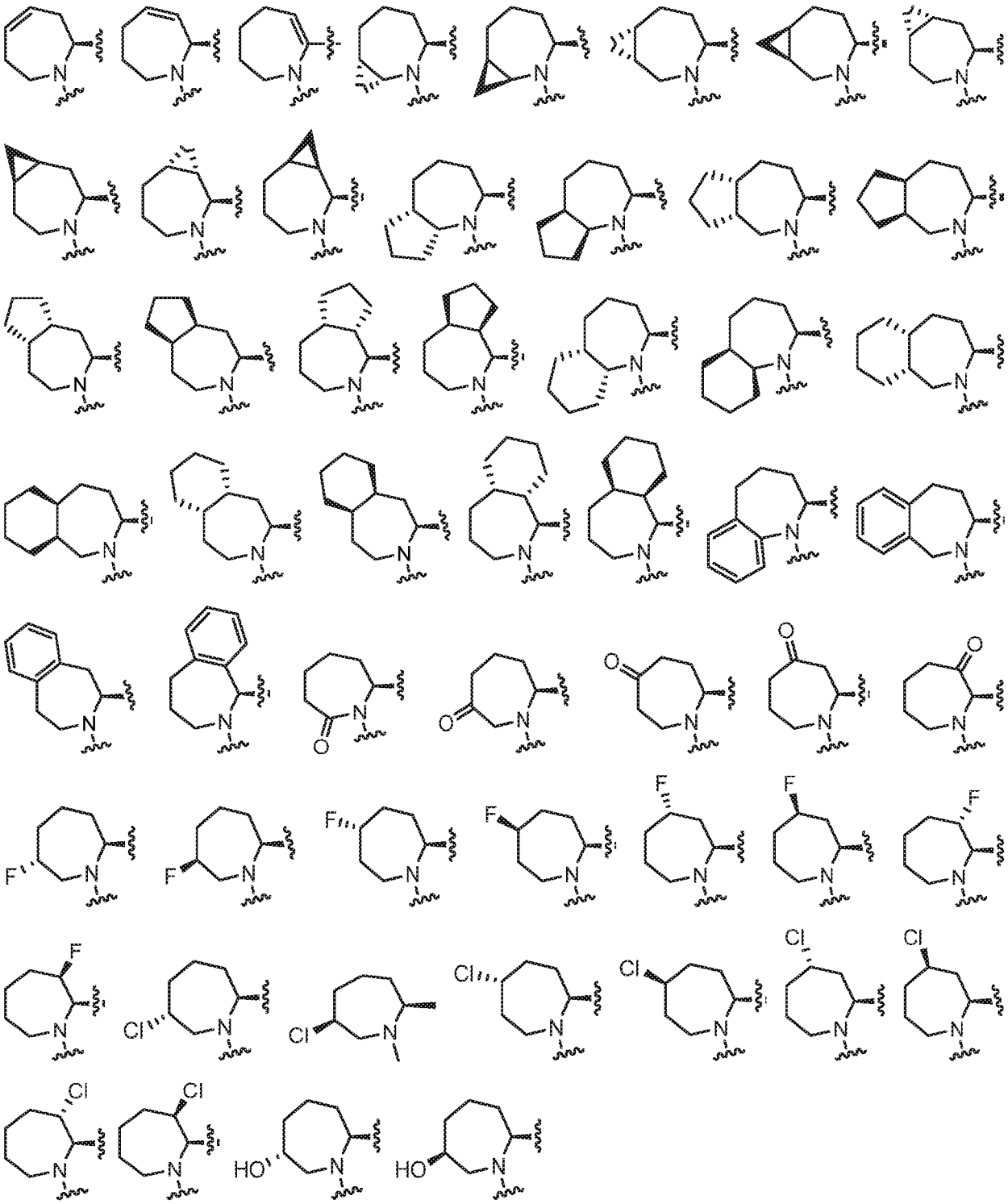


FIG. 4C

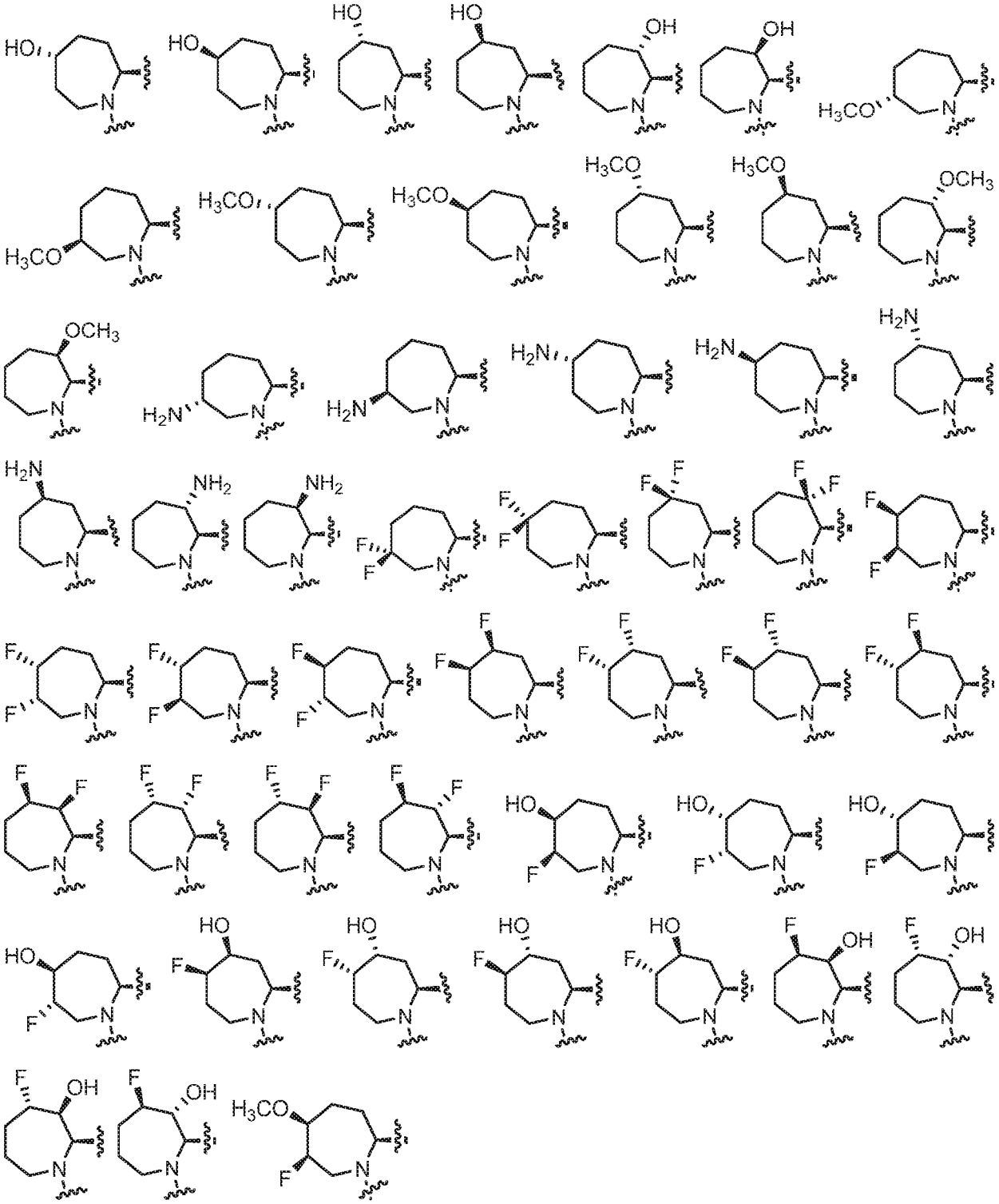


FIG. 4D

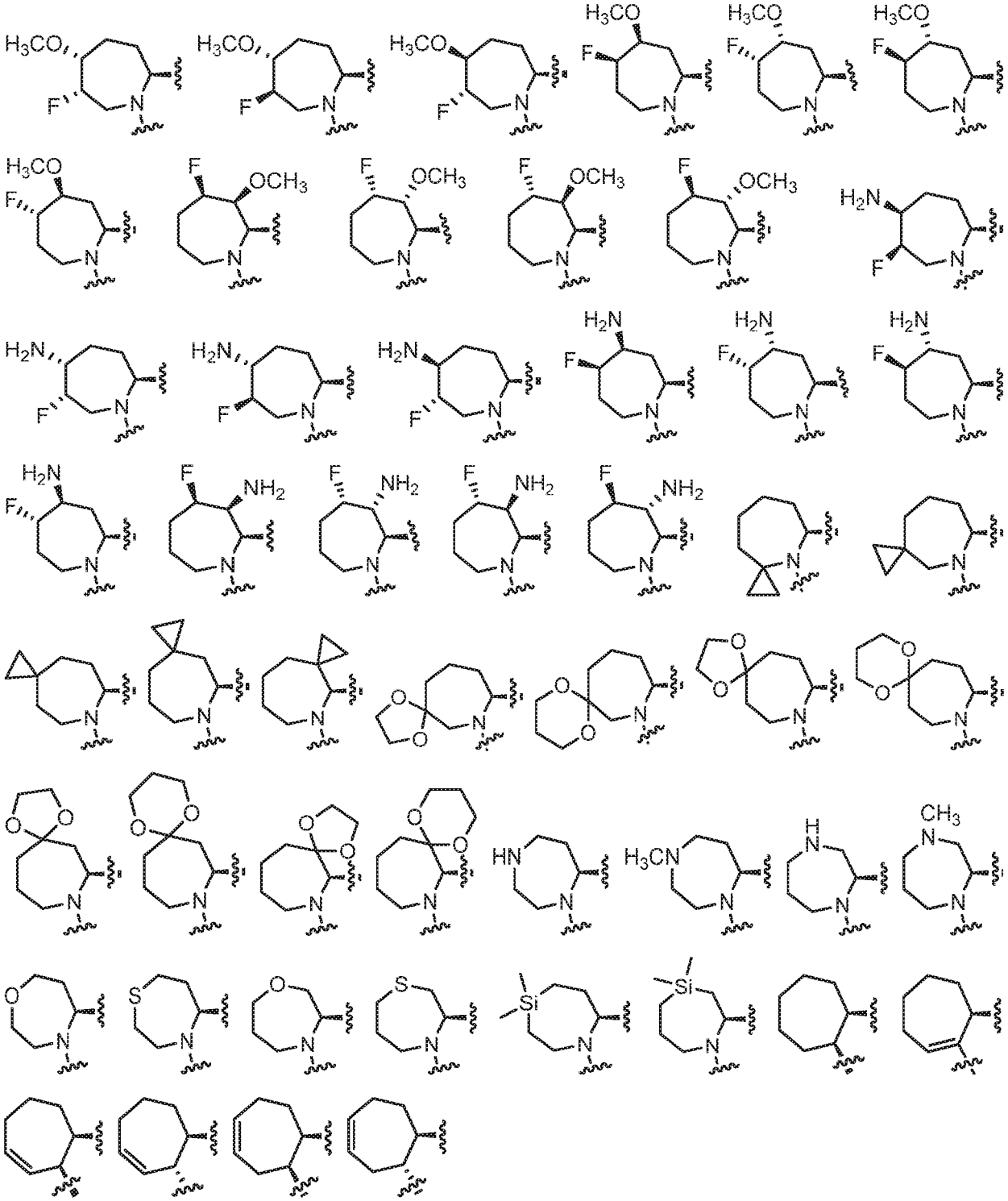


FIG. 4E

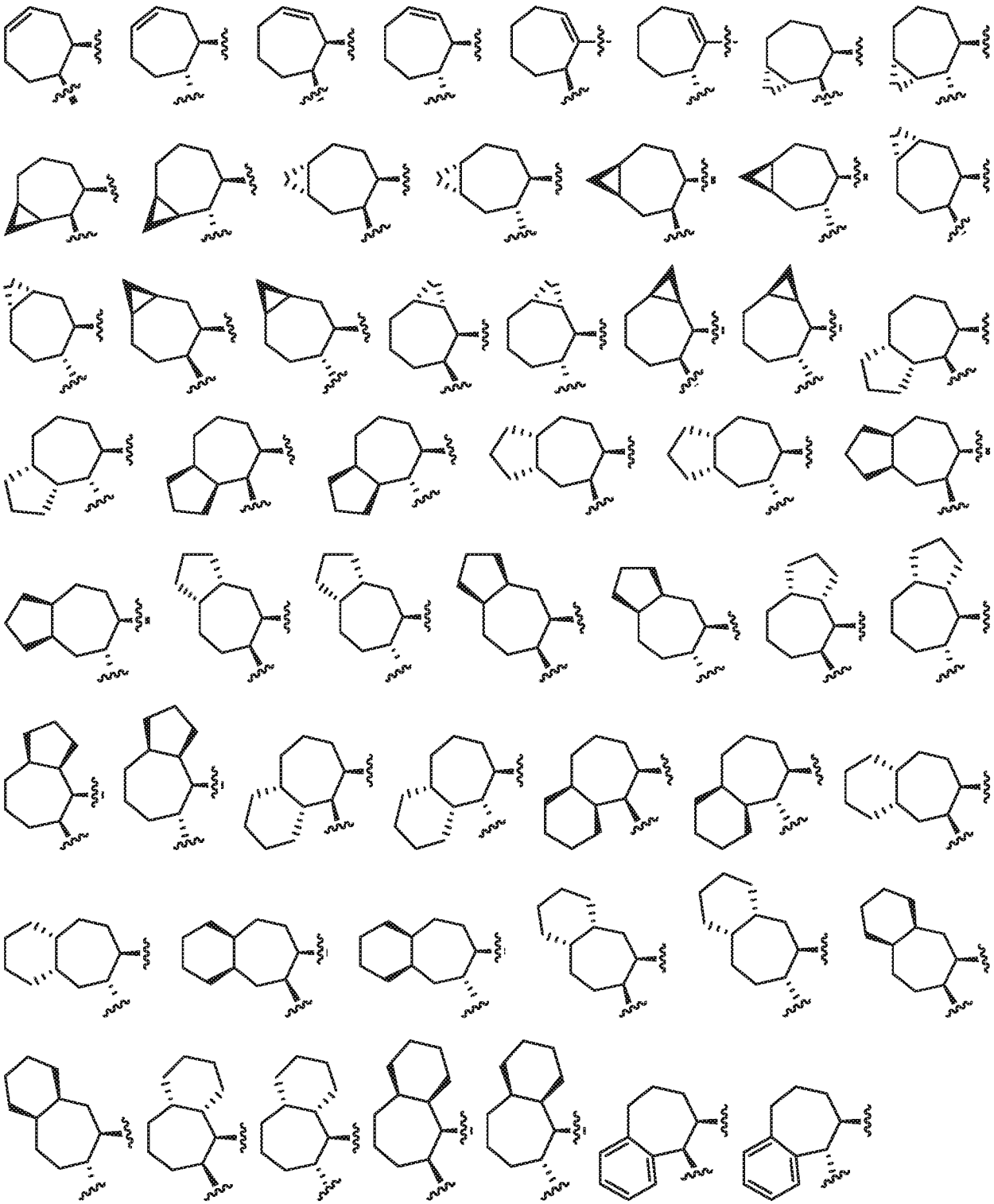


FIG. 4F

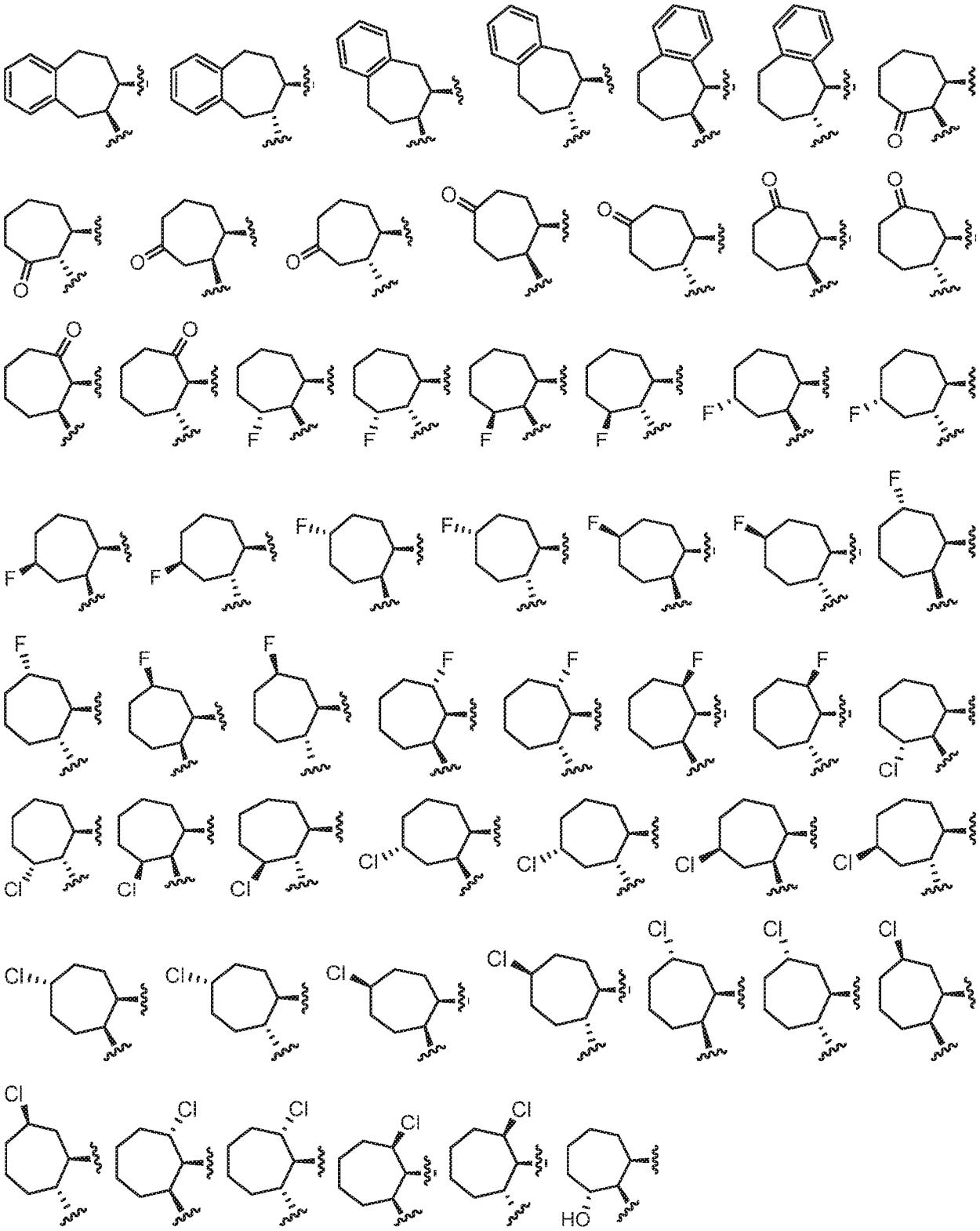
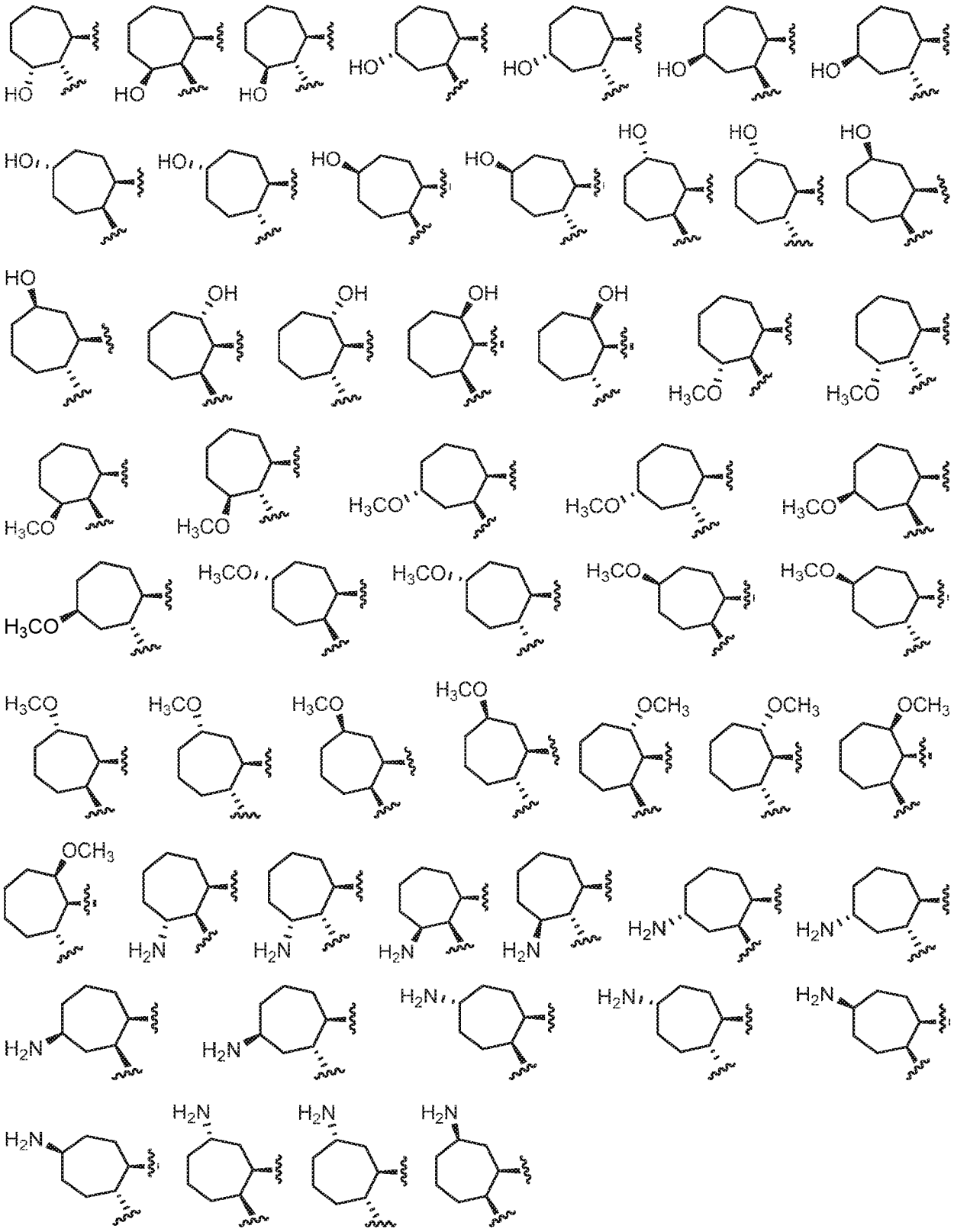


FIG. 4G


HO
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H3CO
H3CO
H3CO
OCH3
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H2N
H2N
H2N
H2N

FIG. 4H

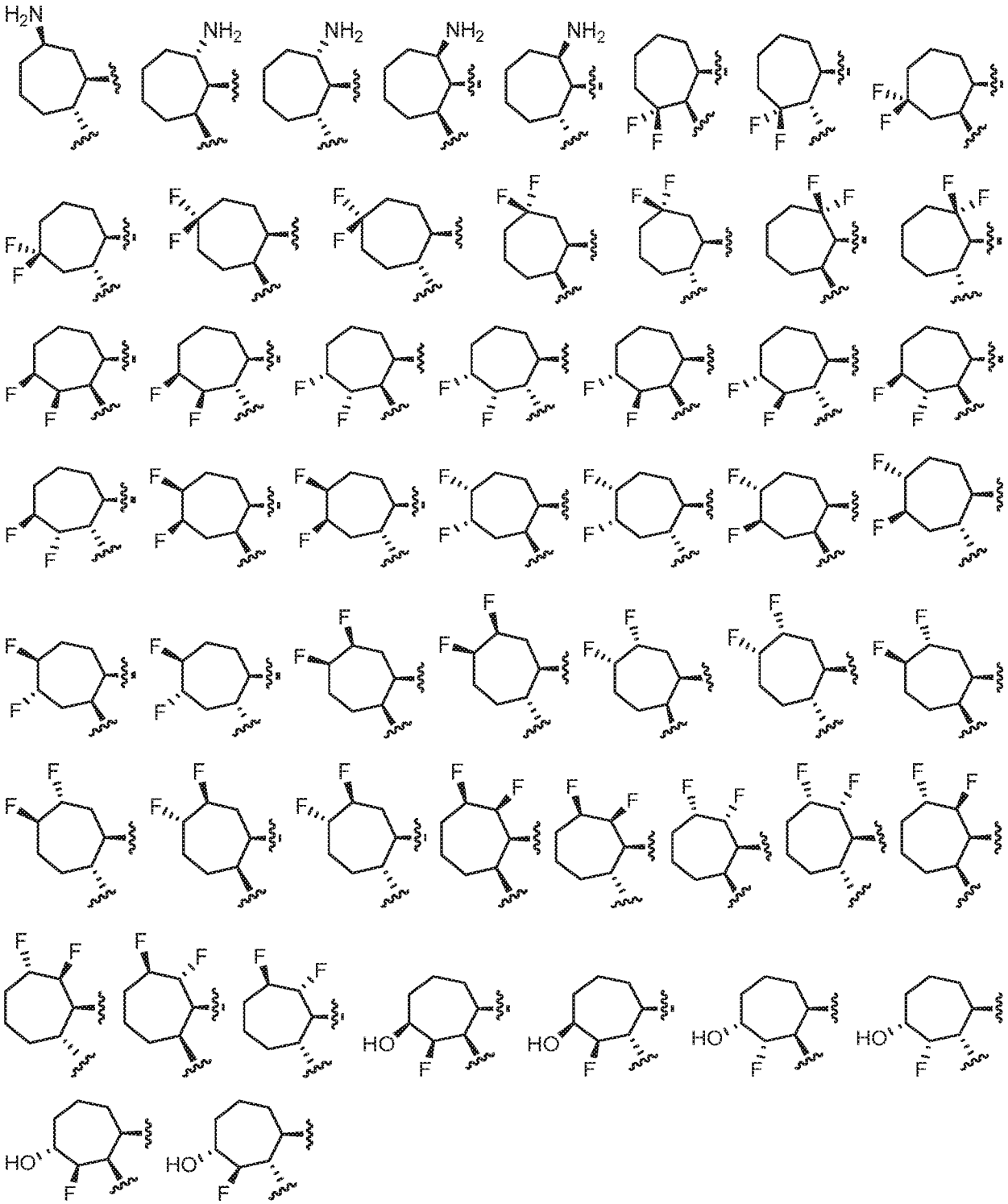


FIG. 4I

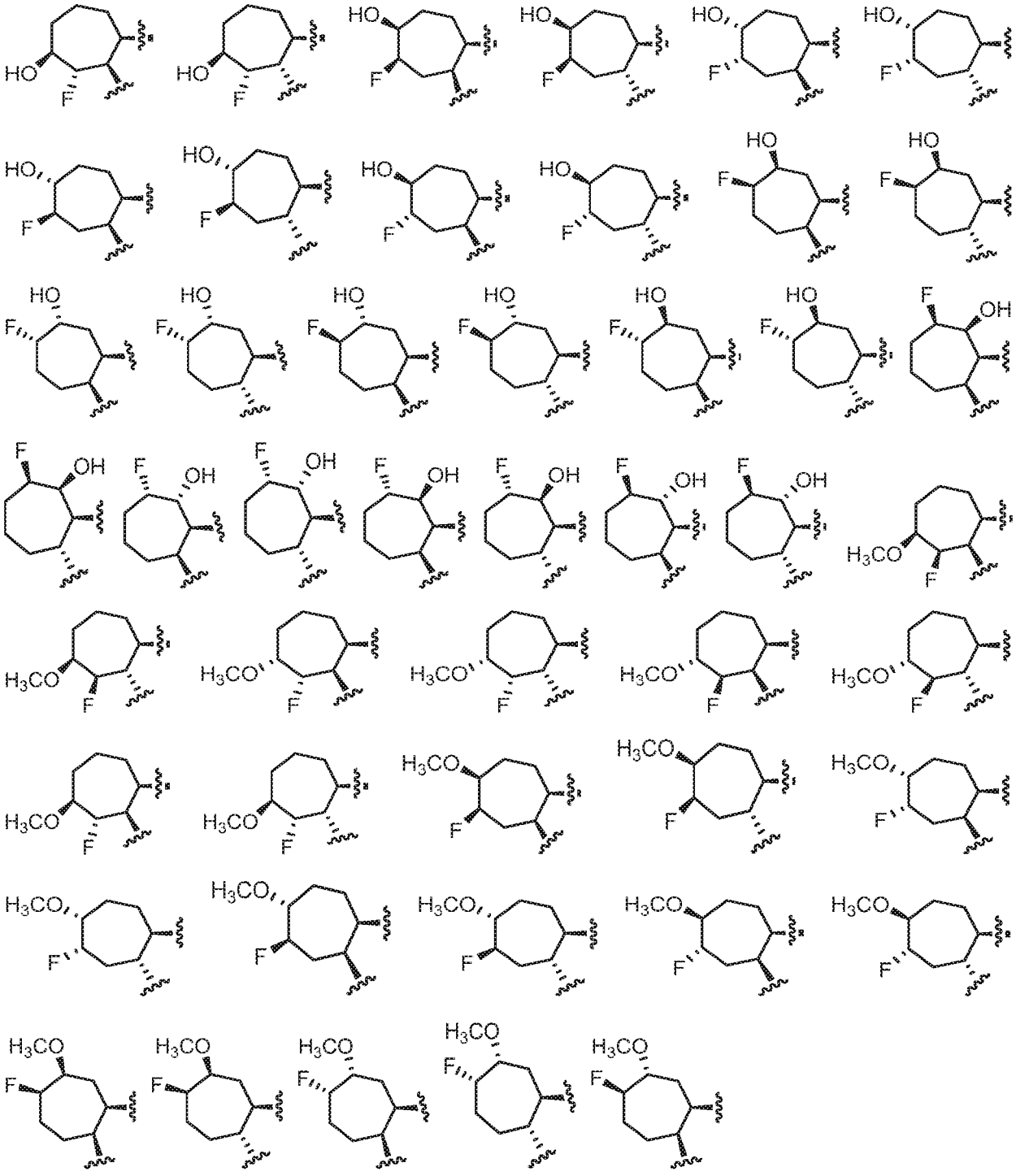


FIG. 4J

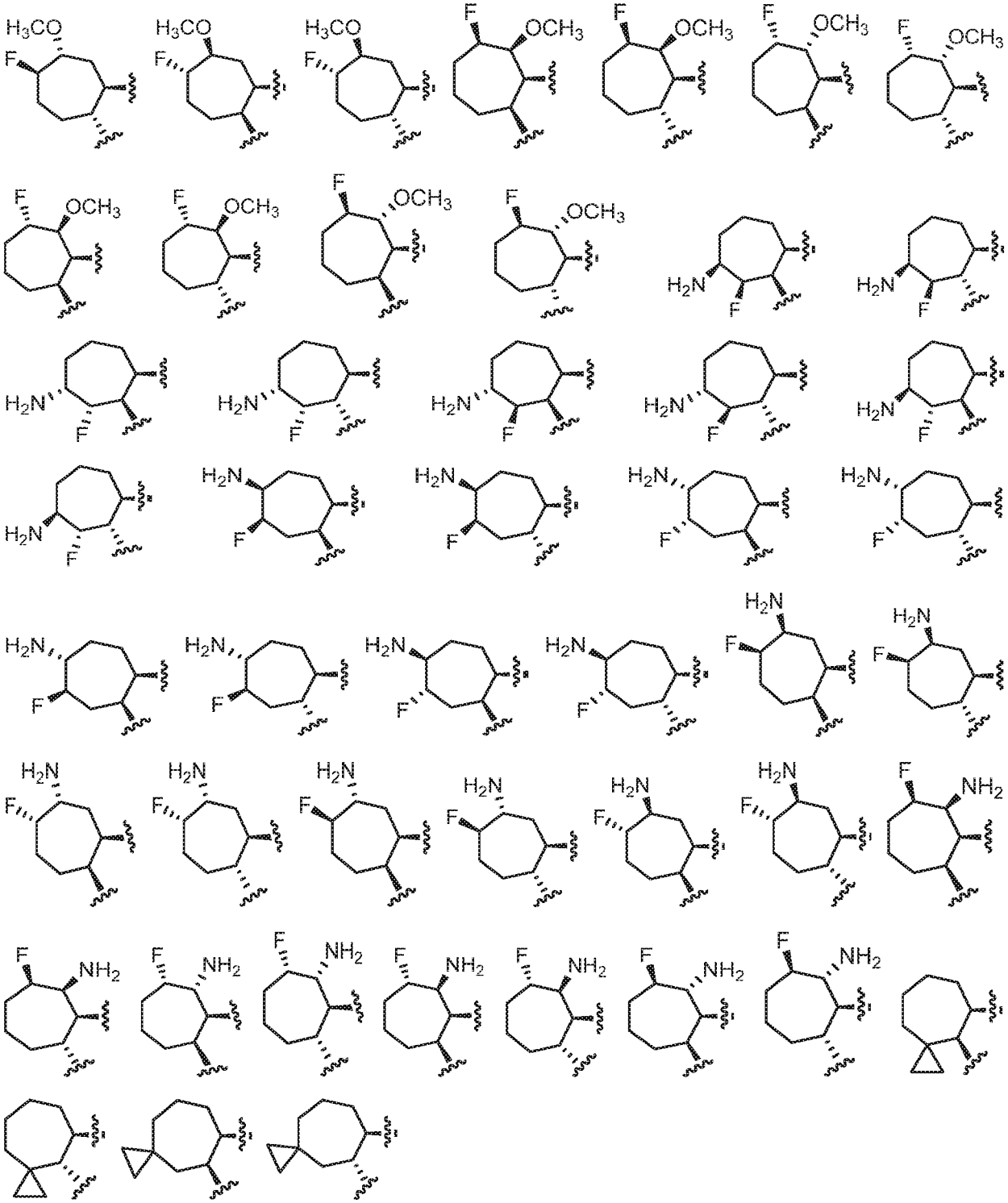


FIG. 4K

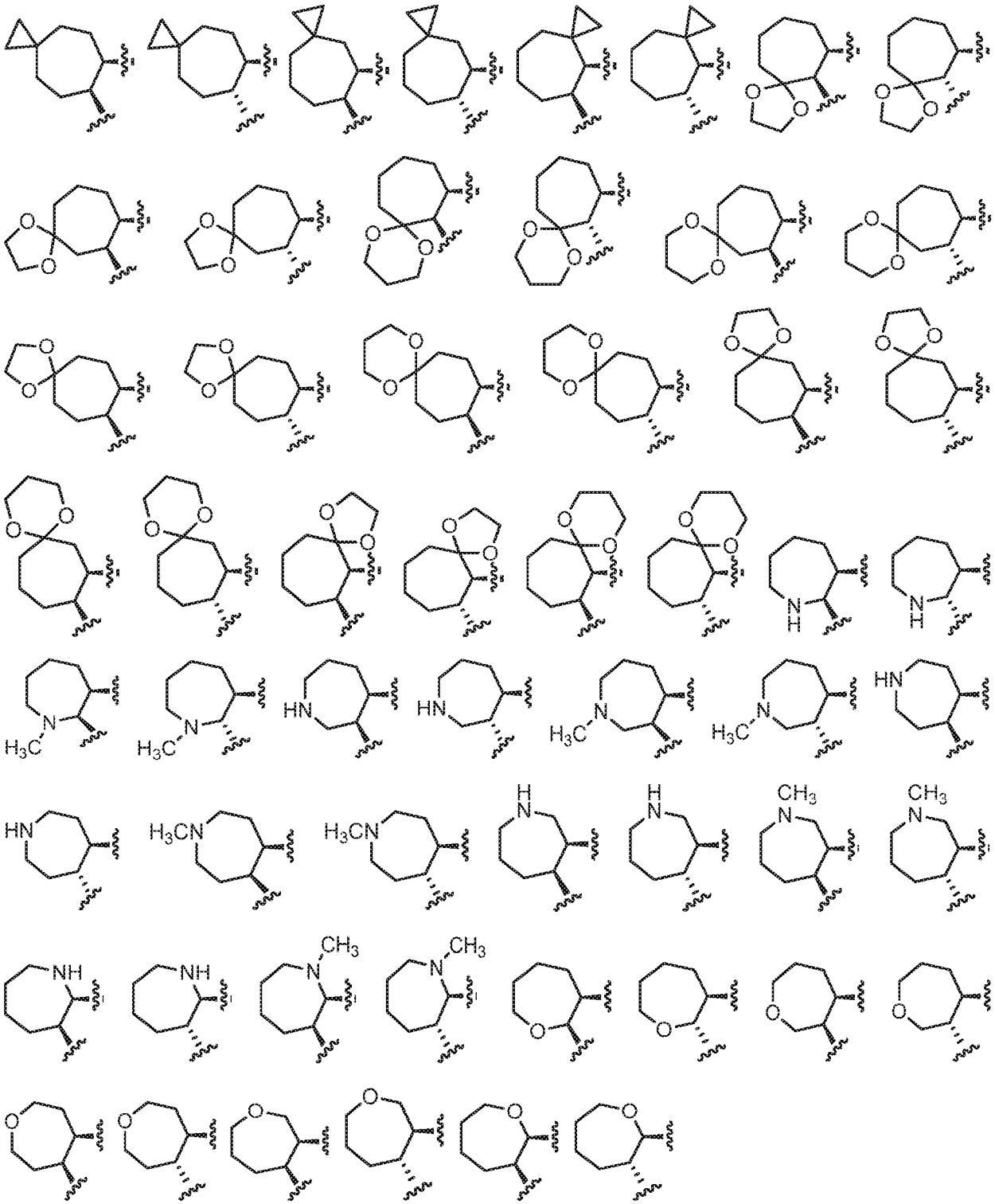


FIG 4L

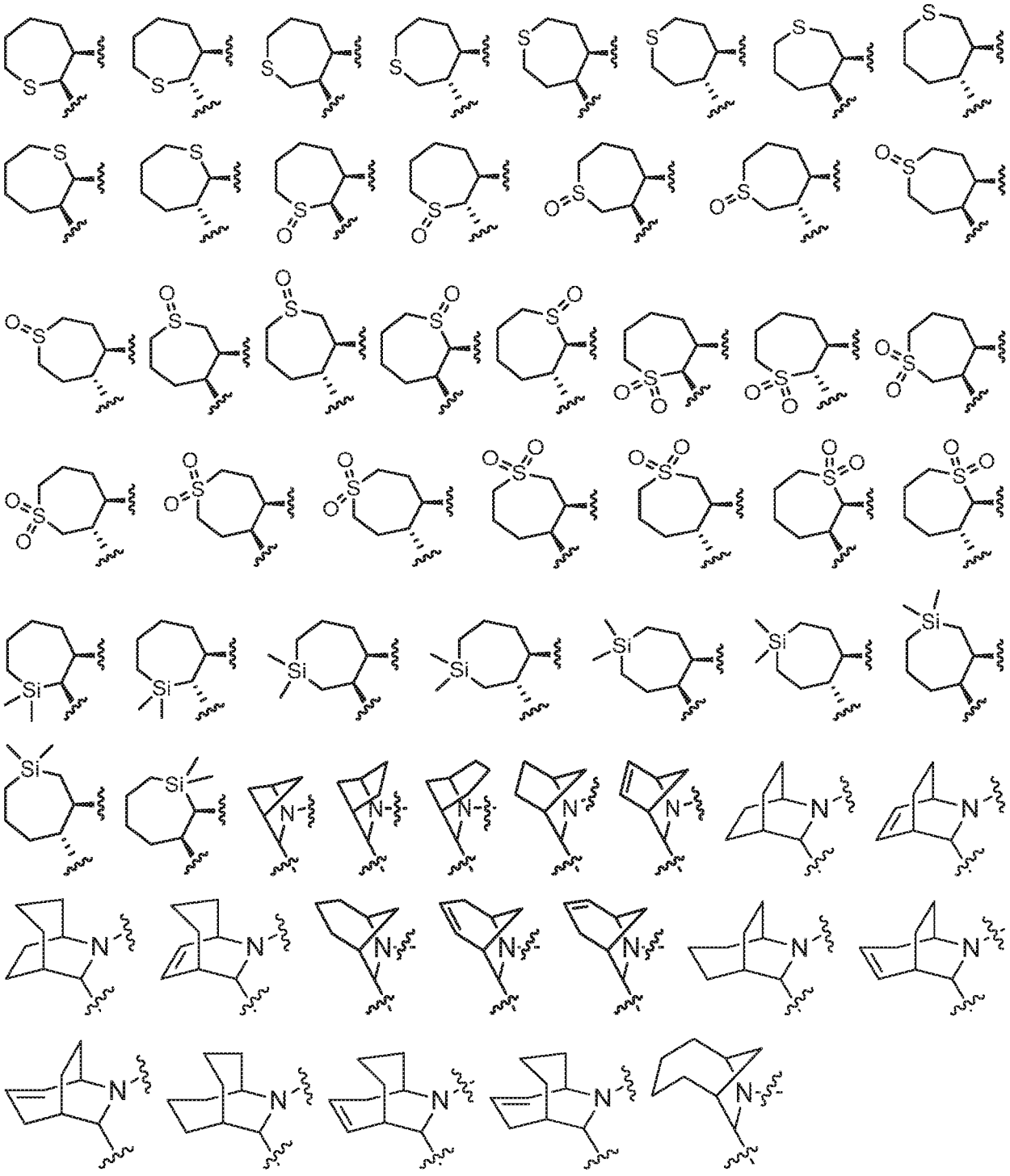


FIG 4M

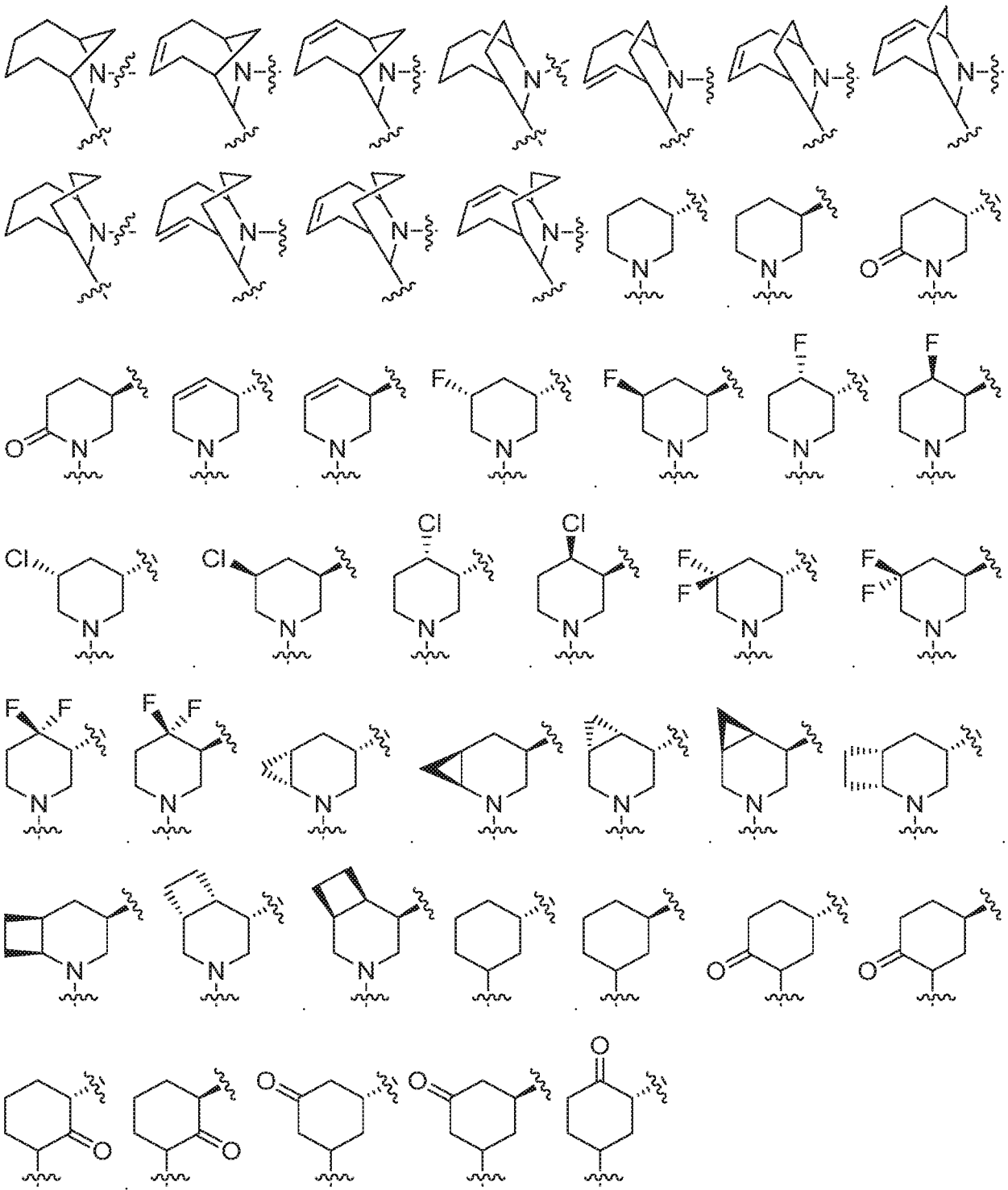
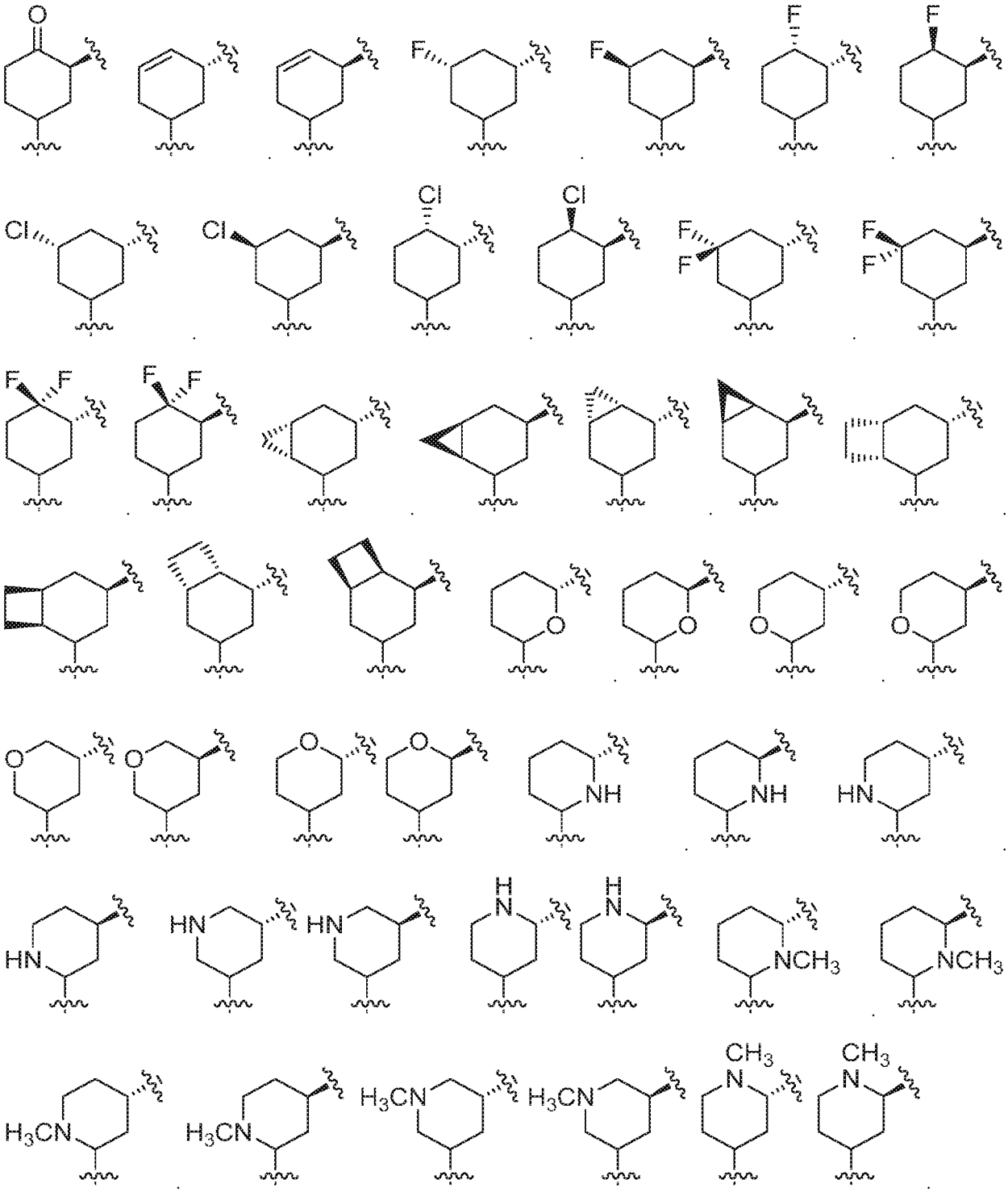


FIG 4N


O
F
F
F
F
Cl
Cl
Cl
Cl
F
F
F
F
F
F
O
O
O
O
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NH
NH
HN
HN
HN
HN
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H3CN
CH3
N
CH3
N

FIG. 5

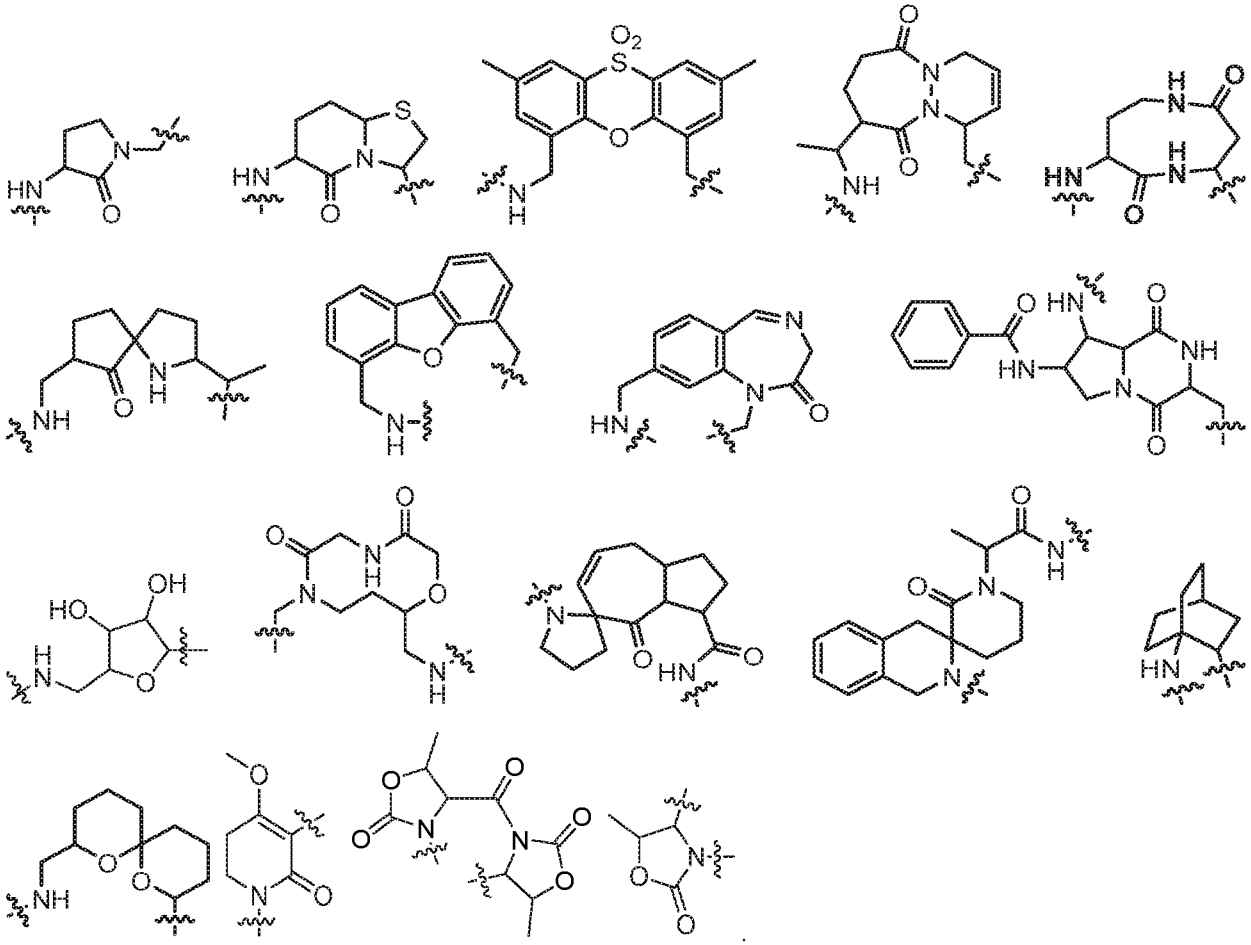

FIG. 6

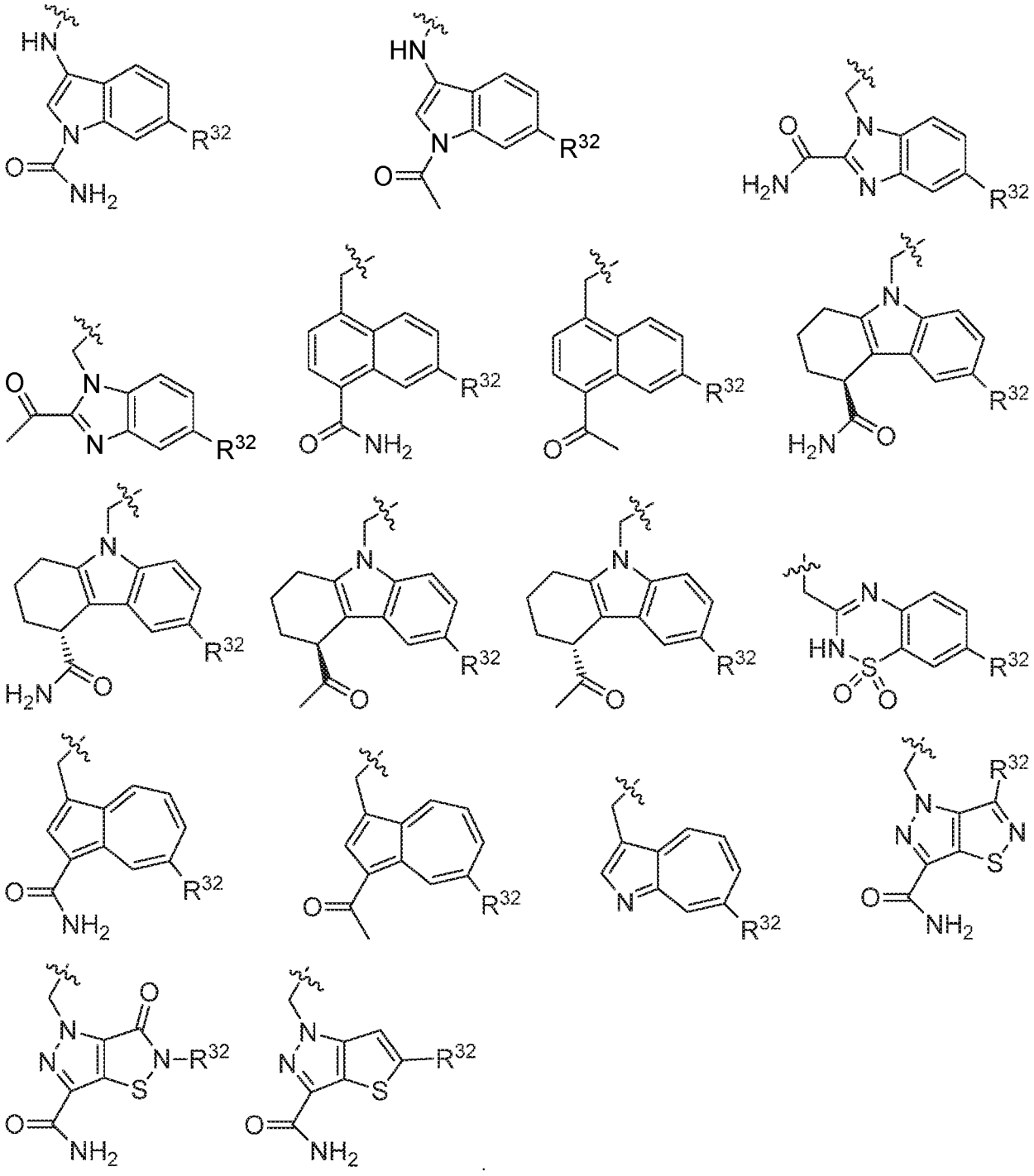

FIG. 7A

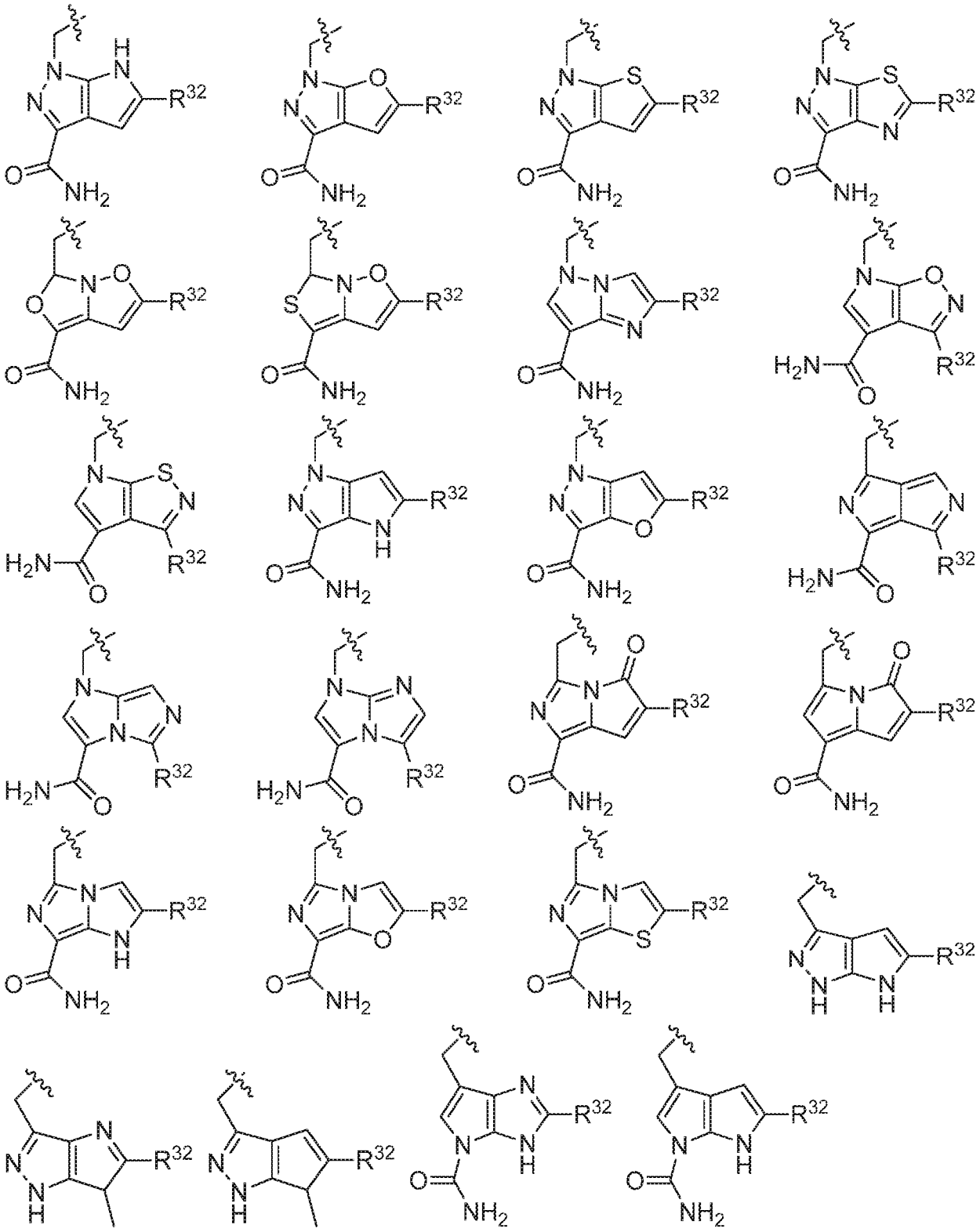

FIG. 7B

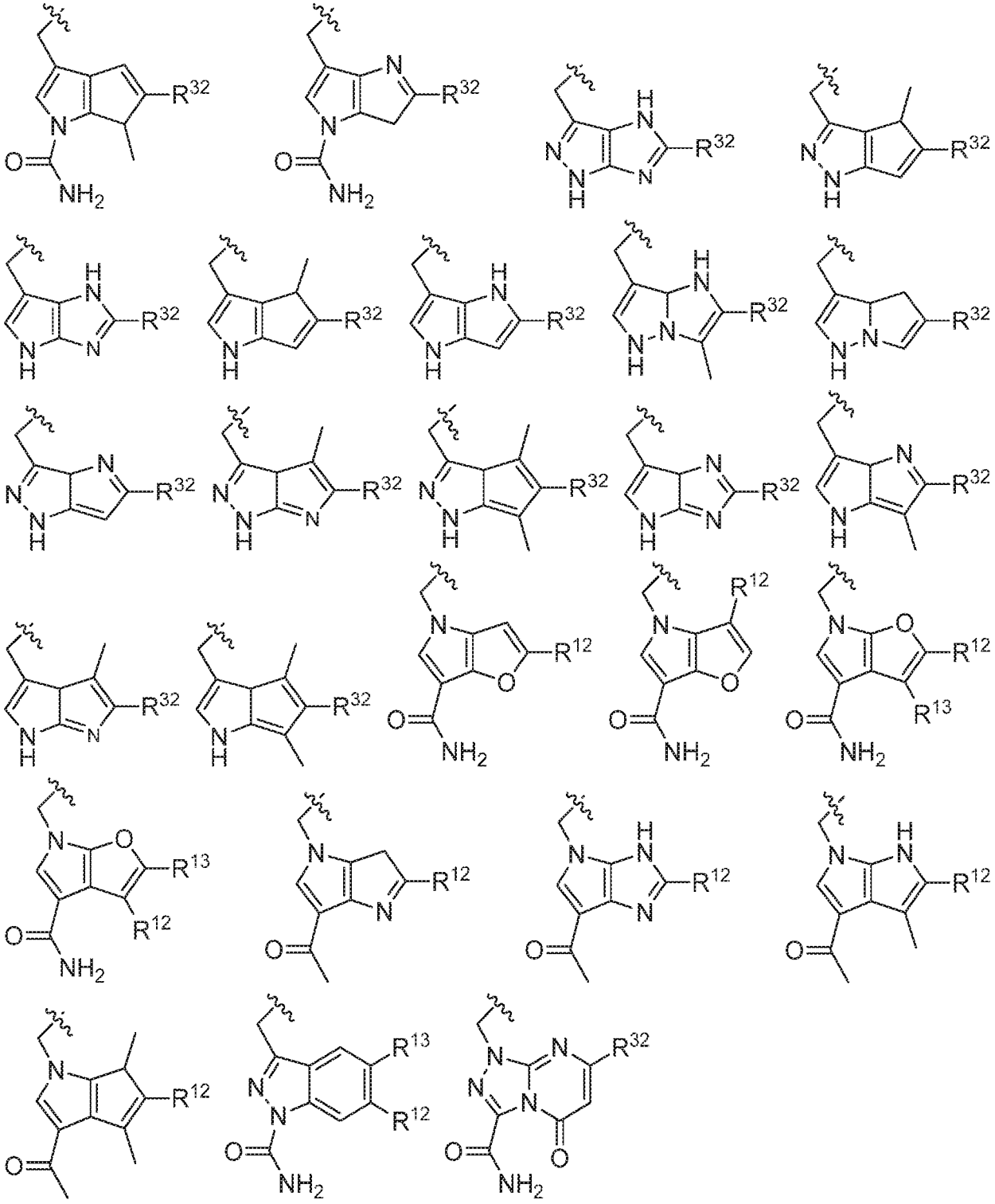

FIG. 7C

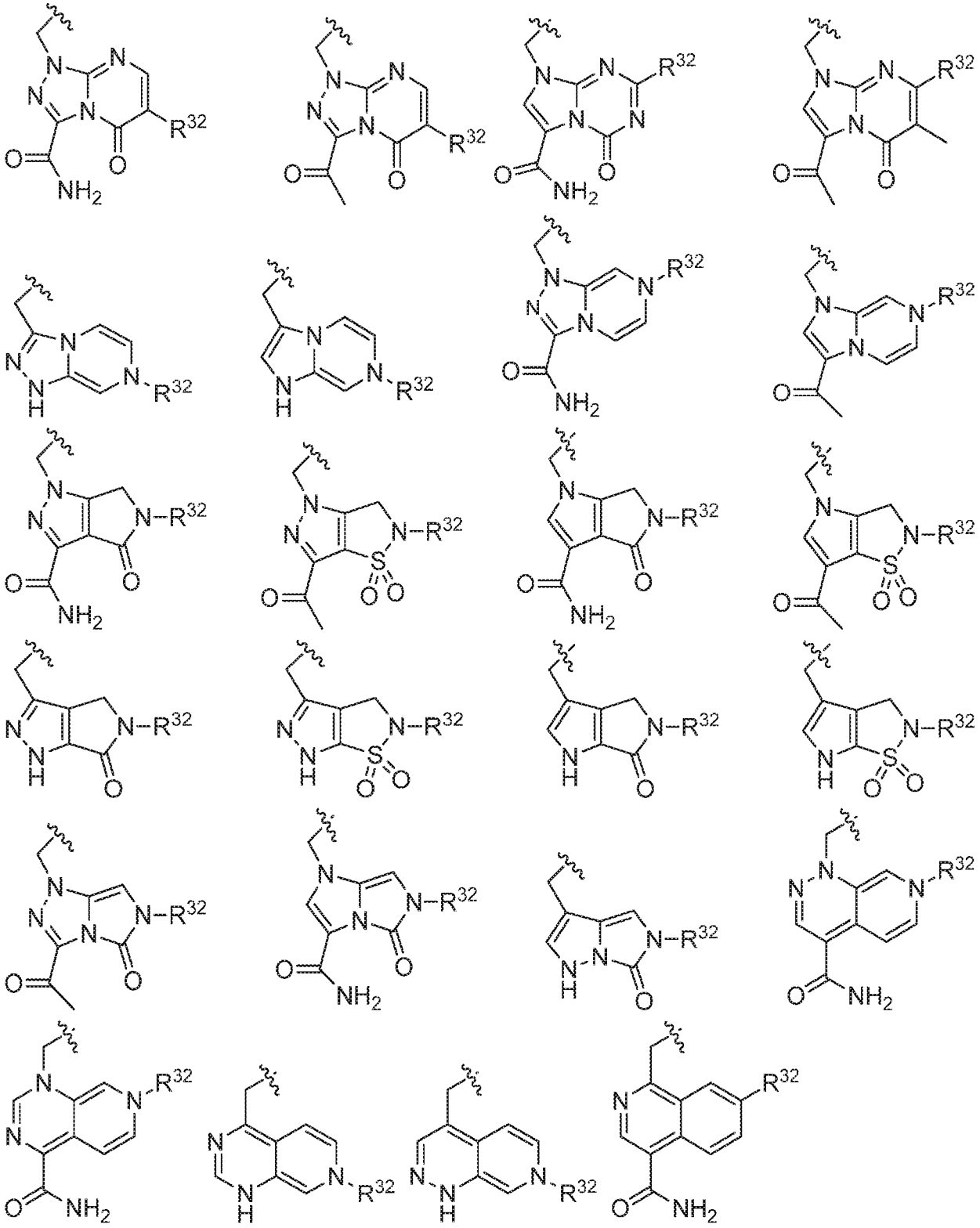

FIG. 7D

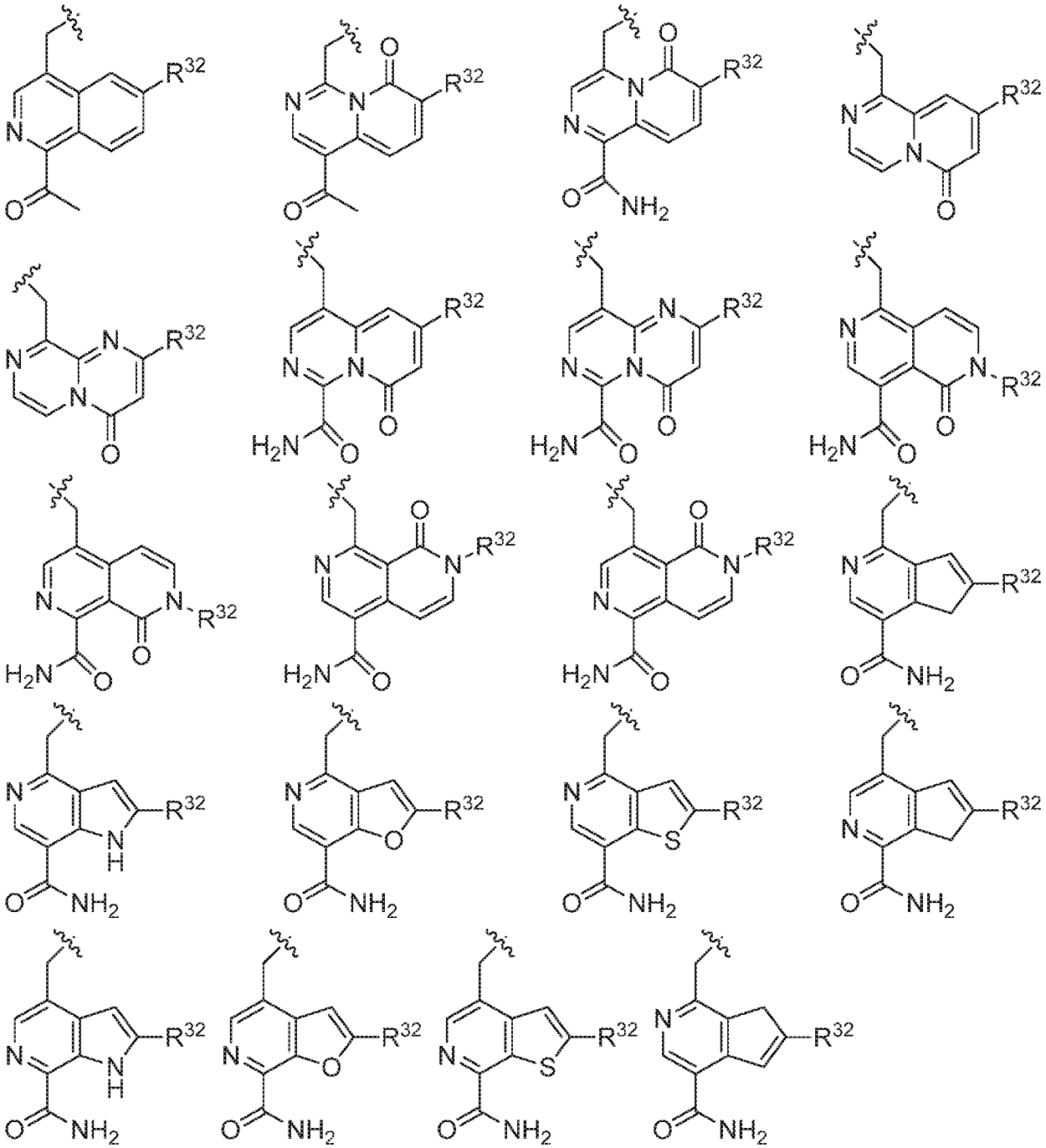

FIG. 7E

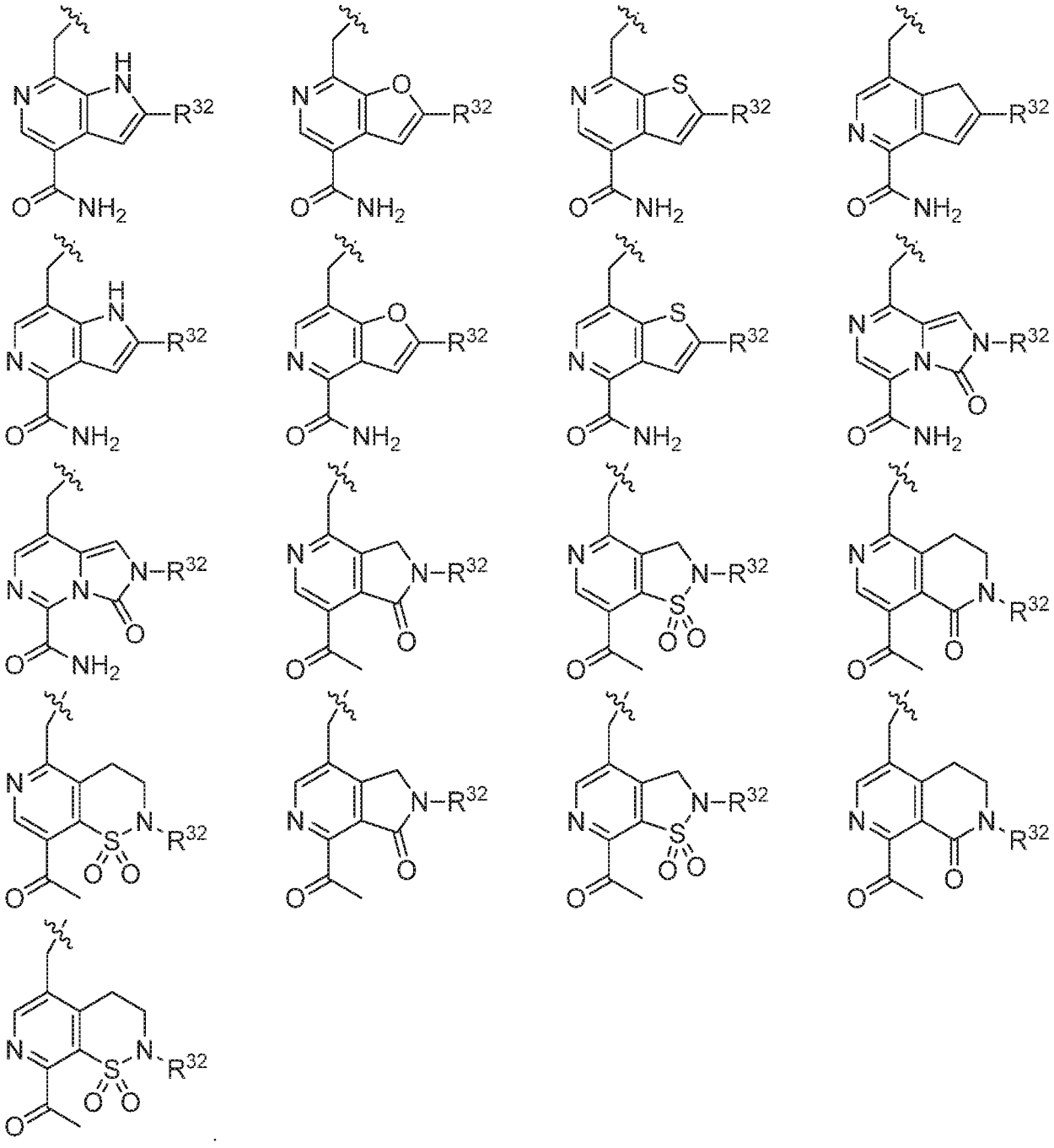

FIG. 8A

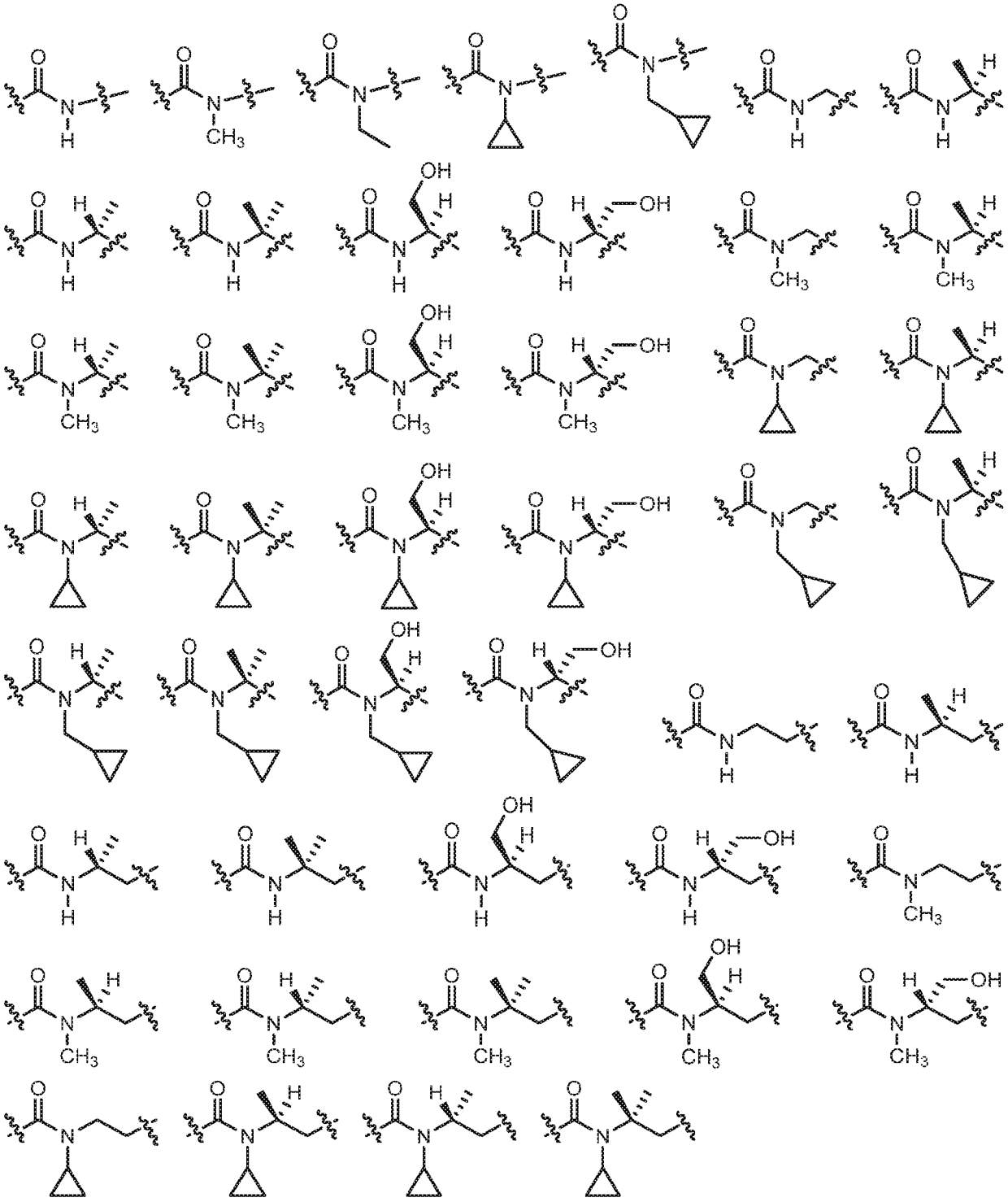

FIG. 8B

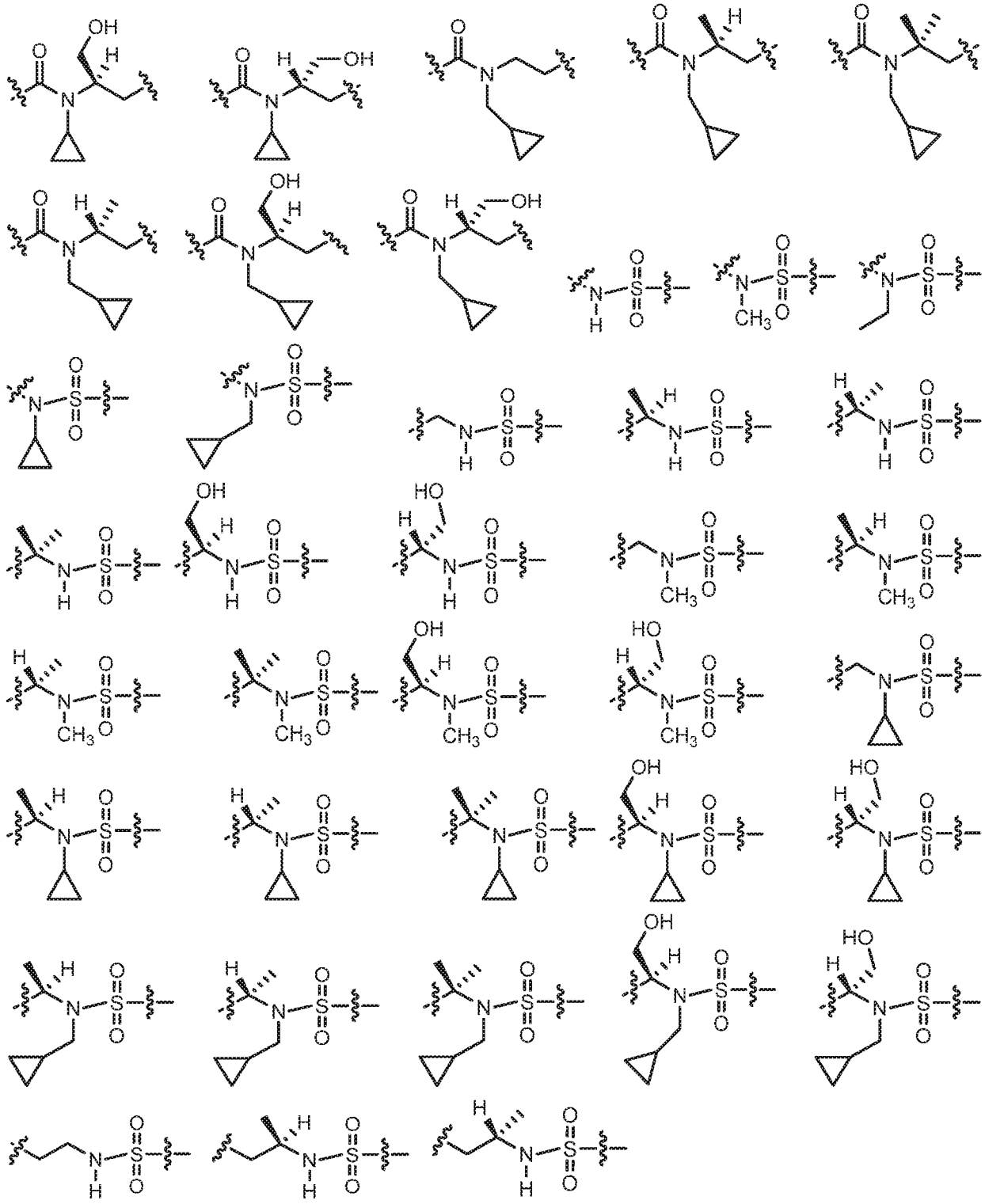

FIG. 8C

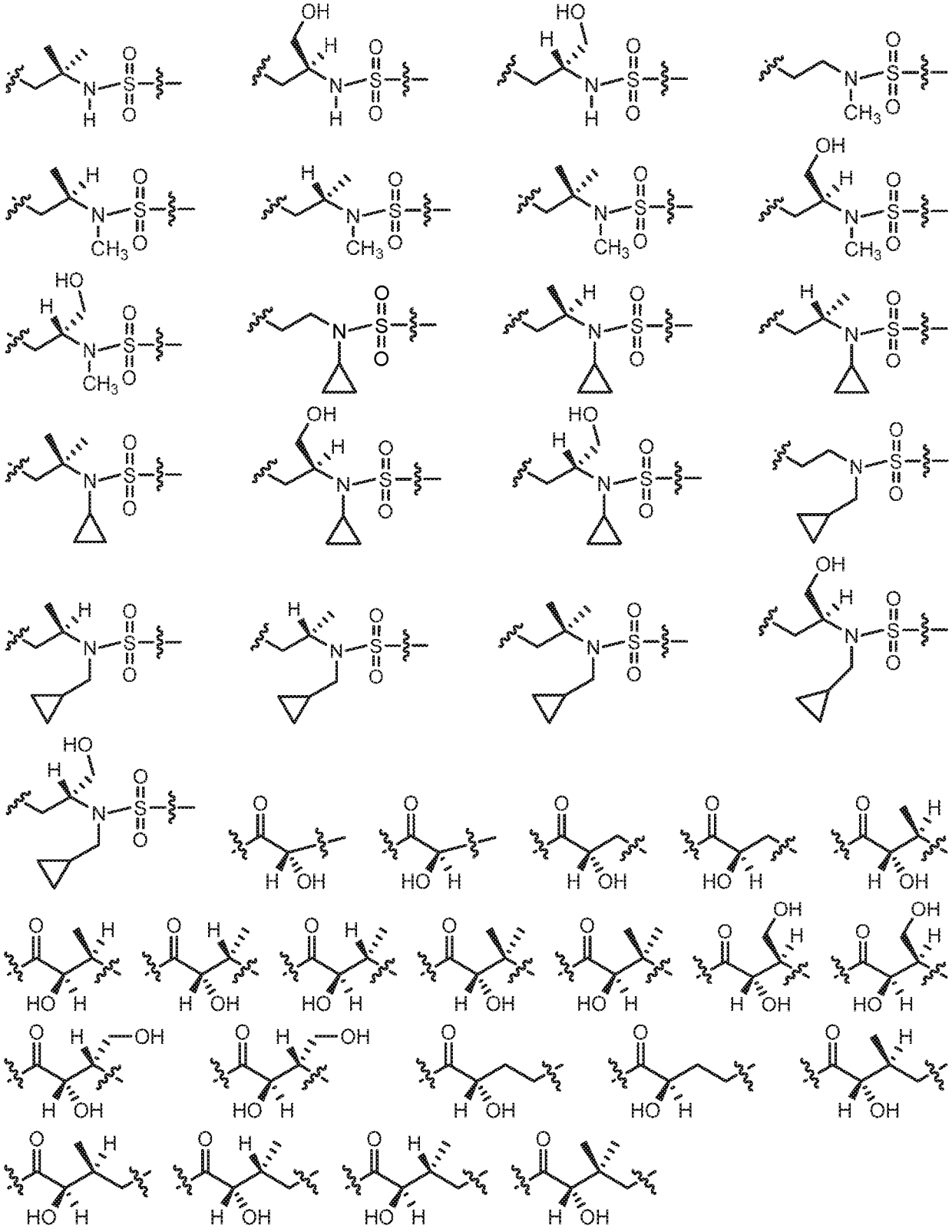

FIG. 8D

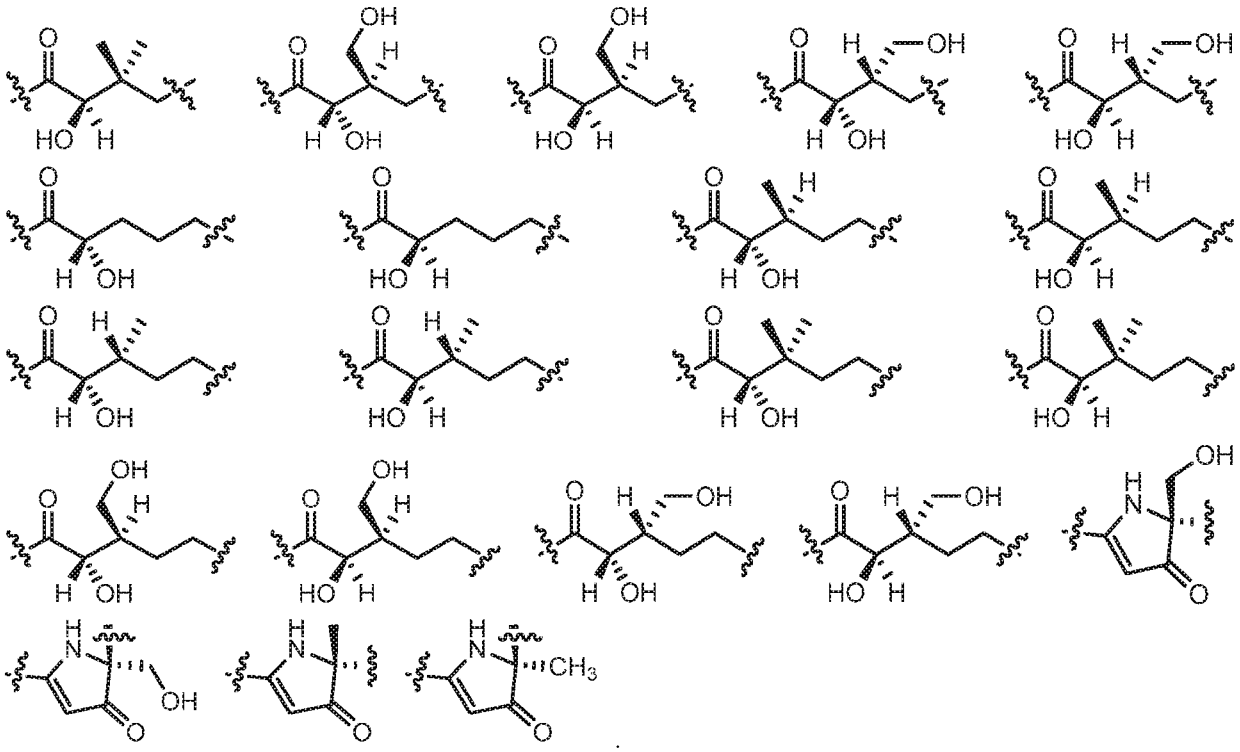

FIG. 9A

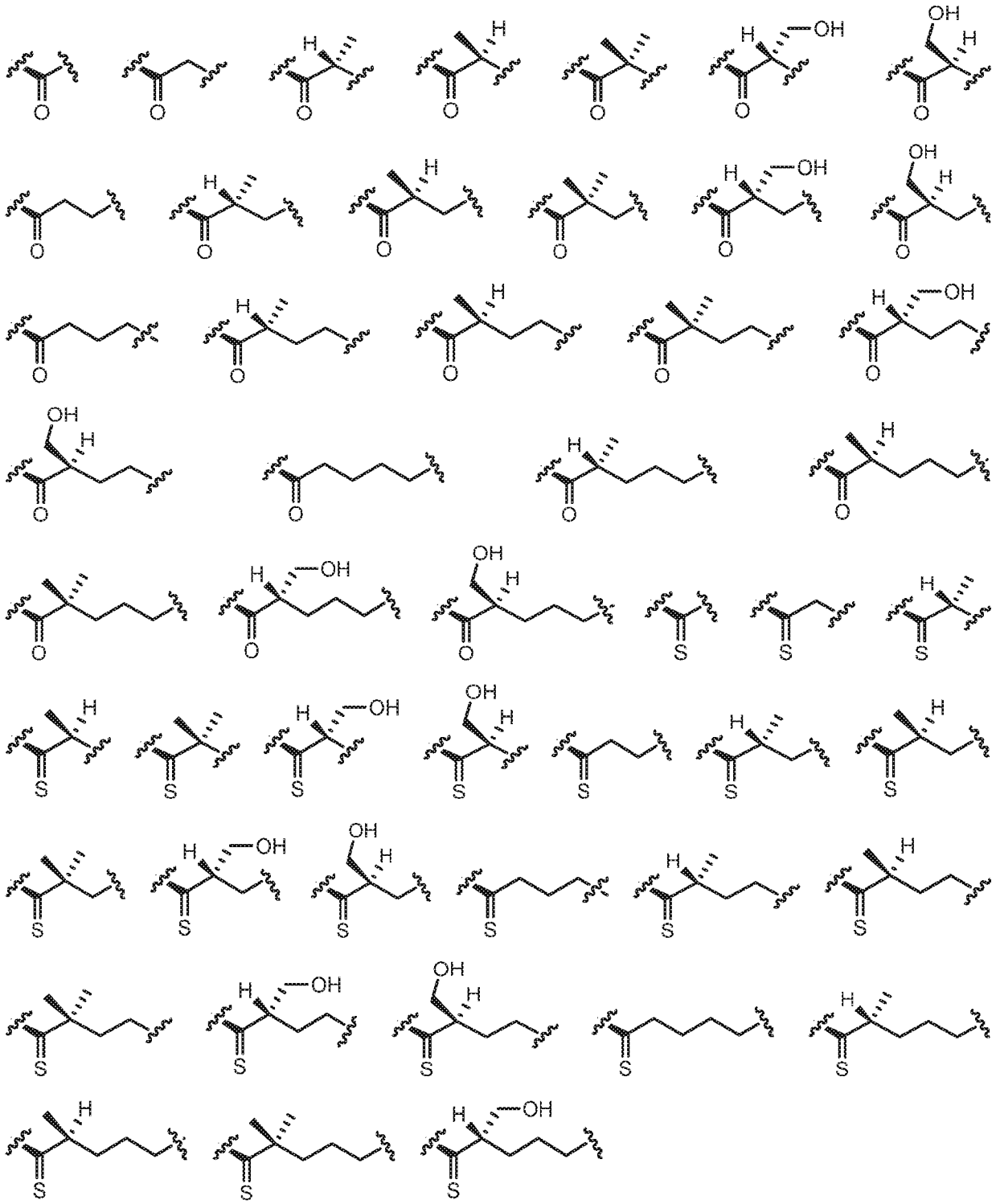

FIG. 9B

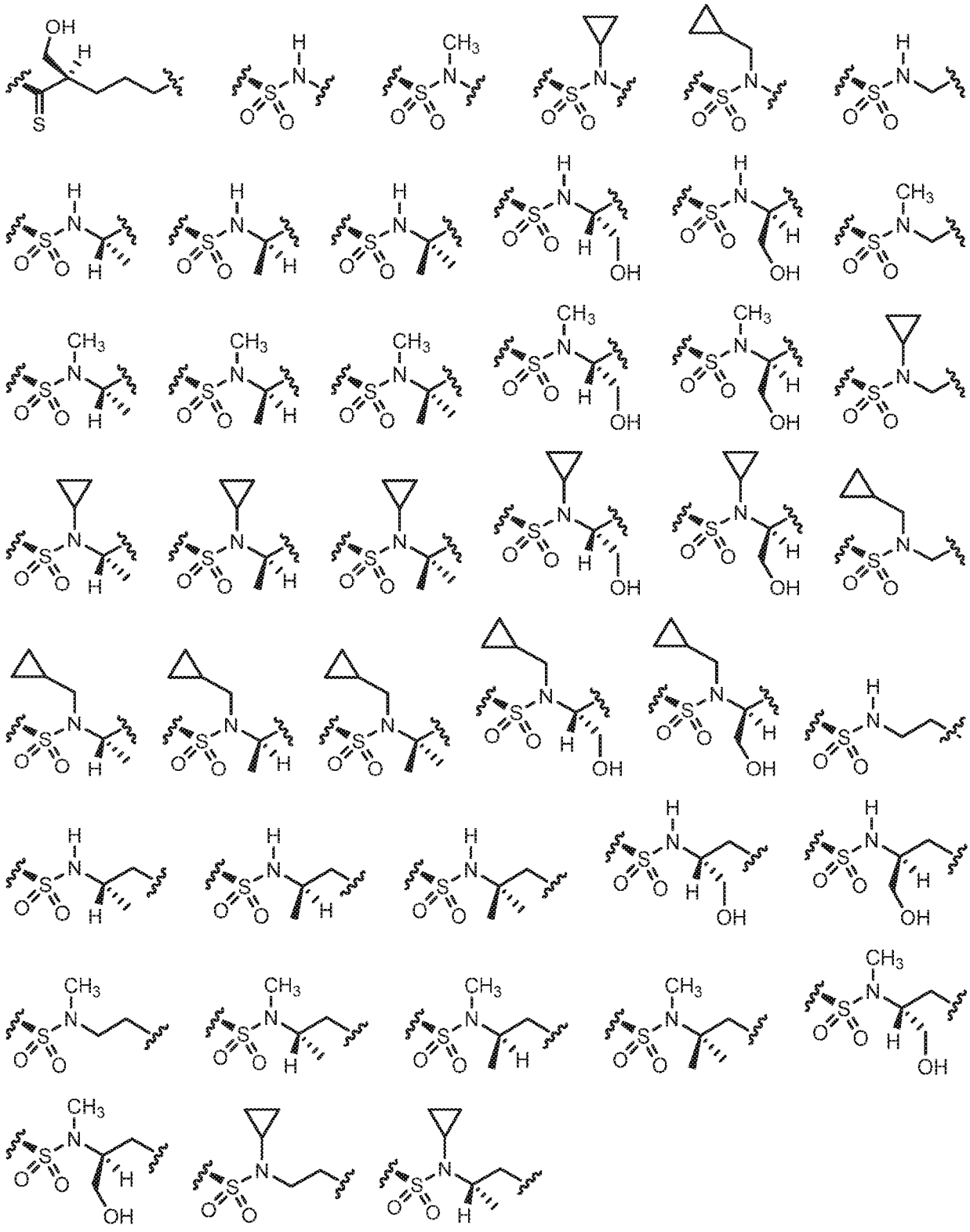

FIG. 9C

FIG. 9D

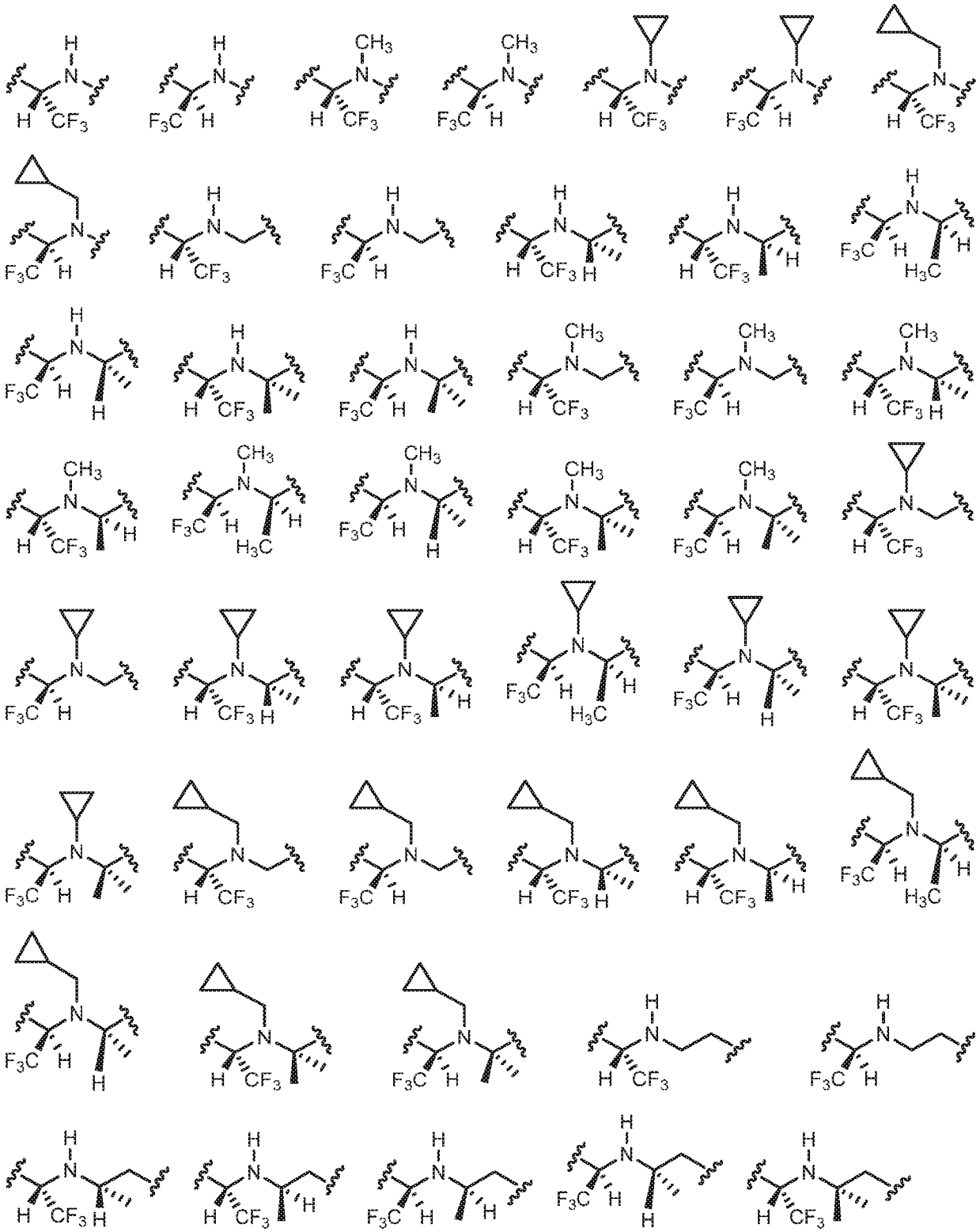

FIG. 9E

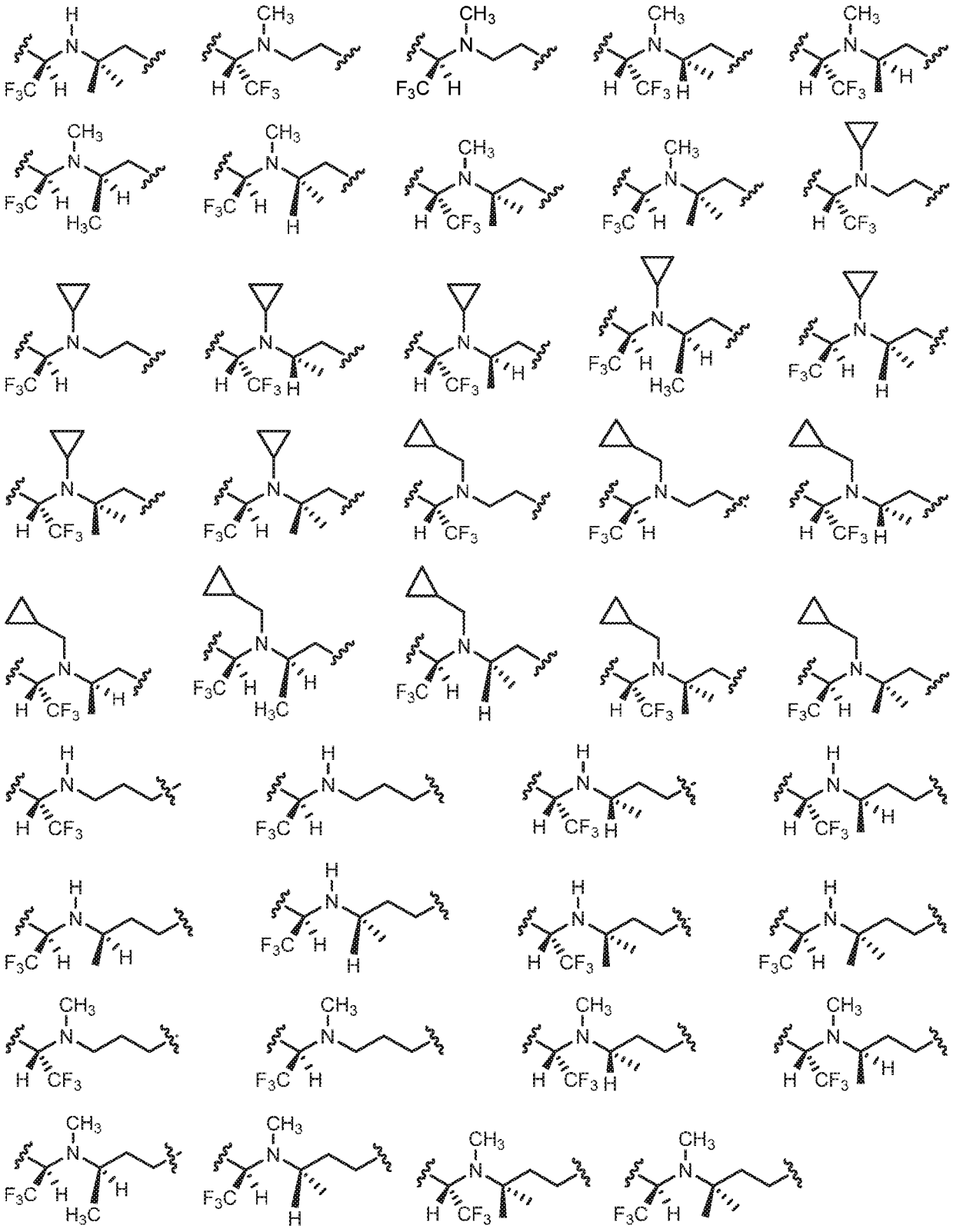

FIG. 9F

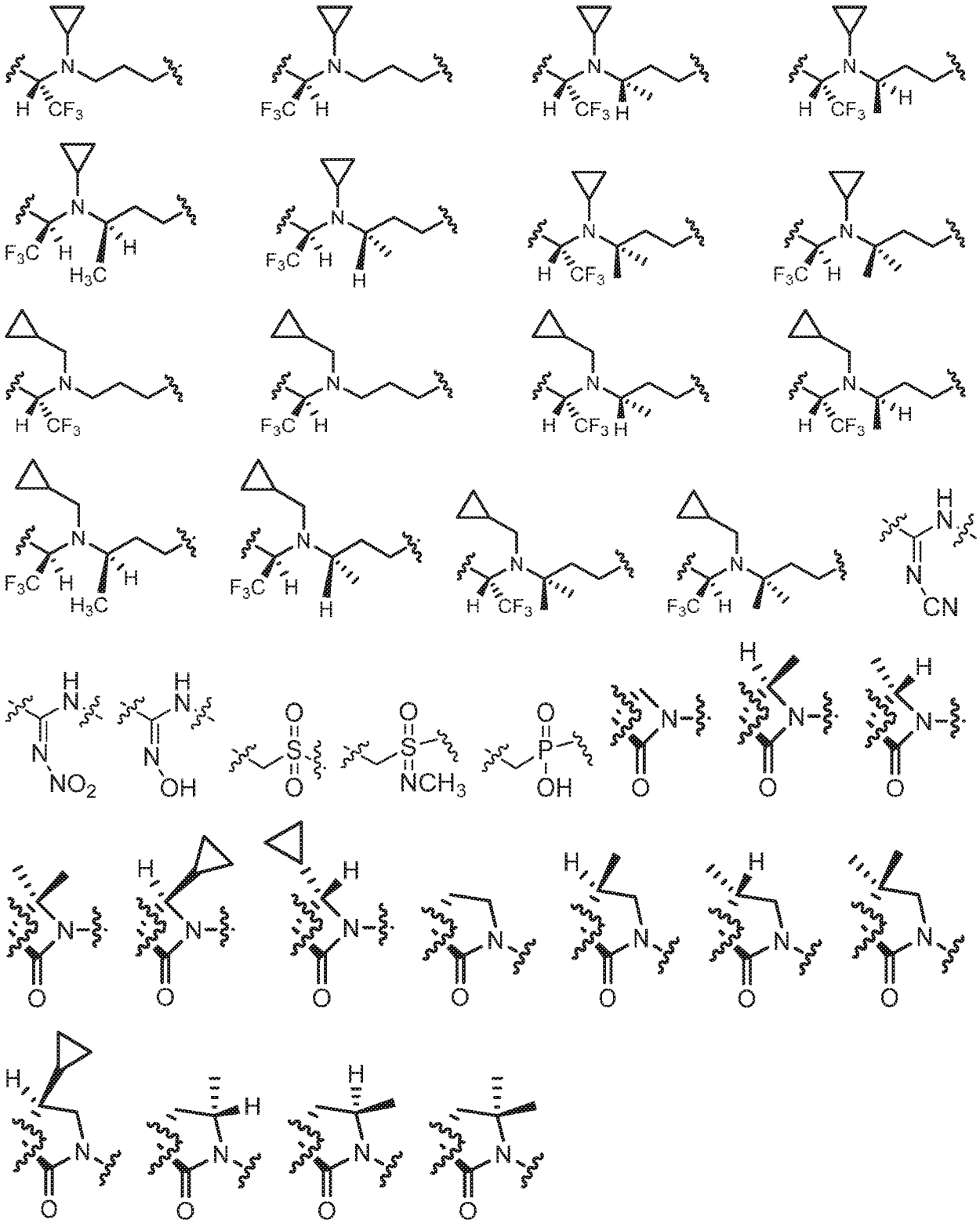

FIG. 9G

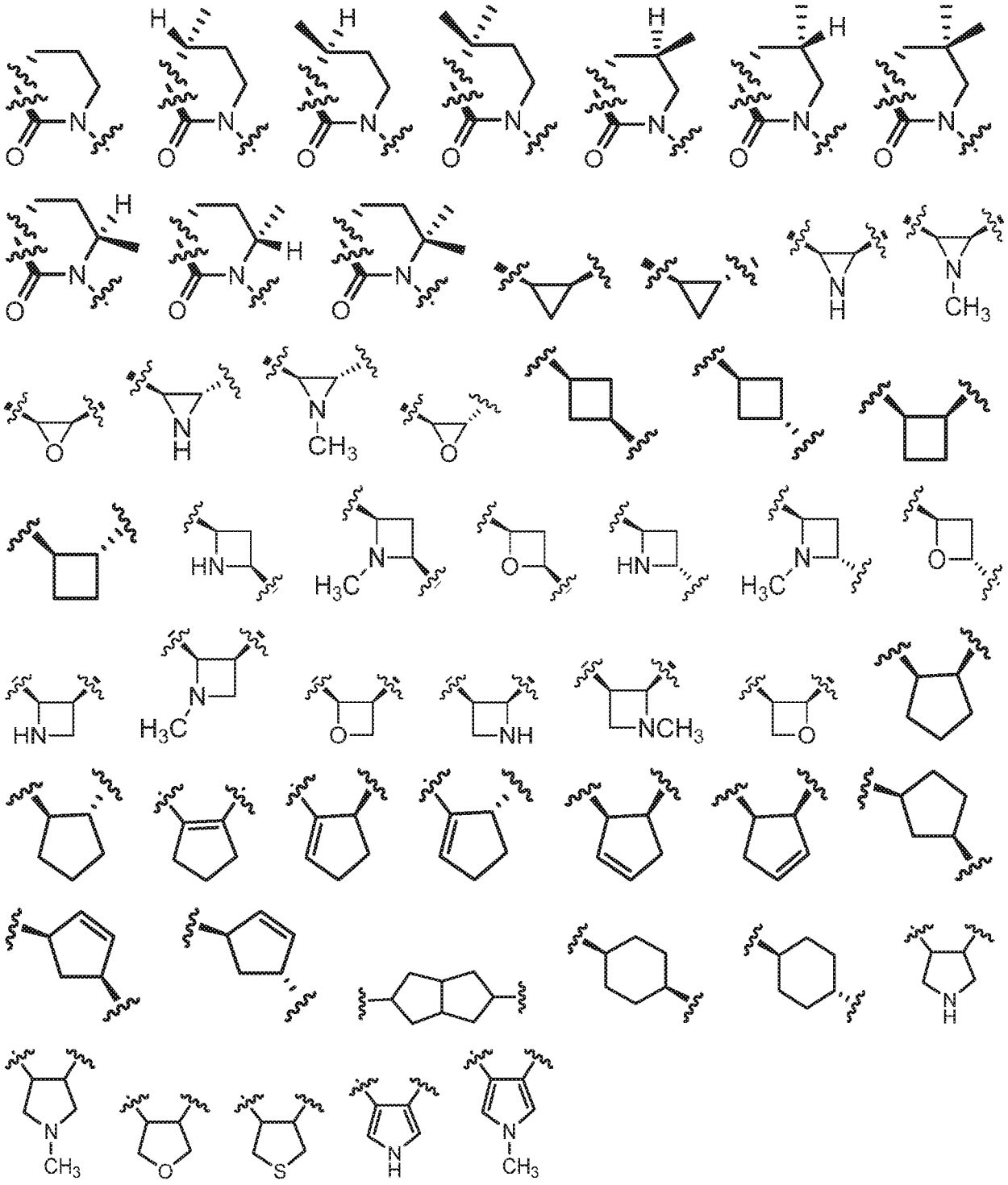

FIG. 9H

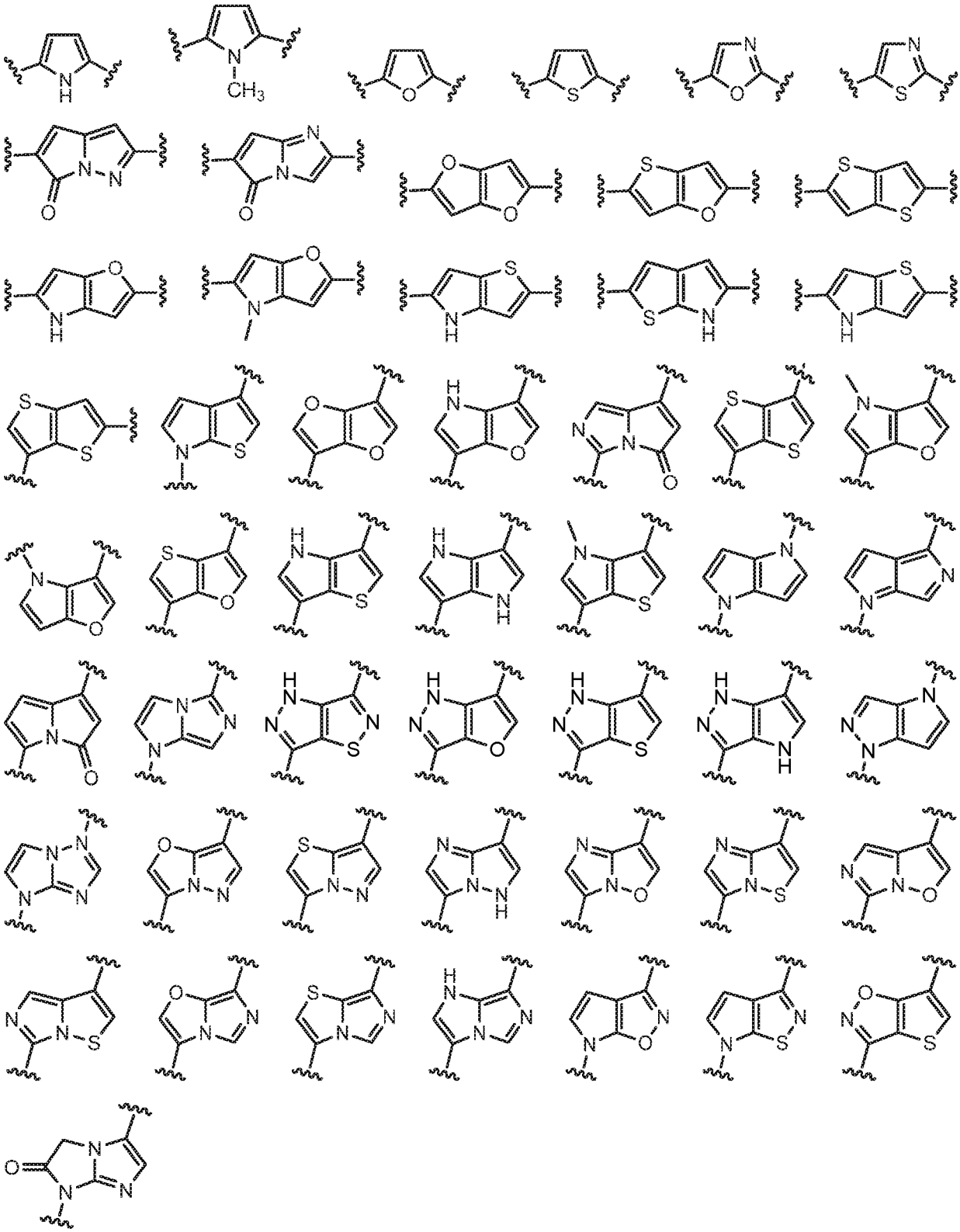

FIG. 9I

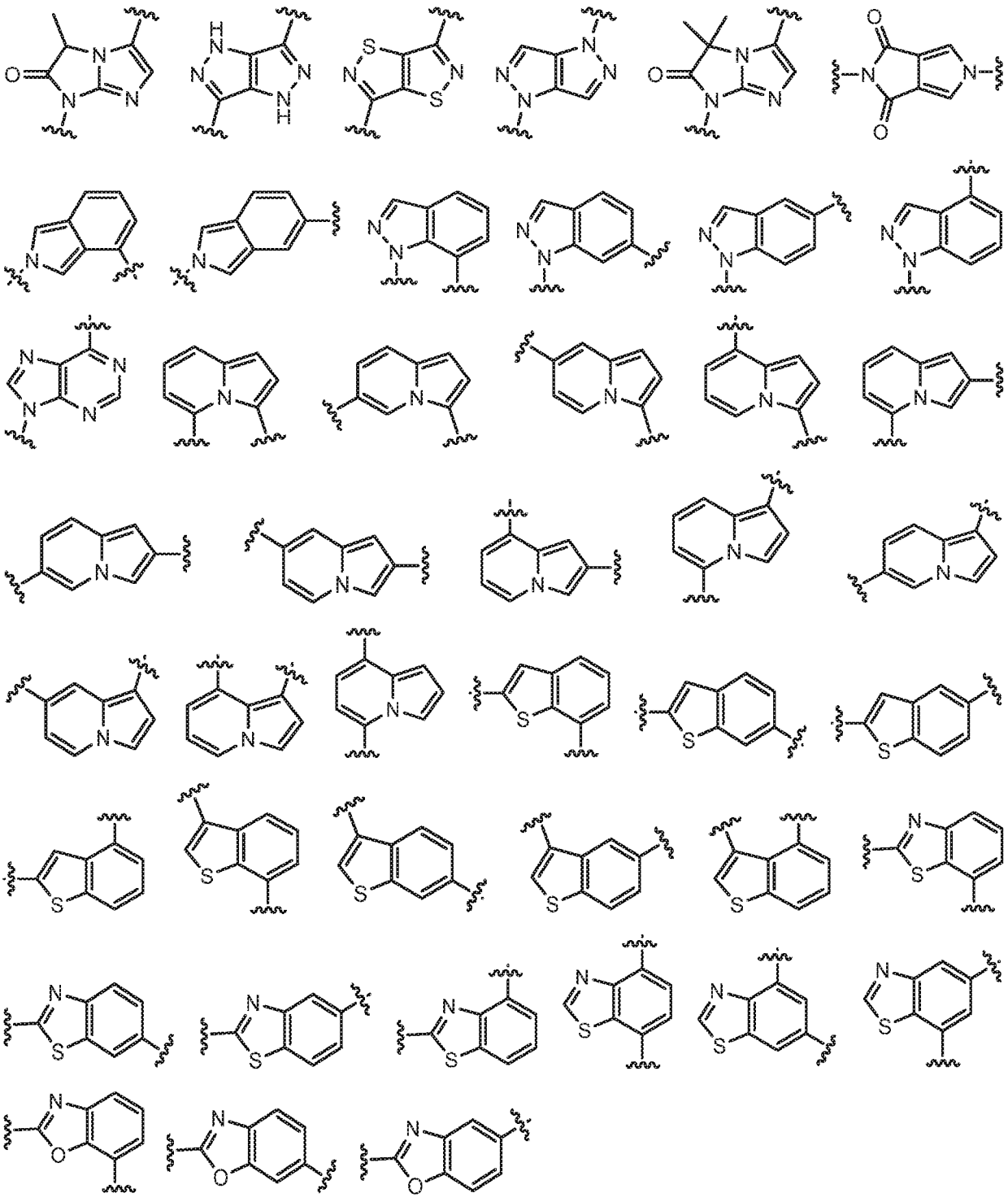

FIG. 9J

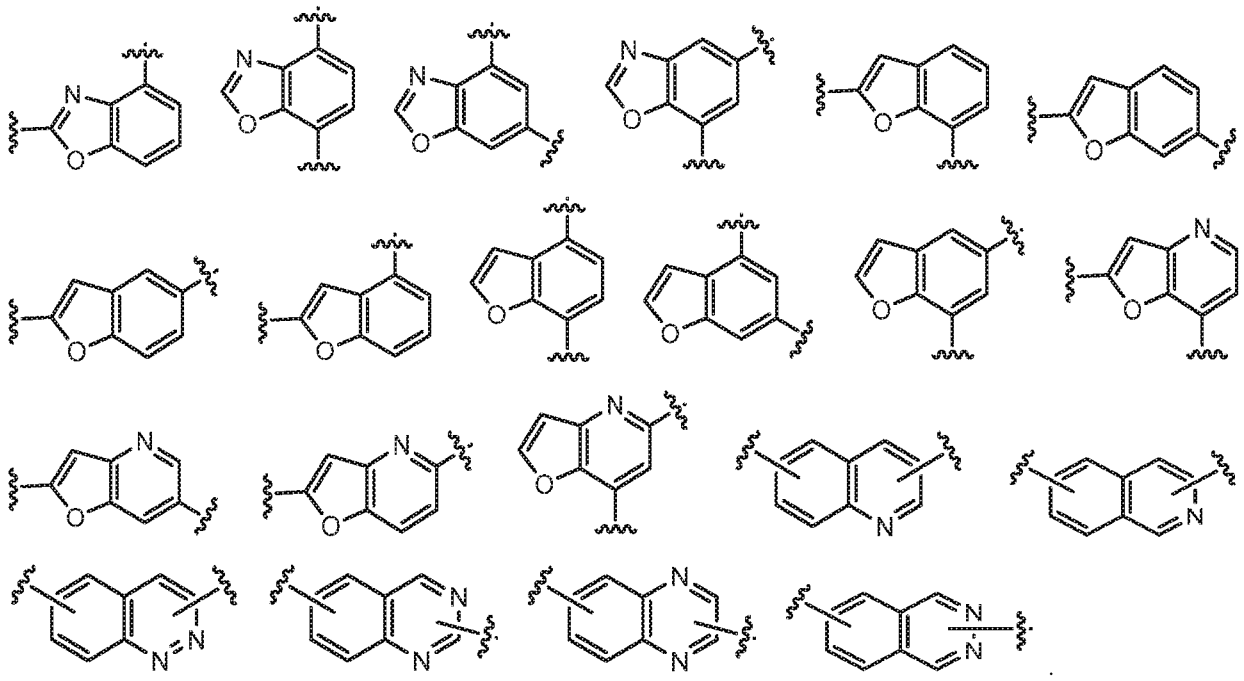

FIG. 10A

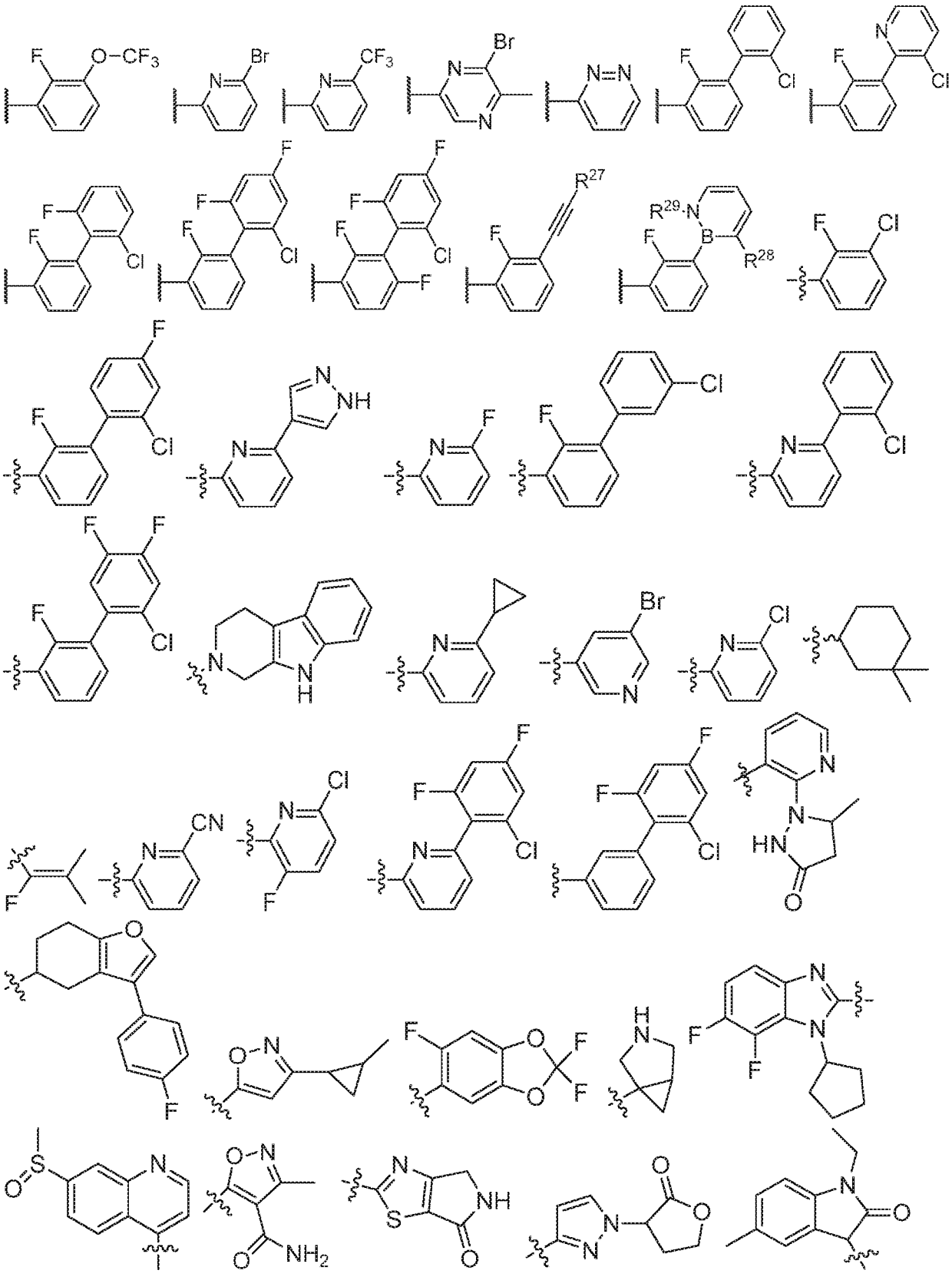

FIG. 10B

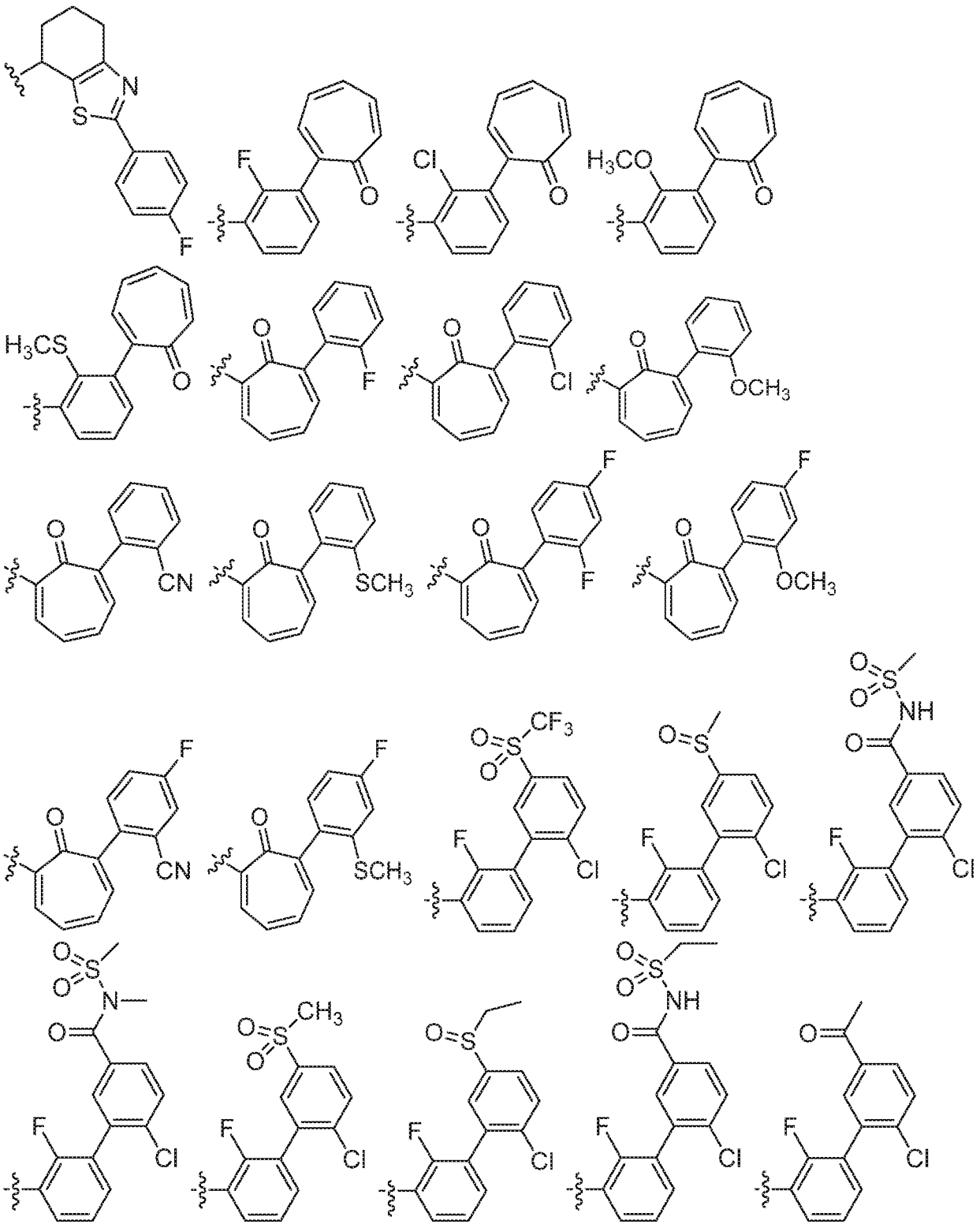

FIG. 10C

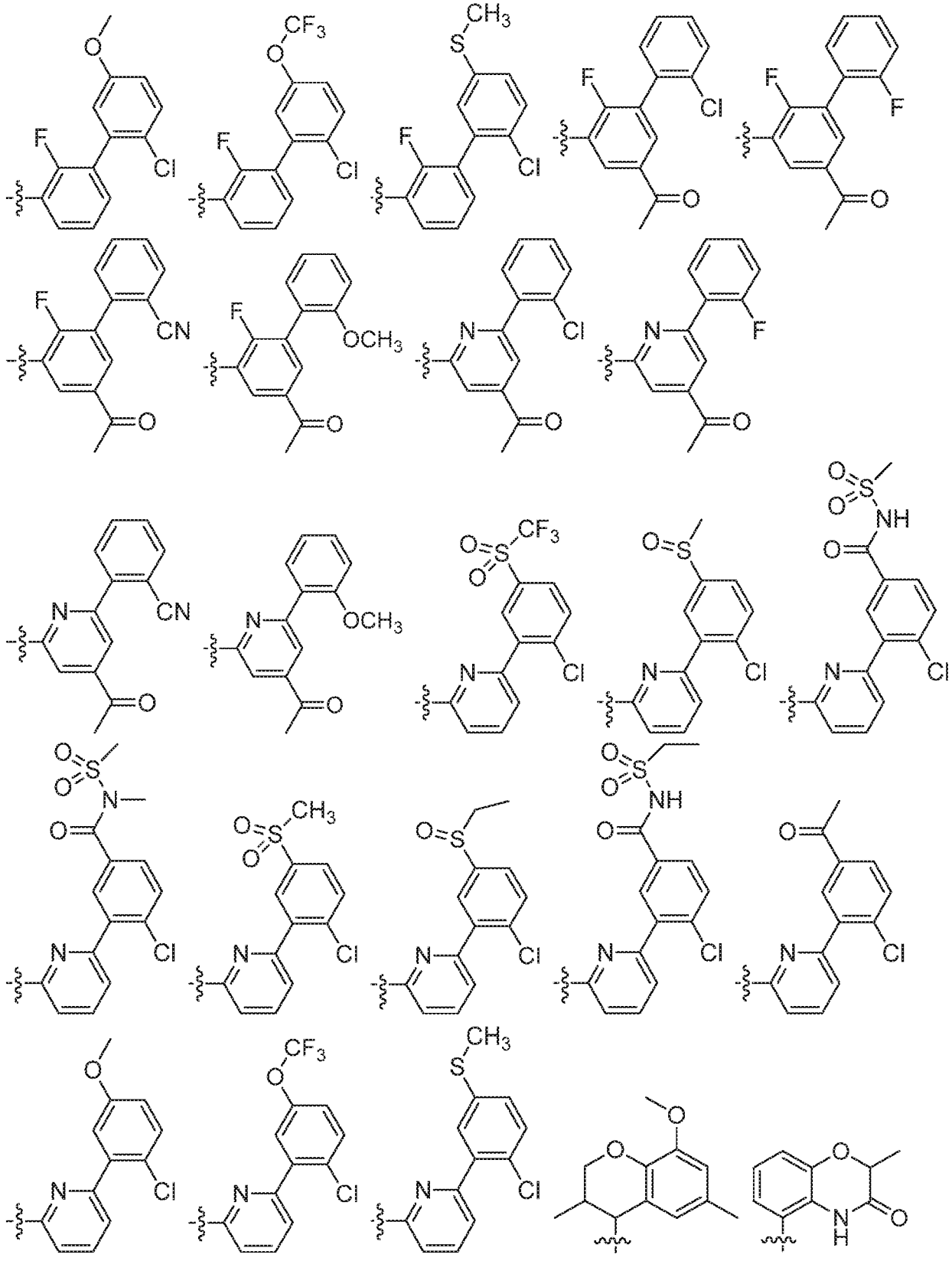

FIG. 10D

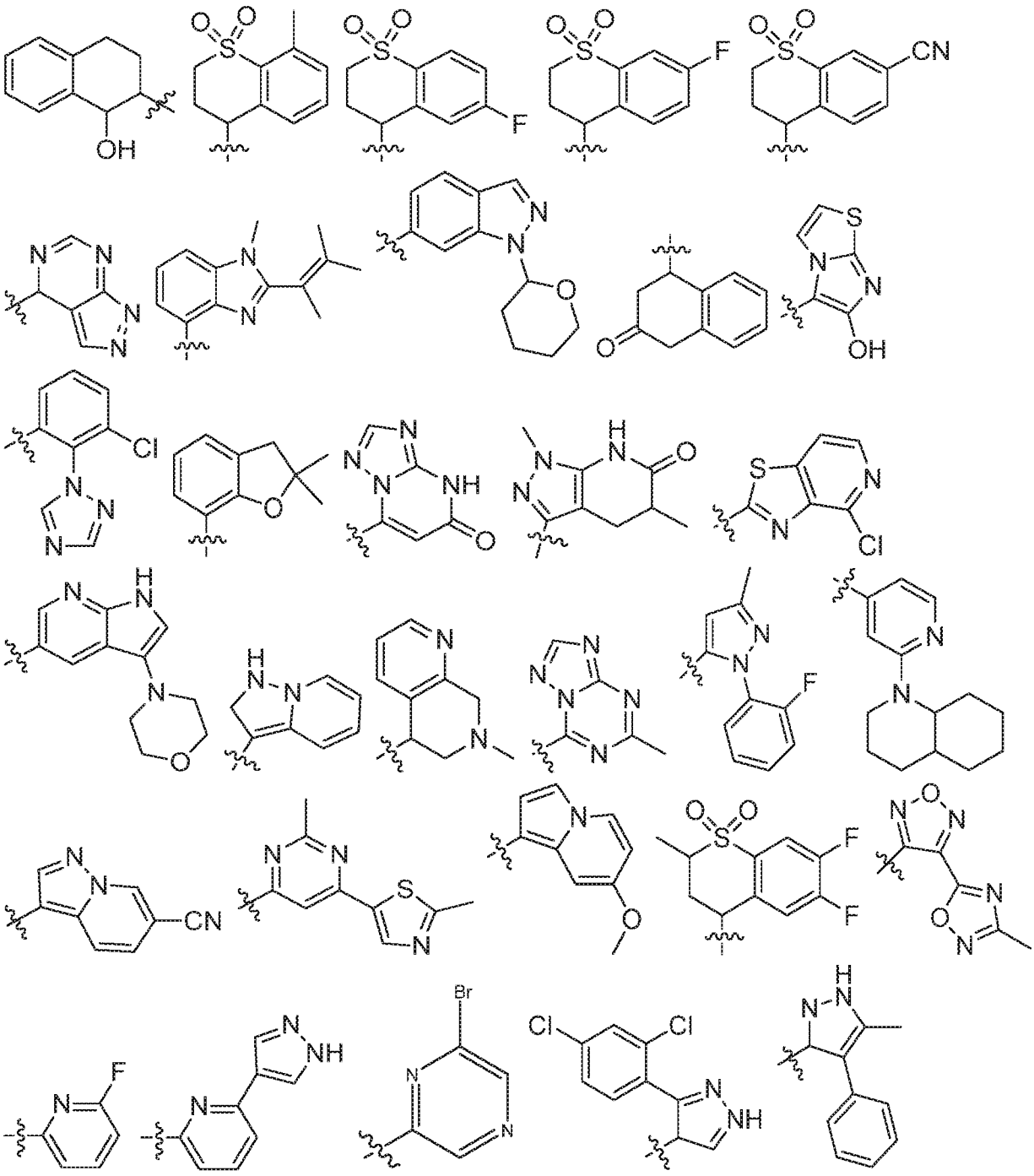

FIG. 11A

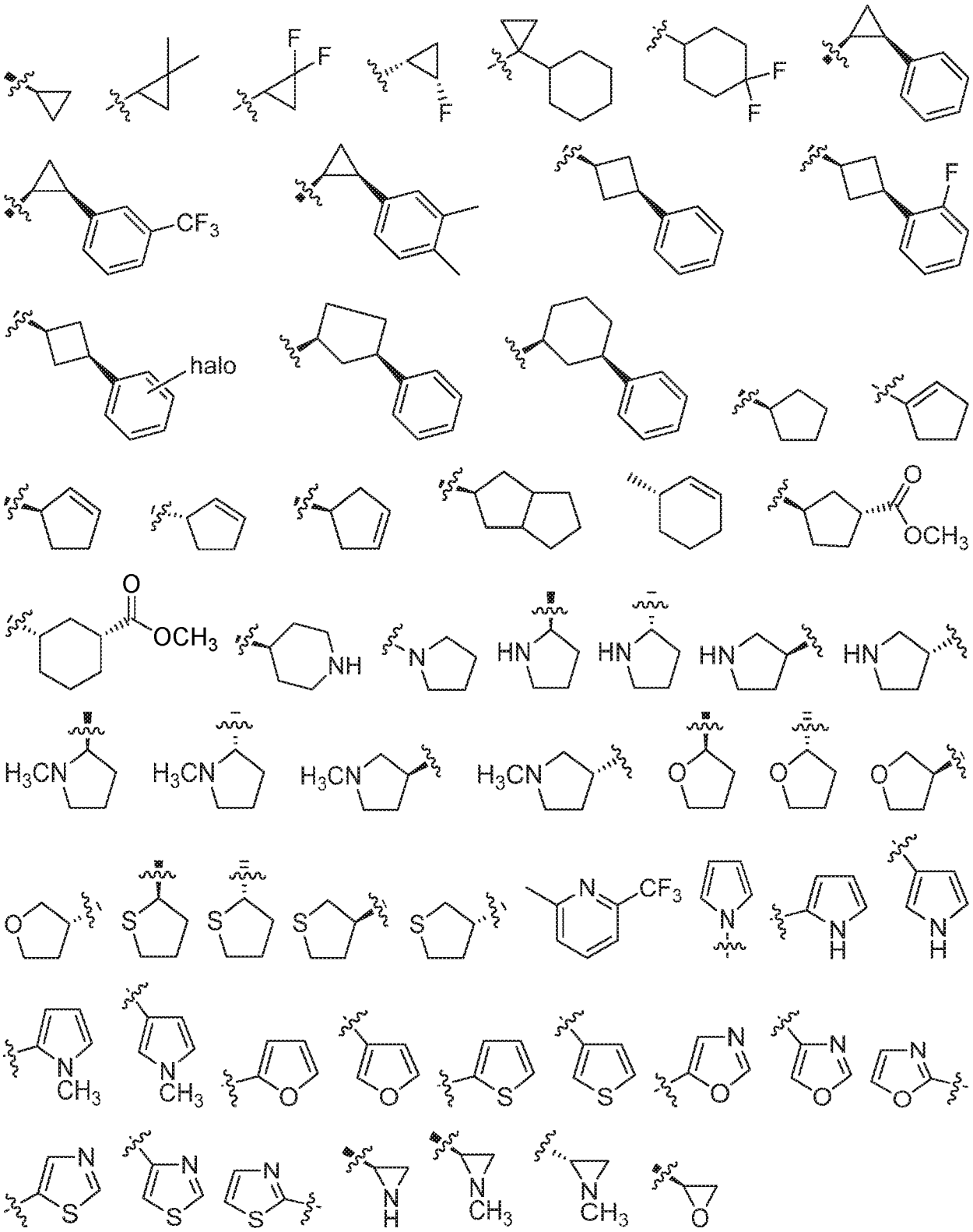
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FIG. 11B

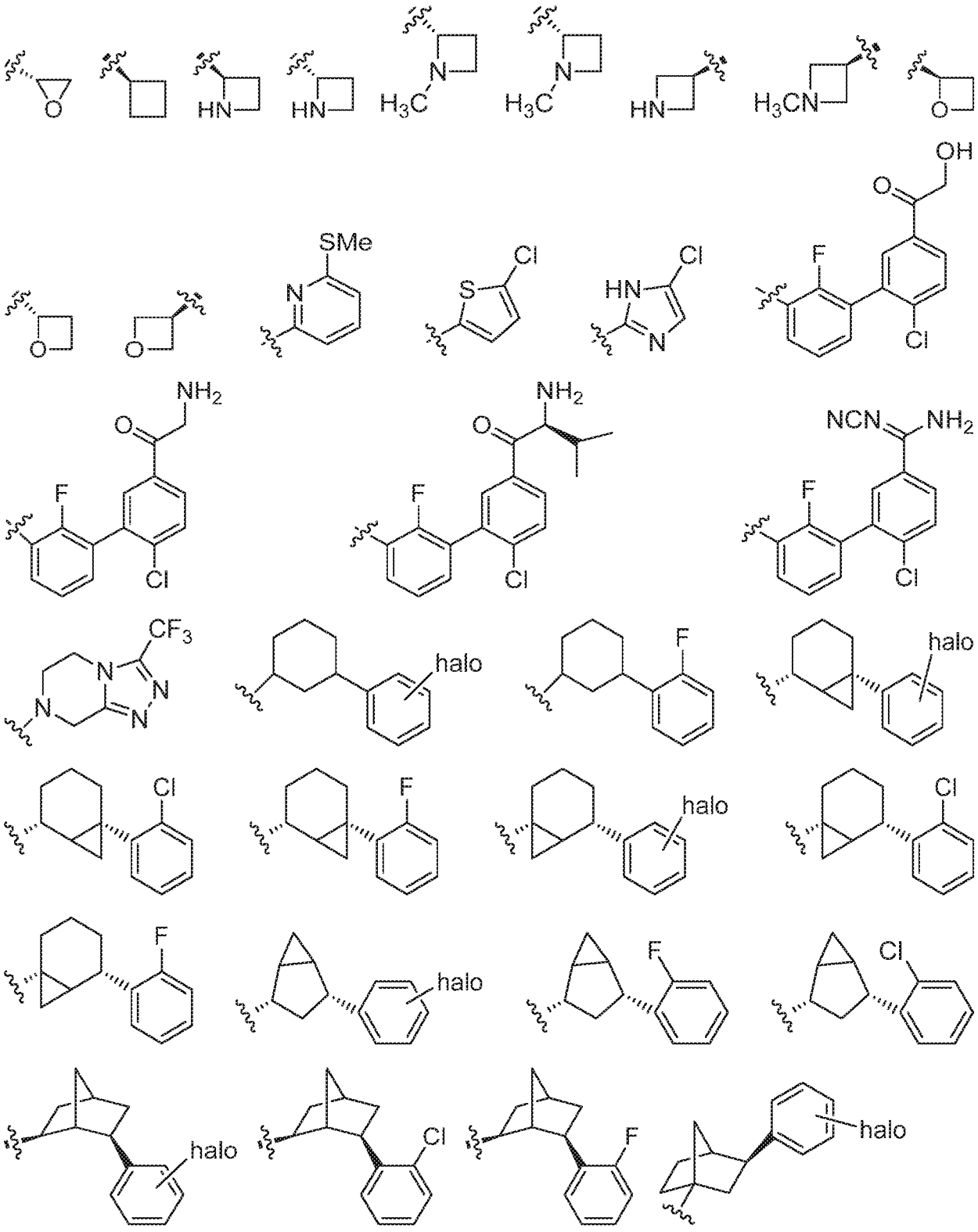
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FIG. 11C

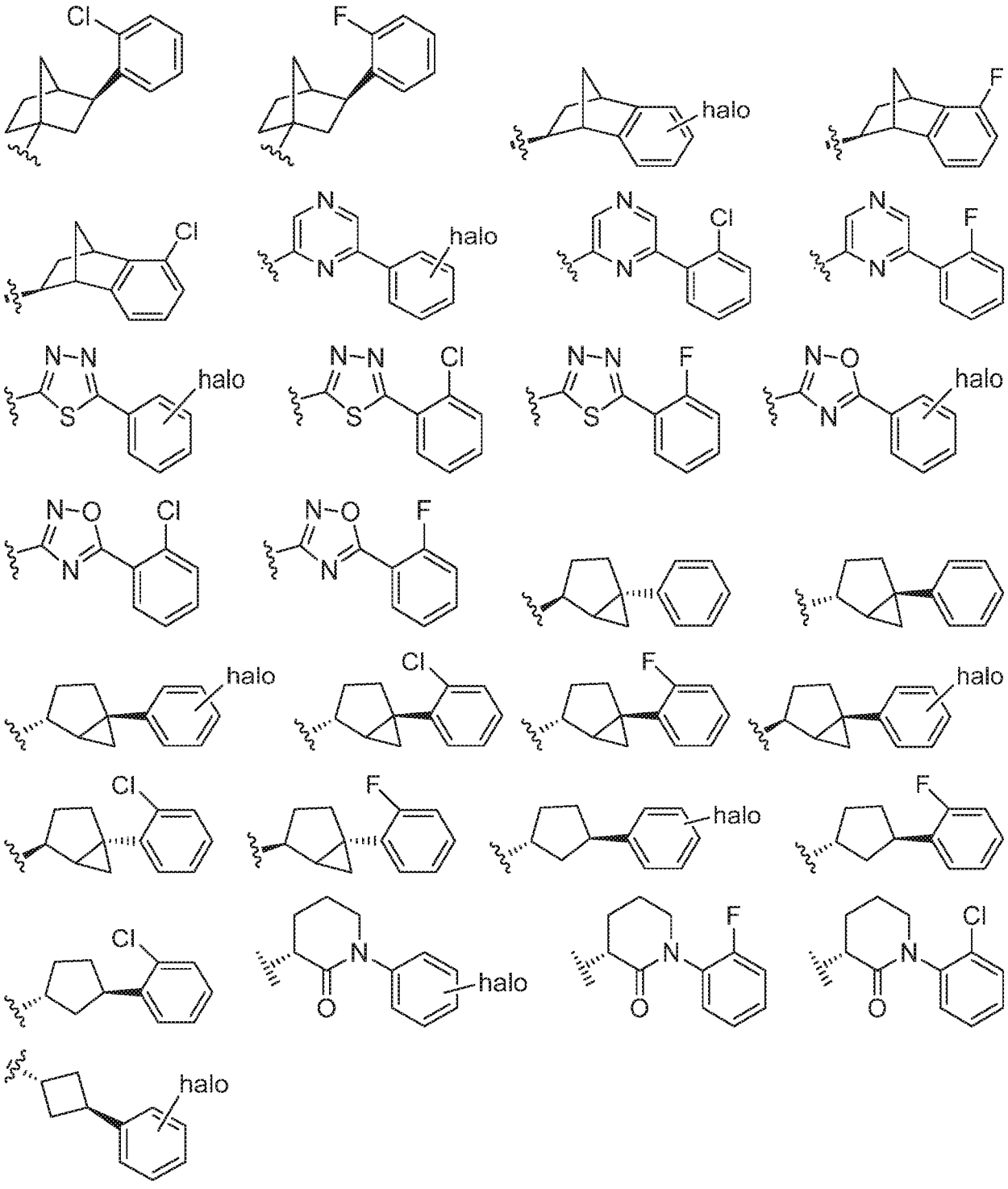
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FIG. 11D

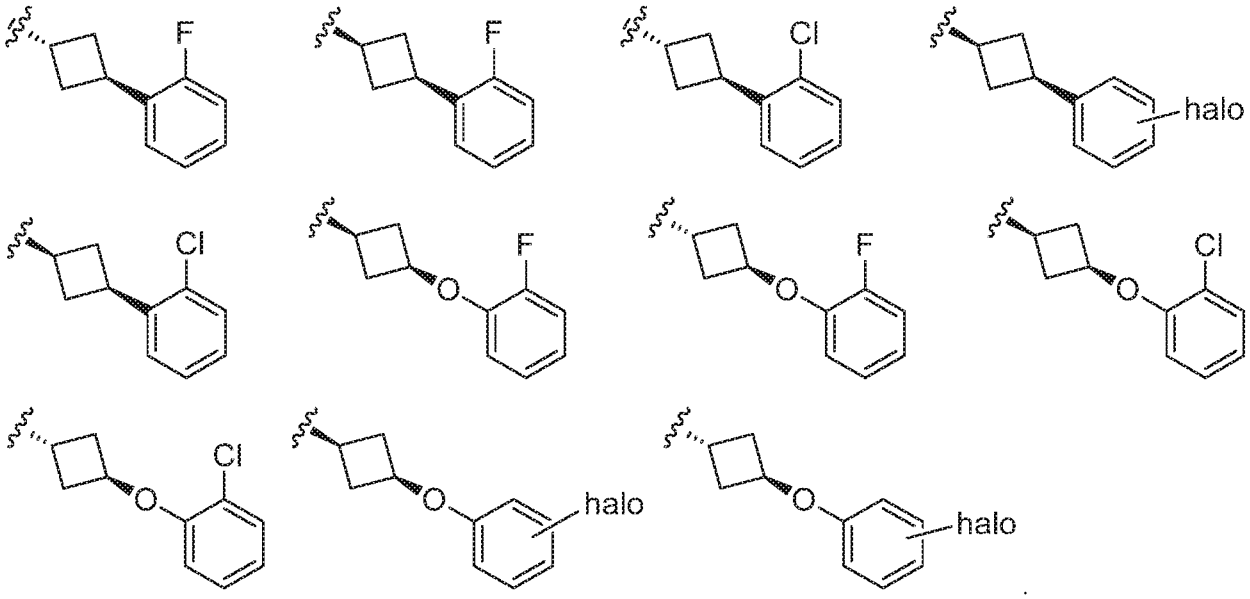

FIG. 12

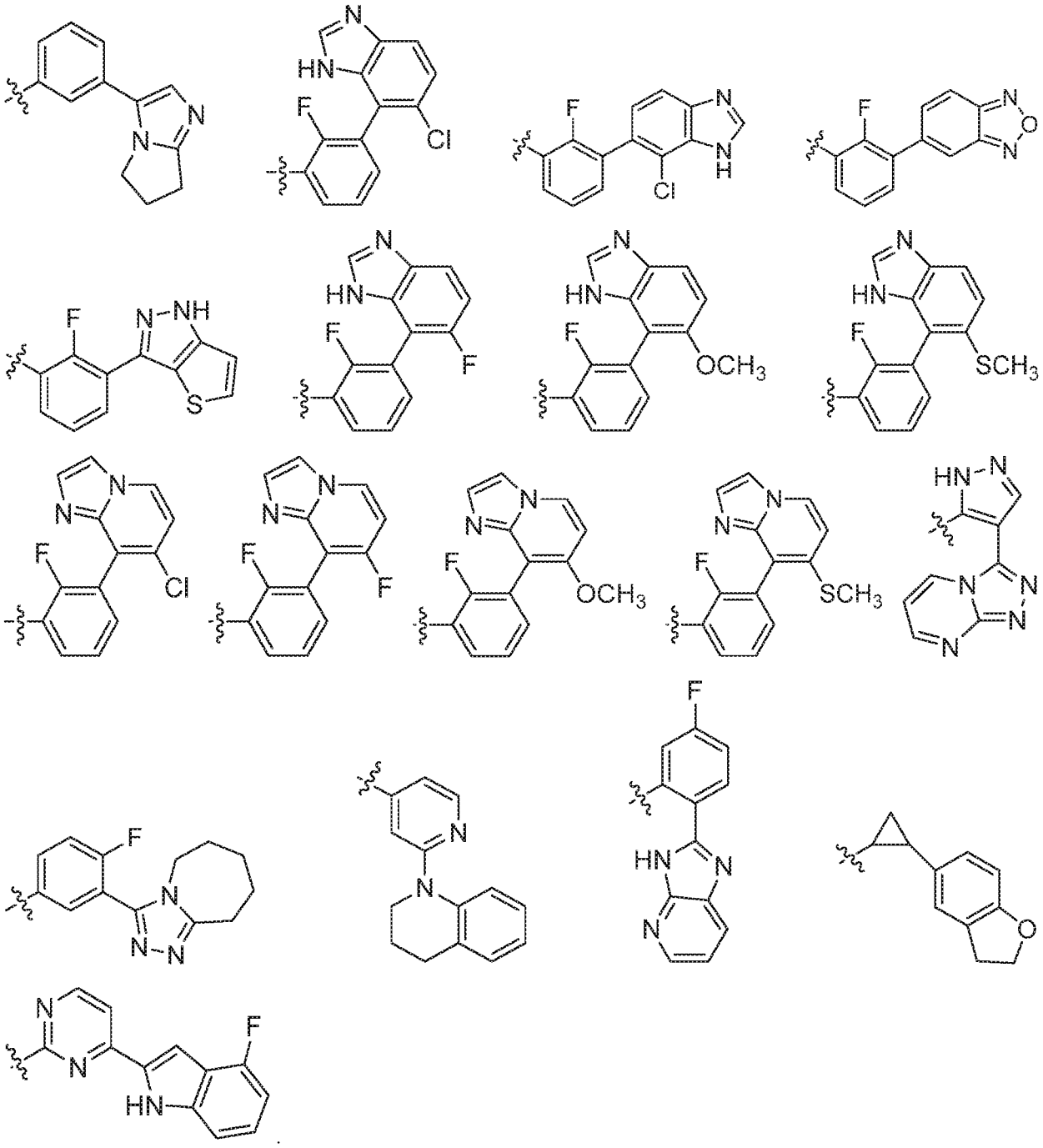

FIG. 13A

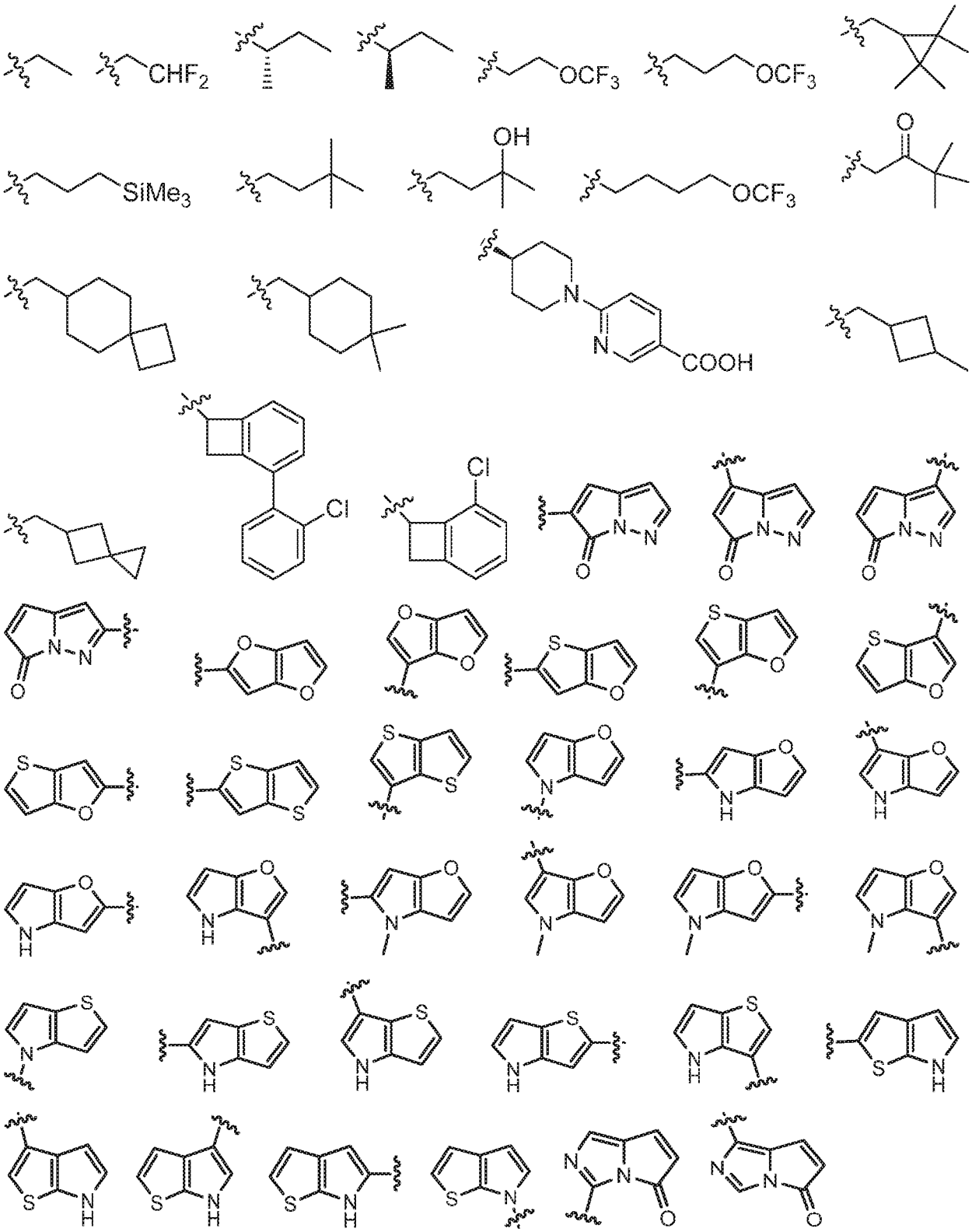

FIG. 13B

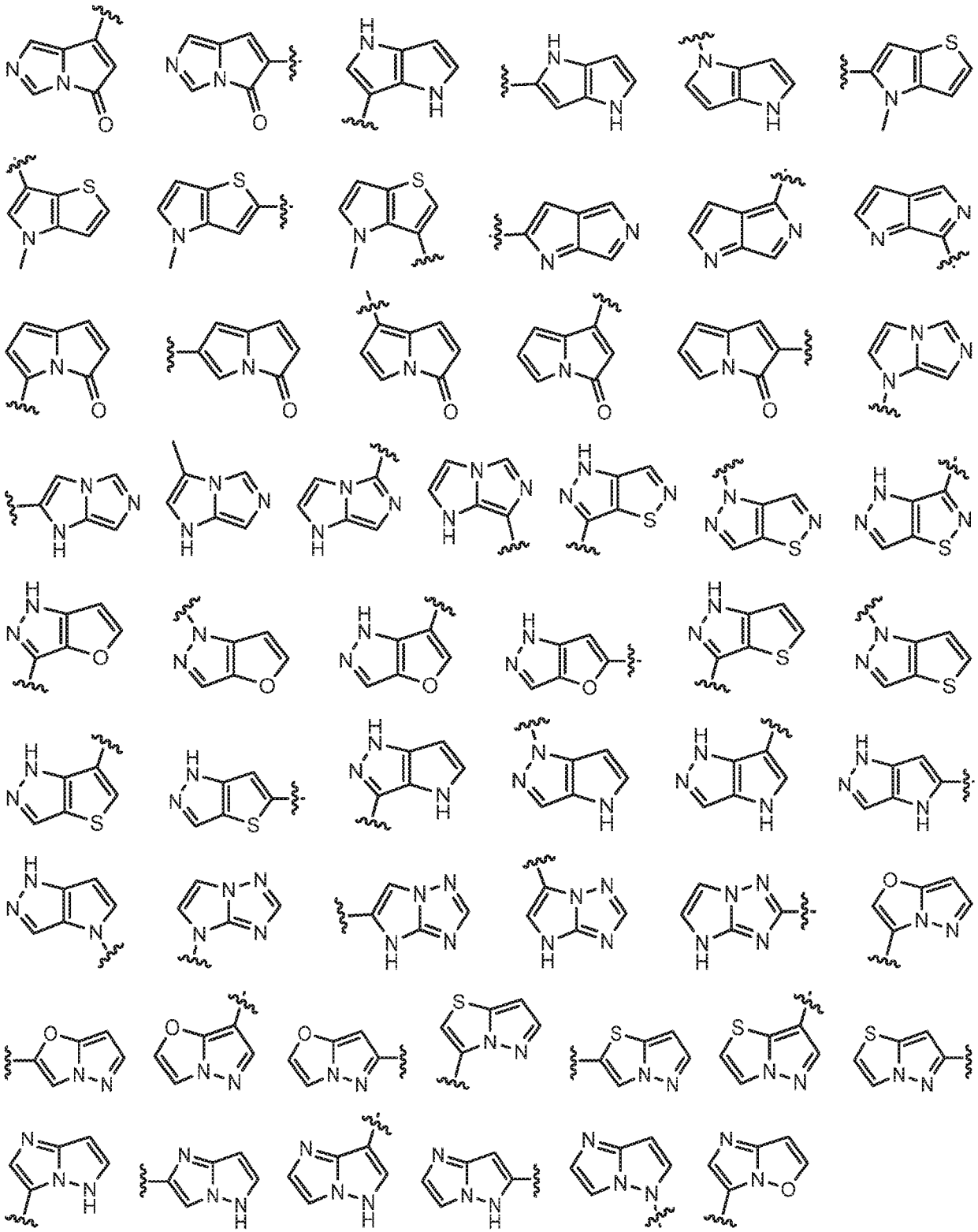

FIG. 13C

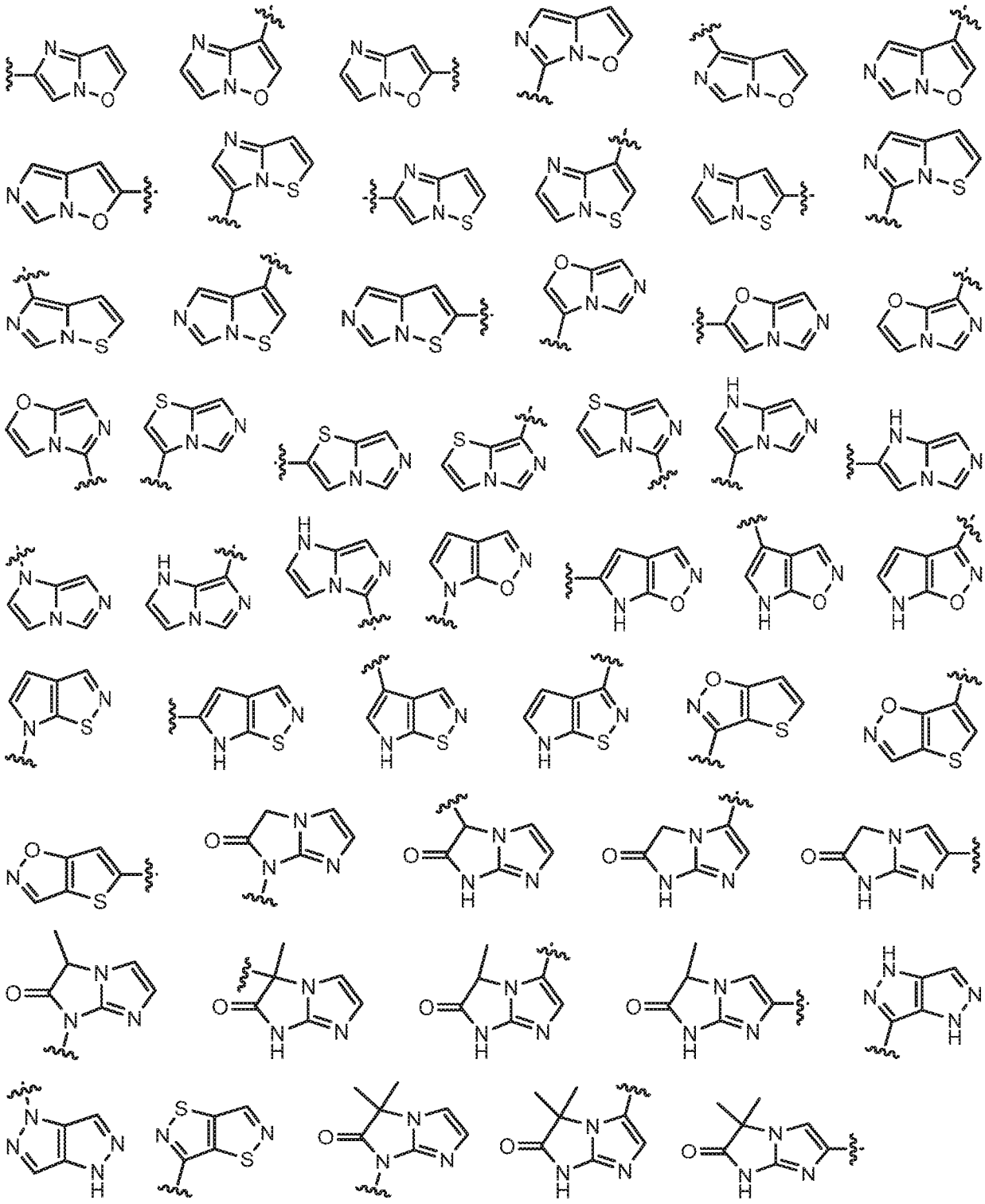

FIG. 13D

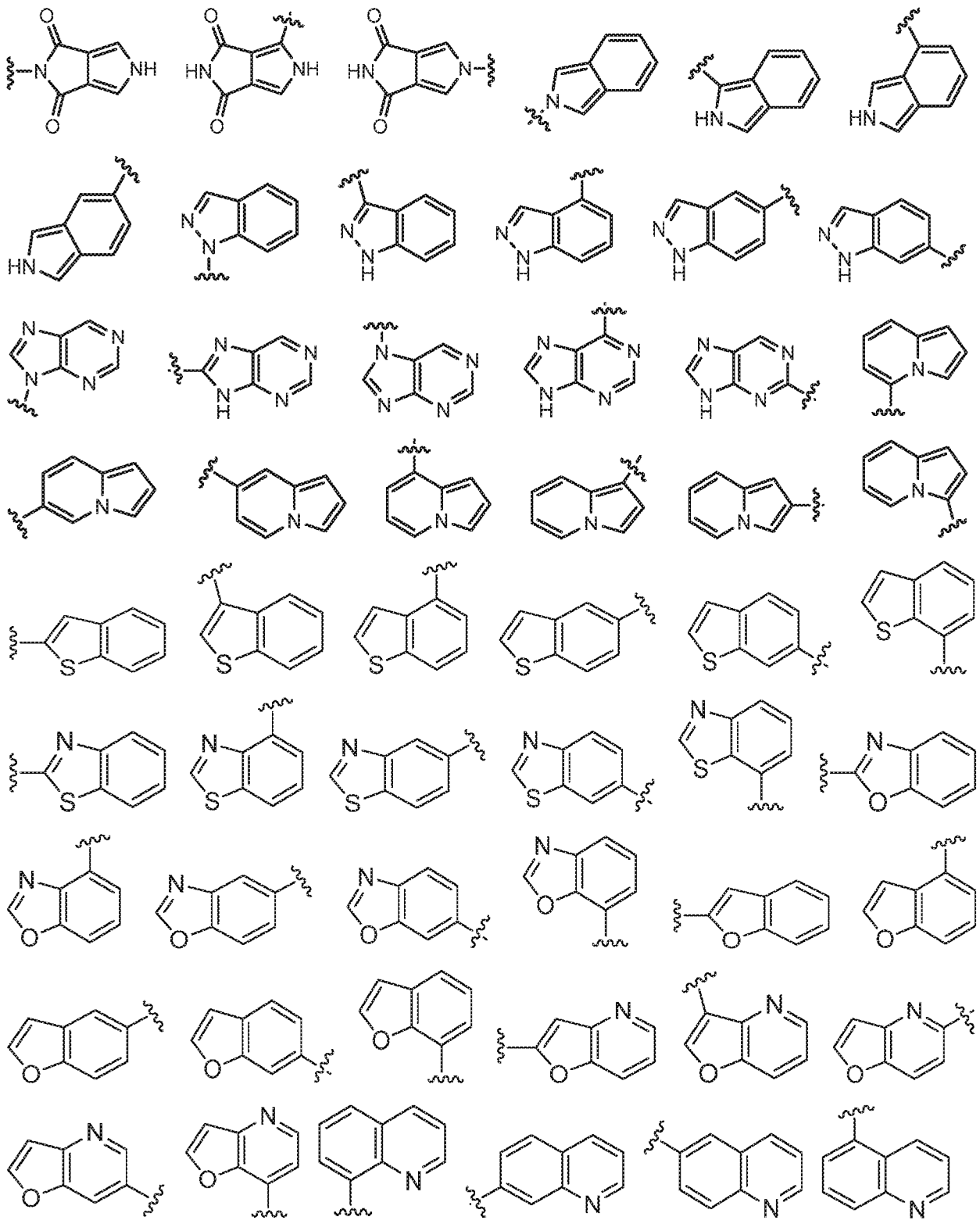

FIG. 13E

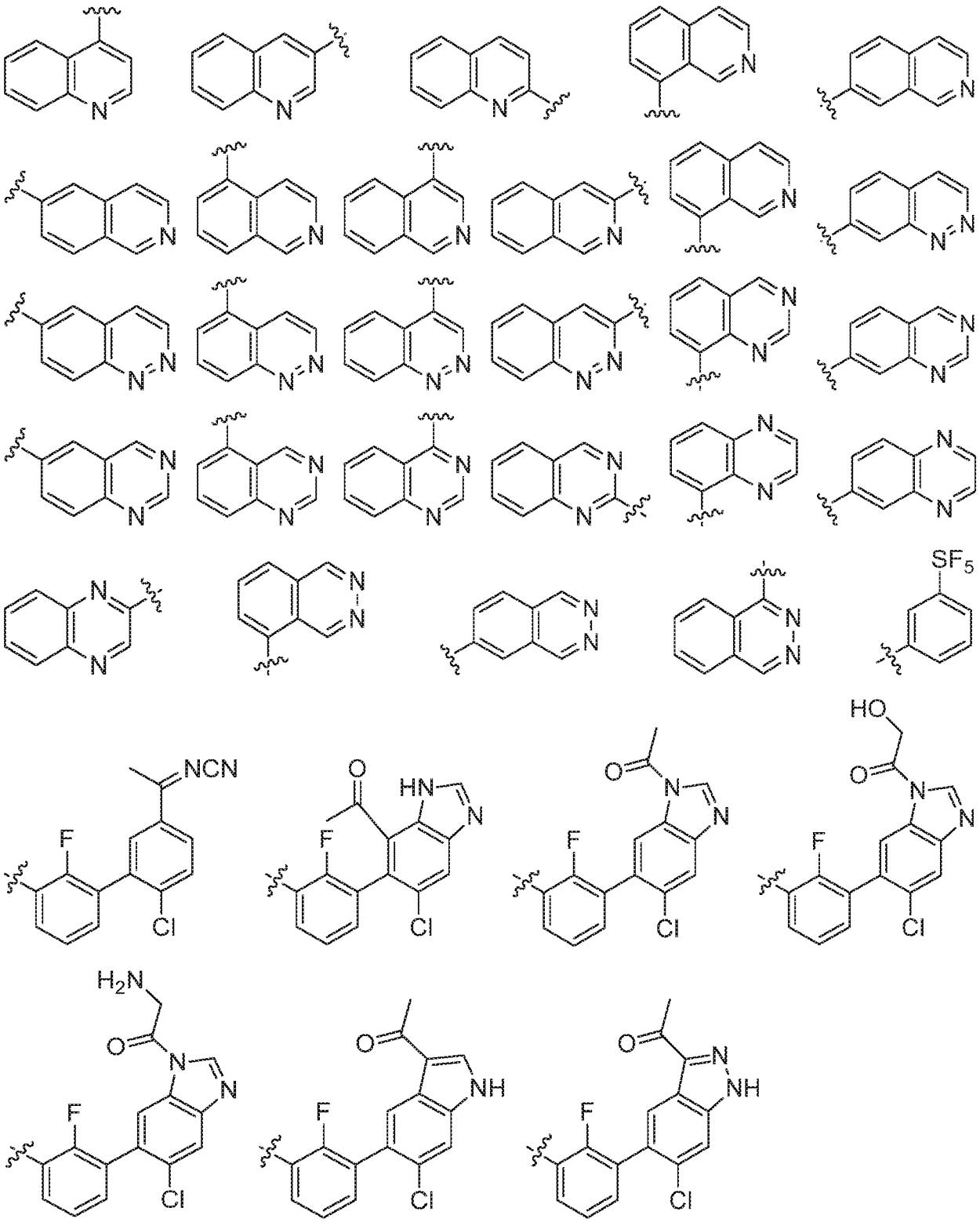

FIG. 13F

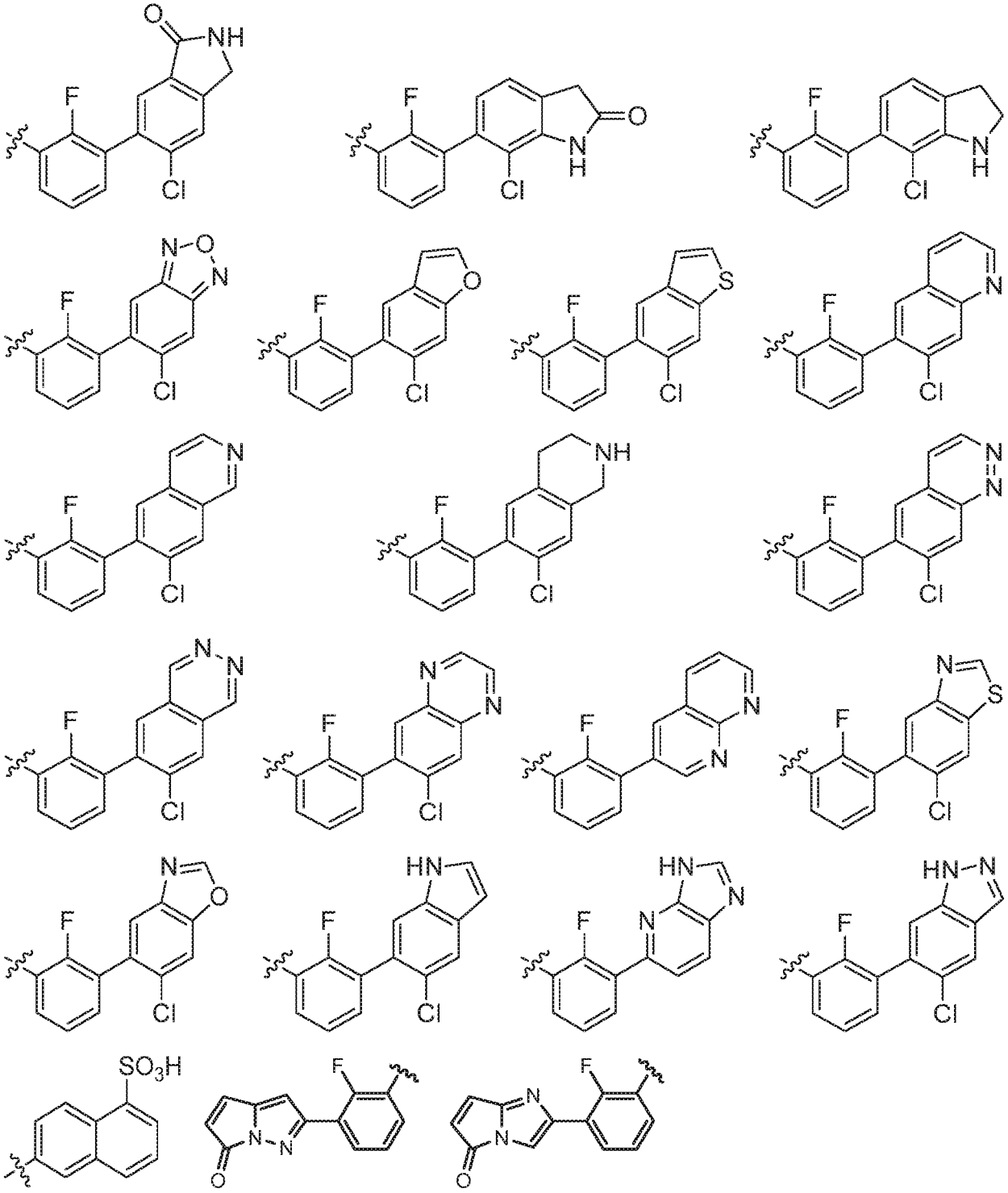

FIG. 13G

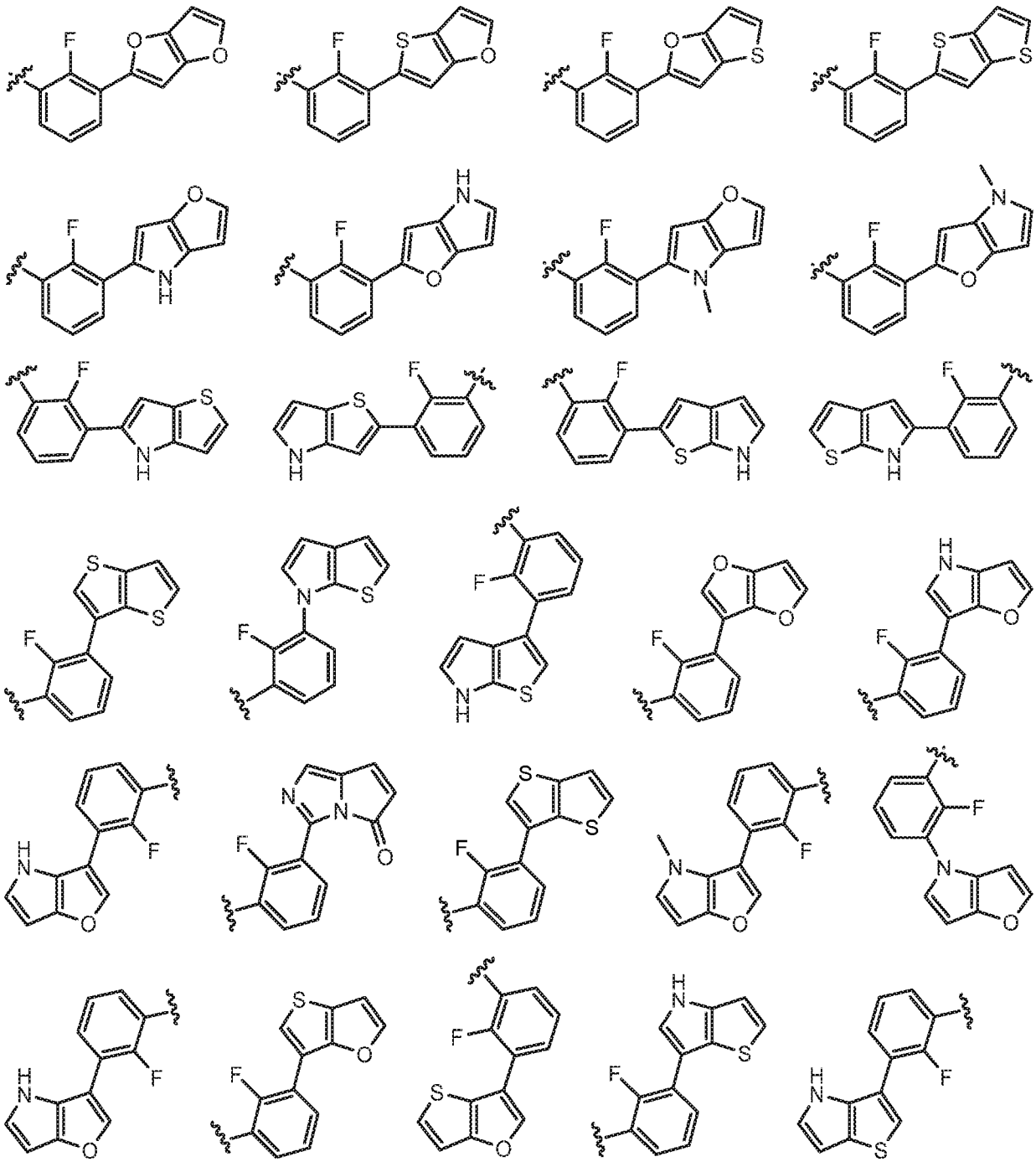

FIG. 13H

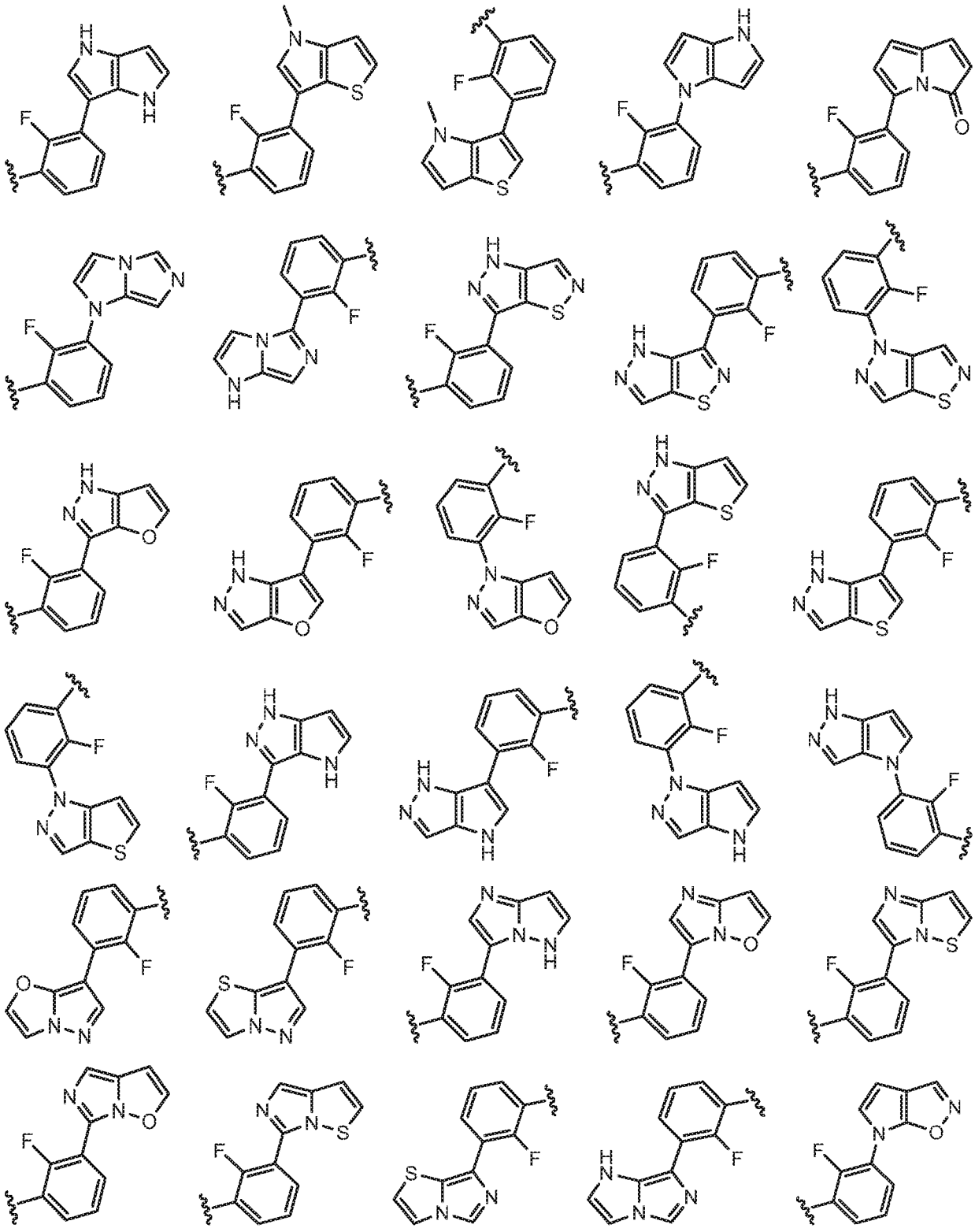

FIG. 13I

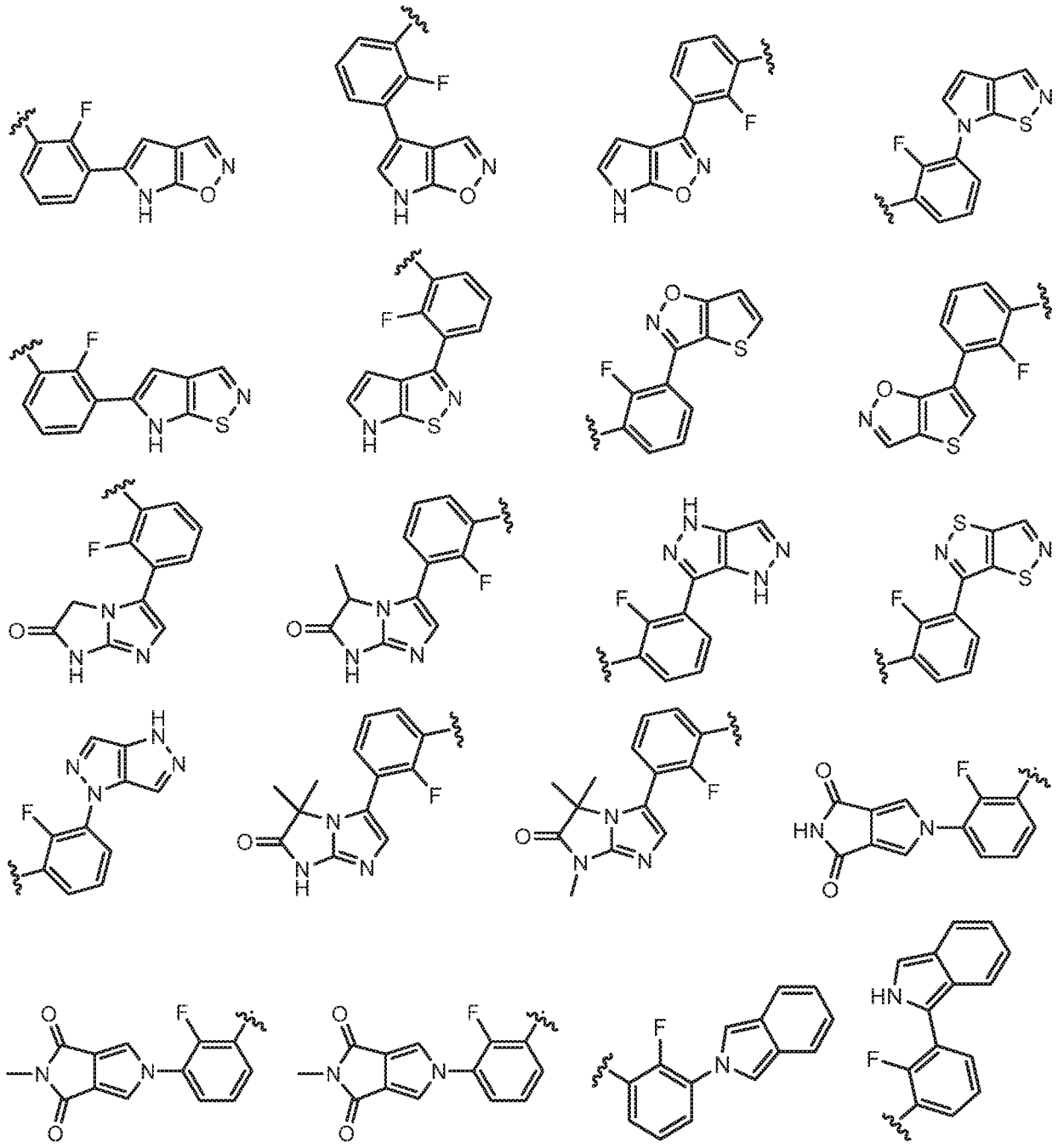

FIG. 13J

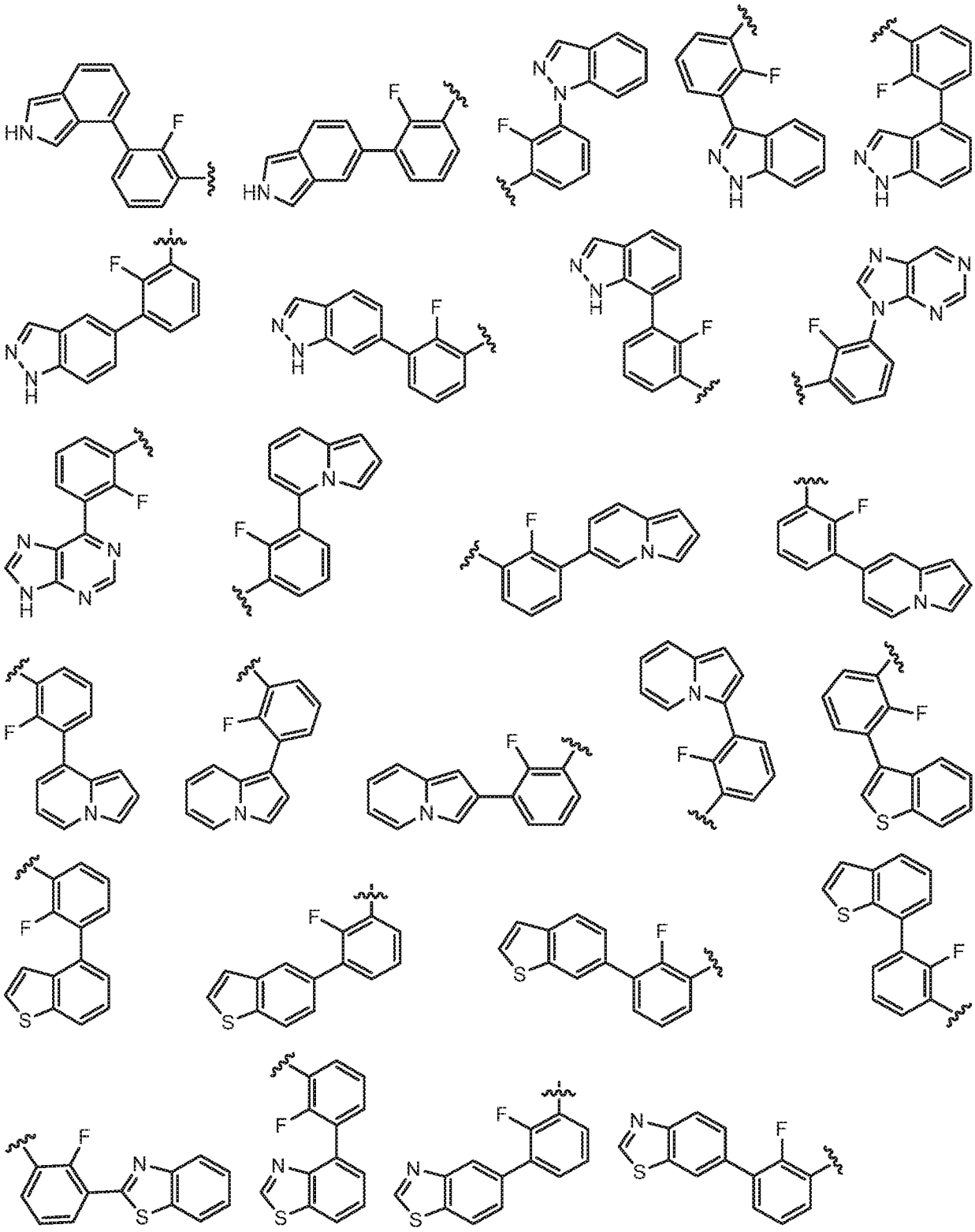

FIG. 13K

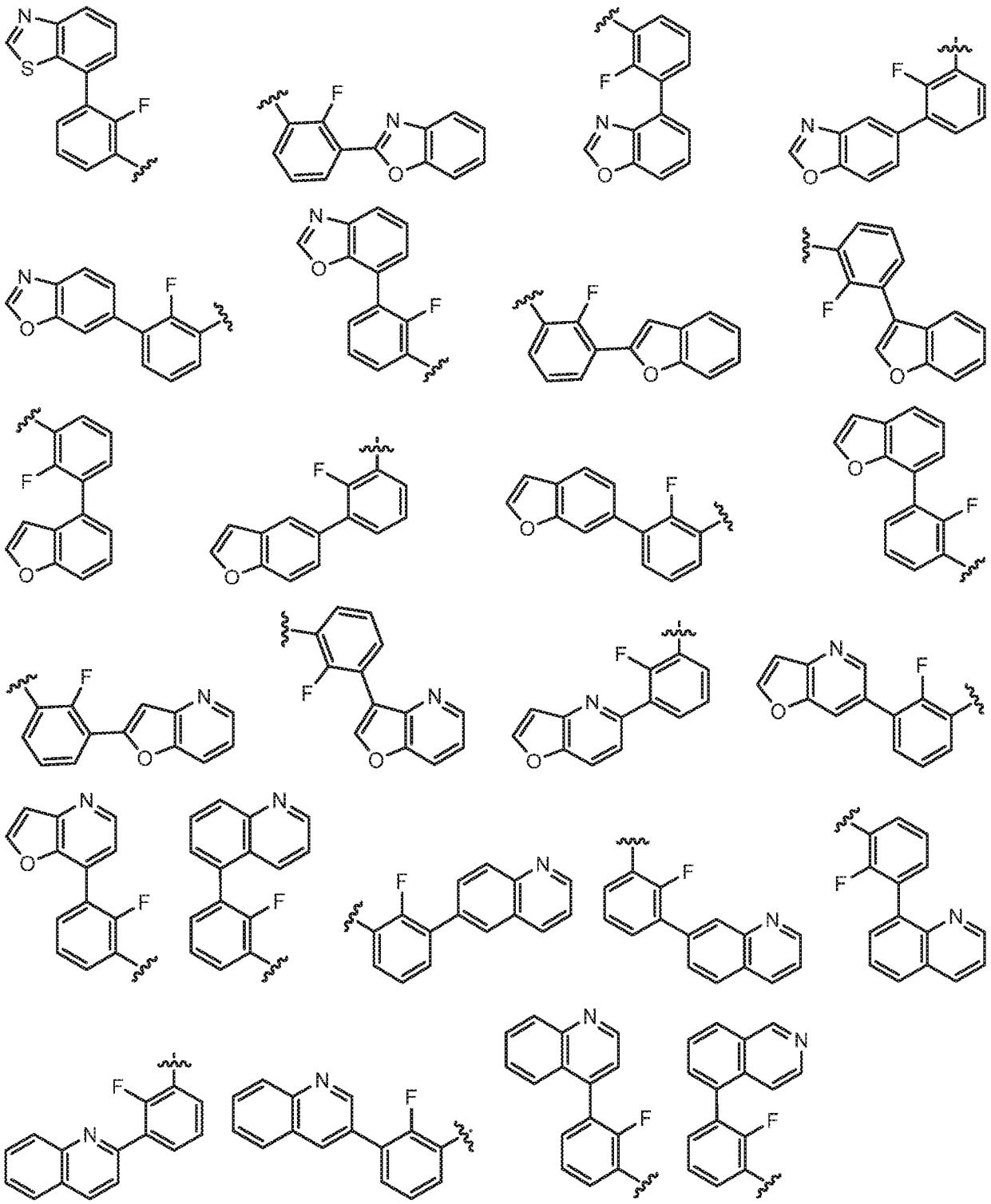

FIG. 13L

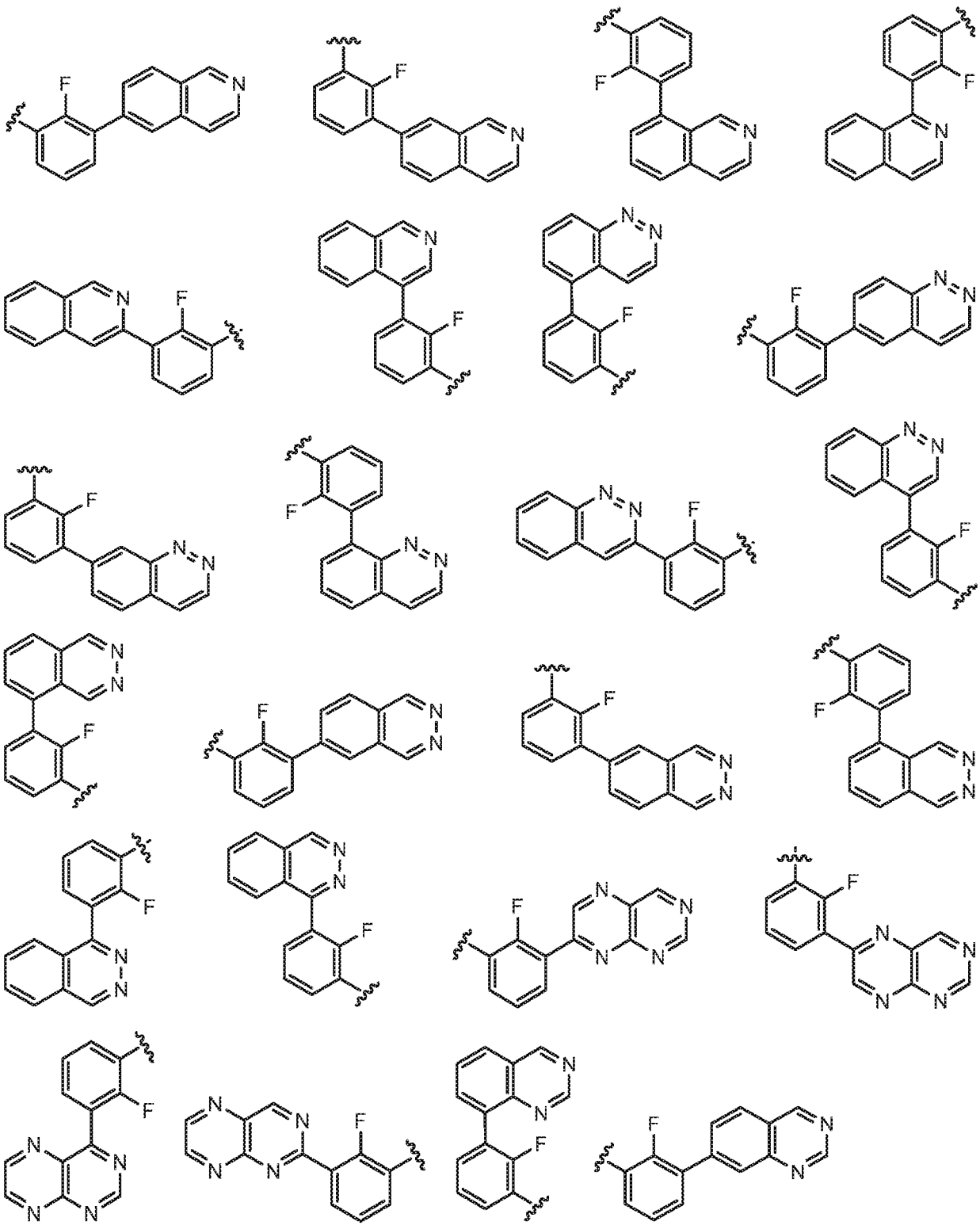

FIG. 13M

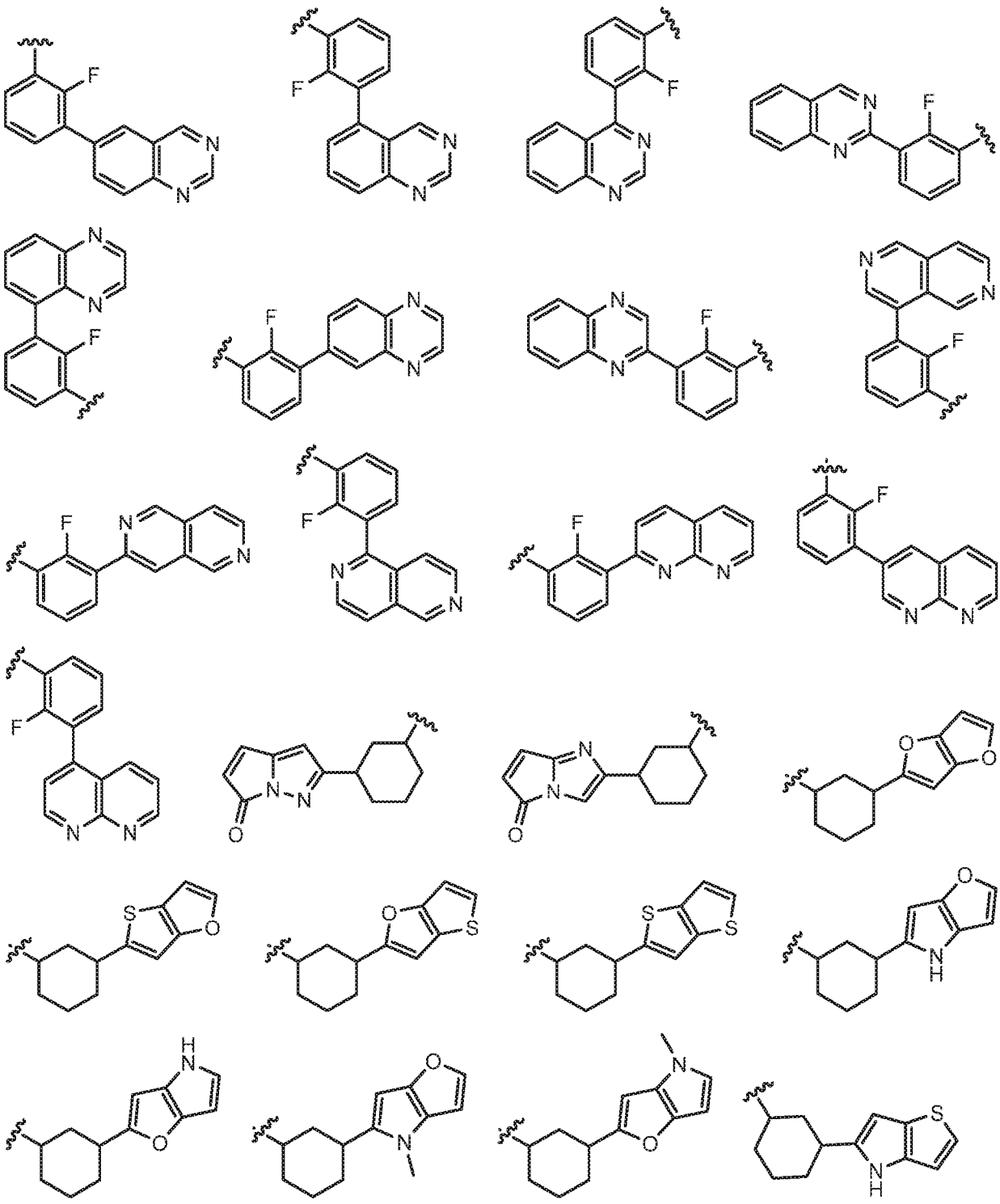

FIG. 13N

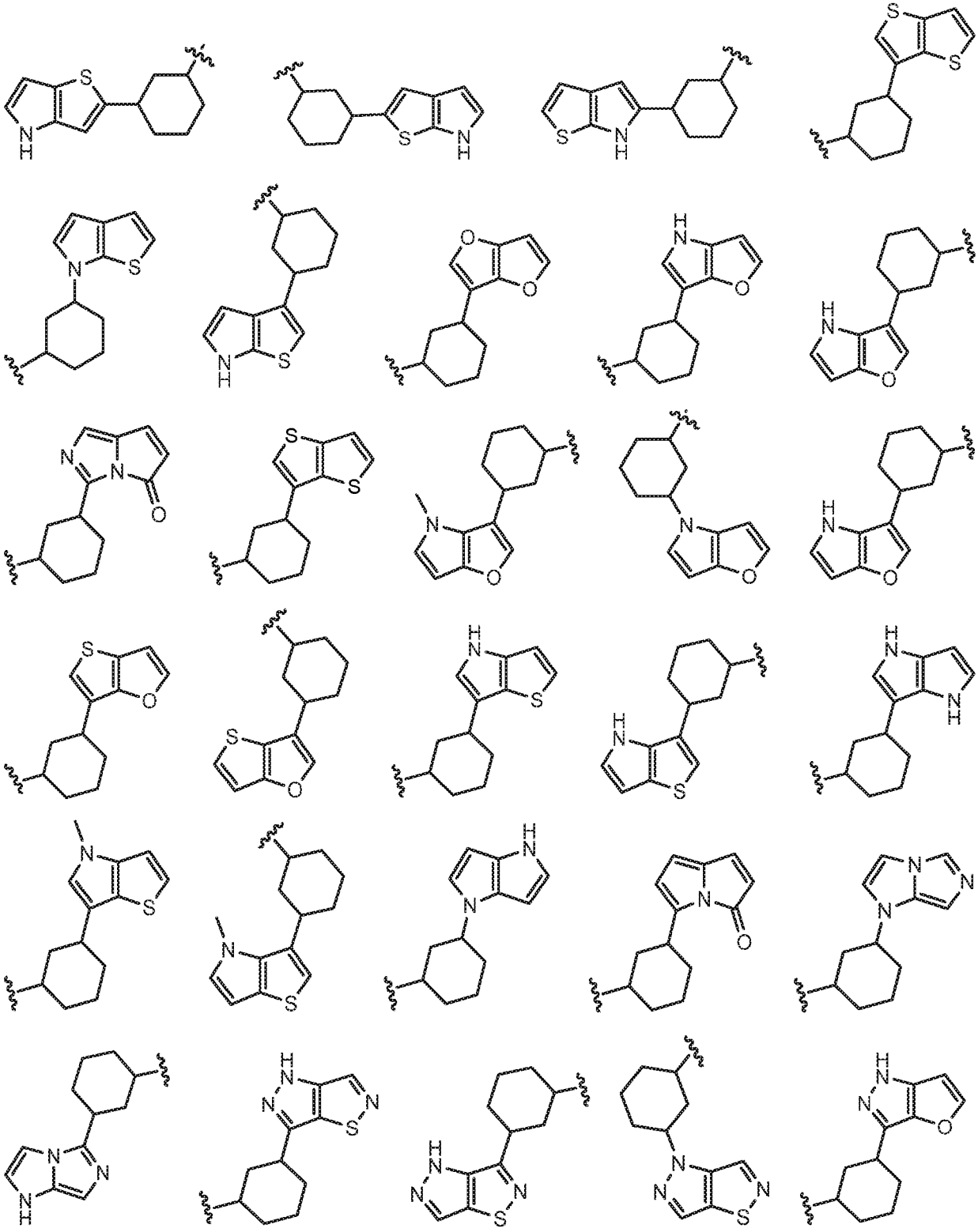

FIG. 13O

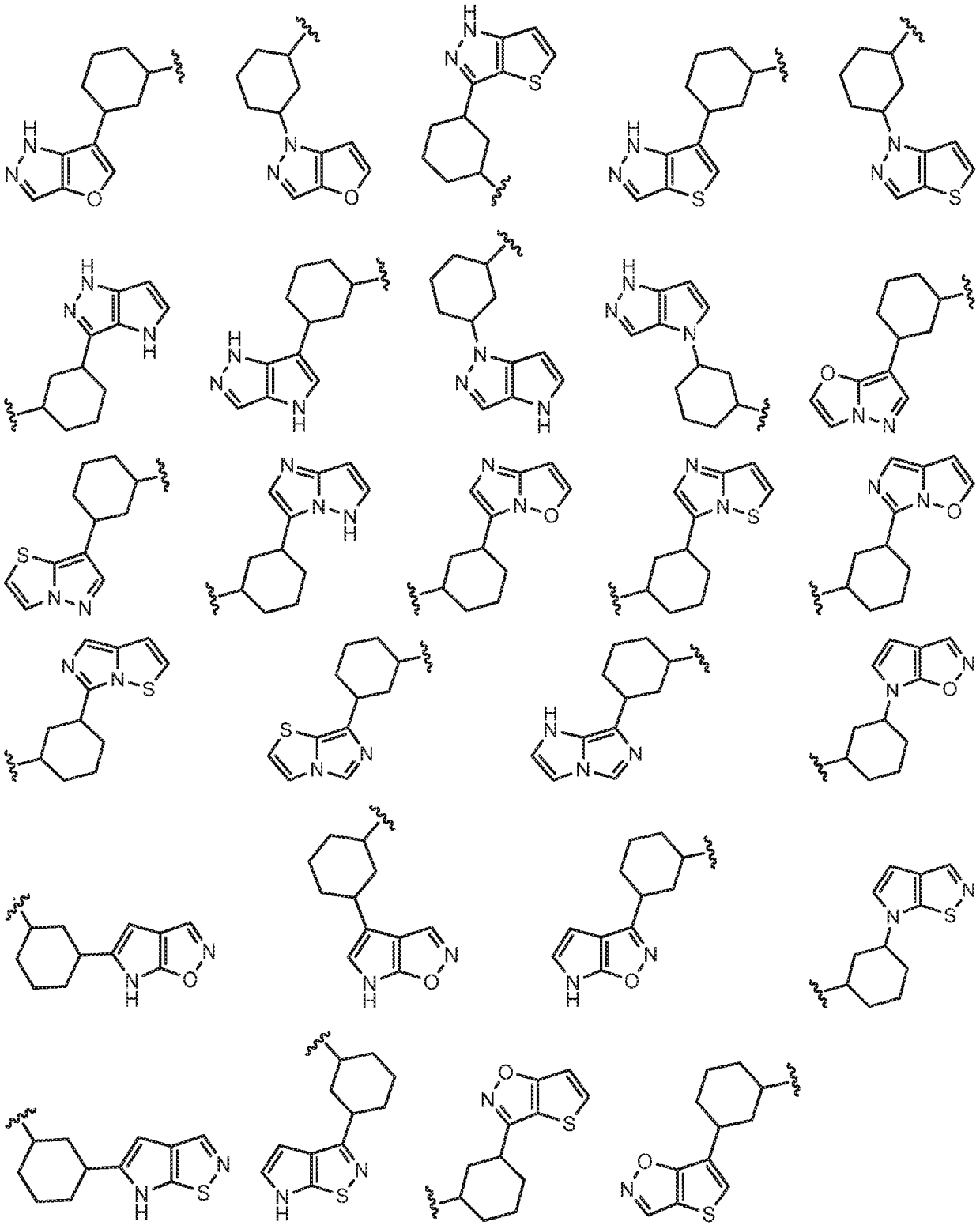

FIG. 13P

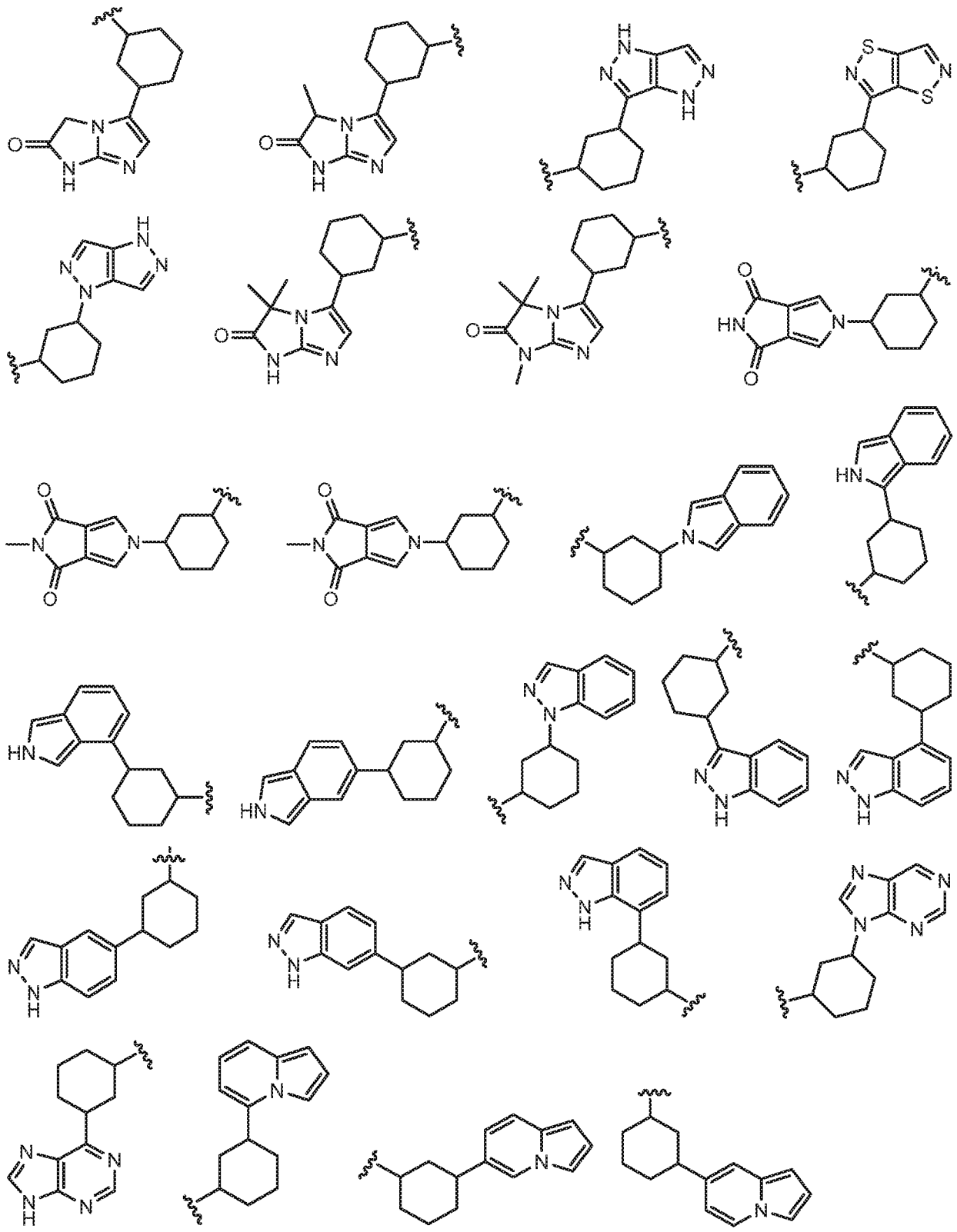

FIG. 13Q

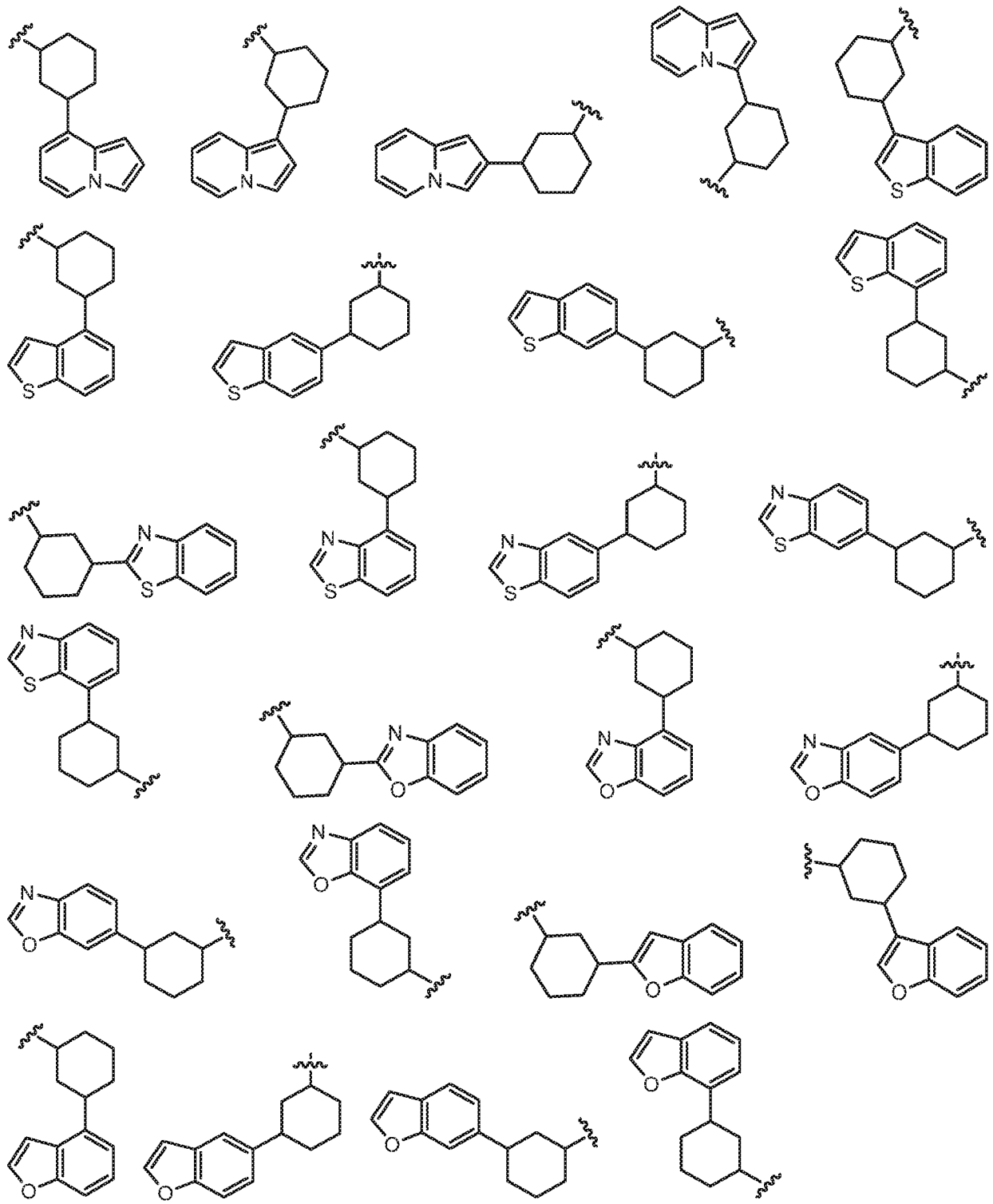

FIG. 13R

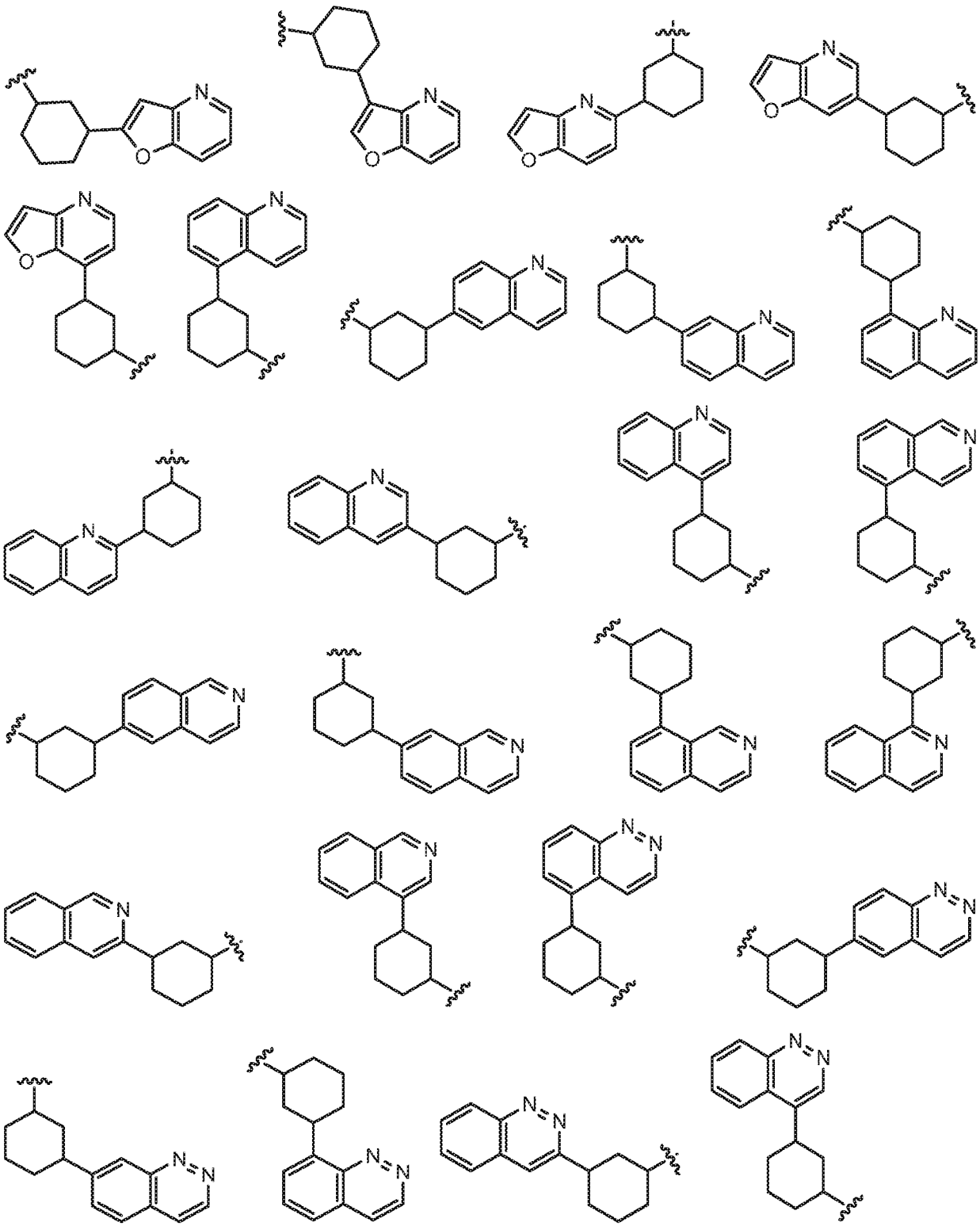

FIG. 13S

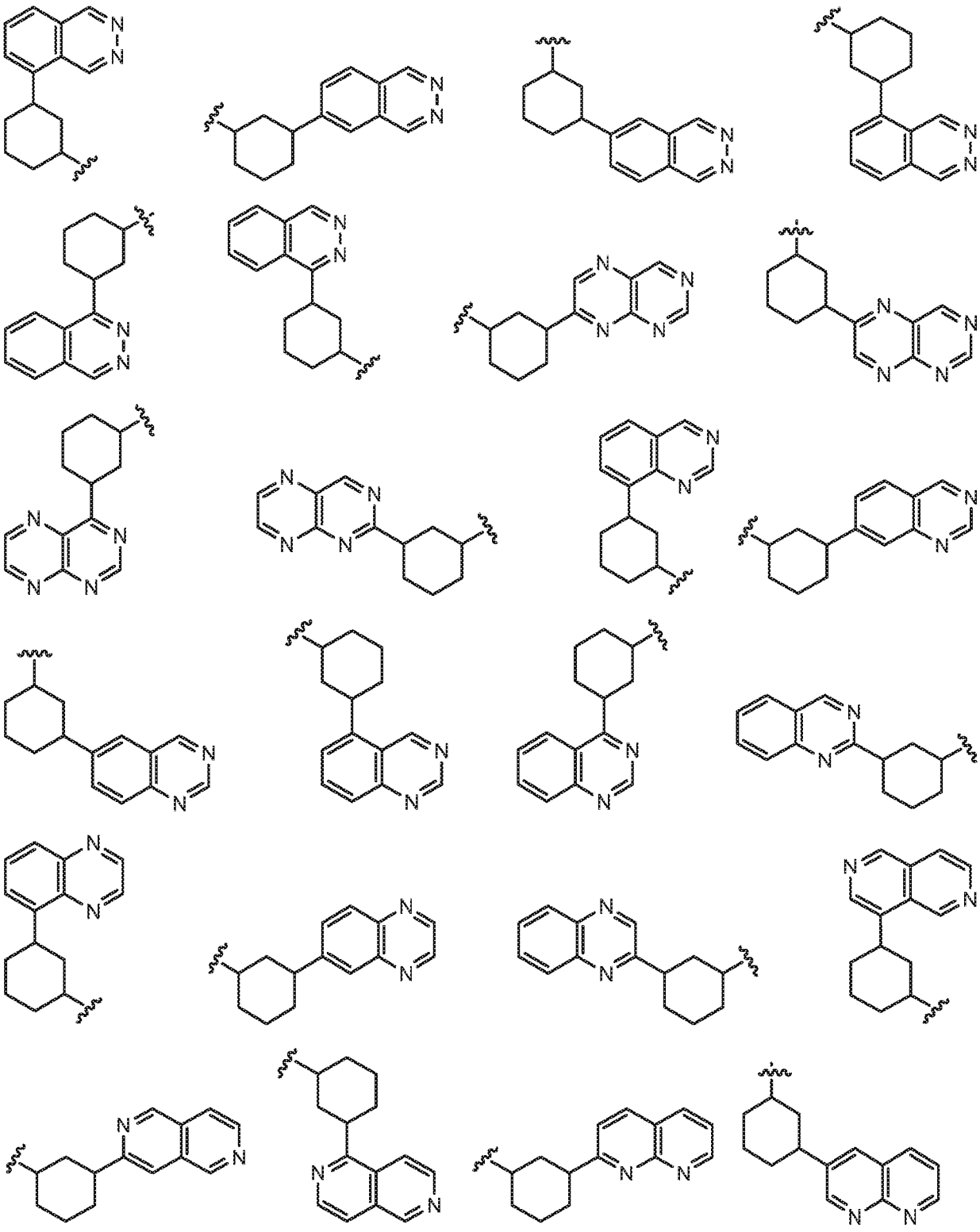

FIG. 13T

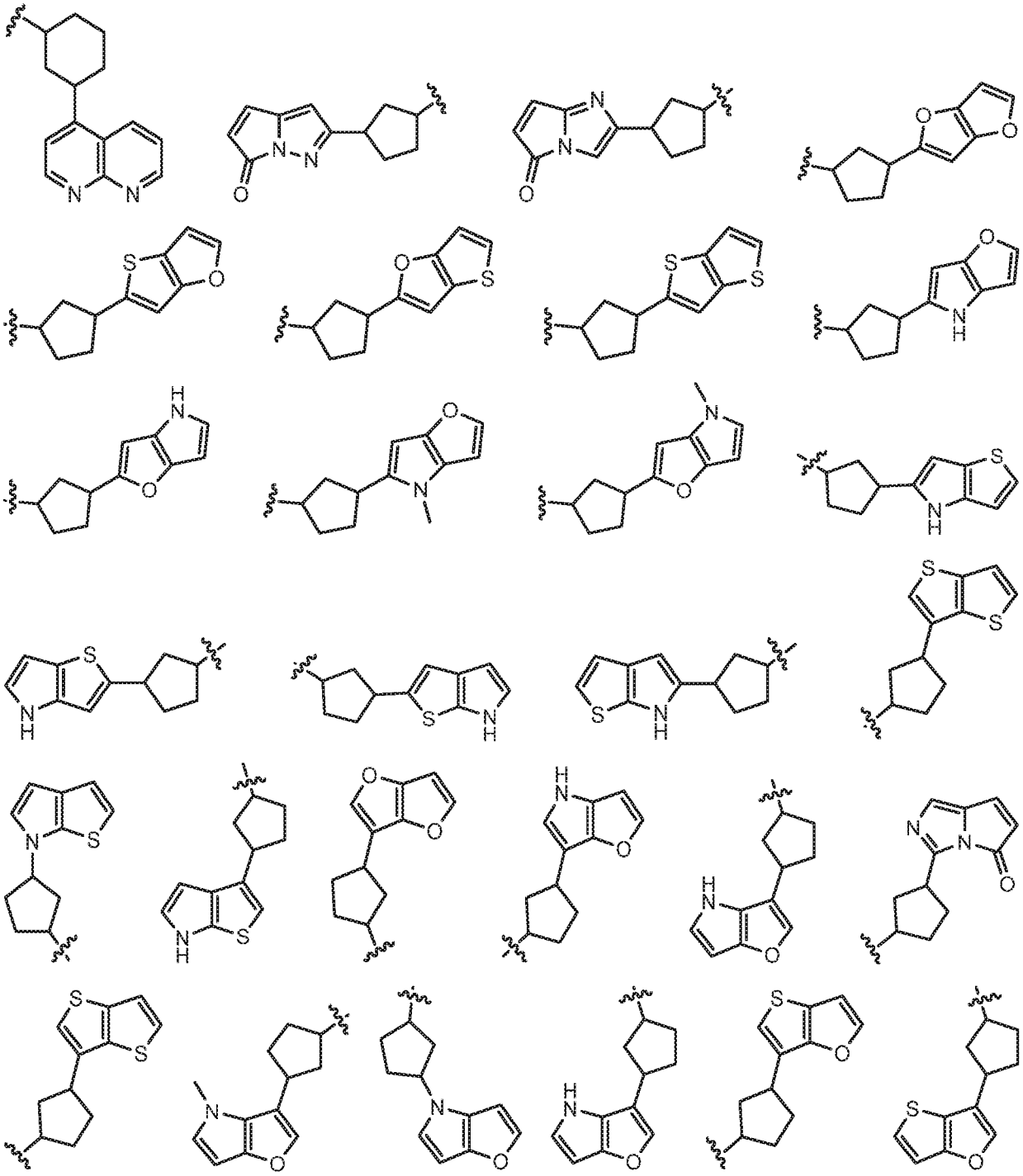

FIG. 13U

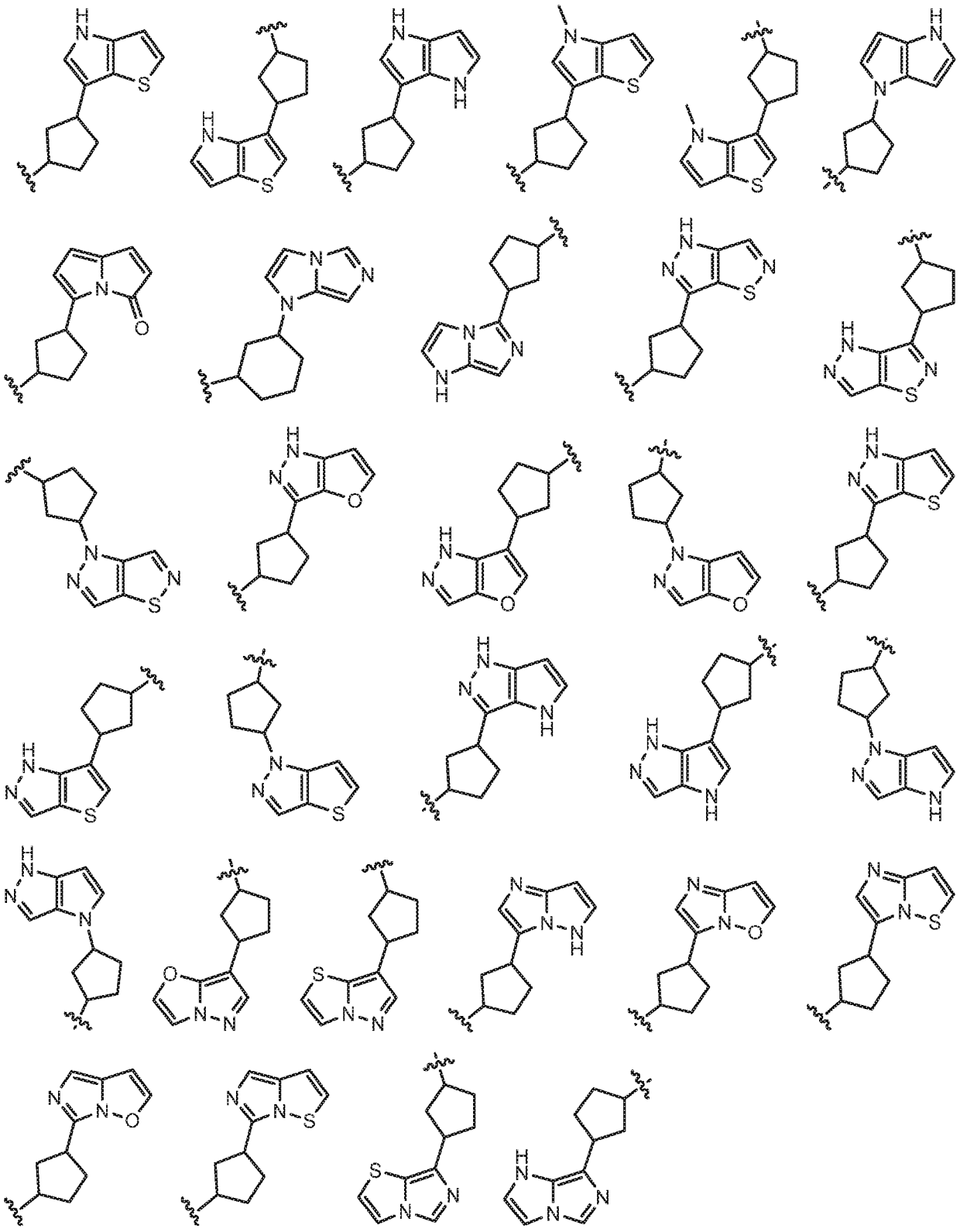

FIG. 13V

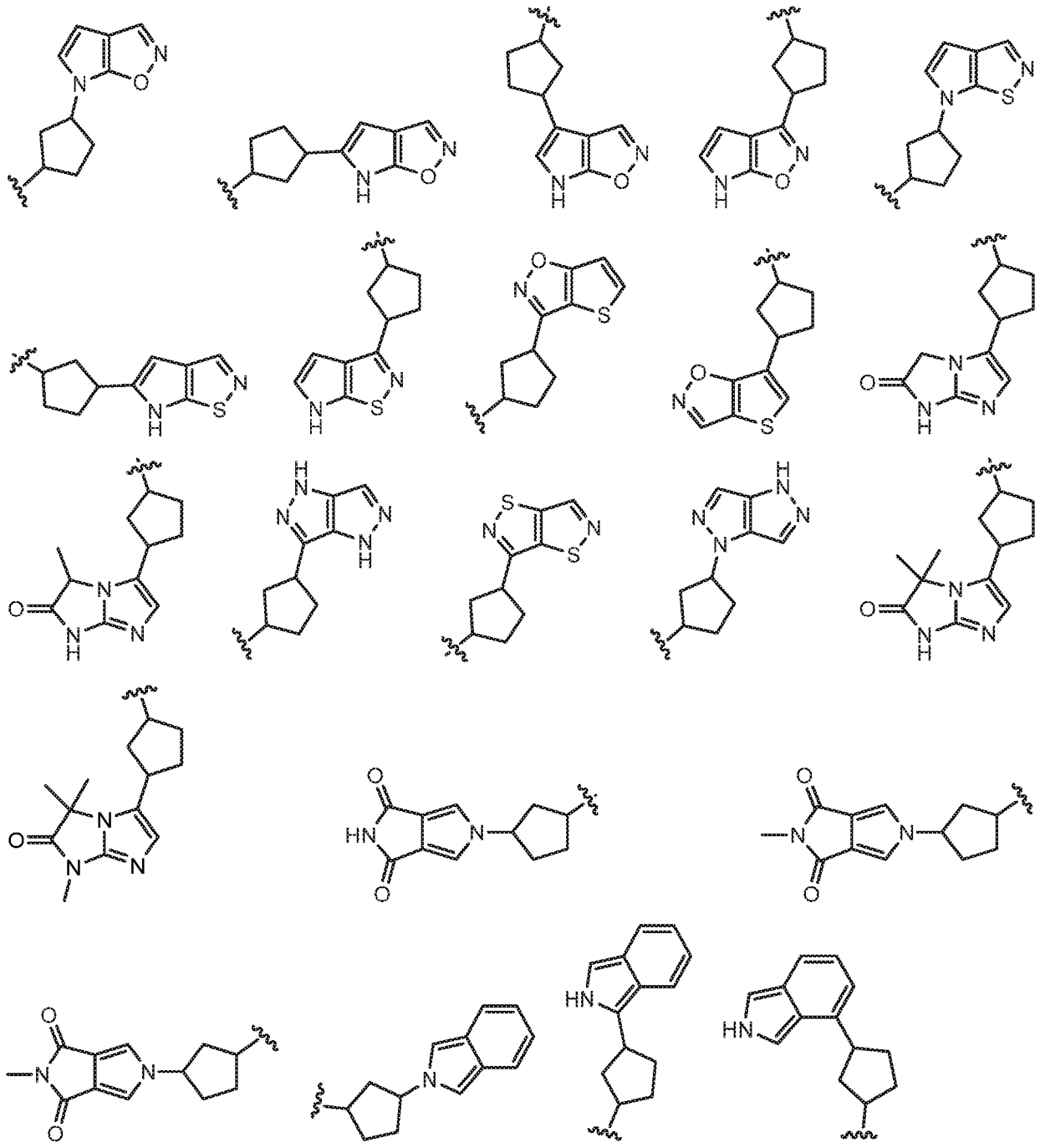

FIG. 13W

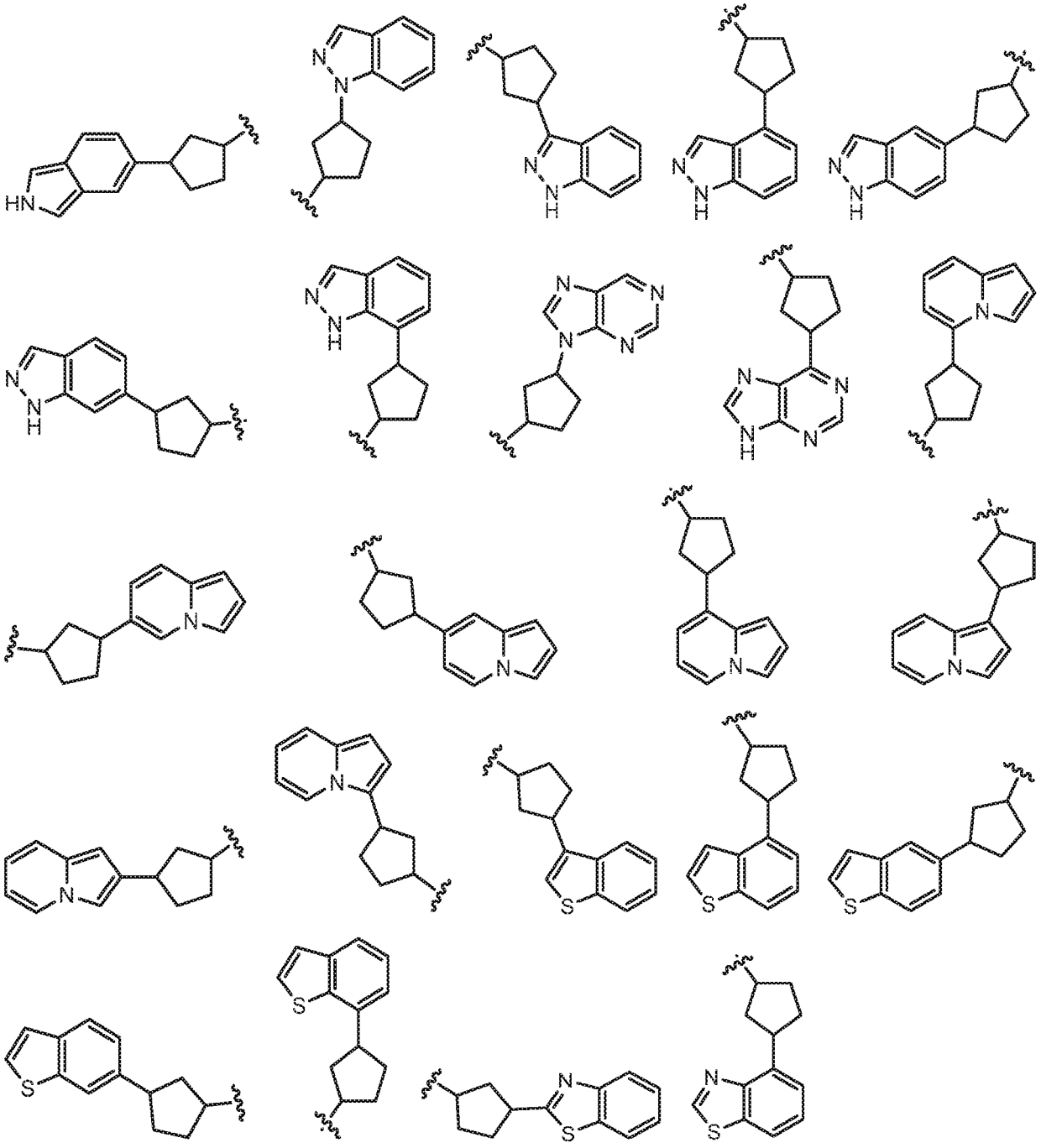

FIG. 13X

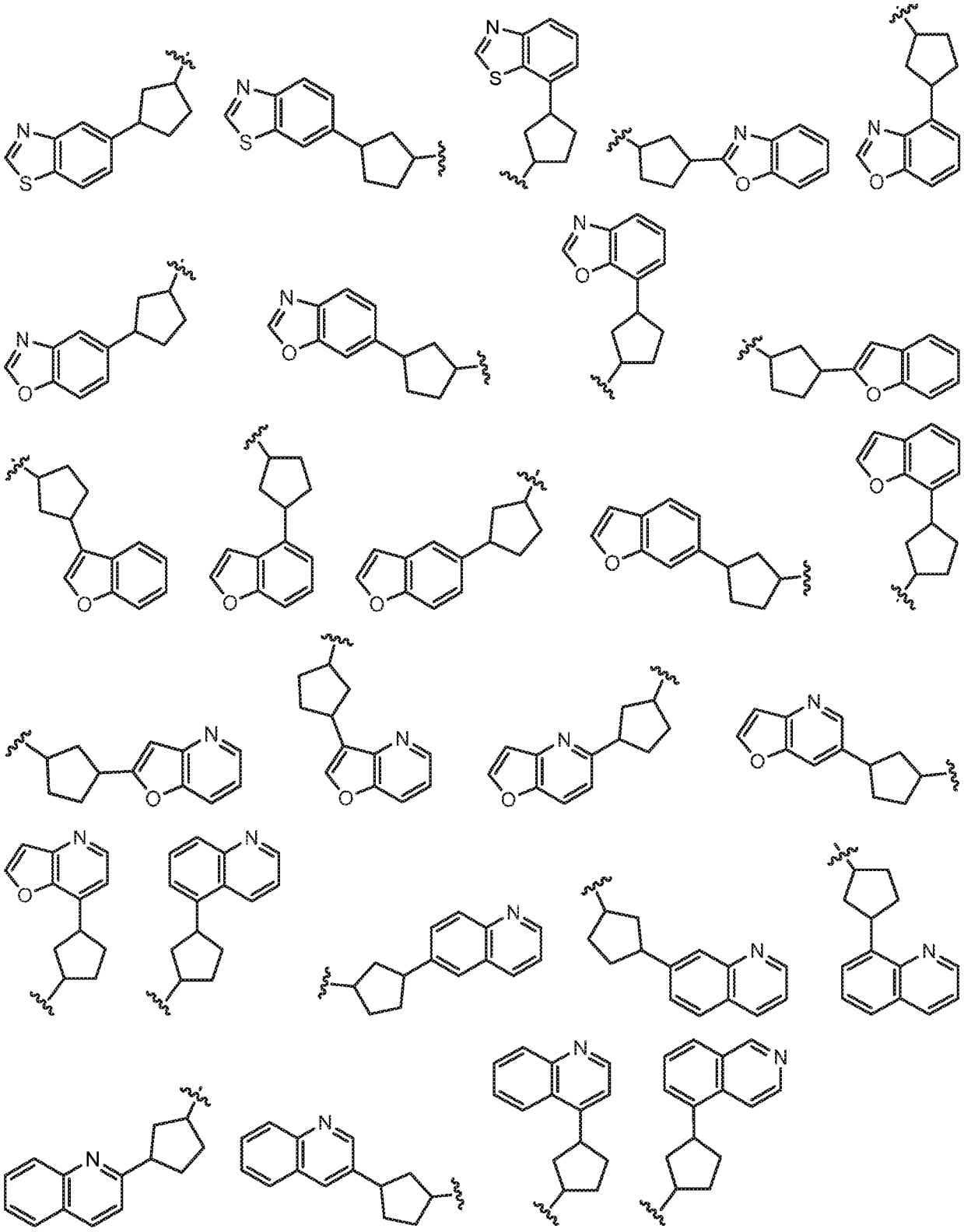

FIG. 13Y

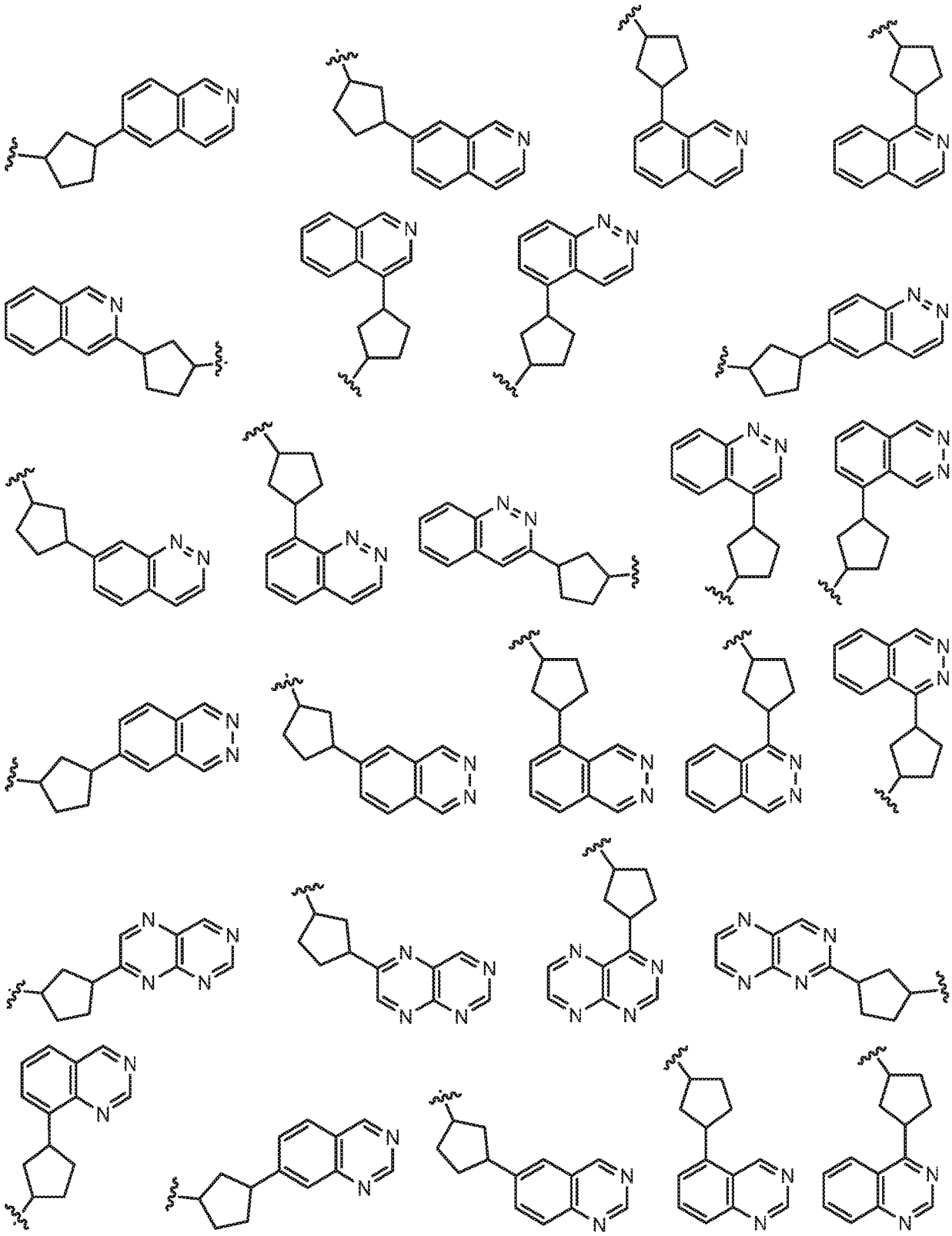

FIG. 13Z

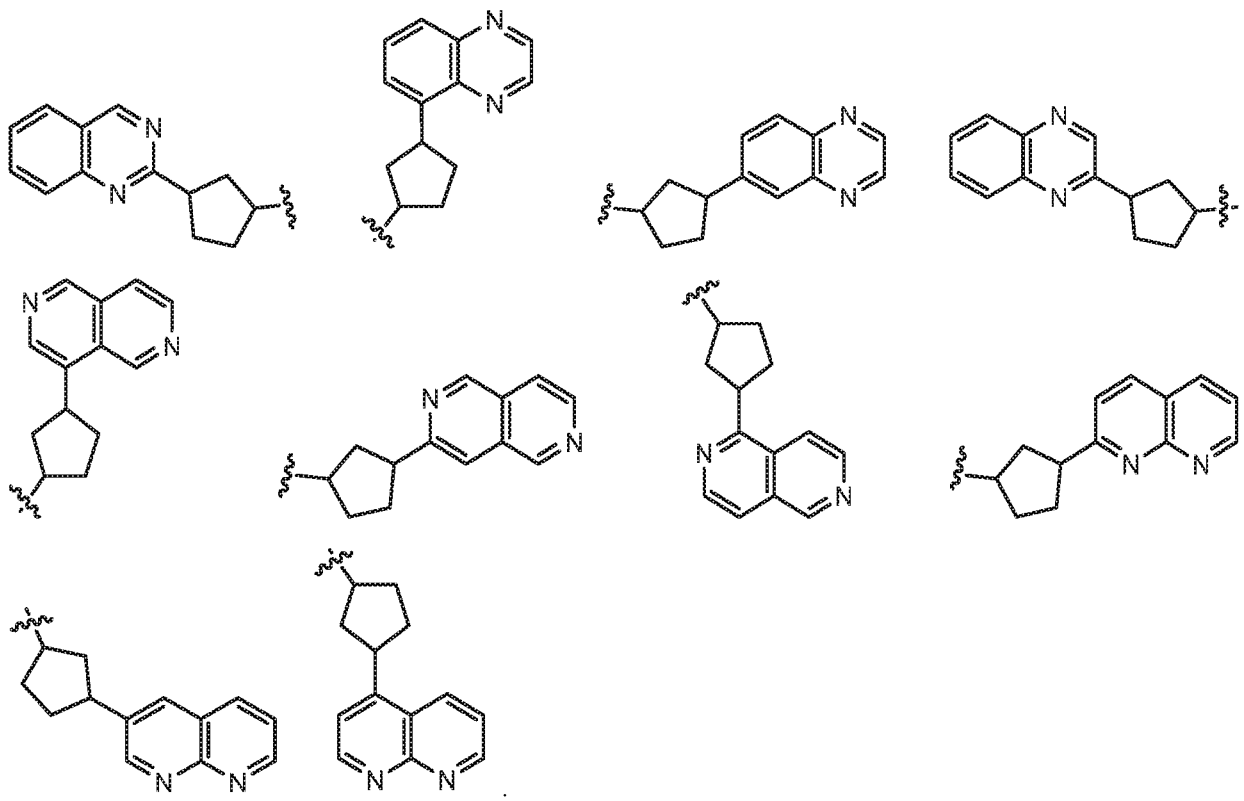

FIG. 14

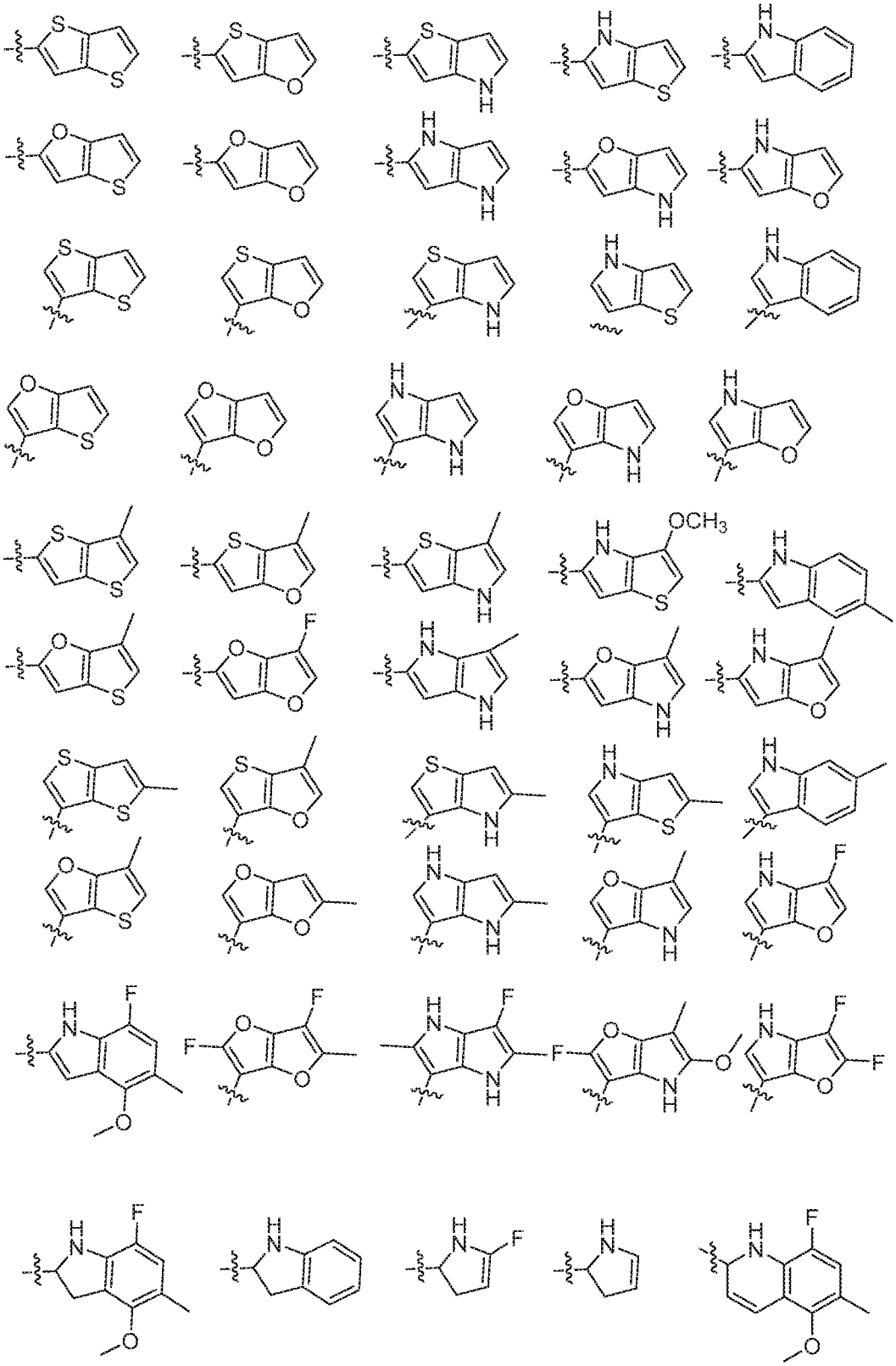

FIG. 15

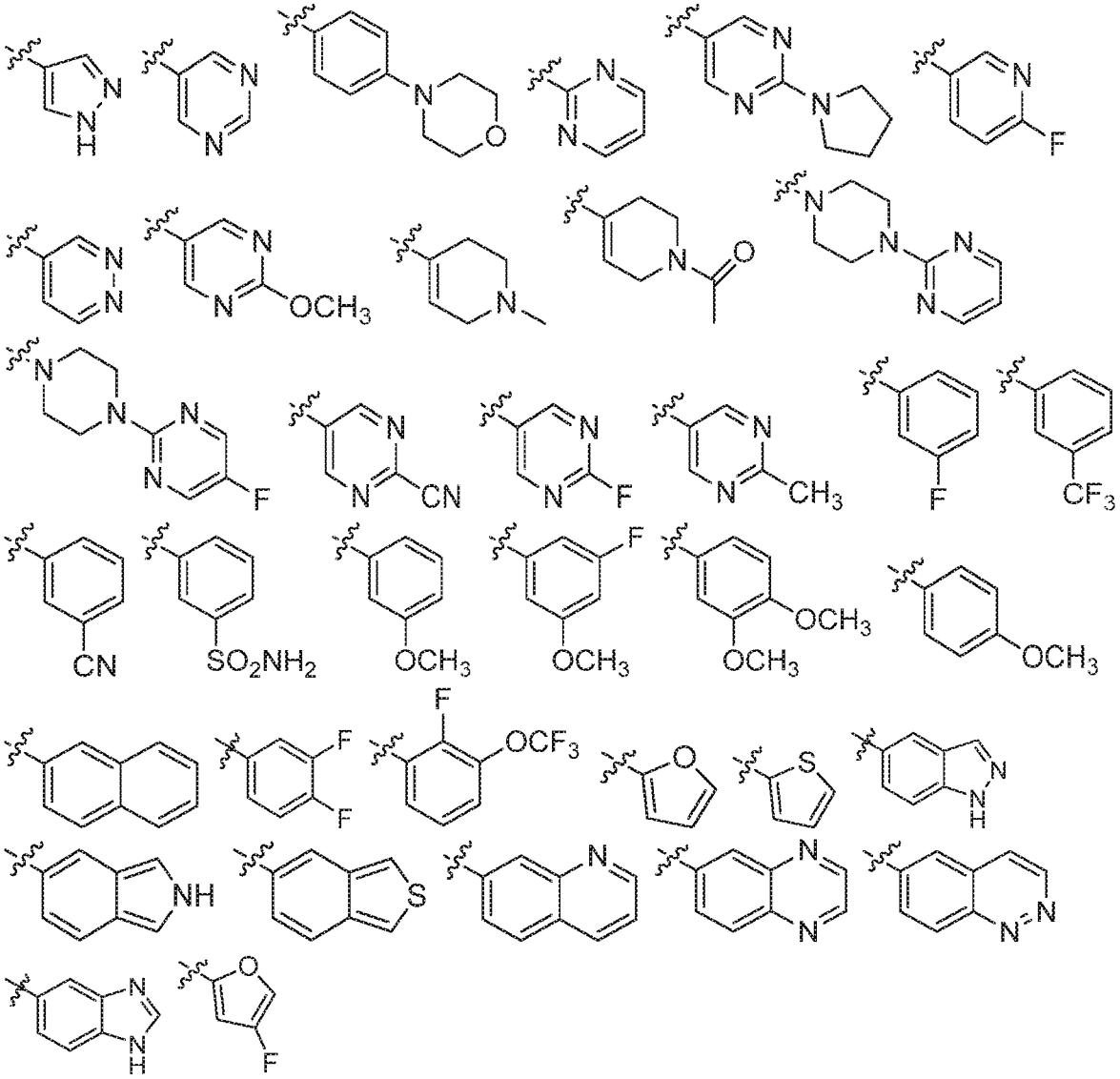
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FIG. 16

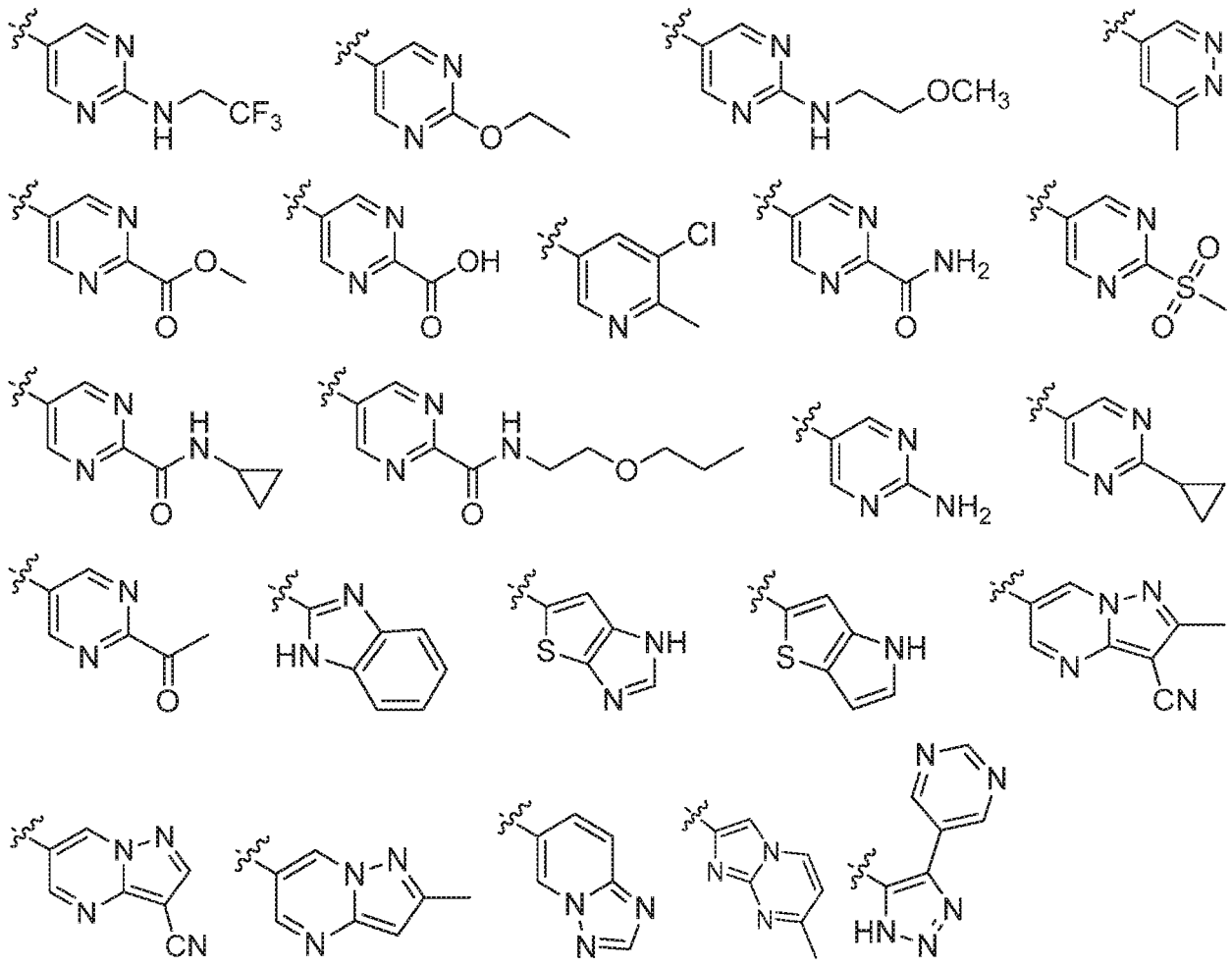


FIG. 17A

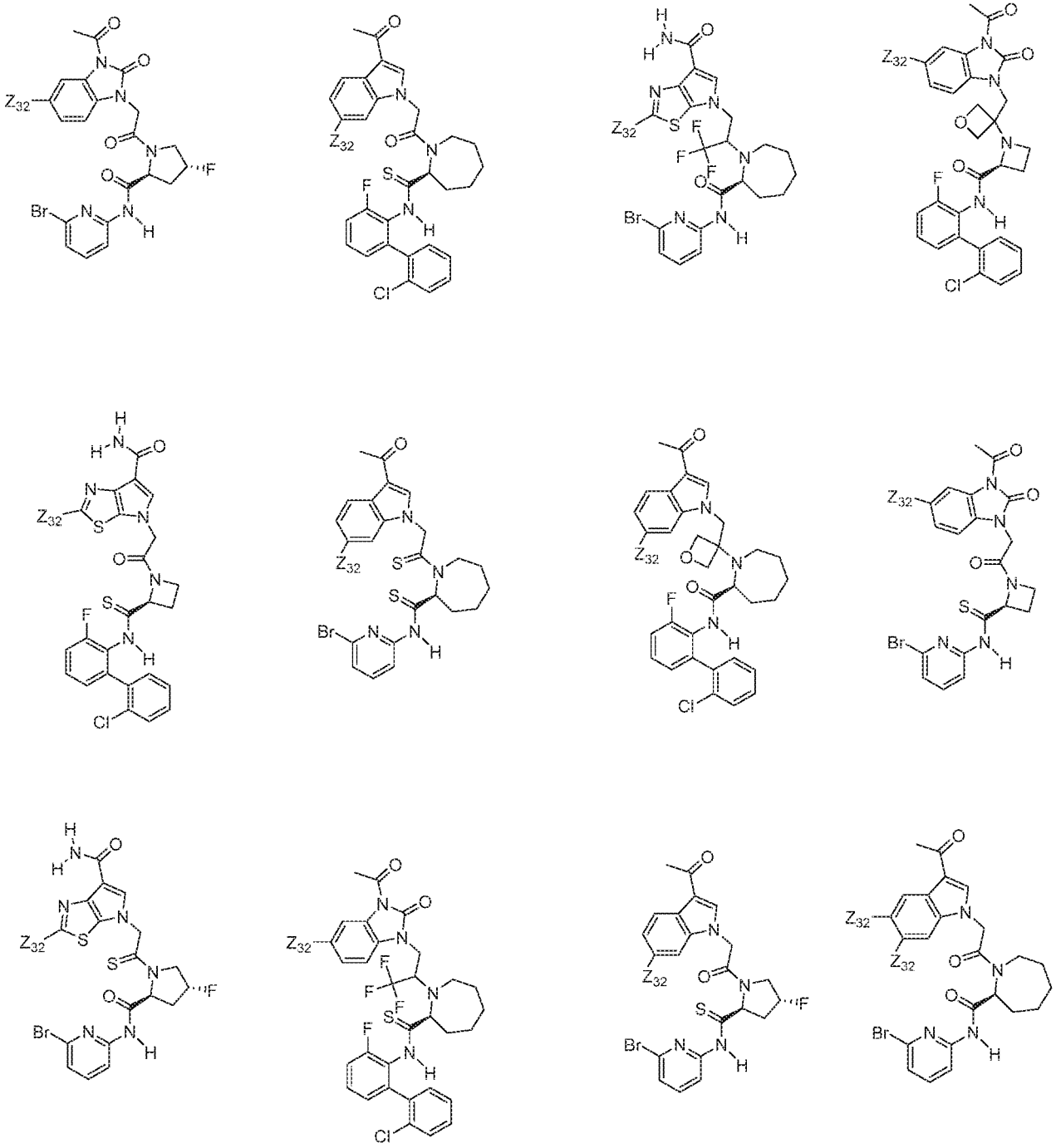


FIG. 17B

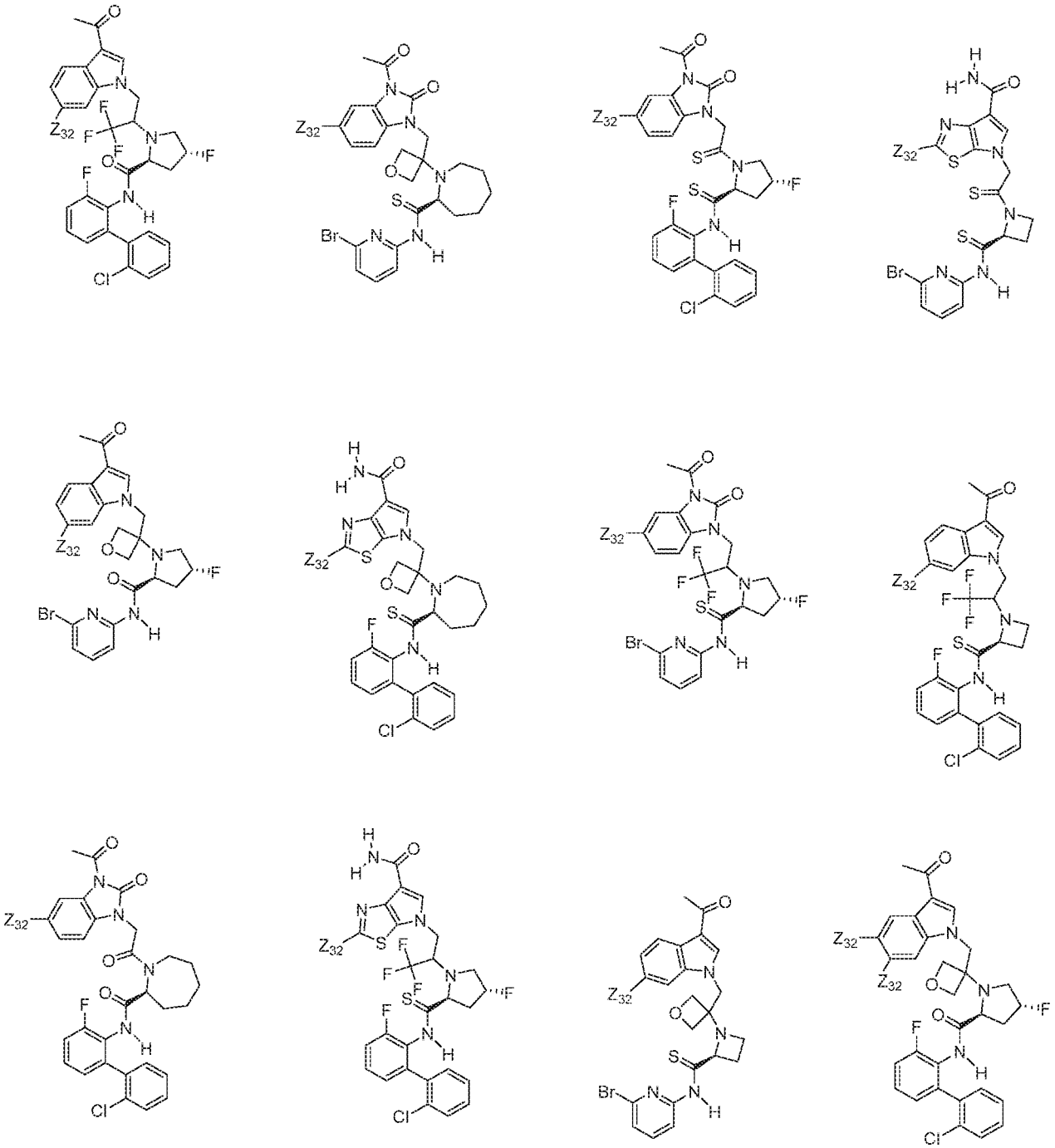


FIG. 17C

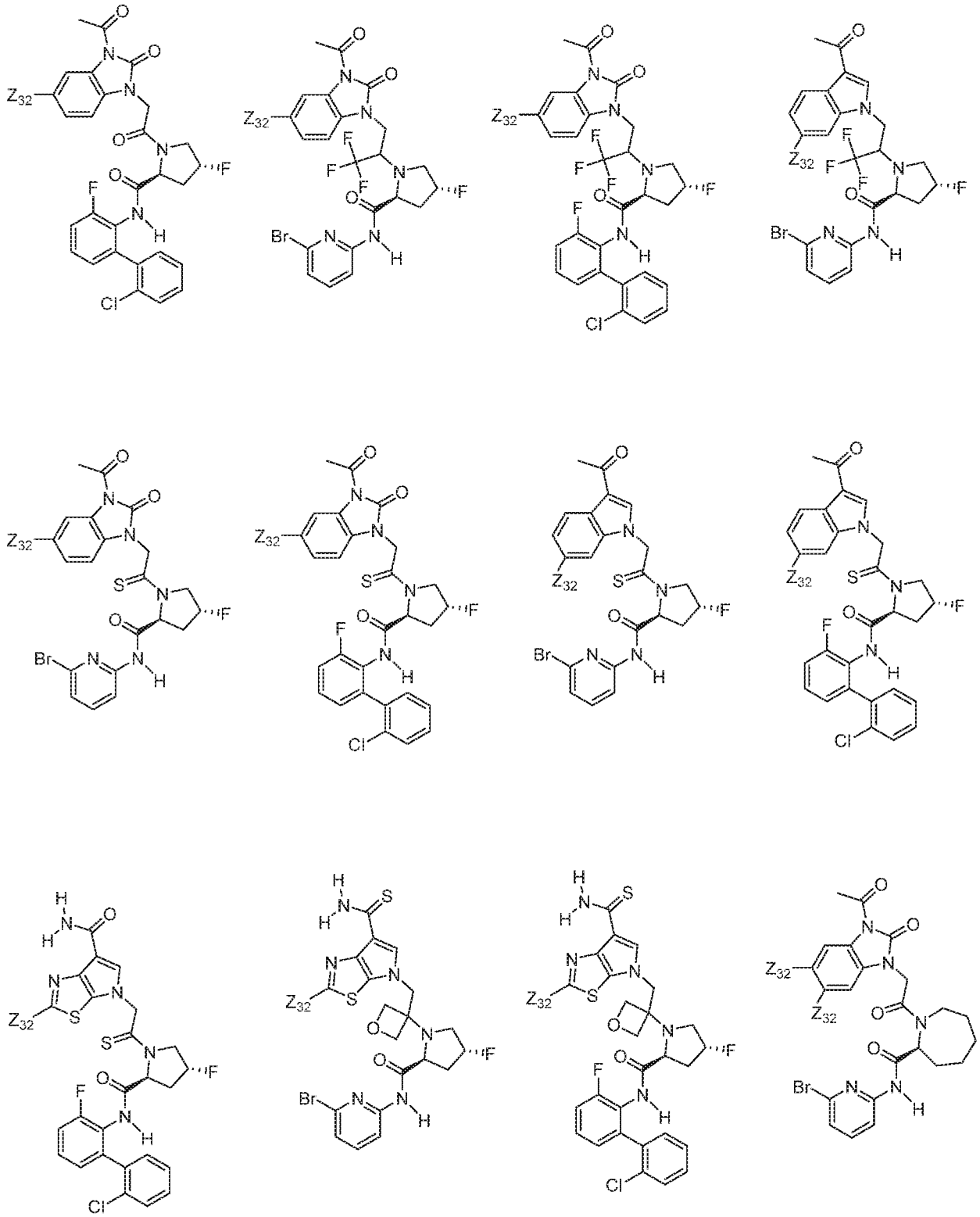


FIG. 17D

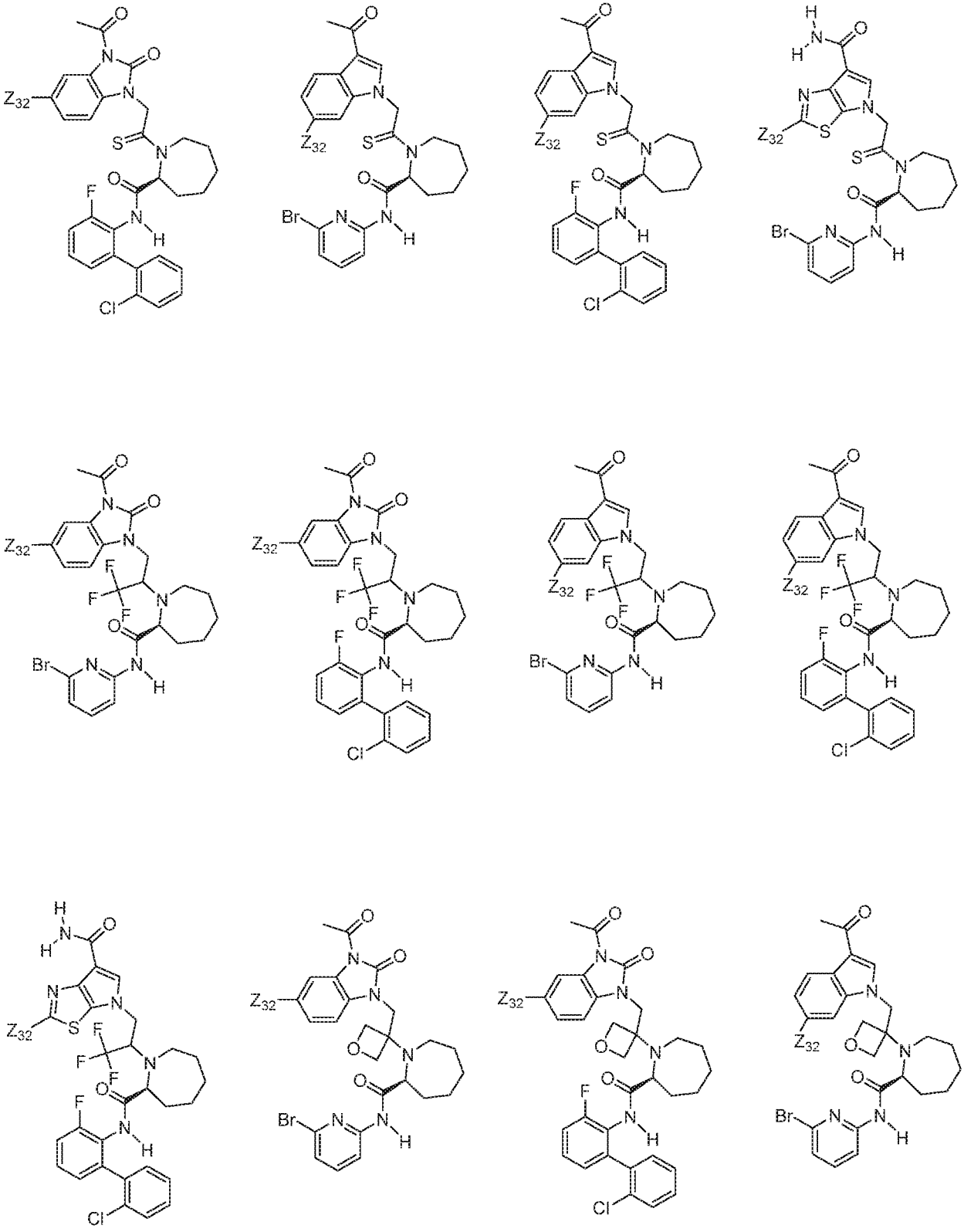


FIG. 17E

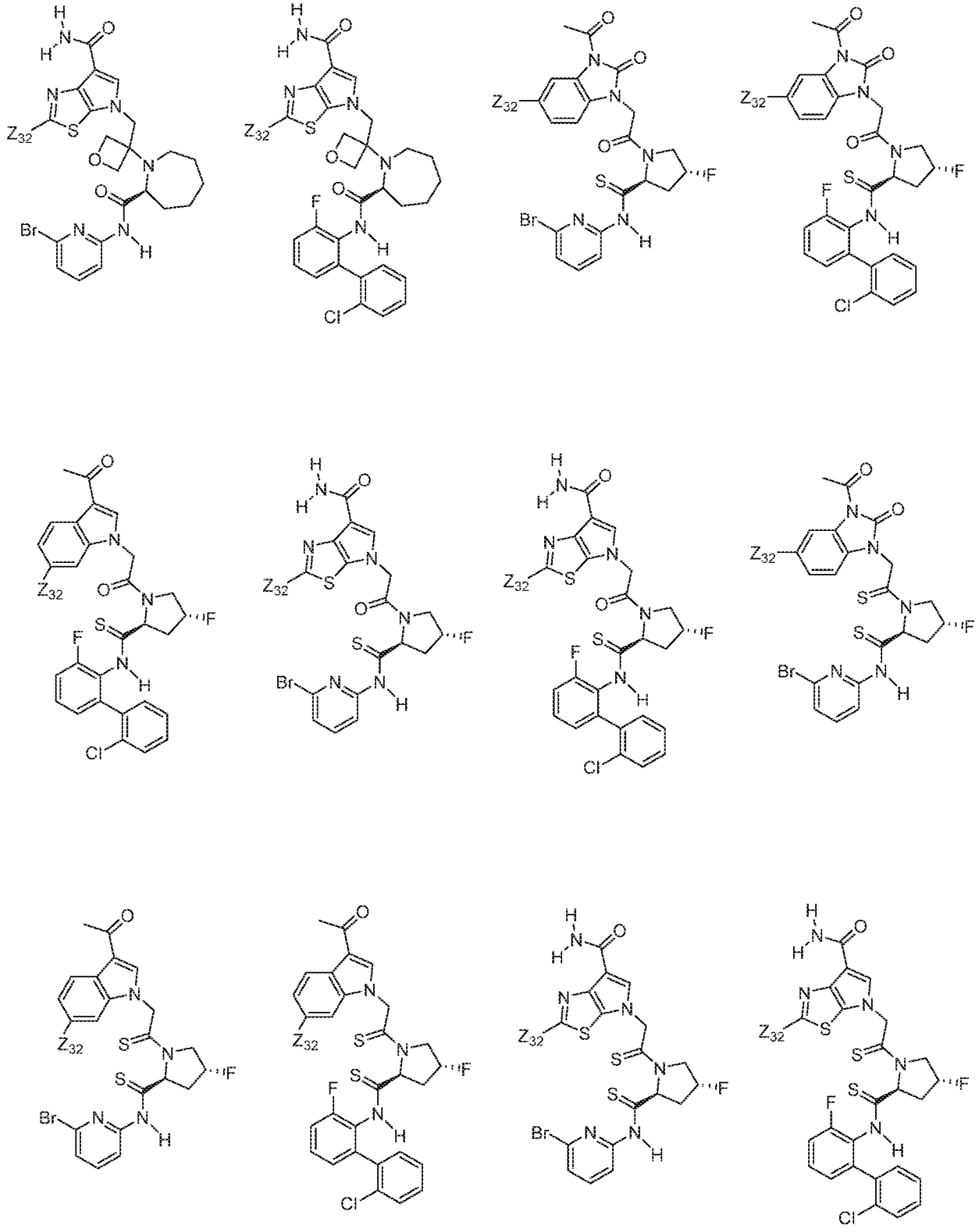


FIG. 17F

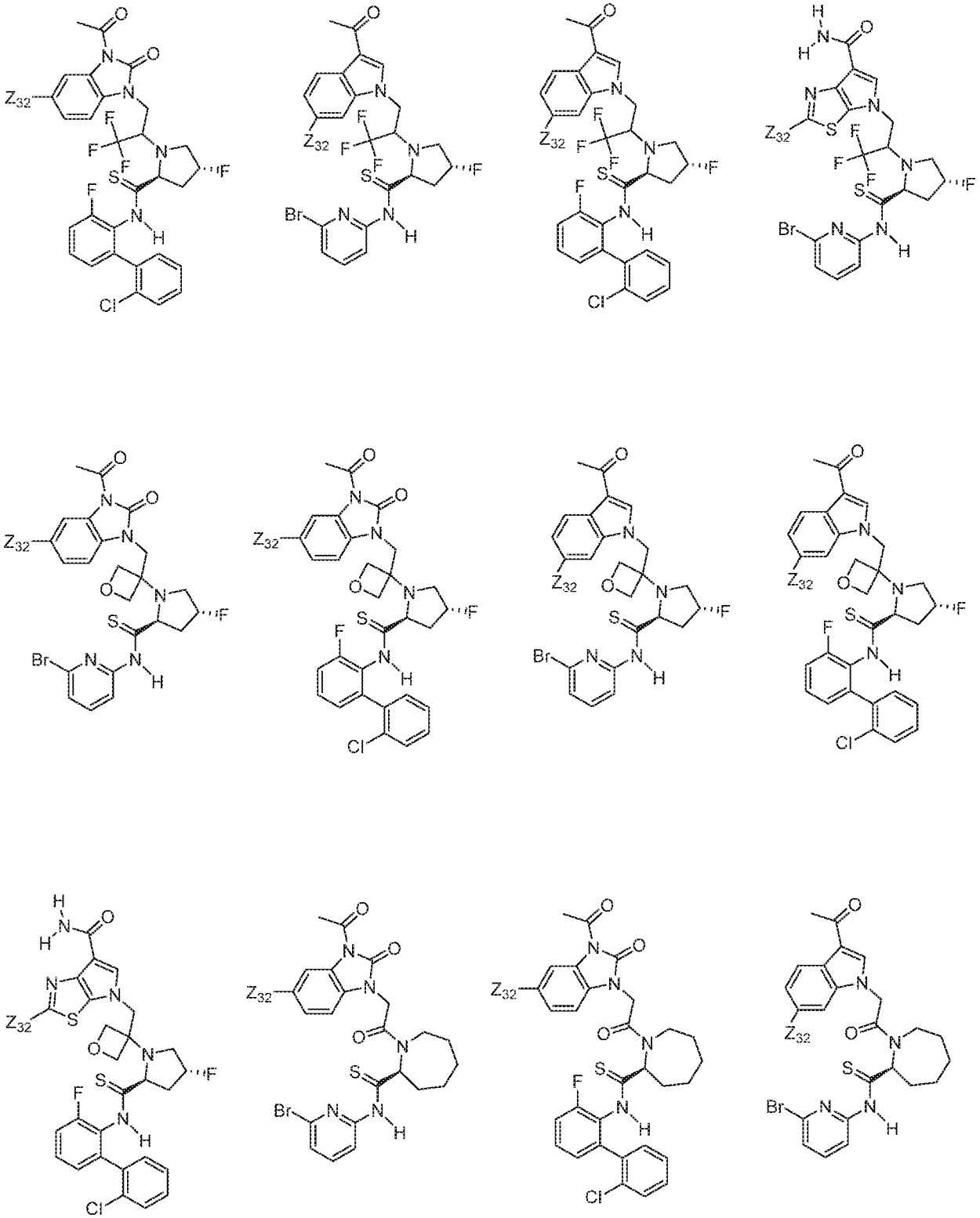


FIG. 17G

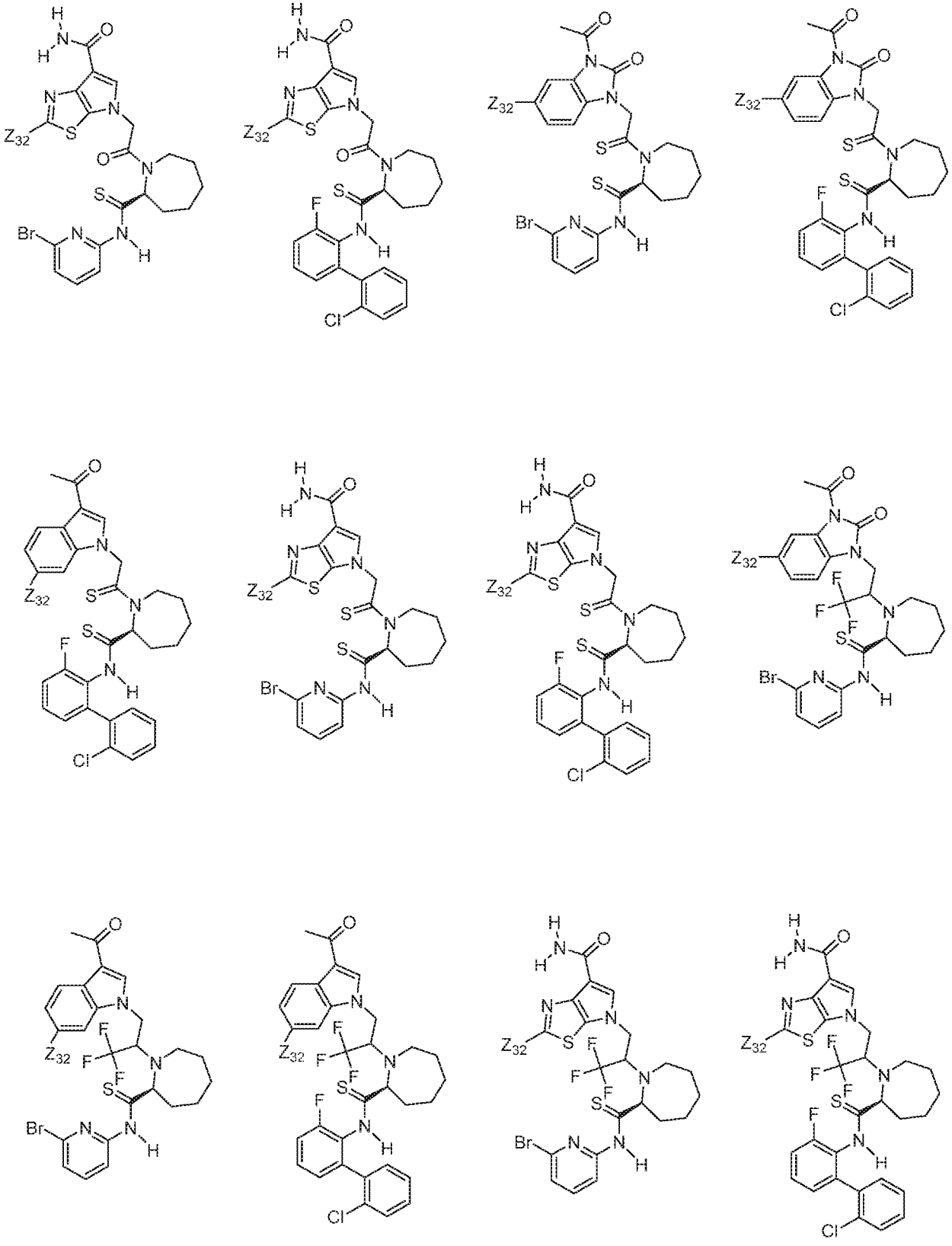


FIG. 17H

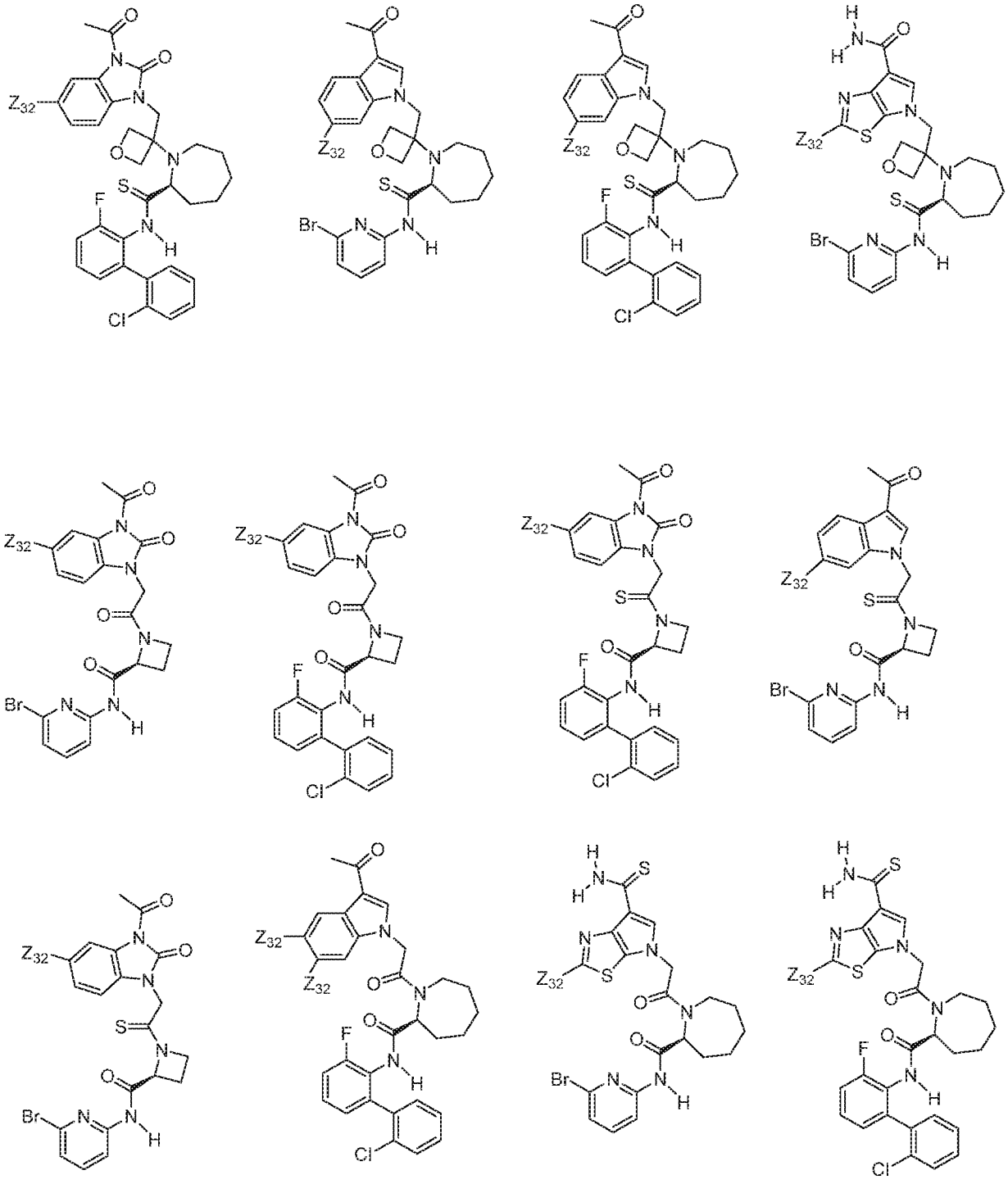


FIG. 17I

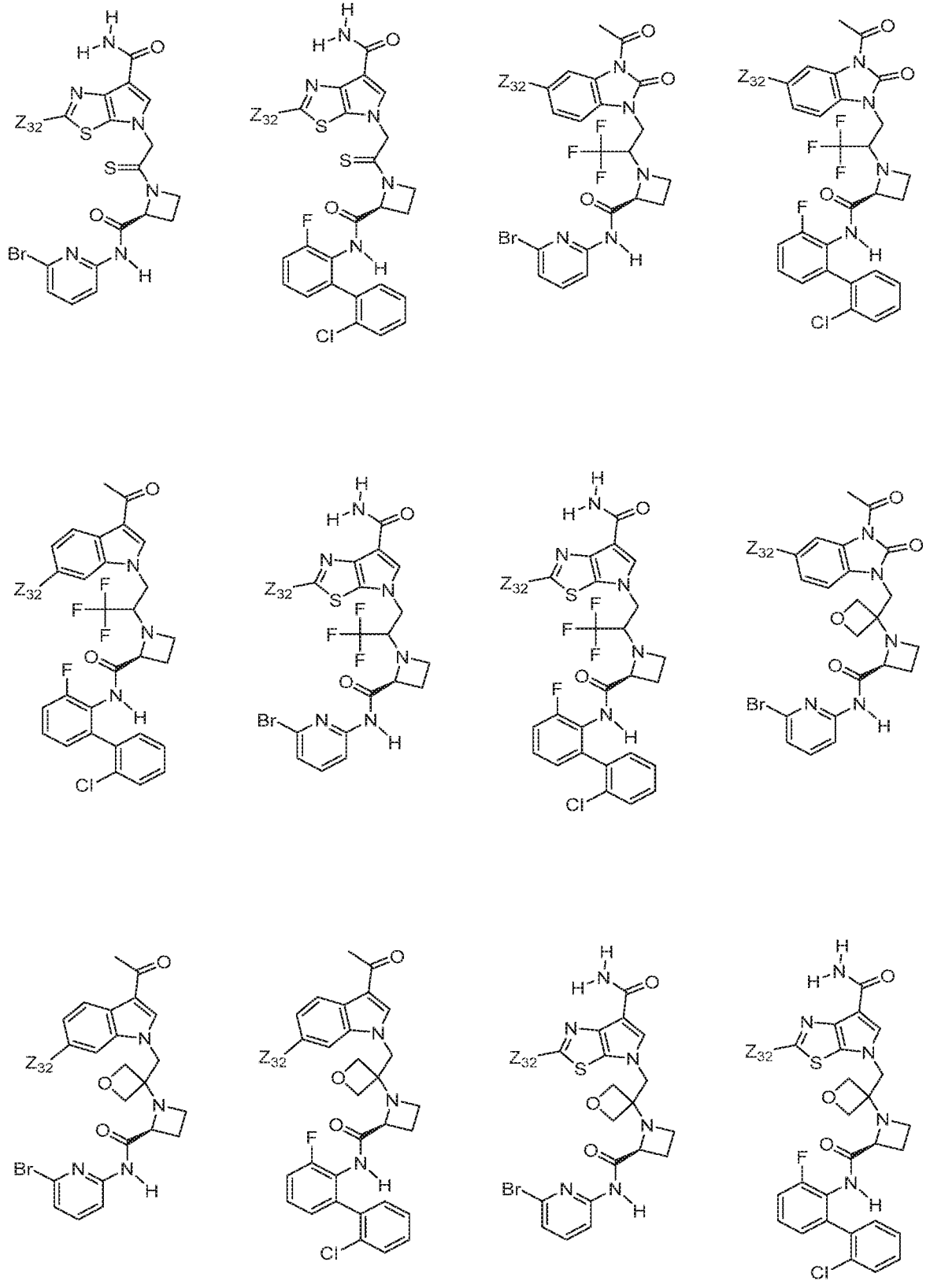


FIG. 17J

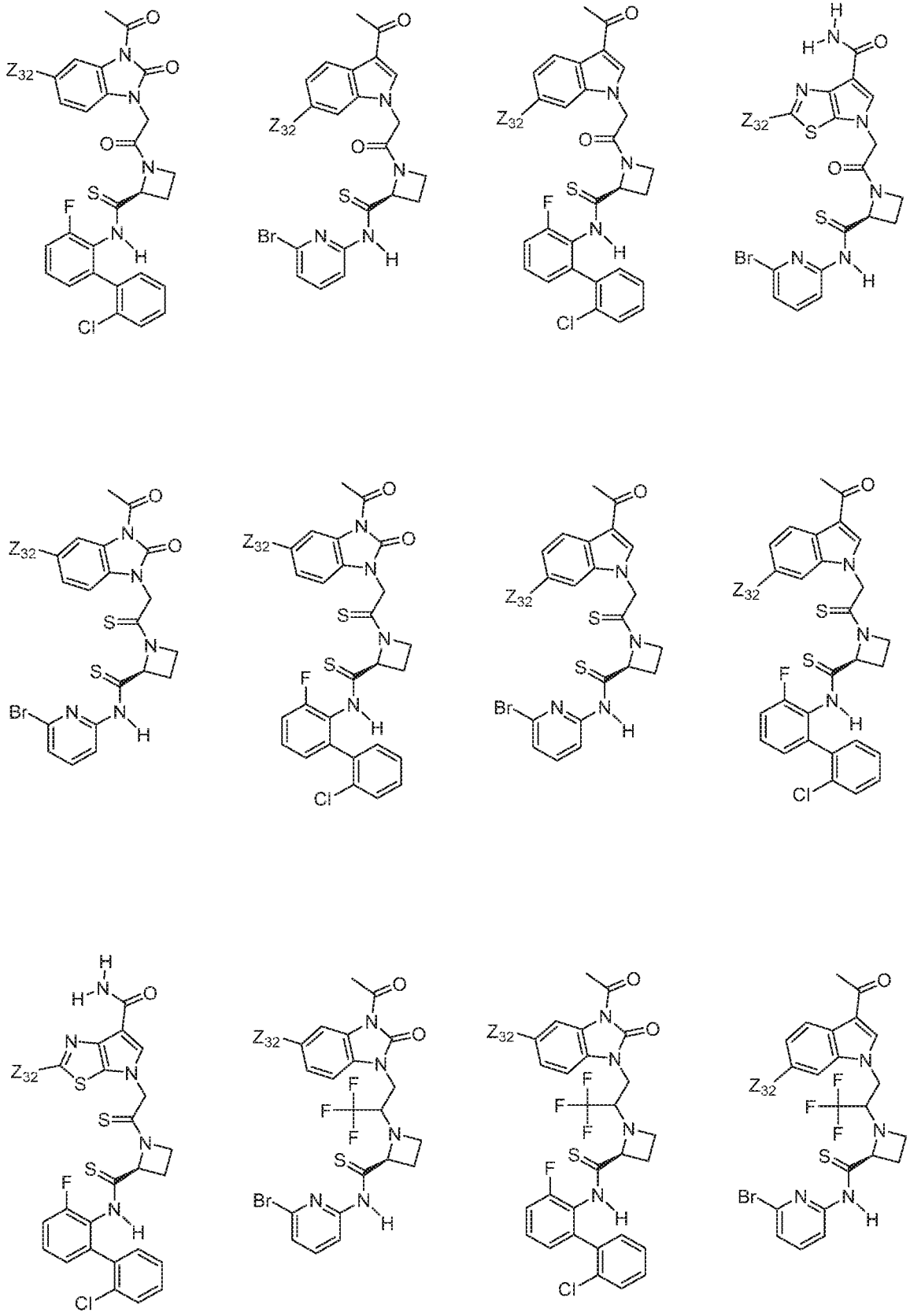


FIG. 17K

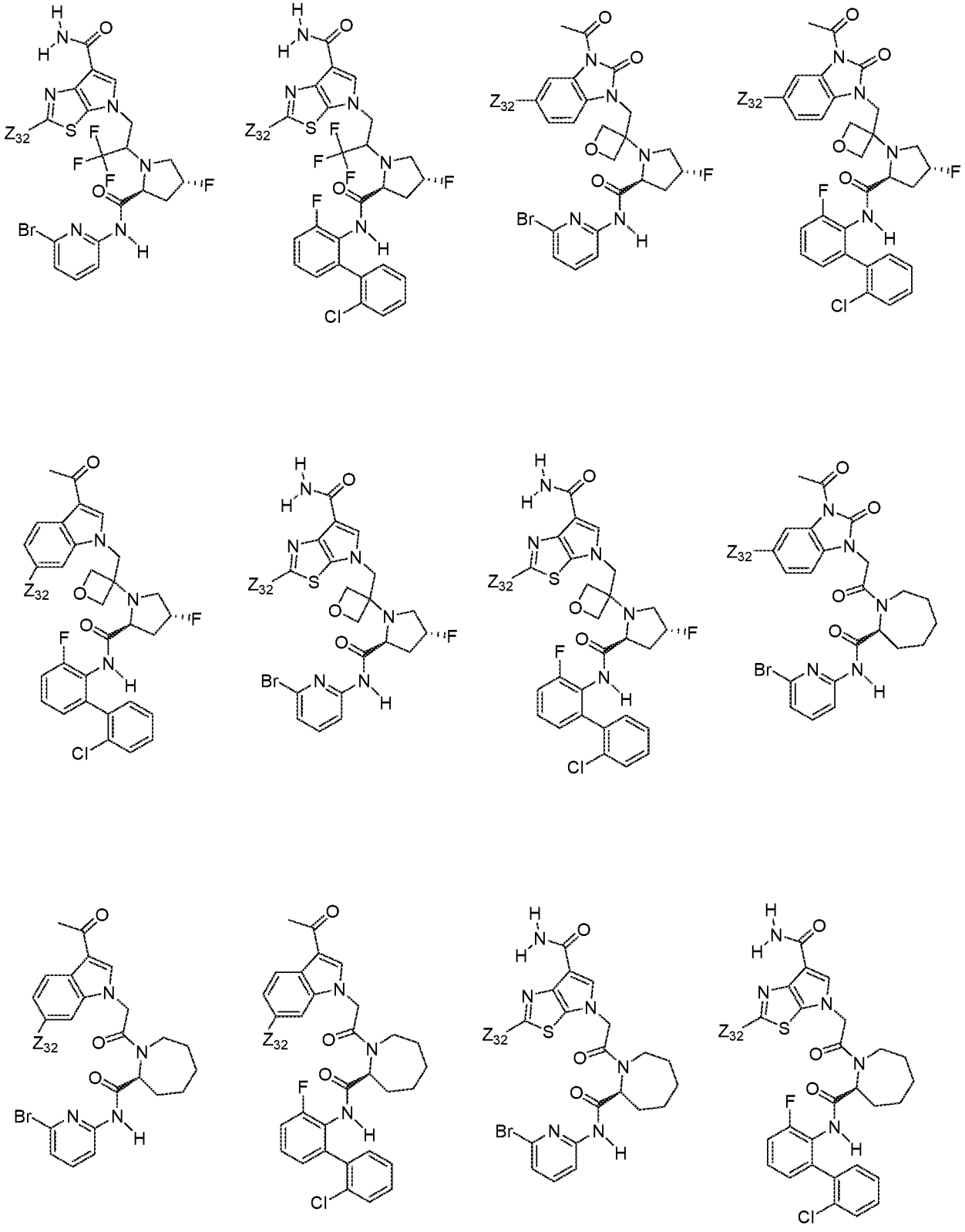
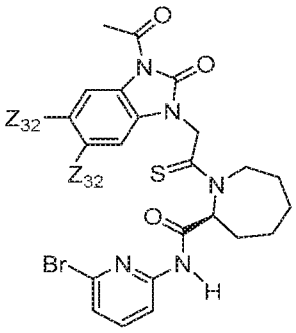
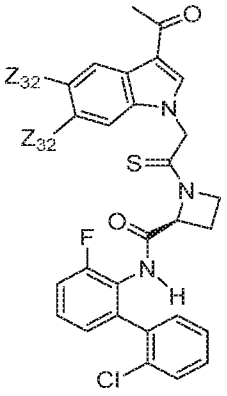
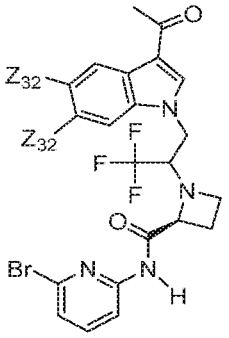
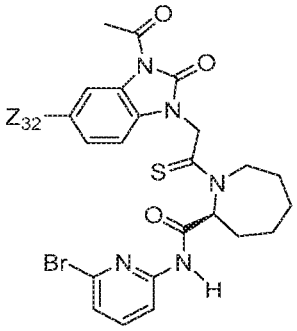


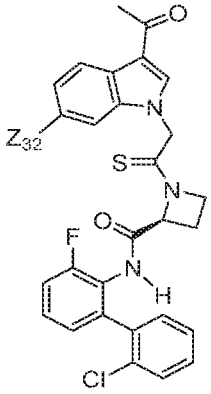
FIG. 17L

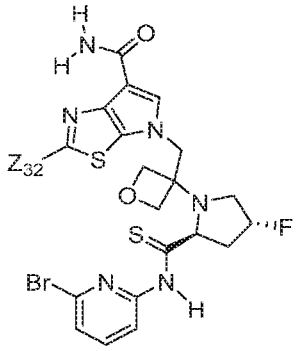


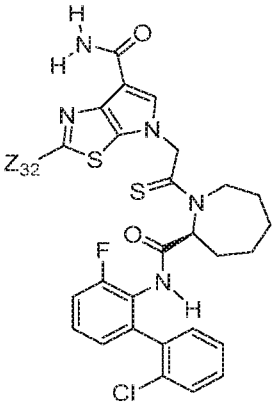


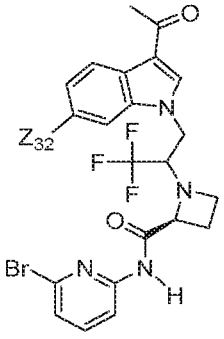












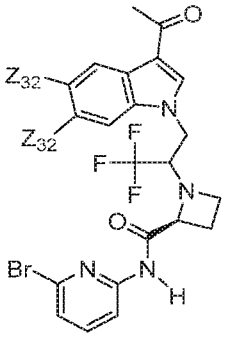


FIG. 17M

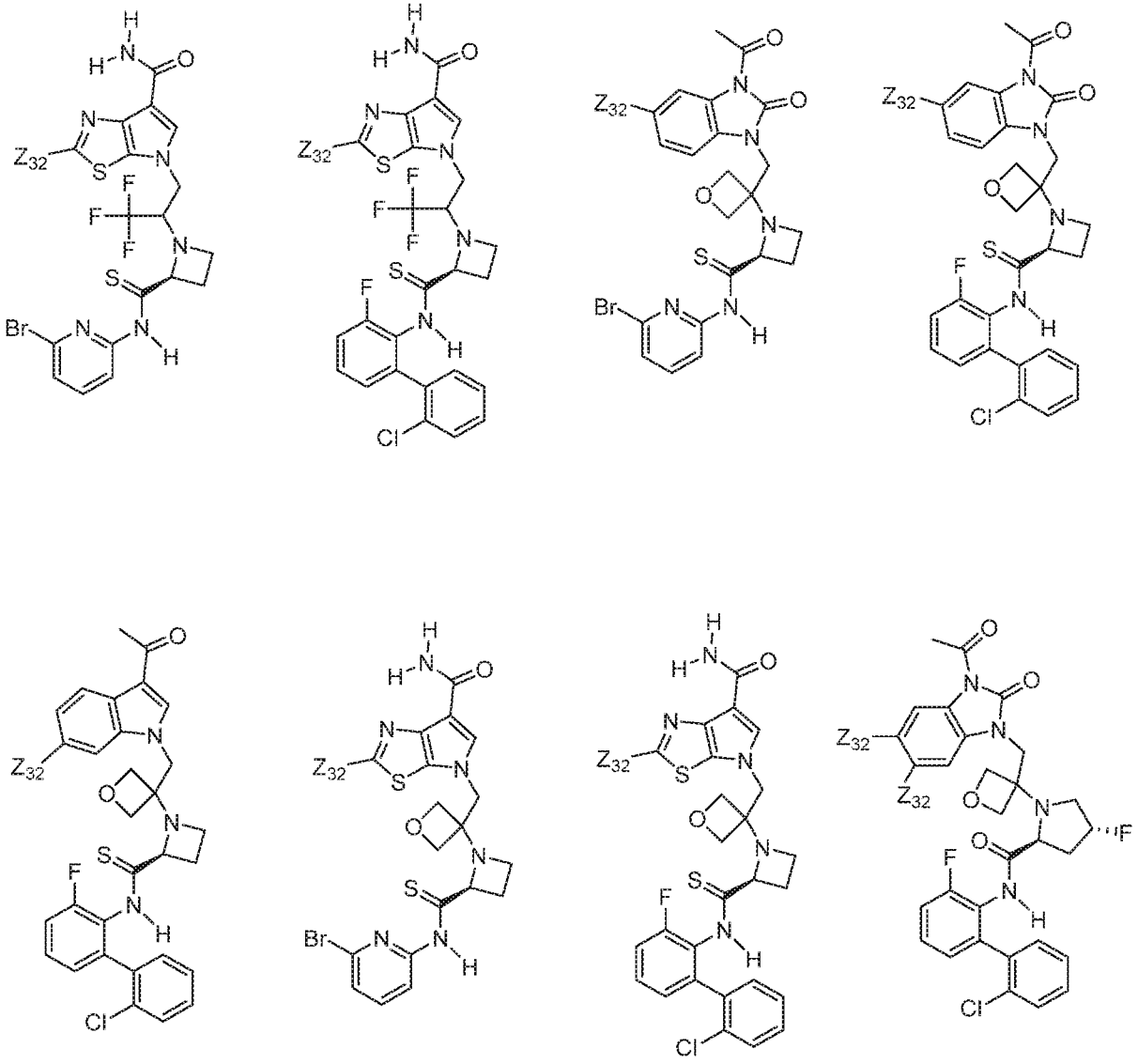
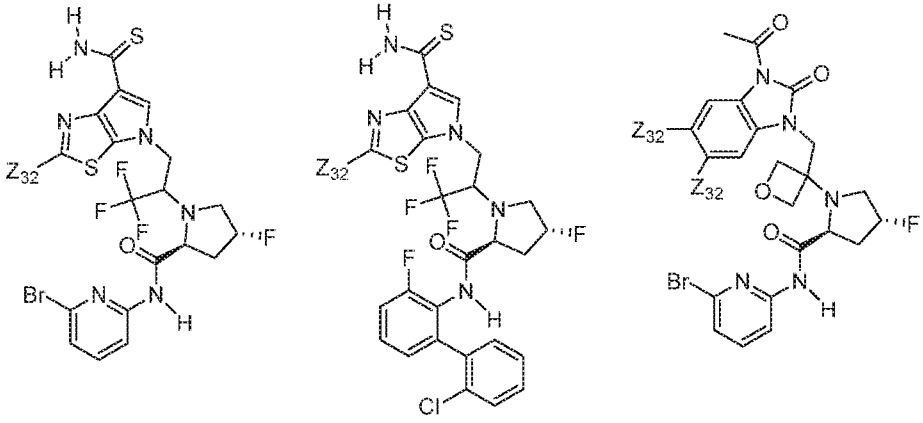


FIG. 17N



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20 16/048788

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.01)
CPC - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.1 1)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.01)
CPC - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.1 1)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/359; 514/408; 514/415; IPC(8) - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.01); CPC - A61K 31/40; A61K 31/167; A61K 31/395; C07D 401/14; C07D 403/14; C07D 471/04 (2016.1 1) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, STN, PubChem, Google Patents, Google Scholar
Search terms used: indole carboxamide pyrroline cyclopropylene fatty liver

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0295884 A1 (ALTMANN et al) 22 November 2012 (22.11.2012) entire document	1, 3-10
A	US 2005/0267108 A1 (HSIEH et al) 01 December 2005 (01.12.2005) entire document	1, 3-10
A	US 2005/0228000 A1 (SMALLHEER et al) 13 October 2005 (13.10.2005) entire document	1, 3-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December 2016	05 JAN 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCTOSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 201 5)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US201 6/048788

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ¾ Claims Nos.: 11-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1 and 3-10 have been analyzed subject to the restriction that the claims read on a compound of Formula I: or a pharmaceutically acceptable salt thereof, wherein A is selected from A2, where A2 is the first shown structure, where R6 is hydrogen, R8 and R8' are independently hydrogen, X15 is NH, X16 is CR12, X17 is N, R12 is R31, where R31 is hydrogen; B is selected from B1, where B1 is a monocyclic carbocyclic with 4 ring atoms per ring, which is unsubstituted; C is selected from C1, wherein C1 is the first structure shown, where Q1 is N(R1), Q2 is C(R2R2'), Q3 is N(R3), X1 and X2 are independently N; R1, R2, R2', and R3 are independently hydrogen; L is selected from L1, where L1 is a bond; L3 is selected from L4, where L4 is -C(O)-.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3-10

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search tees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/048788

Continued from Box No. Ill Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1 . In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-10 are drawn to compounds of Formula I, methods for the treatment of a host with a disorder, compounds for use to treat a host with a disorder, and use of compounds in the manufacture of a medicament to treat a host with a disorder.

The first invention of Group I+ is restricted based on the proviso that at least one of A , B, C, L, or L3 is selected from A2, B3, C3, L2, or L5; and is restricted to a compound of Formula I: or a pharmaceutically acceptable salt thereof, wherein A is selected from A2, where A2 is the first shown structure, where R6 is hydrogen, R8 and R8' are independently hydrogen, X15 is NH, X16 is CR12, X17 is N, R12 is R31, where R31 is hydrogen; B is selected from B1, where B1 is a monocyclic carbocyclic with 4 ring atoms per ring, which is unsubstituted; C is selected from C1, wherein C1 is the first structure shown, where 0.1 is N(R1), Q2 is C(R2R2'), Q3 is N(R3), X1 and X2 are independently N; R1, R2, R2', and R3 are independently hydrogen; L is selected from L1, where L1 is a bond; L3 is selected from L4, where L4 is -C(O)-; methods for the treatment of a host with a disorder; compounds for use to treat a host with a disorder; and use of compounds in the manufacture of a medicament to treat a host with a disorder. It is believed that claims 1 and 3-10 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I: or a pharmaceutically acceptable salt thereof, wherein A is selected from A2, where A2 is the second shown structure, where R6 is hydrogen, R8 and R8' are independently hydrogen, X18 is CR12, X19 is N, X20 is NH, R12 is R31 , where R31 is hydrogen; B is selected from B1, where B1 is a monocyclic carbocyclic with 4 ring atoms per ring, which is unsubstituted; C is selected from C1, wherein C1 is the structure shown, where Q1 is N(R1), Q2 is C(R2R2'), Q3 is N(R3), X1 and X2 are independently N; R1, R2, R2', and R3 are independently hydrogen; L is selected from L1, where L1 is a bond; L3 is selected from L4, where L4 is -C(O)-; methods for the treatment of a host with a disorder; compounds for use to treat a host with a disorder; and use of compounds in the manufacture of a medicament to treat a host with a disorder. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables A, C, L, L3, and B.

The Groups I+ share the technical features of a compound having the core structure of Formula I; a method for the treatment of a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, comprising administering an effective amount of a compound; a method for the treatment of a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; a compound for use to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy; a compound for use to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease; use of a compound in the manufacture of a medicament to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy; use of a compound in the manufacture of a medicament to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease or a cardiovascular disease; a compound for use to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure; dermatomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy; and a compound for use to treat a host with a disorder selected from paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2012/0295884 A1 to Altmann et al. teach a compound having the core structure of Formua I (Para. [1714];. ..see product...); a method for the treatment of a host with a disorder selected from fatty liver and conditions stemming from fatty liver (Claims 20 and 22,. ..liver fibrosis...; Para. [0017]; Para. [0859]; See Para. [0374] of the applicants specification that describes the disorder selected from fatty liver and conditions stemming from fatty liver as being liver fibrosis.); comprising administering an effective amount of a compound (Claims 20 and 22; Para. [0017]; Para. [0859]); a method for the treatment of a host with age-related macular degeneration (AMD) (Para. [0859]; Claim 23), comprising administering an effective amount of a compound (Para. [0859]; Claim 23); a compound (Para. [1714]) for use to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver (Claims 20 and 22; Para. [0017]; Para. [0859]); a compound (Para. [1714]) for use to treat a host with age-related macular degeneration (AMD) (Para. [0859]; Claim 23), comprising administering an effective amount of a compound (Para. [0859]; Claim 23); a compound for use in the manufacture of a medicament (Para. [1714]; Para. [0860]; Para. [1047]) to treat a host with a disorder selected from fatty liver and conditions stemming from fatty liver (Claims 20 and 22; Para. [0017]; Para. [0859]); and use of a compound in the manufacture of a medicament (Para. [0859]; Claim 23; Para. [1714]; Para. [0860]; Para. [1047]) to treat a host with age-related macular degeneration (AMD) (Para. [0859]; Claim 23).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US201 6/048788

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.