Abstract: Compounds, methods of use, and processes for making inhibitors of complement Factor D comprising Formula I or a pharmaceutically acceptable salt or composition thereof wherein R<sup>1</sup> or R<sup>2</sup> on the A group is an ether substituent (R<sup>2</sup>) are provided. The inhibitors described herein target Factor D and inhibit or regulate the complement cascade. The inhibitors of Factor D described herein reduce the excessive activation of complement.
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ETHER COMPOUNDS FOR TREATMENT OF MEDICAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional U.S. Application No. 62/209,997, filed August 26, 2015 and the entirety of the 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 the immune system, 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 instead 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 phagocytosis 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(¼0), which associates with Factor B to form the (¼3(H/0))B complex. Complement Factor D acts to cleave Factor B within the C3(¼H20)B complex to form Ba and Bb. The Bb fragment remains associated with C3(¼H20) to form the alternative pathway € 3 convertase C3(¼H20)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 b 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 of Factor H, the alternative pathway of the complement cascade is overly activated leading to cellular damage. Inhibition of the alternative pathway under these circumstances 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. Alexion Pharmaceutical’s anti-C5 antibody ecuiizumab (Soliris®) is currently the only complement-specific antibody on the market, and is the first and only approved treatment for paroxysmal nocturnal hemoglobinuria (PNH). Exciluzimab is also approved for atypical hemolytic uremic syndrome (aHUS). However, many
of the patients treated with eculizurab 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 aHUS, hemolytic uremic syndrome (HUS), abdominal aortic aneurysm, hemodialysis complications, hemolytic anemia, or hemodialysis, neuromyelitis (NMO), myasthenia gravis (MG), fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure, dermatomyositis, 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.

[0011] Biocryst Pharmaceuticals US Pat. No. 6653340 titled "Compounds useful in the complement, coagulant 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 BCX1 470 was discontinued due to lack of specificity and short half-life of the compound.


[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 WO1 999/048492 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 WO1 993/020099 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.


[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 dysregulation of the complement cascade, or with undesired result of the complement cascade performing its normal function.

SUMMARY

[0019] In a first embodiment, the invention is the use of a compound of Formula 1, or a pharmaceutically acceptable salt or composition thereof, wherein at least one of R₁² or R₁³ on the A group is an ether substituent (such as those in Figs. 6A, 6B and 6C) including those compounds set out in Table 1, for the treatment of a disorder in a host, typically a human, wherein the disorder is selected from the group disclosed in the Detailed Description, Part IV, Section A. The compounds of Table 1 were first disclosed in PCT Patent Application No. PCT/US201 5/01 7597 and U.S. Patent Application No. 14/63 1,683 titled "Ether Compounds for Treatment of Complement Mediated Disorders," however, not for the indications now provided in the Detailed Description, Part IV, Section A. The compound is provided in an effective amount to treat the disorder, and is optionally provided in a pharmaceutically acceptable carrier. Therefore, in particular, this first embodiment includes uses of compounds to treat a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A.

[0020] Non-limiting examples of disorders described in the Detailed Description, Part IV, Section A include: fatty liver and conditions stemming from fatty liver, nonalcoholic steatohepatitis (NASH), liver inflammation, cirrhosis, liver failure, dermatomyocitis, and amyotrophic lateral sclerosis. In another embodiment of Section A disorders, the active compound is used to modulate an immune response prior to, during, or after surgery or other medical procedure, or as adjunctive therapy to dampen the immune or inflammatory response during a pharmaceutical or biopharmaceutical drug treatment, a blood transfusion, or other allogenic tissue or fluid administration. In one embodiment, a Section A method is provided for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of biotherapeutics (e.g. CAR T-cell therapy) in a host by administering an effective amount of a designated compound herein, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.
[0021] Non-limiting examples of disorders in the Detailed Description, Part IV, Section B of this invention include 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. In one aspect, an active compound or its salt or composition can be used to treat a medical disorder which is mediated by either a dysfunctional complement cascade or a disorder or abnormality of a cell that adversely affects the ability of the cell to engage in or respond to normal complement activity, for example, including but not limited to sparing certain cells from complement mediated lysis. PNH is one example of such a disorder, wherein host blood cells are missing the gene PIG-A that expresses a protein that protects the blood cells from complement mediated lysis. Other embodiments of Section B disorders include complement associated disorders that are induced by antibody-antigen interactions, a component of an immune or autoimmune disorder, hereditary angioedema, capillary leak syndrome, atypical hemolytic uremic syndrome (aHUS), hemolytic uremic syndrome (BUS), abdominal aortic aneurysm, hemodialysis complications, hemolytic anemia and hemodialysis.

[0022] In a second embodiment of the invention, an ether compound is selected from Table 2 or an active compound that is prepared from or consists of moieties selected from Figures 1B, 1C, 2B, 2C, 2D, 2E, 2F, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, and 3N, 5, 6A, 6B or 6C; and optionally 4B, 4C, 4D, 4E, or 4F or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B. In one embodiment, the compound of Table 2 is used to treat a disorder associated with a dysfunction, including increased activity of the complement pathway that includes the administration of an effective amount of a compound selected from Table 2 or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in Table 2 in one embodiment is used to dampen or inhibit detrimental complement activity in a host, by administration of an effective amount in a suitable manner to a host in need thereof. Therefore, in particular, this second embodiment includes
compound species, and uses of these species to treat disorders selected from the group disclosed in the Detailed Description, Part IV, Section A or B.

[0023] In a third embodiment of the invention, an ether compound is provided selected from Table 3 or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B. In one embodiment, the compound of Table 3 is used to treat a disorder associated with a dysfunction, including increased activity, of the complement pathway that includes the administration of an effective amount of a compound selected from Table 3 or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in Table 3 in one embodiment is used to dampen or inhibit detrimental complement activity in a host, by administration of an effective amount in a suitable manner to a host in need thereof. Therefore, in particular, this third embodiment includes compound species and uses of these species to treat a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B.

[0024] In a fourth embodiment of the invention, an ether compound is provided that is prepared from or consists of moieties selected from Figures 1D, 1E, 5, 6A, 6B, 6C, 7A, 7B, 7C, 7D, 7E, and 8; and optionally 4B, 4C, 4I), 4E, or 4F or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A. In one embodiment, the compound that is prepared from or consists of moieties selected from Figures 1D, 1E, 5, 6A, 6B, 6C, 7A, 7B, 7C, 7D, 7E, and 8; and optionally 4B, 4C, 4D, 4E, or 4F is used to treat a disorder associated with a dysfunction, including increased activity, of the complement pathway that includes the administration of an effective amount of the compound or an embodiment of the active compound, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in one embodiment provided herein is used to dampen or inhibit
detrimental complement activity in a host, by administration of an effective amount in a suitable
manner to a host in need thereof. Therefore, in particular, this fourth embodiment includes uses of
these compounds to treat disorder selected from the group disclosed in the Detailed Description,
Part IV, Section A.

[0025] In a fifth embodiment of the invention, an ether compound is provided that is
prepared from or consists of moieties selected from Figures 1B, 1C, 1D, 1E, 3A, 3B, 3C, 3D, 3E,
3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 5, 6A, 6B, 6C, 6D, 6E, and 7F; and optionally
4B, 4C, 4D, 4E, or 4F or a pharmaceutically acceptable composition, salt, isotopic analog or
prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a
human, including a disorder selected from the group disclosed in the Detailed Description, Part
IV, Section A or B. In one embodiment, the compound that is prepared from or consists of moieties
selected from Figures 1B, 1C, 1D, 1E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N,
3O, 3P, 3Q, 5, 6A, 6B, 6C, 6D, 6E, and 7F; and optionally 4B, 4C, 4D, 4E, or 4F, is used to treat
a disorder associated with a dysfunction, including increased activity, of the complement pathway
that includes the administration of an effective amount of the compound or an embodiment of the
active compound, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically
acceptable carrier, as described in more detail below. 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. The compound in one embodiment
provided herein is used to dampen or inhibit detrimental complement activity in a host, by
administration of an effective amount in a suitable manner to a host in need thereof. Therefore, in
particular, this fifth embodiment includes compound species and uses of these species to treat
disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B.

[0026] In a sixth embodiment of the invention, an ether compound is provided that is
prepared from or consists of moieties selected from Figures 1B, 1C, 1D, 1E, 3A, 3B, 3C, 3D, 3E,
3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 5, 6A, 6B, 6C, 6D, 6E, 7G, and 8; and optionally
4B, 4C, 4D, 4E, and 4F, or a pharmaceutically acceptable composition, salt, isotopic analog or
prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a
human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A. In one embodiment, the compound that is prepared from or consists of moieties selected from Figures 1B, 1C, 1D, 1E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3P, 3Q, 5, 6A, 6B, 6C, 6D, 6E, 7G, and 8; and optionally 4B, 4C, 4D, 4E, and 4F is used to treat a disorder associated with a dysfunction, including increased activity, of the complement pathway that includes the administration of an effective amount of the compound or an embodiment of the active compound, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in one embodiment provided herein is used to dampen or inhibit detrimental complement activity in a host, by administration of an effective amount in a suitable manner to a host in need thereof. Therefore, in particular, this sixth embodiment includes uses of these species to treat disorder selected from the group disclosed in the Detailed Description, Part IV, Section A.

[0027] In a seventh embodiment of the invention, an ether compound as described and used herein is selected from those depicted in Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G and 9H, and Figures 6D and 6E, or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B. In one embodiment, the compound of Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figures 6D and 6E, is used to treat a disorder associated with a dysfunction, including increased activity of the complement pathway that includes the administration of an effective amount of a compound selected from Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figures 6D and 6E, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in Figure 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figures 6I) and 6E, in one embodiment is used to dampen or inhibit detrimental complement activity in a host, by administration of an effective amount in a suitable manner to a host in need.
thereof. Therefore, in particular, this seventh embodiment includes compound species, and uses of these species to treat disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B.

[0028] In an eighth embodiment of the invention, a compound is provided that is prepared from or consists of moieties selected from Figures 1D, 1E, 5, 6E, 7A, 7B, 7C, 7I), 7E, and 8; and optionally 4B, 4C, 4D, and 4E, or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A. In one embodiment, the compound that is prepared from or consists of moieties selected from Figures 1D, 1E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 5, 6E, 7A, 7B, 7C, 7D, 7E, 7F, 7G, and 8; and optionally 4B, 4C, 4D, and 4E, is used to treat a disorder associated with a dysfunction, including increased activity, of the complement pathway that includes the administration of an effective amount of the compound or an embodiment of the active compound, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below. 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. The compound in one embodiment provided herein is used to dampen or inhibit detrimental complement activity in a host, by administration of an effective amount in a suitable manner to a host in need thereof. Therefore, in particular, this eighth embodiment includes uses of a compound that is prepared from or consists of moieties selected from Figures 1B, 1C, 1D, 1E, 5, 6E, 7A, 7B, 7C, 7D, 7E, and 8; and optionally 4B, 4C, 4D, and 4E, to treat disorders selected from the group disclosed in the Detailed Description, Part IV, Section A.

[0029] In a ninth embodiment of the invention, an ether compound as described and used herein is selected from those depicted in Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G and 9H, and Figures 6A, 6B, and 6C or a pharmaceutically acceptable composition, salt, isotopic analog or prodrug thereof, for the treatment of an immune or inflammatory disorder in a host, typically a human, including a disorder selected from the group disclosed in the Detailed Description, Part IV, Section A or B. In one embodiment, the compound of Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figure 6A, 6B, and 6C is used to treat a disorder associated with a dysfunction, including increased
activity of the complement pathway that includes the administration of an effective amount of a
compound selected from Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figures 6A, 6B, and 6C
or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier,
as described in more detail below. 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. The compound in Figure 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and
Figures 6A, 6B, and 6C in one embodiment is used to dampen or inhibit detrimental complement
activity in a host, by administration of an effective amount in a suitable manner to a host in need
thereof. Therefore, in particular, this seventh embodiment includes compound species, and uses of
these species to treat disorder selected from the group disclosed in the Detailed Description, Part
IV, Section A or B.

[0030] Compounds disclosed herein or used as described herein may be administered in
any desired route according to the direction of the healthcare provider, for example, oral, topical,
parenteral, by inhalation or spray, sublingual, via implant, including ocular implant, transdermal,
via buccal administration, rectal, as an ophthalmic solution, injection, including ocular injection,
intravenous, intra-aortal, intracranial, subdemiai, intraperitoneal, subcutaneous, transnasal,
sublingual, or rectal or by other means, in dosage unit formulations optionally containing
conventional pharmaceutically acceptable carriers, and in an immediate or controlled release
fashion. For use in the eye, any of the compounds described herein can be administered to the eye
in any desired form of administration, including via intravitreal, intrastromal, intracameral, sub-
tenon, sub-retinal, retro-bulbar, peribulbar, suprachoroidal, choroidal, subchoroidal, conjunctival,
subconjunctival, episcleral, posterior juxtascieralscleral, circumcorneal, and tear duct injections,
or through a mucus, mucin, or a mucosal barrier, in an immediate or controlled release fashion.

[0031] The compounds of Formula I as described in PCT Patent Application No.
Treatment of Complement Mediated Disorders," are of the formula:
and the pharmaceutically acceptable salts and compositions thereof, wherein:

[0032] Q¹ is NO¹ or C(R¹R³³);  
[0033] Q² is C(R²R³³), C(R²R³³)C(R²R³³), S, O, N(R²) or C(R²R³³);  
[0034] Q³ is N(R³), S, or C(R³³);  
[0035] X¹ and X² are independently N, CH, or CZ, or X¹ and X² together are C=C; and  
[0036] wherein Q¹, Q², Q³, X¹, and X² are selected such that a stable compound results.  
[0037] It is clear that when q is 0, — was is not a double bond.

[0038] R and R' (see Fig. 5) are independently selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryi, 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 core ring includes one or more chiral carbon atoms. The invention includes the use of compounds with 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.

[0039] Z is F, Cl, N₂, CH₃, CH₂D, CHD₂, or CDs.

[0040] R¹, R¹', R², R²', R³, and R³' are independently selected at each occurrence, as appropriate, and only where a stable compound results, from hydrogen, halogen, hydroxy!, nitro, cyano, amino, Ci-Cealkyl, C2-C6alkenyl, C2-C6alkynyl, Ci-Cealkoxy, C2-C6alkynyl, C2-Cealkanoyi, Ci-Cethioalkyl, hydroxyCi-Cealkyl, ammoCi-Cealkyl, -Co-C4alkylNR 9⁹R 1⁰, -C(0)OR 9, -OC(0)R 9, -NR⁹C(O)R 1⁰, -C(O)NR 9⁹R 1⁰, -OC(O)NR 9⁹R 1⁰, -NR⁹C(O)OR 1⁰, C1-C2haloalkyl, and Ci-C2haloalkoxy, where R⁹ and R 1⁰ are independently selected at each occurrence from hydrogen, Ci-C6alkyi, (C3-C7cycloalkyl)Co-C4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), and -0-Co-C4alkyl(C3-C7cycloalkyl).

[0041] In alternative embodiments, R¹ and R¹' or R³ and R³' 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 selected from N, O, or S; R² and R³ may be taken together to form a 3- to 6-membered carbocyclic spiro ring; or R² and R³′ may be taken together to form a 3- to 6-membered heterocyclic spiro ring; each of which spiro ring may be unsubstituted or substituted with 1 or more substituents independently selected from halogen (and in particular F), hydroxy¹, cyano, -COOH, C₁-C₄alkyl (including in particular methyl), C₂-C₄alkenyl, C₂-C₄alkynyl, (Vinyl)oxy, C₂-C₄alkanoyl, hydroxyC₂-C₄alkyl, (mono- and di-C₂-C₄alkylamino)C₂-C₄alkyl, -CO-C₂-C₄alkyl(C₁-C₇cycloalkyl), -O-Co-C₂-C₄alkyl(C₁-C₇cycloalkyl), C₁-Ohaioalkyl, and C¹-C₇haioalkoxy.

[0042] In alternative embodiments, R¹ and R² may be taken together to form a 3-membered carbocyclic ring; R¹ and R² 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 selected from N, O, and S; or R² and R³, 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 selected from halogen (and in particular F), hydroxyl, cyano, -COOH, C₁-C₄alkyl (including in particular methyl), C₂-C₄alkenyl, C₂-C₄alkynyl, C₂-C₄alkanoyl, hydroxyC₂-C₄alkyl, (mono- and di-C₂-C₄alkylamino)C₂-C₄alkyl, -CO-C₂-C₄alkyl(C₁-C₇cycloalkyl), -O-Co-C₂-C₄alkyl(C₁-C₇cycloalkyl), C₁-C₂haloalkyl, and C₁-C₇haloalkoxy.

[0043] In alternative embodiments, R¹ and R¹′, R² and R²′, or R³ and R³′ can be taken together to form a carbonyl group. In alternative embodiments, R¹ and R² or R² and R³ can be taken together to form a carbon-carbon double bond.

[0044] Non-limiting examples of the ring are illustrated, for example, in Figure 5 (any of which can be otherwise substituted with R¹, R¹′, R², R²′, R³, and R³′).

[0045] In an alternate embodiment, the ring is replaced by one of the following core structures:
wherein \( q \) is 0, 1, 2 or 3, \( r \) is 1, 2 or 3, \( \cdots \) is a single or double bond. Examples of core structures are provided on Fig. 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, and Figure 5.

[0046] \( A \) is a group selected from:
Examples of "A" groups are in Figures 1B, 1C, 1D, and 1E.

R\textsuperscript{4} is selected from -CHO, -CONH\textsubscript{2}, O\textsubscript{2}alkanoyl, hydrogen, -SO\textsubscript{2}NH\textsubscript{2}, -C(CH\textsubscript{2})\textsubscript{2}F, -CH(CF\textsubscript{3})NH\textsubscript{2}, Ci-C\textsubscript{2}alkyl, -Co-C\textsubscript{4}alkyl(C\textsubscript{3}-C\textsubscript{7}cycloalkyl), -C(0)Co-C\textsubscript{2}alkyl(C\textsubscript{3}-C\textsubscript{7}cycloalkyl),

R\textsubscript{5} and R\textsubscript{6} are independently selected from -CHO, -C(0)NH\textsubscript{2}, -C(0)NH(CH\textsubscript{3}), C\textsubscript{2}-Cealkanoyl, hydrogen, hydroxyi, halogen, cyano, cyanoimino, Ci-C\textsubscript{2}alkyi, Ci-C\textsubscript{2}alkoxy, -Co-C\textsubscript{2}alkyi(mono- and di-Ci-C\textsubscript{4}alkylamino), Ci-C\textsubscript{2}haloalkyl, and Ci-C\textsubscript{2}haloalkoxy.

Each of which R\textsuperscript{4} other than hydrogen, -CHO, and -CONH\textsubscript{2}, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyi, cyano, cyanoimino, Ci-C\textsubscript{2}alkyi, Ci-C\textsubscript{2}alkoxy, -Co-C\textsubscript{2}alkyi(mono- and di-Ci-C\textsubscript{4}alkylamino), Ci-C\textsubscript{2}haloalkyl, and Ci-C\textsubscript{2}haloalkoxy.

R\textsuperscript{5} and R\textsuperscript{6} are independently selected from -CHO, -C(0)NH\textsubscript{2}, -C(0)NH(CH\textsubscript{3}), C\textsubscript{2}-Cealkanoyl, hydrogen, hydroxyi, halogen, cyano, nitro, -COOH, -SO\textsubscript{2}NH\textsubscript{2}, vinyl, Ci-Cealkyl (including methyl), C\textsubscript{2}-Cealkenyl, Ci-C\textsubscript{2}alkoxy, -Co-C\textsubscript{4}alkyl(C\textsubscript{3}-C\textsubscript{7}cycloalkyl), -C(0)Co- C\textsubscript{4}alkyl(C\textsubscript{3}-C\textsubscript{7}cycloalkyl), -P(0)(OR\textsubscript{9})\textsubscript{2}, -OC(0)R\textsubscript{9}, -C(0)OR\textsubscript{9}, -C(0)N(CH\textsubscript{2}CF\textsubscript{2}R\textsubscript{3})(R\textsubscript{10}), -NR\textsuperscript{2}C(0)R\textsubscript{10}, phenyl, or 5- to 6-membered heteroaryl.
Each R and R other than hydrogen, hydroxy!, cyano, and -COOH is unsubstituted or optionally substituted. For example, R and R other than hydrogen, hydroxy!, cyano, and -COOH may be substituted with one or more substituents independently selected from halogen, hydroxy!, amino, imino, cyanoimino, C1-C2alkyl, Ci-C4alkoxy, -Co-Caalkylfmono- and di-Ci-Gtalkylamino), Ci-C2haloalkyl, and Ci-C2halaalkoxy.

R is hydrogen, halogen, hydroxyl, Ci-Gialkyl, -Co-C4alkyl(C3-C7cycloalkyl), or Ci-C4alkoxy; or R and R may be taken together to form an oxo, vinyl, or imino group.

R is hydrogen, Ci-C6alkyl, or -Co-C4alkyl(C3-C7cycloalkyl).

R and R are independently selected from hydrogen, halogen, hydroxyl, C1-Cealkyl, -Co-C4alkyl(C3-C7Cycloalkyl), Ci-Cealkoxy, and (C1-C4alkylamino)Co-C2alkyl; or R and R are taken together to form an oxo group; or R and R can be taken together with the carbon that they are bonded to form a 3-raemembered carbocyclic ring.

R is absent or may be independently selected from halogen, hydroxyl, nitro, cyano, Ci-Cealkyl, Ci-C2haloalkenyl, Ci-C2alkanoyl, Ci-Cealkoxy, -Co-C4alkyl(mono- and di-Ci-Cealkylamino), -Co-C4alkyl(C3-C7cycloalkyl), Ci-C2halaalkyl, and Ci-C2halaalkoxy.

R is hydrogen, Ci-Cealkyl, 0-C6alkenyl, C2-C6alkanoyl, -S02Ci-C6alkyl, (mono- and di-Ci-C6alkylamino)Ci-C4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), -Co-C4alkyl(C3-C7heterocycloalkyl), -Co-C4alkyl(aryl), Co-C4alkyl(heteroaryl), and wherein R other than hydrogen is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, amino, -COOH, and -C(0)O-Ci-C4alkyl.

X is N or CR.

X is N or CR.

X is N or CR.

X is N or CR.

No more than 2 of X, X, X, and X are N.

One of R or R is R. In one embodiment, one of R and R is selected from R and the other of R and R is selected from R. In an alternative embodiment, R and R are each independently selected from an R moiety.

R is selected from hydrogen, halogen, hydroxy!, nitro, cyano, amino, -COOH, C1-C2halaalkyl, Ci-C2halaalkoxy, Ci-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), C2-C6alkenyl, C2-Cealkanoyl, Ci-Cealkoxy, C2-Cealkenyloxy, -C(0)OR, Ci-Cethioalkyl, -Ct>C4alkyl!NR'R. SUBSTITUTE SHEET (RULE 26)
-C(O)NR R 1 0 , -SO2R 9 , -SO2NR R 1 0 , -OC(O) R 1 9 and -C(NR 9 )NR 1 0 , each of which R 1 0 other than hydrogen, halogen, hydroxy!, nitro, cyano, C1-C2 haloalkyl, and Ci-Ci haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxy!, nitro, cyano, amino, -COOH, -CONH 2 Ci-C2 haloalkyl, and Ci-C2 haloalkoxy, and each of which R 1 0 is also optionally substituted with one substituent selected from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently selected from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxy!, nitro, cyano, Ci-Ce alkyl, Ci-Ce alk enyl, C2-C6 alk en yl, Ci-Ce alk oxy, (mono- and di-Ci-C6 alk ylam ino)Co-C4 alk yl, Ci-Ce alk y lester, -Co-C4 alk yl(C3-C7 cycloalk yl), Ci-Ci haloalkyl, and Ci-C2 haloalkoxy;

[0063] R 3 2 is selected from -0(CH2)i-4R 3 3 , -OC2-C4 alk en yl!R 3 3 , -OC2-C4 alk ynylR 3 3 , -0(CH2)wparacyclophane, -O(CH3)1-4P(O)(OR)2 11bR 2 3 b , -0(CH2)2I-4S(0)(OR)2 111R 2 2 2 , -0(CH2)1-4S(0)NR 3 2 1R 2 3 5 , -0(CH2)3i-4S0 3 NR 3 2 1R 2 2 2 , -0(CH2)1-4S0 3 NR 3 2 1R 2 3 5 , -O(C2-C7 cycloalk yl), -O(aryl), -O(heteroaryl), and -O(heterocycle) and each group can be optionally substituted as further described herein. In certain places within the specification, R 3 2 is referred to as z3 2 .

[0064] When A is an indole or indazole and X 1 2 is N, X 1 3 is CR 1 3, wherein R 1 3 is R 3 2.

[0065] When A is an indole or indazole and X 3 1 is N, X 1 2 is CR 1 2, wherein R 1 2 is R 3 2.

[0066] R 1 1, R 1 4, and R 1 5 are independently selected at each occurrence from hydrogen, halogen, hydroxy!, nitro, cyano, -0(PO)(OR)2 12 , -0(PO)(OR) 9 2 2 , Ci-Ce alk yl, C8-C6 alk en yl, C2-Ce alk yn yl, C2-C6 alk en yl (aryl), C2-C6 alk en yl (cycloalk yl), C2-C6 alk en yl (heterocycle), C2-C6 alk en yl (heteroaryl), C2-C6 alk en yl (aryl), C2-C6 alk en yl (cycloalk yl), C2-C6 alk en yl (heterocycle), C2-C6 alk en yl (heteroaryl), C2-C6 alk en yl, Ci-Ce alk oxy, Ci-Ce thioalk yl, -Co-Osaikyi (mono- and di-Ci-Ce alk ylam ino), -Co-C4 alk yl(C3-C7 cycloalk yl), -Co-C4 alk oxy(C3-C7 cycloalk yl), Ci-C2 haloalk yl, and Ci-C2 haloalk oxy.

[0067] L is a bond or is selected from the formulas

\[
\text{\begin{align*}
\text{\begin{array}{c}
\text{O} \\
R_{18} & R_{18} \\
\text{N} \\
R_{17} & m \\
\text{S} \\
R_{18} & R_{18} \\
\text{O} \\
R_{18} & R_{18} \\
\end{array}}
\end{align*}}
\]

and

\[
\text{\begin{align*}
\text{\begin{array}{c}
\text{N} \\
R_{18} & R_{18} \\
\text{S} \\
R_{17} & m \\
\text{O} \\
R_{18} & R_{18} \\
\text{O} \\
R_{18} & R_{18} \\
\end{array}}
\end{align*}}
\]

where R 1 7 is hydrogen, Ci-Ce alk yl, or -C6-C4 alk yl(C3-C7 cycloalk yl) and R 1 8 and R 1 8 3 are independently selected from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3.
[0068] Linkers are also illustrated in Figures 4B, 4C, 4D, 4E, 4F, and 4G.

[0069] B 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 heteroaomis independently selected from N, O, and S and from 4 to 7 ring atoms per ring; C2-C6alkenyl; C2-Calkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C4alkyl)(bi phenyl), and B is unsubstituted or substituted with one or more substituents independently selected from R33 and R34, and 0 or 1 substituents selected from R35 and R36.

[0070] R33 is independently selected from halogen, hydroxyl, -COOH, cyano, Ci-Cealkyl, C2-C6aikanoyl, Ci-Cealkoxy, -Co-C4alkylNR(R)10, -SO2R9, Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0071] R34 is independently selected from nitro, C2-C6alkenyl, Ci-Cealkynyl, Ci-Cethioalkyl, -J(C3-C6cycloalkyl), -B(OH)2, -JC(0)NR9R21, -JOSO2OR21, -C(CH21-4S(0)NR21, -JOP(0)(OR21)(OR22), -J-P(0)(OR21)(OR22), -JOP(0)(OR21)R22, -JOP(0)R21R22, -J-P(0)R21R22, JSP(0)(OR21)(OR22), -JSP(0)(OR21)R22, -JNR9P(0)(NHR21)(NHR22), -JNR9P(0)(OR21)(NHR22), -JNR9P(0)(OR21)XOR22, -J-C(S)R21, -JNR21SO2R22, -J-NR9S(O)NR3422, -J-NR9SO2NR10R22, -JSQ2NR9COR22, -JSO2NR9CQNR22, -JMR21SO2R22, JJC(0)NR21SO2R22, -JCNH2NR22, -JCNH2NR9S(O)NR22, -JOC(0)NR21R22, -JNR31C(0)OR22, -J-NR21O(0)R22, -(CH2)1-4C(0)NR21R22, -J-C(0)NR21R25, -J-NR31C(0)NR21, -J-C(0)R21, -J-NR9C(O)NR10R22, -CCR21, -(CH2)1-40C(0)R21, and -JC(0)OR23; each of which R34 may be unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)2, -Si(CH3)3, -COOH, -CONH2, -P(0)(OH)2, Ci-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), Ci-Cealkoxy, -Co-C2alkyl(mono- and di-Ci-C4alkylamino), Ci-Cealkyester, Ci-C4alkylamino, Ci-CUhdroxyalkyl!, Ci-C2haloalkyl!, and Ci-C2haloalkoxy.

[0072] R35 is independently selected from napthyl, napthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl containing 1 or 2 heteroaomis selected from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroaomis independently selected from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R35 is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, Ci-Cealkyl, C2-C6aikaney, C2-C6alkanoyl, Ci-Cealkoxy, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, Ci-Cealkyester, -Co-C4alkyl(C3-C7cycloalkyl), -SO2R9, Ci-C2haloalkyl, and Ci-C2haloalkoxy.

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[0073] R^5 is independently selected from tetrazolyi, (phenyl)Co-Cialkyl, (phenyl)Ci-
C2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms
independently selected from N, O, B, and S, each of which R^5 is unsubstituted or substituted with
one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, Ci-Cealkyl,
C2-C6alkenyl, C2-C6aikanoyi, Ci-Cealkoxy, (mono- and di-Ci-C6alkyiamino)Co-C4alkyl, Ci-
Cealkyiester, -Co-C4alkyl(C 3-C7cycloalkyl), -SO2R^9, -OSi(CH3)2C(CH3)3, -Si(CH3)2C(CH3)3, Ci-
C2haloalkyl, and Ci-C2haoalkoxy.

[0074] In one additional alternative embodiment B is selected from:

[0075] In one additional alternative embodiment R^3a is selected from:

[0076] In one embodiment R^1 is selected from F, Cl, Br, and Ci-Cealkyl.

[0077] In one embodiment R^1 is selected from hydroxyl and Ci-Cealkoxy.

[0078] In one embodiment R^1 is selected from C2-C6alkynyl, C2-C6aikanoyl, and Ci-
C6thioalkyl.

[0079] In one embodiment R^1 is selected from aminoCi-Cealkyl and -Co-C4alkylNR^9R^10.

[0080] R^21 and R^22 are independently selected at each occurrence from hydrogen, hydroxyl,
cyano, amino, Ci-C6alkyl, Ci-C6haoalkyl, Ci-Cealkoxy, (C3-C7cycloalkyl)Co-C4alkyl,
(phenyl)Co-C4alkyl, -Ci-C4alkylOC(0)OCi-C6alkyl, -Ci-C4alkylOC(0)OCi-C6alkyl, -Ci-
C4aikyiC(0)OC!-C6aiky, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3
heteroatoms independently selected from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each R\textsuperscript{21} and R\textsuperscript{22} can be optionally substituted.

[0081] R\textsuperscript{23} is independently selected at each occurrence from Ci-Cealkyl, Ct-Cehaioalkyl, (aryl)Co-C4alkyl, (C\textsubscript{3}-C\textsubscript{7}cycloalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each R\textsuperscript{3} can be optionally substituted.

[0082] R\textsuperscript{23a} is independently selected at each occurrence from (C\textsubscript{3}-C\textsubscript{7}cycloalkyl) and each R\textsuperscript{23a} can be optionally substituted.

[0083] R\textsuperscript{23b} is independently selected at each occurrence from hydroxy, Ci-C6alkoxy,Ci-C6alkyl, (C\textsubscript{3}-C\textsubscript{7}cycloalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, -0(\(\text{C}^4\text{H}4\)2-40(0 H)\text{S}8-78, -OC(R\textsuperscript{23c})20C(0)OR\textsuperscript{23d}, -GC(R\textsuperscript{25c})2QC(G)R\textsuperscript{23d}, an N-linked amino acid or an N-linked amino acid ester, and each R\textsuperscript{23b} can be optionally substituted.

[0084] R\textsuperscript{23c} is independently selected at each occurrence from hydrogen, d-Cealkyl, C2-C8alkenyl, C2-Csalkynyl, (aryl)Co-C4alkyl, (aryl)C2-C8alkenyl- or (aryljCVCgalkynyl; or two R\textsuperscript{23c} groups can be taken together with the carbon that they are bonded to form a 3-6 membered heterocycloalkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, or a 3-6 membered carbocyclic ring, and each R\textsuperscript{23c} can be optionally substituted.

[0085] R\textsuperscript{23d} is independently selected at each occurrence from Ci-Csalkyl, C\textsubscript{2}-C8alkenyl, C2-Csalkynyl, (aryl)Co-C4alkyl, (aryOCa-Csalkenyl or (aryl)C2-C8alkynyl, and each R\textsuperscript{23d} can be optionally substituted.

[0086] R\textsuperscript{24} and R\textsuperscript{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\textsuperscript{24} and R\textsuperscript{25} can be optionally substituted.

[0087] J is independently selected at each occurrence from a covalent bond, Ci-C4alkylene, -OGi-C4alkylene, C2-C4alkenylen, and C2-C4alkynylene.

[0088] The present invention thus includes at least the following features:

(a) An ether compound of Formula I, including those compounds listed in Table 1, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or
preventing a disorder listed in the Detailed Description, Part IV, Section A, 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, dermatomyositis; amyotrophic lateral sclerosis; and cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy);

(b) An ether compound of Table 2 or Table 3 or an active compound that is prepared from or consists of moieties selected from Figures 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8 and optionally 4B, 4C, 4D, 4E or 4F, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing a disorder listed in the Detailed Description, Part IV, Section A, 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, dermatomyositis; amyotrophic lateral sclerosis; and cytokine or inflammatory reactions in response to the administration of biotherapeutics (e.g. CAR T-cell therapy);

(c) An ether compound of Table 2 or Table 3 or an embodiment of the active compound as described in Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing a disorder listed in the Detailed Description, Part IV, Section B of this invention, including but not limited to paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, 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,

(d) A pharmaceutically acceptable composition of an ether compound of Table 2 or Table 3 or an ether compound that is prepared from or consists of moieties selected from Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8 and optionally 4B, 4C, 4D, 4E or 4F, or its pharmaceutically acceptable salt in a pharmaceutically acceptable carrier,

(e) An ether compound selected from Table 2 or Table 3 or a compound that is prepared from or consists of moieties selected from Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F, as described
herein, and pharmaceutically acceptable salts, prodrugs and pharmaceutically acceptable compositions thereof,

(i) An ether compound selected from Table 2 or Table 3 or a compound that is prepared from or consists of moieties selected from Figure IB, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing disorders mediated by the complement pathway, and for example, cascade Factor D;

(g) Use of a compound of Formula I, including those compounds listed in Table 1, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, Section A, 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, dermatomyositis; amyotrophic lateral sclerosis; and cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy);

(h) Use of a compound of Table 2 or Table 3 that is prepared from or consists of moieties selected from Figure IB, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8 and optionally 4B, 4C, 4D, 4E or 4F, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, Section A, 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; dermatomyositis; amyotrophic lateral sclerosis, and cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy);

(i) Use of a compound of Table 2 or Table 3 or a compound that is prepared from or consists of moieties selected from Figure IB, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F as described herein, and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, Section B of this invention, including but not limited to paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration
(AMD), retinal degeneration, other ophthalmic diseases (e.g., geographic atrophy), a respirator}' disease or a cardiovascular disease;

(j) A process for manufacturing a medicament intended for the therapeutic use for treating or preventing a disorder listed in the Detailed Description, Part IV, Section A or Section B, or generally for treating or preventing disorders mediated by complement cascade Factor D, including age-related macular degeneration (AMD), retinal degeneration, paroxysymai nocturnal hemoglobinuria (PNFI), C3 glomerulonephritis, multiple sclerosis (MS), and rheumatoid arthritis (RA) and other disorders described further herein characterized in that a compound selected from Table 2 or Table 3 or a compound that is prepared from or consists of moieties selected from Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8 and optionally 4B, 4C, 4D, 4E or 4F, is used in the manufacture;

(k) A compound selected from Table 2 or Table 3 or a compound that is prepared from or consists of moieties selected from Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F, as described herein in substantially pure form (e.g., at least 90 or 95%):

(l) An ether compound of Formula 1, including those compounds listed in Table 1, as described herein, and pharmaceutically acceptable salts and prodrugs 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;

(m) An ether compound of Table 2 or Table 3 or a compound that is prepared from or consists of moieties in Figure 1B, 1C, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 5, 6A, 6B, 6C, or 8, and optionally 4B, 4C, 4D, 4E or 4F, as described herein, and pharmaceutically acceptable salts and prodrugs 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 alloergic tissue or fluid administration,

(n) An ether compound that is prepared from or consists of moieties selected from Figures 1D or 1E; 5; 6A, 6B or 6C; 7A, 7B, 7C, 7D or 7E; and 8; and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing a disorder listed in the Detailed Description, Part IV, Section A, 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; dermatomyositis; amyotrophic lateral sclerosis; and cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy);

(o) An ether compound that is prepared from or consists of moieties selected from one of the following groups: (i) any of Figures 1B, 1C, 1D or 1E; Figure 5; Figures 6A, 6B, 6C or 6D, and Figure 7F; optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (ii) Figures 1B, 1C, 1D, 1E or IF; Figure 5, Figure 6D, Figure 7A, 7B, 7C, 7D, 7E, 7F or 7G; and Figure 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G, (iii) Figures 1A, IB, IC, 1D, 1E, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3i, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G, and 6D; (iv) i A, IB, IC, 1D, 1E, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3i, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q, 7G, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (v) Figures 1A, IB, IC, 1D, 1E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3i, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q, 6A, 6B, 6C, 6D or 6E, 7G and optionally Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G and; (vi) Figures IB, IC, 1D or IE; Figure 5; Figures 6E, any of Figures 7A, 7B, 7C, 7D, 7E, 7F or 7G and 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G, or (vii) Figures 9A-9H and any of Figures 6A, 6B, 6C, 6D, or 6E; as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing a disorder listed in the Detailed Description, Part IV, Section A, 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, dermatomyositis; amyotrophic lateral sclerosis; and cytokine or inflammatory reactions in response to the administration of biotherapeutics (e.g. CAR T-cell therapy);
(p) An ether compound that is prepared from or consists of moieties selected from one of the following groups: (i) any of Figures 1B, 1C, 1D or 1E; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E and Figure 7F, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G (ii) Figures 1B, 1C, 1D, 1E or 1F; Figure 5. Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G; and Figure 8, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G (iii) Figures 1B, 1C, 1D, 1E, IF, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, or 6D, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G (iv) Figures 1B, 1C, 1D, 1E, IF, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6A, 6B, 6C, 6D, 6E, and 7F, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (v) Figures 1B, 1C, 1D, 1E, 1F, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6A, 6B, 6C, 6D, 6E, and 7G, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (vi) Figures 1B, 1C, 1D or 1E; Figure 5; Figures 6E; any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G, and 8, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; or the species of (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and any one of Figures 6A, 6B, 6C, 6D, 6E; as described herein, and pharmaceutically acceptable salts and prodrugs thereof, for use in treating or preventing a disorder listed in the Detailed Description, Part IV, Section Bof this invention, including but not limited to paroxysmal nocturnal hemoglobinuria (PNFI), C3 glomerulonephritis, 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;

(q) A pharmaceutically acceptable composition of a compound of any species consisting of moieties selected from one of the following groups: (i) any of Figures 1B, 1C, 1D or 1E; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E and Figure 7F; optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (ii) Figures 1B, 1C, 1D, 1E or 1F; Figure 5. Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G; and Figure 8; optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G (iii) Figures 1B, 1C, 1D, 1E, IF, and 6D, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4F, or 4G (iv) Figures 1B, 1C, 1D, 1E, IF, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6A, 6B, 6C, 6D, 6E, 7F, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (v) Figures 1B, 1C, 1D, 1E, IF, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6A, 6B, 6C, 6D, 6E.
6B, 6C, 6D, 6E, 7G, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (vi) Figures 1B, IC, 1D or IE; Figure 5; Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G and 8; optionally including a moieties of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G, or (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and any one of Figures 6A, 6B, 6C, 6D, 6E; or its pharmaceutically acceptable salt in a pharmaceutically acceptable carrier; (r) A compound that is prepared from or consists of moieties selected from one of the following groups (i) any of Figures 1B, IC, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q; Figure 5; optionally any one of Figures 6A, 6B, 6C, 6D or 6E; Figure 7F and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (ii) Figures 1B, IC, ID, IE or IF; Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G; and Figure 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G, (iii) Figures 1B, IC, ID, IE, IF, 2B, 2C, 2I) or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P, 3Q, and 6D, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) Figures 1A, 1B, IC, ID, IE, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P, 6A, 6B, 6C, 6D or 6E, 7F and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; or (v) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figure 6D, as described herein, and pharmaceutically acceptable salts, prodaigs and pharmaceutically acceptable compositions thereof; (s) A compound that is prepared from or consists of moieties selected from one of the following groups (i) any of Figures 1B, IC, 1D or IE; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E and Figure 7F; optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F or 4G; (ii) Figures 1B, IC, ID, IE or IF; Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G; and Figure 8; optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F or 4G; (iii) Figures 1-4 and 6D; (iv) Figures 1A, 1B, IC, ID, IE, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P, 6A, 6B, 6C, 6D or 6E, 7F and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (v) Figures 1B, IC, 1D, IE, IF, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P, 3Q, 6A, 6B, 6C, 6D, 6E, 7G, optionally including a moiety of Figures 4A, 4B, 4C, 4D, 4E, 4F, or 4G, (vi) Figures 1B, 1C, 1D or IE; Figure 5; Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G and 8; optionally including a moiety of Figures 4, or (vii) Figures 9A-9H, and Figure 6D, as described herein, and pharmaceutically acceptable salts and prodrugs.
thereof, for use in treating or preventing disorders mediated by the complement pathway, and
for example, cascade Factor D;

(t) Use of a compound that is prepared from or consists of moieties selected from Figures 1D or
IE, 5; 6A, 6B or 6C; 7A, 7B, 7C, 7D or 7E; and 8; optionally including a moiety of Figure 4A,
4B, 4C, 4D or 4E as described herein, and pharmaceutically acceptable salts and prodrugs
thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the
Detailed Description, Part IV, Section A, 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; dermatomyositis, amyotrophic lateral sclerosis; and
cytokine or inflammatory reactions in response to biotherapeutics (e.g. CAR T-cell therapy);

(u) Use of a compound of that is prepared from or consists of moieties selected from (i) any of
Figures 1B, 1C, 1D or 1E; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E and Figure 7F;
optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E (ii) Figures 1B, 1C, 1D, 1E or
IF; Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G; and Figure 8; and
optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E; (iii) Fig. 1A, 1B, 1C, 1D, 1E,
2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, and
and 6D and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) any of Figures 1B, 1C, 1D or 1E;
Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, Figures 6A,
6B, 6C, 6D or 6E; Figure 7F and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E,
4F or 4G; (v) any of Figures 1B, 1C, 1D or 1E; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3J, 3K,
3L, 3M, 3N, 3O, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E, Figure 7G and optionally
including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (vi) Figures 1B, 1C, 1D or 1E;
Figure 5; Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G and 8; optionally
including a moiety of Figure 4A, 4B, 4C, 4D, or 4E; or (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F,
9G, 9H, and Figure 6D, as described herein, and pharmaceutically acceptable salts and
prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder
listed in the Detailed Description, Part IV, Section A, 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; dermatomyositis;
amyotrophic lateral sclerosis, and cytokine or inflammatory reactions in response to
biotherapeutics (e.g. CAR T-cell therapy);
(v) Use of a compound that is prepared from or consists of moieties selected from (i) any of Figures IB, IC, ID or IE; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E and Figure 7F, optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E (ii) Figures 1B, IC, ID, IE or IF; Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G, and Figure 8; and optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E; (iii) Fig. 1A, IB, IC, ID, IE, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3F1, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q, and and 6D and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) any of Figures 1B, IC, ID or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E; Figure 7F and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (v) any of Figures IB, 1C, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E; Figure 7G and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (vi) Figures 1B, 1C, 1D or IE; Figure 5: Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G and 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D, or 4E; or (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and Figure 6D, as described herein, and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, Section B of this invention, including but not limited to paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (MID), retinal degeneration, other ophthalmic diseases (e.g., geographic atrophy), a respiratory disease or a cardiovascular disease;

(w) A process for manufacturing a medicament intended for the therapeutic use for treating or preventing a disorder listed in the Detailed Description, Part IV, Section A or Section B, or generally for treating or preventing disorders mediated by complement cascade Factor D, including age-related macular degeneration (AMD), retinal degeneration, paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, multiple sclerosis (MS), and rheumatoid arthritis (RA) and other disorders described further herein characterized in that a compound selected for use is a compound that is prepared from or consists of moieties selected from (i) any of Figures IB, 1C, 1D or IE; Figure 5; any one of Figures 6A, 6I3, 6C, 6I), 6E and Figure 7F; optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E (ii) Figures 1B, IC, 1D, 1E or 1F; Figure 5, Figure 6I, any of Figures 7A, 7B, 7C, 7I), 7E, 7F, or 7G, and Figure 8; and optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E; (iii) Fig. 1A, IB,
1C, 1D, 1E, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, and and 6D and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) any of Figures 1B, IC, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, Figures 6A, 6B, 6C, 6D or 6E; Figure 7F and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (v) any of Figures 1B, IC, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E; Figure 7G and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (vi) Figures 1B, IC, 1D or IE; Figure 5: Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G and 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D, or 4E; or (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and Figure 6D, as described herein is used in the manufacture;

(x) A compound that is prepared from or consists of moieties selected from (i) any of Figures 1B, IC, 1D or IE; Figure 5; any one of Figures 6A, 6B, 6C, 6D, 6E, and Figure 7F; optionally including a moiety of Figures 4A, 4B, 4C, 4D or 4E; (ii) Figures 1B, IC, 1D, 1E or IF; Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F or 7G, and Figure 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E; (iii) 1A, 1B, IC, 1D, IE, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, and 6D, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) Fig. 1A, 1B, IC, 1D, 1E, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P or 3Q, and 7F and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; or (v) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and Figure 6D as described herein as described herein in substantially pure form (e.g., at least 90 or 95%);

(y) A compound that is prepared from or consists of moieties selected from Figures 1D or IE; 5; 6A, 6B or 6C; 7A, 7B, 7C, 7D or 7E; and 8; optionally including a moiety of Figures 4A, 4B, 4C, 4D, or 4E; as described herein, and pharmaceutically acceptable salts and prodrugs 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; and
(z) A compound of that is prepared from or consists of moieties selected from (i) any of Figures IB, 1C, 1D or 1E; Figure 5; any one of Figures 6A, 6B, 6C, 6D or 6E and Figure 7F; optionally including a moiety of Figure 4A, 4B, 4C, 4I or 4E (ii) Figures 1B, 1C, 1D, 1E or IF, Figure 5, Figure 6D, any of Figures 7A, 7B, 7C, 7D, 7E, 7F, or 7G; and Figure 8; optionally including a moiety of Figures 4A, 4B, 4C, 4I or 4E (iii) 1A, IB, 1C, ID, 1E, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q, and 6D, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) Figures IB, 1C, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E; Figure 7F and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (v) Figures IB, 1C, 1D or IE; Figure 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 30, 3P or 3Q; Figures 6A, 6B, 6C, 6D or 6E, Figure 7G and optionally including a moiety of Figure 4A, 4B, 4C, 4D, 4E, 4F or 4G; (vi) Figures IB, 1C, 1D or IE; Figure 5; Figures 6E; and any of Figures 7A, 7B, 7C, 7D, 7E, 7F or 7G and 8; optionally including a moiety of Figure 4A, 4B, 4C, 4D or 4E; or (vii) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G or 9H, and Figure 6D as described herein, and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for treating or preventing a disorder listed in the Detailed Description, Part IV, Section Bof this invention, including but not limited to paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulonephritis, rheumatoid arthritis, multiple sclerosis, age-related macular deg and pharmaceutically acceptable salts and prodrugs 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.

(aa) For each of (a) through (z) 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.

(bb) In another embodiment, any moiety of "A" (Fig. 1B, C, D or E), any moiety of "B" ((Fig. 2 B, C, D, or E), Fig 7 (A, B, C, D, E, F or G) or Fig. 8); any moiety of the core ((Fig. 3 B, C,
D, E, F, G, H, I, J, K, L, M, N, 0, P or Q) or Fig. 5), any moiety of Linker (Fig. 4 B, C, D, E, F, or G) and any moiety of R² (Fig. 6 A, B, C, D or E) can be combined to treat an indication of Section A; and the assembly of moieties from the Figures and each active compound made therefrom 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;

(cc) In another embodiment, any moiety of "A" (Fig. 1 B, C, D or E); any moiety of "B" ((Fig. 2 B, C, D, or E), Fig 7 (A, B, C, D, E, F or G) or Fig. 8); any moiety of the core ((Fig. 3 B, C, D, E, F, G, H, I, J, K, L, M, N, 0, P or Q) or Fig. 5), any moiety of Linker (Fig. 4 B, C, D, E, F, or G) and any moiety of R² (Fig. 6 A, B, C, D or E) can be combined to treat an indication of Section B with the proviso that there is at least one moiety selected from Fig 1 (B or C); or Fig. 7F; Fig 4G; or Fig. 6D; and the assembly of moieties from the Figures and each active compound made therefrom 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

[0089] FIG. 1A is an illustration of Formula I which highlights the location of the A ring.

[0090] FIG. 1B and 1C provide non-limiting embodiments of the A ring, wherein R^2 is defined below.

[0091] FIG. 1D and 1E illustrate non-limiting embodiments of the A ring of Fig. 1A, wherein R^4, R^5, R^6, R^7, R^8, R^9, R^11, R^12, R^13, R^14, R^16, R^19, X^11, X^12, X^13, and X^14 are defined below.

[0092] FIG. 2A illustrates the location of the B ring of Formula 1.

[0093] FIGS. 2B, 2C, 2D and 2E provide certain embodiments of the B ring, wherein "halo" can be F, Cl, Br, or I.

[0094] FIG. 3A illustrates the location of the Central Core of Formula 1.

[0095] FIGS. 3B, 3C, 3D, 3E, 3F, 3G, 3H, 31, 3J, 3K, 3L, 3M, 3N, 3G, 3P, and 3Q provide non-limiting embodiments of the Central Core ring (C ring), wherein q is 0, 1, 2 or 3, r is 1, 2 or 3, \( \equiv \equiv \equiv \) is a single or double bond, and R^44, R^47, R^45, R^45 are defined below wherein each group can be optionally substituted.

[0096] FIG. 4A illustrates the location of the Linker in Formula 1.

[0097] FIGS. 4B, 4C, 4D, 4E, 4F and 4G, provide non-limiting specific embodiments of the Linker (L), wherein R^17, R^18, R^18, and m are defined below.

[0098] FIG. 5 provides non-limiting specific embodiments of the Central Core ring, wherein R, R', and R^3 are defined below.

[0099] FIGS. 6A, 6B, 6C, 6D and 6E provide non-limiting specific embodiments of R^10, wherein R^10 is defined below.

[0100] FIGS. 7A, 7B, 7C, 7D, 7E, 7F and 7G provide non-limiting specific embodiments of the B ring, wherein R^27, R^28, and R^29 are defined below.

[0101] FIG. 8 provides non-limiting specific embodiments of the B ring.

[0102] FIGS. 9A, 9B, 9C, 9D, 9E, 9F, 9G and 9H provide non-limiting examples of compounds included in the present invention, wherein Z^32 is the same as R^32 as used herein.
DETAILED DESCRIPTION

1. TERMINOLOGY

[0103] 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.

[0104] The compounds in any of the Formulas described herein include enantiomers, mixture of enantiomers, diasteromers, tautomers, racemates and other isomers, such as rotamers, as if each is specifically described, unless otherwise indicated in the text or drawing or otherwise indicated in context. "Formula I" includes all subgeneric groups of Formula I, such as Formula 1A and Formula 1B and also includes pharmaceutically acceptable salts of a compound of Formula I, unless clearly contraindicated by the context in which this phrase is used. "Formula I" also includes all subgeneric groups of Formula I, such as Formulas 1C - ID, and Formulas II - XXX, and also includes pharmaceutically acceptable salts of all subgeneric groups of Formula I, such as Formulas 1A, - ID, and Formulas II - XXX, unless contraindicated by the context in which this phrase is used.

[0105] 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. 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.

[0106] The present invention includes compounds with at least one desired isotopie 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. 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, $^{36}$Cl, $^{125}$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.

[0107] 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. AUG, 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).

[0108] 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 embodiment, 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.

[0109] In one embodiment, the substitution of a hydrogen atom for a deuterium atom can be provided in any of A, B, L, or central core. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group selected from any of $R$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$, $R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{27}$, $R^{28}$, $R^{29}$, $R^{30}$, $R^{31}$, $R^{32}$, $R^{33}$, $R^{34}$, $R^{35}$, $R^{36}$, $R^{37}$, $R^{38}$, $R^{39}$, $R^{40}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, $R^{46}$, $R^{47}$, $R^{48}$, $R^{49}$, $R^{50}$, $R^{51}$, $R^{52}$, $R^{53}$, $R^{54}$, $R^{55}$, $R^{56}$, $R^{57}$, $R^{58}$, $R^{59}$, $R^{60}$ and $R^{107}$. For example, when any of R groups are, or contain for example through
substitution, methyl, ethyl, or methoxy, the aikyi residue may be deuterated (in non-limiting embodiments, CDs, CH2CD3, CD2CD3, CDH2, CD2H, CDs, CHDCH2D, CH2CD3, CHDCHD2, OCDH2, OCD2H, or OCD3 etc.). 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.

[0110] The substitution of a hydrogen atom for a deuterium atom occurs within an R group when at least one of the variables within the R group is hydrogen (e.g., ^2H or D) or alkyl. For example, when any of R groups are, or contain for example through substitution, methyl or ethyl, the alkyl residue may be deuterated (in non-limiting embodiments, CDs, CH2CD3, CD2CD3, CDH2, CD2H, CDs, CHDCH2D, CH2CD3, CHDCHD2, etc.).

[0111] The compound of the present invention may form a solvate with solvents (including water). Therefore, in one embodiment, the invention includes a sovated 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. Non-limiting 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, de-acetone, DMSO-^d6. A solvate can be in a liquid or solid form.

[0112] A dash ("-"+) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -(C=())NFl2 is attached through carbon of the keto (C=0) group.

[0113] 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. Alternatively, oxygen substitution can mean that an atom is oxidized, for example, sulfur can be oxidized to sulfoxide or sulfone; nitrogen can be oxidized to nitrooxide, or carbon or phosphorus may be partially or fully oxidized. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates.
[0114] 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. Non-limiting 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.

[0115] 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, Cl, Br or I); cyano; hydroxyl; nitro, azido; alkanoyl (such as a C2-C0 alkanoyl group), carboxamide; alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxio such as phenoxy; alkythio including those having one or more thioether linkages; alkylsulfonyl; alkylsulfonyl groups including those having one or more sulfonylethoxyl linkages; aminoalkyl groups including groups having one or more N atoms; aryI (e.g., phenyl, biphenyi, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); aryalkyl 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 aryalkyl group; aryalkoxy, for example, having 1 to 3 separate or fused rings with benzyloxy being an exemplary aryalkoxy 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, thiazoiiy, triazinyl, oxazoyl, isoxazoyl, imidazoyl, indoyl, benzofuranyl, benzothiazoyl, tetrahydrofuranyl, tetrahydropryanyl, piperidinyi, morpholinyl, piperezinyl, and pyrroloidinyl. 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 selected from halogen, hydroxyl, amino, cyano, -CHO, -COOH, -COONH2, Ci-Cealkyl, Cz-Cealkenyl, C?.-C6alkynyl, -Ci-C6alkoxy, C?.-C6alkanoyl, Ci-Cealkylester, (mono- and di-Ci-C6alkylammonio)Co-C2alkyl, Ci-C2haoalkyl, hydroxyCi-Cealkyl, ester, carbamate, urea, sulfonamide, -Ci-C6alkyl(heterocyclo), -Ci-C6alkyl(heteroaryl), -Ci-C6alkyl(C3-C5cycloalkyl), 0-Ci-C6aikyi(C3-C7cycloalkyl), B(OH)3, phosphate, phosphonate and Ci-C2haoalkoxy.
[01:16] "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, or Ci-Ce. 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 C1-C6 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-C4 alkyl 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-C» alkyl is used herein in conjunction with another group, for example, (C3-C7 cycloalkyl)Co-C4 alkyl, or -Co-C4 alkyl(C3-C7 cycloalkyl), 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 - O-Co-C4 alkyl(C3-C7 cycloalkyl). 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.

[01:17] 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 terras alkyl, alkenyl, alkynyl, alkoxy, alkanoyl, alkenoxy, haloalkyl, aminoalkyl, alkyiene, alkenylene, alkynylene, etc. can all be considered to include the cyclic forms of alkyl, unless unambiguously excluded by context.

[01:18] "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. Non-limiting examples are C2-C5 alkenyl, Ca-Calkenyl and C2-Calkenyl. 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.

[01:19] "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-Calkynyl. 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.

[0120] "Alkylene" is a bivalent saturated hydrocarbon. Alkenyles, for example, can be a 1 to 8 carbon moiety, 1 to 6 carbon moiety, or an indicated number of carbon atoms, for example Ci-C4alkylene, Ci-Cmlkylene, or Ci-C2alkylene.

[0121] "Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenyles, 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.

[0122] "Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynyles, 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.

[0123] "Alkoxy" is an alkyl group as defined above covalently bound through an oxygen bridge (-O-). 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-methylpentenoxy. 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.

[0124] "Alkenyloxy" is an alkenyl group as defined covalently bound to the group it substitutes by an oxygen bridge (-O-).

[0125] "AlkanoyP is an alkyl group as defined above covalently bound through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, that is C₂.alkanoy is a CH₃(C=O)ₘ group. In one embodiment, the alkanoy group is optionally substituted as described above.

[0126] "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 -O(C=O)alkyl or a group of the formula -(C=O)Oalkyl.
[0127] "Amide" or "carboxamide" is -C(0)NR²R³ wherein R¹ and R² are each independently selected from hydrogen, alkyl, for example, C₁-C₆alkyl, alkenyl, for example, C₂-C₆alkynyl, alkylnyl, for example, C₂-C₆alkynyl, -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, R¹ and R² can form a C₃-C₇heterocyclic ring. In one embodiment, the R¹ and R² groups are each independently optionally substituted as described above.

[0128] "Carbocyclic group", "carboyclic ring", or "cydioalkyl" 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. Cycioalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents can have a cycioalkyl group, which is attached as a spiro group. Examples of carbocyclic rings include cyclohexityl, cyclohexyl, cyclopentyl, cyclopentyl, cyclobutyl, and cyclopropyl rings. In one embodiment, the carbocyclic ring is optionally substituted as described above. In one embodiment, the cycioalkyl is a partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. In another embodiment, the cycioalkyl is a saturated group containing all carbon ring atoms.

[0129] "Carboyclic-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, -O-, linker.

[0130] "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, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0131] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0132] "Hydroxyalkyl" is an alkyl group as previously described, substituted with at least one hydroxyl substituent.

[0133] "Aminoalkyl" is an alkyl group as previously described, substituted with at least one amino substituent.

[0134] "Halo" or "halogen" indicates independently any of fluoro, chloro, bromo or iodo.

[0135] "Aryl" indicates an aromatic group containing only carbon in the aromatic ring or rings. In one embodiment, the aryl groups contain 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 selected 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.

[0136] 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, 5, 6, 7 to 10 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, 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, and S) or a bicycle having 6 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), 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 sulfur. 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. Chera. Soc. (1960) 82:5566. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropryanyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, piperidonyl, morpholino, thiomorpholino, thioxanyl, piperaziny1, homopiperaziny1, azetidiny1, oxetany1, thietany1, homopiperidiny1, oxepany1, thiepany1, oxazepiny1, diazepiny1, thiazepiny1, 2-pyrroliny1, 3-pyrroliny1, indoliny1, 2H-pyrany1, 4H-pyrany1, dioxany1, 1,3-dioxoiany1, pyrazoliny1, dithiany1, dithiolany1, dihydroprany1, dihydrothiery1, dihydrofurany1, dihydroisouquinoliny1, tetrahydroisouquinoliny1, pyrazoliny1imidazoliny1, imidazoliny1, 2-oxa-5-azabicyclo[2.2.2]octany1, 3-oxa-8-azabicyclo[3.2.1]octany1, 8-oxa-3-azabicyclo[3.2.1]octany1, 6-
oxa-3-azabicyclo[3.1.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyclo[3.1.1]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl, quinolizinyl, N-pyridyl ureas, and pyrrolopyrirdaine. 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 (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiaraorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

[0137] "Heterocyclicoxy group" is a monocyclic heterocyclic ring or a bicyclic heterocyclic group as described previously linked to the group it substitutes via an oxygen, -O-, linker.

[0138] "Heteroaryi" indicates a stable monocyclic aromatic ring which contains from 1 to 3, or in some embodiments from 1, 2 or 3 heteroatoms selected from N, O, S, B or P with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 4 to 7 or 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms selected 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 heteroaryi groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryi groups are 8- to 10-membered heteroaryi groups, that is, groups containing 8 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and 0 atoms in the heteroaryi group exceeds 1, these heteroatoms are not adjacent to one another. In one embodiment, the total number of S and 0 atoms in the heteroaryi group is not more than 2. In another embodiment, the total number of S and 0 atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryi 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, isothiazoyl, 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, quinazolinyi, quinoxaiinyl, naphthyridinyi, tetrahydrofuranyl, and furoypyridinyl. Heteroaryi groups are optionally substituted independently with one or more substituents described...
"Heteraryoxy" is a heteroaryl group as described bound to the group it substituted via an oxygen, -O-, linker.

"Heterocycloalkyl" is a saturated ring group. It may have, for example, 1, 2, 3, or 4 heteroatoms independently selected from N, S, and O, 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 morpholiny1, piperaziny1, piperidiny1, and pyrroliny1.

The term "mono- and/ or di-alkylamino" indicate a secondary or tertiary alkylamino group, wherein the alkyl groups are independently selected 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.

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.

"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.

A "pharmacetically acceptable salt" is a derivative of the disclosed compound in which the parent compound is modified by making inorganic and organic, non-toxic, 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, ethanoi, isopropanol,
or aceionitrile are typical, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0144] 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, g'lycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esyiic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-(CH₂)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).

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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 pharmacologic or pharmacokinetic properties of the parent. Prodrug strategies exist which provide choices in
modulating the conditions for \textit{in vivo} generation of the parent drug, all of which are deemed included herein. Non-limiting examples of prodrug strategies include covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylaion, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others.

[0149] "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, inraaortial, transdermal, polymeric controlled delivery, non-polymeric controlled delivery, nano or microparticles, liposomes, and/or topical contact.

[0150] 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


![Chemical Structure Image]

as well as the pharmaceutically acceptable salts and compositions thereof. In one embodiment, the invention is the use of 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 ether substituent, including those compounds set out in Table 1, for the treatment of a disorder in a host, typically a human, wherein the disorder is selected from the group disclosed in the Detailed Description, Part IV, Section A.

[0152] Formula I can be considered to have a central core, an L substituent, a B substituent (which can be an L-B substituent), and a (C=0)A substituent. Non-limiting examples of compounds falling within Formula I with variations in the variables e.g., A, B, $R^{1}$-$R^{3}$, the central core, and L, are illustrated below. The disclosure includes the use of all combinations of these definitions so long as a stable compound results. In one embodiment, the compound of Formula I is selected from the compounds in Table 1 below.

[0153] 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 Terfiány Nitrogen
Compounds to N-Oxides Using Sodium Percarbonate as Oxygen Source, Synlett, 2261-2663, 2006

[0154] In one embodiment, a sulfur atom in a selected compound as described herein can be oxidized to form a sulfoxide of a sulfone. For example, the compound 1,3,5-triazol-2,4,6-triphosphorine-2,2,4,6,6-tetrachloride (TAPC) is an efficient promoter for the oxidation of sulfides to sulfoxides. See, Bahrami, M. et al., "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", Synlett, 1557-1561 (2010). Sulfides can be oxidized to sulfones using, for example, niobium carbide as the catalyst, 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", Synlett, 1557-1561 (2010).


One skilled in the art will appreciate that other heteroatoms, 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 II - XXX

[0155] In one aspect, the disclosure includes the use, as further described herein, of a compound or salt of Formula II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII, XXIX and XXX. The variables shown in Formula II-XXX carry the definitions set forth in the SUMMARY section for Formula I or any of the definitions set forth in this disclosure.
m is 0 or 1.

Formula XX

Formula XXI

Formula XXII

m is 0 or 1

Formula XXIII

m is 0 or 1

Formula XXIV

Formula XXV

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Additionally, the disclosure includes the use of compounds and salts of Formula I and pharmaceutically acceptable compositions thereof, and any of its subformuia (II-XXX) in which at least one of the following conditions is met in the embodiments described below.

The \( R_{2}^{2} \) and \( R_{3}^{3} \) Ether Substituents

[0157] In one embodiment, the invention is the use of a compound of Formula I, or a pharmaceutically acceptable salt or composition thereof, wherein \( R_{12}^{12} \) or \( R_{13}^{13} \) on the A group is an ether substituent, including those compounds set out in Table 1, for the treatment of a disorder in
a host, typically a human, wherein the disorder is selected from the group disclosed in the Detailed Description, Part IV, Section A. In other embodiments, the R_{32} group is as illustrated in Figures 6A, 6B, 6C, 6D or 6E.

[0158] One of R^{12} or R^{13} is R^{32}. In one embodiment, one of R^{12} and R^{13} is selected from R^{31} and the other of R^{12} and R^{13} is selected from R^{32}. In an alternative embodiment, R^{12} and R^{13} are each independently selected from an R^{32} moiety. In certain places within the specification R^{32} is referred to as Z_{32}.

[0159] R^{31} is selected from hydrogen, halogen, hydroxy, nitro, cyano, amino, -COOH, C2-C6alkoxy, C3-C6alkyl, -Co-C4alkyl(C3-C7cycloalkyl), C2-C6alkenyl, C2-Cealkenyl, C2-Cealkynoyl, C2-C6alkenyloxoy, -C(0)OR, Ci-Cethioalkyi, -Co-C4alkyiNR(0)R, -C(0)NR, -SO2R, -SO2NR, -QC(0)R, and -C(NR)NR, each of which R^{31} other than hydrogen, halogen, hydroxy, nitro, cyano, Ci-C2haloalkyl, and Ci-C2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxy!, nitro, cyano, amino, -COOH, -CONH2, C1-C2haloalkyl, and Ci-Cihaloalkoxy, and each of which R^{31} is also optionally substituted with one substituent selected from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently selected from N, O, and S, which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxy, nitro, cyano, Ci-C6alkyl, C2-Cealkenyl, Cz-C4aikanoyl, Ci-C6alkoxy, (mono- and di-Ci-C6alkylaraino)Co-C4alkyl, Ci-Cealkylester, -Co-C4alkyl(C3-C7cycloalkyl), Ci-C2.haloalkyl, and Ci-C2haloalkoxy;

[0160] R^{32} is selected from -0(CH2)i-4R^{2a}, -O,C(=2-C4alkeny)NR^{2a}, -OC2-C4alkynylR^{23}, -0(CH2)wparacyclophone, -0(CH2)i-4S(0)(R^{2b})R^{2b}, -0(CH2)i-4S(0)NR^{2}R^{22}, -0(CH2)i-4S((i)NR^{25}, -0(CH2)i-4S()2NR^{21}R^{22}, -0(CH2)i-4S02NR^{23}R^{22}, -O(C3-C7cycloalkyl), -O(aryl), -O(heteroaryl), and -O(heterocycle) and each group can be optionally substituted as further described herein. In some embodiments, R^{32} is -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each group can be optionally substituted.

[0161] R^{21} and R^{22} are independently selected at each occurrence from hydrogen, hydroxy, cyano, amino, Ci-C6alkyl, Ci-C6haloalkyl, Ci-Cealkoxy, C3-Cydoalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, -Ci-C4alkylOC(0)OCi-C6alkyl, -Ci-C4alkyi0C(0)Ci-C6alkyl, -Ci-C-
C4alkylC(0)OCi-C6alkyi, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and (5- or 6-membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each R21 and R22 can be optionally substituted.

[0162] R23 is independently selected at each occurrence from Ci-Cealkyl, Ci-Cohaloalkyl, (aryl)Co-C4alkyl, (C3-C7cycloalkyl)Co-C4alkyl, (phenyl)Co-C4alkyl, (4- to 7-membered heterocycloalkyl)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and (5- or 6-membered unsaturated or aromatic heterocycle)Co-C4alkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each R23 can be optionally substituted.

[0163] R23a is independently selected at each occurrence from (Ci-CTCycioalkyl), and each R23a can be optionally substituted.

[0164] R23b is independently selected at each occurrence from hydroxy!, Ci-Calkoxy,Ci-Cealkyl, (C3-C7cycloalkyl)Co-C4alkyl, (p-phenyl)Co-C4alkyl, -O(-(1-H)2-O(1-H))20C2-R23d, -C(C(R23c)2)C(0)R23d, an N-linked amino acid or an N-linked amino acid ester, and each R23c can be optionally substituted.

[0165] R23c is independently selected at each occurrence from hydrogen, Ci-Calkyl, C2-Calkenyl, C2-C8alkynyl, (aryl)Co-C4alkyl, (aryl)C2-Calkenyl- or (aryl)C2-Calkynyl; or two R23c groups can be taken together with the carbon that they are bonded to form a 3-6 membered heterocycloalkyi having 1, 2, or 3 heteroatoms independently selected from N, O, and S, or a 3-6 membered carbo cyclic ring, and each R23c can be optionally substituted.

[0166] R23d is independently selected at each occurrence from Ci-Calkyl, C2-Calkenyl, C2-Calkynyl, (aryl)Co-C4alkyl, (aryl)C2-Calkenyl or (aryl)C2-Calkynyl, and each R23d can be optionally substituted.

[0167] R24 and R25 are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyi group, or a 6- to 10- membered bicyclic heterocyclic group having fused, spiro, or bridged rings, and each R24 and R25 can be optionally substituted.

[0168] When A is indole or indazole and X12 is N, X13 is CR13, wherein R13 is R32.

[0169] When A is an indole or indazole and X13 is N, X12 is CR12, wherein R12 is R32.

[0170] Non limiting examples of R13 include the structures of Figure 6.

[0171] As shown in Figure 6, in one embodiment, two R23b groups in a 0(CH2)i-
4P (0)R 23bR3b moiety can come together to form a heterocyclic ring that can be optionally substituted with an R 100 group, wherein R 108 is aryl, heteroaryl, alkyl, cycloalkyl, heterocyclic, alkenyl or alkynyl. See for example: HepDirect (Cyclic l-aryi-l,3-propanoyl esters) Prodrugs: Activation via CYP-mediated oxidation of the benzylic carbon. See Hecker, S. J. et al. J. Med. Chem. 2007, 50, 3891-3896.

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

[0172] In one embodiment, \textbf{R}^{12} is \textbf{R}^{32}.
[0173] In one embodiment, \textbf{R}^{13} is \textbf{R}^{32}.
[0174] In one embodiment, \textbf{R}^{12} is -0(CH2)-4R 23a.
[0175] In one embodiment, \textbf{R}^{12} is -OC2-C4alkenylR 23a.
[0176] In one embodiment, \textbf{R}^{12} is ~OC2-C4alkynylR 23.
[0177] In one embodiment, \textbf{R}^{12} is -0(CH2)i-4paracyclophane.
[0178] In one embodiment, \textbf{R}^{12} is -0(CH2)i-4P(0)R 23bR23b.
[0179] In one embodiment, \textbf{R}^{12} is -0(CH2)i-4S(0)NR 23R 23.
[0180] In one embodiment, \textbf{R}^{12} is -0(CH2)i-4S(0)NR 24R 25.
[0181] In one embodiment, \textbf{R}^{12} is ~0(CH2)i4S0 3NR 23R 22.
[0182] In one embodiment, \textbf{R}^{12} is ~0(CH2)i4S0 2NR 24R 25.
[0183] In one embodiment, \textbf{R}^{12} is -Q(CH2),4S0 2NR 24R 25.
[0184] In one embodiment, \textbf{R}^{12} is -O(aryl).
[0185] In one embodiment, \textbf{R}^{12} is optionally substituted -0(CH2),4R 23a.
[0186] In one embodiment, \textbf{R}^{12} is optionally substituted -OC2-C4alkenylR 23a.
[0187] In one embodiment, \textbf{R}^{12} is optionally substituted -OC2-C4alkynylR 23.
[0188] In one embodiment, \textbf{R}^{12} is optionally substituted -0(CH2)i-4paracyclophane.
[0189] In one embodiment, \textbf{R}^{12} is optionally substituted -0(CH2)i-4P(0)R 23bR 23b.
[0190] In one embodiment, \textbf{R}^{12} is optionally substituted -Q(CH2)i4S(0)NR 21R 22.
[0191] In one embodiment, \textbf{R}^{12} is optionally substituted -Q(CH2)i4S(0)NR 24R 23.
[0192] In one embodiment, \textbf{R}^{12} is optionally substituted -0(CH2)i-4S02NR 23R 22.
[0193] In one embodiment, \textbf{R}^{12} is optionally substituted -0(CH2)i4S02 NR 24R 23.
[0194] In one embodiment, \textbf{R}^{12} is optionally substituted -O(C3-C7cycloalkyl).
[0195] In one embodiment, \textbf{R}^{12} is optionally substituted -O(aryl).
[0196] In one embodiment, $R_{12}^3$ is optionally substituted -O(heteroaryl).

[0197] In one embodiment, $R_{12}^3$ is optionally substituted -O(heterocycle).

[0198] In one embodiment, $R_{13}^3$ is optionally substituted -O(CH$_2$i-4$R^3$)$_2$.

[0199] In one embodiment, $R_{13}^3$ is optionally substituted -OC$_2$C$_4$alkenyl$R^{23}$.

[0200] In one embodiment, $R_{13}^3$ is optionally substituted -OC$_2$C$_4$alkynyl$R^{23}$.

[0201] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4paracyclophane.

[0202] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4P(0)R$^{23b}$)$_2$.

[0203] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4S(0)NR$^{23}$R$^{22}$.

[0204] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4S(0)NR$^{23}$R$^{25}$.

[0205] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4S02NR$^{23}$R$^{22}$.

[0206] In one embodiment, $R_{13}^3$ is optionally substituted -0(CH$_2$i-4S02NR$^{24}$R$^{25}$.

[0207] In one embodiment, $R_{13}^3$ is optionally substituted -0(C3-C7cycloalkyl).

[0208] In one embodiment, $R_{13}^3$ is optionally substituted -O(aryl).

[0209] In one embodiment, $R_{13}^3$ is optionally substituted -O(heteroaryl).

[0210] In one embodiment, $R_{13}^3$ is optionally substituted -O(heterocycle).

[0211] In one embodiment, $R_{12}^3$ is -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S.

[0212] In one embodiment, $R_{12}^3$ is -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S.

[0213] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4R$^{23a}$.$R^{23b}$.

[0214] In one embodiment, $R_{13}^3$ is -OC$_2$C$_4$alkenyl$R^{23a}$.

[0215] In one embodiment, $R_{13}^3$ is -OC$_2$C$_4$alkynyl$R^{23}.$

[0216] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4paracyclophane.

[0217] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4P(0)R$^{23b}$)$_2$.

[0218] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4S(0)NR$^{23}$R$^{22}$.

[0219] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4S(0)NR$^{24}$R$^{25}$.

[0220] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4S02NR$^{23}$R$^{22}$.

[0221] In one embodiment, $R_{13}^3$ is -0(CH$_2$i-4S02NR$^{24}$R$^{25}$.

[0222] In one embodiment, $R_{13}^3$ is -0(C3-C7cycloalkyl).

[0223] In one embodiment, $R_{13}^3$ is -O(aryl).
In one embodiment, R is 0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S.

In one embodiment, R is 0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S.

In one embodiment, the disclosure provides compounds of Formula I, wherein:

one of R and R is H and the other of R and R is R, where

R is 0(CH2)i-4p-paracyclophane, -0(CH2)i-4P(0)RbR1aR2bR2iS(0)NRbR2bR2i, -0(CH2)i-4S(0)NRbR2bR2i, -0(CH2)i-4S02NRbR2bR2i, -0(C3-C7cycloalkyl), -O(aiyl), -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each group can be optionally substituted;

wherein R, R, R, R, R, and R are as defined in the summary section above.

In another embodiment, the disclosure provides compounds of Formula I, wherein:

R, R, R, and R are all hydrogen;

R is fluoro and R is hydrogen, -Co-C4alkyl(C3-C7cycloalkyl), or -O-Co-C4alkyl(C3-C7cycloalkyl);

R is hydrogen, halogen, or C1-C2alkyl;

R, R, R, and R are independently selected at each occurrence from hydrogen, halogen, hydroxy!, amino, Ci-C4alkyl, Ci-C4alkoxy, -Co-C2alkyl(mono- and di-Ci-C2alkylamino), trifluoromethyi, and trifluoromethoxy;

X is CR; and

R is 0(CH2)i-4i44, QC2-C4aikenyiR, QC2-C4alkynylR, -0(C34)i-4paracyclophane, -0(CH2)i-4P(O)RbR1aR2bR2iS(0)NRbR2bR2i, -0(CH2)i-4S(0)NRbR2bR2i, -0(CH2)i-4S02NRbR2bR2i, -0(C3-C7cycloalkyl), -O(aryl), -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each group can be optionally substituted;

wherein R, R, R, R, R, and R are as defined in the summary section above.
In one embodiment, the disclosure provides compounds of Formula I, wherein;

m is O or 1;

R^2 is halogen, R^2 is hydrogen or halogen, and R^2 is hydrogen, halogen, -CO-C4alkyl(C3-C7cycloalkyl), or -0 -Co-C4alkyl(C3-C7cycloalkyl);

R^6 is -C(0)Ci-C4alkyl, -C(0)NH 2, -C(0)CF 3, -C(0)(C 2-C7cycloalkyl), or -ethyl(cyanoimino);

one of R^12 and R^13 is selected from hydrogen, halogen, C4aikyl, C4alkoxy, trifluoromethyl, and trifluoromethoxy; the other of R^12 and R^13 is R^32, where

R^32 is -0(CH 2) 4R^23a, -OC 2-C4alkeny1R^23a, -OC2-C4alkynylR^23, -O(CH 2);

4paracyclophane, -(CH 2)i4P(0)R^23b, -0(CH 2)i4S(0)NR^23R^22, -0(CH 2)i4S(0)NR^24R^25,

-0(CH 2)MSO2NR^23b, -0(CH 2)i4S0 2NR^24R^25, -(0-C3-C7cycloalkyl), -O(aryl), -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each group can be optionally substituted;

wherein R^21, R^22, R^23, R^23a, R^23b, R^24, and R^25 are as defined in the summary section above.

In one embodiment, the disclosure provides compounds of 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^22, where

R^32 is -0(CH 2) 4R^23a, -OC 2-C4alkeny1R^23a, -OC2-C4alkynylR^23, -O(CH 2);

4paracyclophane, -(CH 2)i4P(0)R^23b, -0(CH 2)i4S(0)NR^23R^22, -0(CH 2)i4S(0)NR^24R^25,

-0(CH 2)i4S0 2NR^23b, -0(CH 2)i4S0 2NR^24R^25, -(0-C3-C7cycloalkyl), -O(aryl), -0(4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and -0(5- or 6-membered unsaturated or aromatic heterocycle) having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and each group can be optionally substituted;

wherein R^21, R^22, R^23, R^23a, R^23b, R^24, and R^23 are as defined in the summary section above.

In one embodiment, R^12 may be unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH) 2, -Si(CF 3) 3, -COOH, -COM 12, -P(0)(OH) 2, Cl-Cealkyl, Cl-Cealkoxy, -Co-C 2alkyl(mono- and di-
Ci-C4alkylamino), Ci-Ceaikyiester, Ci-C4alkylamino, Ci-C4hydroxylalkyl, Ci-C2haloalkyl, and Ci-C2haloalkoxy.

Central Core Moiety

[0250] The central core moiety in Formula I is illustrated below:

![Central Core Moiety Diagram]

wherein:

[0251] \( Q^1 \) is \( N(R^1) \) or \( C(R^1 R^2) \);
[0252] \( Q^2 \) is \( C(R^2 R^2') \), \( C(R^2 R^2') C(R^2 R^2') \), \( S, O, N(R^2) \) or \( C(R^2 R^2') 0 \);
[0253] \( Q^3 \) is \( N(R^3), S, \) or \( C(R^3 R^3') \);
[0254] \( X^1 \) and \( X^2 \) are independently \( N, CH, \) or \( CZ \), or \( X^1 \) and \( X^2 \) together are \( C=C \); and
[0255] wherein \( Q^1, Q^2, Q^3, X^1, \) and \( X^2 \) are selected such that a stable compound results.

[0256] Non-limiting examples of the ring are illustrated in Figure 5 (any of which can be otherwise substituted with \( R^1, R^1', R^2, R^2', R^3 \), and \( R^3' \)).

[0257] In an alternate embodiment, the ring is replaced by one of the following core structures:

![Core Structures Diagram]

wherein \( q \) is 0, 1, 2 or 3, \( r \) is 1, 2 or 3, \( \equiv \equiv \) is a single or double bond.

[0258] It is clear that when \( q \) is 0, \( \equiv \equiv \) is not a double bond.
Any of the structures illustrated herein, e.g., A, B, L or central core can be optionally substituted with 0, 1, 2, 3, or 4, as appropriate, and independently, selected from R£:

[0260] R and R' are independently selected from H, aiaky, cycloaiaky, cycloaiakyiaiaky, heterocycle, heterocycloalkyl, aryl, aralkyl, 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 erabodiraents in which the chiral carbon can be provided as an enantiomer, or raixtures 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.

[0261] Z is F, Cl, NH2, CH3, CH3D, CHS)h or CD,.

[0262] R, R', R2, R3, and R3 are independently selected at each occurrence, as appropriate, and only where a stable compound results, from hydrogen, halogen, hydroxyl, nitro, cyano, amino, Ci-Cealkyl, C2-Cealkeny, C2-Cealkylyl, Ci-Cealkoxy, C2-Cealkynyl, C2-Cealkanoyl, Ci-Cethioalkyl, hydroxyCi-Cealkyl, aminoCi-Cealkyl, -Co-CealkylnR 9 R10, -C(O)OR 9, -OC(O)R 9, -NR9C(O)R10, -C(0)NR¼ 1, -OC(0)NR9R10, -NR9C(O)OR 10, C1-
C\text{haloalkyl}, and C\text{1-haloalkoxy}, where \(R^9\) and \(R^{10}\) are independently selected at each occurrence from hydrogen, \(\text{C}_1\text{-C}_6\text{alkyl},\) \((\text{C}_3\text{-C}_7\text{cycloalkyl})\text{Co-C}_4\text{alkyl},\) \(-\text{Co-C}_4\text{alkyl}(\text{C}_3\text{-C}_7\text{cycloalkyl}),\) and \(-\text{O-C}_4\text{alkyl}(\text{C}_3\text{-C}_7\text{cycloalkyl}).\)

[0263] Examples of central cores include, but are not limited to
Non-limiting Central Core Embodiments

[0266] In alternative embodiments, \( R^1 \) and \( R^3 \) 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 selected 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 selected from halogen (and in particular F), hydroxyl,
cyano, -COOH, C₁–C₄alkyl (including in particular methyl), C₂–C₄alkenyl, C₁–C₄alkoxy, C₂–C₄alkanoyl, hydroxyC₁–C₄alkyl, (mono- and di-C₁–C₄alkylamino)C₀–C₄alkyl, -Co-C₄alkyl(C₃–C₇cycloalkyl), -0-Co-C₄alkyl(C₃–C₇cycloalkyl), Cᵢ-C₂haloalkyl, and Cᵢ-C₂haloalkoxy.

[0267] In alternative embodiments, R¹ and R² may be taken together to form a 3-membered carbocyclic ring; R¹ and R² 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 selected from N, O, and S; or R² and R³, 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 substituied with 1 or more substituents independently selected from halogen (and in particular F), hydroxyl, cyano, -COOH, C₁-C₄alkyl (including in particular methyl), C₂-C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₂-C₄alkanoyl, hydroxyC₁-C₄alkyl, (mono- and di-C₁-C₄alkylamino)C₀-C₄alkyl, -Co-C₄alkyl(C₃-C₇cycloalkyl), -0-Co-C₄alkyl(C₃-C₇cycloalkyl), Cᵢ-C₂haloalkyl, and Cᵢ-C₂haloalkoxy.

[0268] In one embodiment, the central core moiety is proline.

[0269] In one embodiment, the central core moiety is 4-fluoroproline.

[0270] In one embodiment, R¹, R¹', R², R³, and R³', if present, are all hydrogen; and R² is fluoro.

[0271] In one embodiment, R¹, R¹', R²', and R³', if present, are all hydrogen; and R² is fluoro and R³ is -Co-C₄alkyl(C₃-C₇cycloalkyl) or -0-Co-C₄alkyl(C₃-C₇cycloalkyl).

[0272] In one embodiment, R¹ and R² are taken together to form a 3- to 6-membered cycloalkyl group, and R¹', R²', R³, and R³', where present, are all hydrogen.

[0273] In one embodiment, R¹, R¹', R³, and R³', if present, are all hydrogen, and R² and R²' are taken together to form a 5- or 6-membered heterocycloalkyl group having 1 or 2 oxygen atoms.

[0274] In one embodiment, R¹ is hydrogen and R² is fluoro.

[0275] In one embodiment, R¹ and R² are joined to form a 3-membered ring.
[0276] The disclosure includes the use of compounds of Formula I in which the central pyrrolidine is vinyl substituted, for example:

\[
\begin{align*}
\text{Structure} \quad \text{(Example of Vinyl Substitution)}
\end{align*}
\]

[0277] In one embodiment, the compound of Formula I has the structure:

\[
\begin{align*}
\text{Structure} \quad \text{(Example of Second Heteroatom Addition)}
\end{align*}
\]

[0278] 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:

\[
\begin{align*}
\text{Structure} \quad \text{(Example of Substituent Joining)}
\end{align*}
\]

[0279] 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:

\[
\begin{align*}
\text{Structure} \quad \text{(Example of Heterocyclic Ring Formation)}
\end{align*}
\]
Central Core L–B Substituents

[0281] The central core L substituents and B substituents in Formula I are illustrated below:

[0282] L is a bond or is selected from the formulas:

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

[0283] B 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\textsubscript{2}-C\textsubscript{6}alkenyl; C\textsubscript{2}-Cealkynyl; -(Co-C4alkyl)(aryl); -(Co-C4alkyl)(heteroaryl); or -(Co-C\textsubscript{4}alkyl)(biphenyl).

[0284] Each of which B is unsubstituted or substituted with one or more substituents independently selected from R\textsuperscript{33} and R\textsuperscript{34}, and 0 or 1 substituents selected from R\textsuperscript{35} and R\textsuperscript{36}.
[0285] R₃ is independently selected from halogen, hydroxyl, -COOH, cyano, Ci-Cealkyl, C₂-C₆alkanoyl, Ci-Cealkoxy, -Co-C₄alkyloSiR₃, -SO₂R, Ci-C₂haloalkyl, and Ci-C₂haloalkoxy;

[0286] R₄ is independently selected from nitro, Ci-Cealkenyln, C₂-C₆alkynyl, Ci-Cethioalkyl, -JC₃-C₇cycloalkyl, -B(OH)₂, -JC(0)NR₉R₂⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻˓
J is independently selected at each occurrence from a covalent bond, \( \text{C}_1\text{-C}_4\text{alkylene}, \) -\( \text{O}\text{C}_1\text{-C}_4\text{alkylene}, \) \( \text{C}_2\text{-C}_4\text{alkenylen}, \) and \( \text{C}_2\text{-C}_4\text{alkynylene}. \)

Examples of B moieties include, but are not limited to:

\( \text{N}=\text{N}, \) \( \text{N}=\text{N}, \) \( \text{N}=\text{N}, \) and \( \text{N}=\text{N}, \) and
**Non-Limiting L-B Embodiments**

[0291] In one embodiment, -L-B- is

\[
\begin{align*}
R^{26} \text{ and } R^{27} \text{ are independently selected from hydrogen, halogen, hydroxy!, nitro, cyano, } & \\
& \text{Ci-C}_6\text{alkyl, Ci-CSaikenyl, C2-C}_6\text{alkanoyl, Ci-C}_6\text{alkoxy, Ci-Cethioalkyl, -Co-C4alkyl(mono- and di-} \\
& \text{Ci-Cealkylaraino), -Co-C4alkyl(C3-C7cycloalkyl), -Co-C4alkoxy(C3-C7cycloalkyl), Ci-} \\
& \text{C}_2\text{haloalkyl, C1-C2haioalkoxy, and Ci-C2haloalkylthio.}
\end{align*}
\]

[0292] In another embodiment. -L-B- is

[0293] \( R^{18} \) and \( R^{18} \) are independently selected from hydrogen, halogen, hydroxymethyl, and methyl; and \( m \) is 0 or 1; and

[0294] \( R^{26}, R^{27}, \) and \( R^{28} \) are independently selected from hydrogen, halogen, hydroxy!, nitro, cyano, Ci-Cealkyl, C2-C6alkenyl, C2-C6alkanoyl, C1-C6alkoxy, Ci-Cethioalkyl, (mono- and di-Ci-C6alkylamino)Co-C4alkyl, (C3-C7cycloalkyl)Co-C4alkyL (aryl)Co-C4alkyl-, (heteroaryl)Co-
C\textsubscript{4}alkyl-, and -Co-C\textsubscript{4}alkoxy(C\textsubscript{3}-C\textsubscript{7}cycloalkyl); each of which \(R^\text{26}, R^{\text{27}}, \) and \(R^{\text{28}}\) other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, amino, Ci-C\textsubscript{2}alkoxy, Ci-C\textsubscript{2}alkenyl, (C\textsubscript{3}-C\textsubscript{7}cycloalkyl)Co-C\textsubscript{4}alkyl, and Ci-C\textsubscript{2}alkoxy(C\textsubscript{3}-C\textsubscript{7}cycloalkyl). and

[0295] \(R^{\text{29}}\) is hydrogen, Ci-C\textsubscript{2}alkyl, CiC\textsubscript{2}alkoxy(C\textsubscript{3}-C\textsubscript{7}cycloalkyl) or \(-\text{Si}(C\textsubscript{4})\text{2}C(CH\textsubscript{3})\). 

[0296] In one embodiment, \(m\) is 0.

[0297] In one embodiment, the disclosure further includes the use of compounds and salts of Formula I in which B is 2-fluoro-3-chlorophenyl. In another embodiment, another carbocyclic, aryl, heterocyclic, or heteroaryi group such as 2-bromo-7-pyridin-6-yl, \((2,2,2\text{-}\text{trifluoroethyl})-\text{lH}-\text{pyrazol}-3\text{-}y1, 2,2\text{-}\text{dichlorocyclopropylmethyl}, or 2-fluoro-3-\text{trimethylsilyle} \text{phenyl} is used.

[0298] In another embodiment, B is phenyl, pyridyi, or indanyl each of which is unsubstituted or substituted with one or more substituents independently selected from hydrogen, halogen, hydroxyl, nitro, cyano, Ci-C\textsubscript{2}alkyl, Ci-C\textsubscript{2}alkenyl, C\textsubscript{z}-C\textsubscript{7}cycloalkyl, Ci-C\textsubscript{2}alkoxy, Ci-C\textsubscript{2}alkenyl, (mono- and di-Ci-C\textsubscript{2}alkylamino)Co-C\textsubscript{4}alkyl, (C\textsubscript{3}-C\textsubscript{7}cycloalkyl)Co-C\textsubscript{4}alkyl, -Co-C\textsubscript{4}alkoxy(C\textsubscript{3}-C\textsubscript{7}cycloalkyl), (phenyl)Co-C\textsubscript{2}alkyl, (pyridyl)Co-C\textsubscript{2}alkyl; each of which substituents other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, amino, Ci-C\textsubscript{2}alkyl, Ci-C\textsubscript{2}alkoxy, \(-\text{OSi}(CH\textsubscript{3})\text{2}C(CH\textsubscript{3})\), \(-\text{Si}(d\text{1})\text{2}C(0\text{1})\), Ci-C\textsubscript{2}alkoxy, and G-(\text{Vhaloalkoxy})

[0299] In another embodiment, B is phenyl or pyridyi substituted with 1, 2, or 3 substituents selected from chloro, bromo, hydroxyl, \(-\text{SCF}3\), Ci-C\textsubscript{2}alkyl, Ci-C\textsubscript{2}alkoxy, trifluorom ethyl, phenyl and trifluoromethoxy each of which substituents other than chloro, bromo, hydroxyl, \(-\text{SCF}3\), can be optionally substituted.

[0300] In certain embodiments, B is a 2-fluoro-3-chlorophenyl or a 2-fluoro-3-trifluoromethoxy phenyl group.

[0301] In one embodiment, B is pyridyi, optionally substituted with halogen, Ci-C\textsubscript{2}alkoxy, and trifluorom ethyl.

[0302] In one embodiment, B is phenyl, substituted with 1, 2, or 3 substituents independently selected from halogen, Ci-C\textsubscript{2}alkyl, Ci-C\textsubscript{2}alkoxy, trifluoromethyl, and optionally substituted phenyl.

[0303] In one embodiment, \(R^{\text{23}}\) is independently selected at each occurrence from (C\textsubscript{3}-C\textsubscript{7}cycloalkyi)Co-C\textsubscript{4}alkyl, (phenyl)Co-C\textsubscript{4}alkyl, (4- to 7-membered heterocycloalkyi)Co-C\textsubscript{4}alkyl

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SUBSTITUTE SHEET (RULE 26)
having 1, 2, or 3 heteroatoms independently selected from N, O, and S, and (5- or 6-membered unsaturated or aromatic heterocycle)Co-C4alky! Having 1, 2, or 3 heteroatoms independently selected from N, O, and S.

[0304] In one embodiment, B is selected from Figure 7, wherein \( R^{27} \) is hydrogen, methyl, or trifluoromethyl; \( R^{28} \) is hydrogen or halogen; and \( R^{29} \) is hydrogen, methyl, trifluoromethyl, or \(-\text{Si(CH}_3)_2\text{C(CH}_3)_3\).

[0305] In an alternative embodiment, B is selected from Figure 8.

Central Core (C=0)A Substituent

[0306] The central core (C=0)A substituent in Formula I is illustrated below:

[0307] A is a group selected from:

[68]

SUBSTITUTE SHEET (RULE 26)
[0308] R^4 is selected from -CHO, -CONH2, CVCealkanoyl, hydrogen, -SO2NH2, -((CF_3)_2)F, -CH(CF_3)NH2, Ci-Cealkyl, -Co-C4alkyl(C3-C7Cycloalkyl), -C(0)C o-C_2alkyl(C3-C7cycloalkyl),

![Diagram of chemical structures]

each of which R^4 other than hydrogen, -CHO, and -CONH2, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxy!, cyano, cyanimino, Cj-C2.alkyl, Cj-C2alkoxy,

- -Co-C2alkyl(mono- and di-Ci-C4alkylamino), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0309] R^5 and R^6 are independently selected from -CHO, -C(0)NH_2, -C(0)NH(CH_3), C2-Cealkanoyl, hydrogen, hydroxy!, halogen, cyano, nitro, -COOH, -SO2NH2, vinyl, Ci-C6alkyl

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(including methyl), C2-C6alkenyl, Ci-Cealkoxy, -Co-C4alkyl(C3-C7cycloalkyl), -C(0)Co-C4alkyl(C3-C7cycloalkyl), -P(O)(OR)2, -OC(0)R, -C(0)OR, -C(0)N(CH2CH2R)5(R10), -NR5C(0)R10, phenyl, or 5- to 6-membered heteroaryl.

[0310] Each R5 and R6 other than hydrogen, hydroxyl, cyano, and -COOH is unsubstituted or optionally substituted. For example, R5 and R6 other than hydrogen, hydroxyl, cyano, and -COOH may be substituted with one or more substituents independently selected from halogen, hydroxy!, amino, imino, cyano, cyanimino, Ci-C2alkyl, Ci-Ojalkoxy, -Co-C2alkyl(mono- and di-Ci-Gialkylamino), Ci-C2haloalky! and Ci-C2haloalkoxy.

[0311] R6 is hydrogen, halogen, hydroxyl, Ci-C4alkyl, -Co-C4alkyl(C3-C7cycloalkyl), or Ci-C4alkoxy; or R6 and R6 may be taken together to form an oxo, vinyl, or imino group.

[0312] R7 is hydrogen, Ci-Cealkyl, or -Co-C4alkyl(C3-C7cycloalkyl).

[0313] R8 and R8 are independently selected from hydrogen, halogen, hydroxyl, Ci-Cealkyl, -Co-C4alkyl(C3-C7cycloalkyl), Ci-Cealkoxy, and (Ci-C4alkylamino)Co-C2alky!; or R8 and R8 are taken together to form an oxo group; or R8 and R8 can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring.

[0314] R16 is absent or may include one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, Ci-C6alkyl, C7-C6alkenyl, C2-C6alkanoyl, Ci-Cealkoxy, -Co-C4alkyl(mono- and di-Ci-Cealkylamino), -Co-C4alkyl(C3-C7cycloalkyl), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0315] R19 is hydrogen, Ci-Cealkyl, Ci-Cealkeny!, Ci-Cealkanoyl, -SO2Ci-C4alkyl, (mono- and di-Ci-Cealkylamino)Ci-C4alkyl, -Co-C4alkyl(C3-C7heterocycloalkyl), -Co-C4alkyl(aryl), Co-C4alkyl(heteroaryl), and wherein R19 other than hydrogen is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxy!, amino, -COOH, and -C(0)OC1-C1alky!.

[0316] X11 is N or CR11.

[0317] X12 is N or CR.

[0318] X13 is N or CR13.

[0319] X14 is N or CR14.

[0320] No more than 2 of X11, X12, X13, and X14 are N.

[0321] R11, R14, and R15 are independently selected at each occurrence from hydrogen, halogen, hydroxyl nitro, cyano, -0(PO)(OR)2, -(PO)(GR)2, Ci-Cealky!, C2-C6alkenyl, C2-
Cealkynyl, C2-Cealkenyl(aryl), C2-C6aikenyi(cycloalkyi), C2-C6alkenyl(heterocycle), C2-C6alkenyl(heteroaryl), C2-C6alkynyl, C2-C6alkynyl(aryl), C2-C6alkynyl(cycloalkyi), C2-C6alkynyl(heterocycle), C2-C6alkynyl(heteroaryl), C2-C6alkoxy, C2-Cethioalkyl, -Co-C4alkyl(mono- and di-C2alkylamino), -Co-C4alkyl(C3-C7cycloalkyl), -Co-C4alkoxy(C3-CTcycloalkyl), Ci-C2haloalkyl and Ci-C2haloalkoxy.

[0322] In one embodiment, R5 and R6 are independently selected from -CHO, -C(0)NH2, -C(0)NH(CF3), CVCealkanoyl, and hydrogen.

[0323] In one embodiment, each R5 and R6 other than hydrogen, hydroxyl, cyano, and -COOH is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, amino, imino, cyano, cyanoimino, Ci-Cialkyl, Ci-Cialkoyi, -Co-C2alkyl(mono- and di-C2alkylamino), Ci-C2haloalkyl, and Ci-C2haloalkoxy.

[0324] In one embodiment, R8 and R8' are independently hydrogen or methyl.

[0325] In one embodiment, R8 and R8' are hydrogen.

[0326] In one embodiment, R7 is hydrogen or methyl.

[0327] In one embodiment, R7 is hydrogen.

**Embodiments** of Formulas IA, IB, IC, and ID

[0328] 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 to be used within the invention and can be applied to any of the Formulas I-XY,X.

[0329] In one aspect, this disclosure includes the use of compounds and salts of Formula IA:

![Chemical Structure](image)

(IA) where

R6, R13, and B may carry any of the definitions set forth herein for this variable.
[0330] In another aspect, this disclosure includes the use of compounds and salts of Formula IB, IC, and ID.

[0331] 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.

[0332] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ is H, R² is F, R⁶ is alkanoyl, R¹₂ is R³₂, R⁵₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, R¹₃ is H, and B is heteroaryl.

[0333] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ and R² are joined to form a 3 membered ring, R⁵ is alkanoyl, R¹₂ is R³₂, R¹₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, R¹₃ is H, and B is heteroaryl.

[0334] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ is H, R² is F, R⁶ is amide, R¹₂ is R³₂, R³₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, R¹₃ is H, and B is heteroaryl.

[0335] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ and R² are joined to form a 3 membered ring, R⁶ is amide, R¹₂ is R³₂, R³₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, R¹₃ is H, and B is heteroaryl.

[0336] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ is H, R² is F, R⁶ is alkanoyl, R¹₂ is H, R¹₃ is R³₂, R³₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, and B is heteroaryl.

[0337] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m=0, R¹ and R² are joined to form a 3 membered ring, R⁶ is alkanoyl, R¹₂ is H, R¹₃ is H, R³₂ is -0(CH₂)i-4P(0)R ²³bR ²³b, and B is heteroaryl.
In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ is H, R² is F, R⁶ is amide, R¹₂ is H, R¹₃ is R²₃, R₃₂ is -O(CH₂)₄P(0)R, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ and R² are joined to form a 3 membered ring, R⁶ is amide, R¹₂ is H, R¹₃ is \( \nabla \), R₃₂ is -0(CH₂)₄P(0)R, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ is H, R² is F, R⁶ is aikanoyi, R¹₂ is R₃₂, R₃₂ is -0(CH₂)i4P(0)R, R¹₃ is H, and B is phenyl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ and R² are joined to form a 3 membered ring, R⁶ is amide, R¹₂ is R₃₂, R₃₂ is -0(CH₂)i4P(0)R, R¹₃ is H, and B is phenyl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ is H, R² is F, R⁶ is amide, R¹₂ is R₃₂, R₃₂ is -0(CH₂)i4P(0)R, R¹₃ is H, and B is phenyl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ and R² are joined to form a 3 membered ring, R⁶ is amide, R¹₂ is R₃₂, R₃₂ is -0(CH₂)i4P(0)R, R¹₃ is H, and B is phenyl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein m = 0, R¹ and R² are joined to form a 3 membered ring, R⁶ is amide, R¹₂ is R₃₂, R₃₂ is -0(CH₂)i4P(0)R, R¹₃ is H, and B is phenyl.
In some embodiments, uses of structures are provided including Formulas IB and IC, wherein in m=1, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^6 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is amide, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is alkanoyl, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is amide, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is alkanoyl, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is amide, R^{1_2} is H, R^{1_3} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is amide, R^{1_2} is H, R^{1_3} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, and B is heteroaryl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is alkanoyl, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is phenyl.

In some embodiments, uses of structures are provided including Formulas IB and IC, wherein R^1 is H, R^2 is F, R^6 is amide, R^{1_2} is R^{3_2}, R^{3_2} is -O(CH_2)i-4P(0)R^{2_3_3}R^{2_3_3}, R^{1_3} is H, and B is phenyl.
[0358] In some embodiments, uses of staictures are provided including Formulas IB and IC, wherein $m=1$, $R^1$ is H, $R^2$ is F, $R^6$ is amide, $R^{12}$ is $\text{CH}_2$, $R^{32}$ is $\text{CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, $R^{13}$ is H, and B is phenyl.

[0359] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein $m=1$, $R^f$ and $R^2$ are joined to form a 3 membered ring, $R^6$ is amide, $R^{12}$ is $R^{32}$, $R^{32}$ is $\text{-CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, $R^{13}$ is H, and B is phenyl.

[0360] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein $m=1$, $R^1$ is H, $R^2$ is F, $R^6$ is alkanoyl, $R^{12}$ is H, $R^{13}$ is $R^{32}$, $R^{32}$ is $\text{-CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, and B is phenyl.

[0361] In some embodiments, uses of staictures are provided including Formulas IB and IC, wherein $m=1$, $R^1$ is H, $R^2$ is F, $R^6$ is amide, $R^{12}$ is H, $R^{13}$ is $R^{32}$, $R^{32}$ is $\text{-CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, and B is phenyl.

[0362] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein $m=1$, $R^1$ is H, $R^2$ is F, $R^6$ is amide, $R^{12}$ is H, $R^{13}$ is $R^{32}$, $R^{32}$ is $\text{-CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, and B is phenyl.

[0363] In some embodiments, uses of structures are provided including Formulas IB and IC, wherein $m=1$, $R^1$ is H, $R^2$ is F, $R^6$ is amide, $R^{12}$ is H, $R^{13}$ is $R^{32}$, $R^{32}$ is $\text{-CH}(_2)_i\text{P}((0))\text{R}^{23b}\text{R}^{23b}$, and B is phenyl.

[0364] In the above embodiments, uses of staictures are provided including Formulas IB and IC, wherein;

$R^{23b}$ is independently selected at each occurrence from hydroxyl, Ci-C6alkoxy,Ci-C6alkyl, (C3-C7cycloalkyl)C6-C4alkyl, (phenyl)C6-C4alkyl, -$\text{OH}(_2)$2-$\text{O}(_2)$18, -$\text{OC}(R^{23c})2\text{O}(_2)$3, an N-linked amino acid or an N-linked amino acid ester, and each $R^{23b}$ can be optionally substituted;

$R^{23c}$ is independently selected at each occurrence from hydrogen, Ci-Csalkyl, C2-C8alkeny, C2-C2alkynyl, (aryl)Co-C4alkyl, (aryl)C2-C8alkenyl- or (aryl)C2-C8alkynyl; or two $R^{23c}$ groups can be taken together with the carbon that they are bonded to form a 3-6 membered heterocycloalkyl having 1, 2, or 3 heteroatoms independently selected from N, O, and S, or a 3-6 membered carboxylic ring, and each $R^{23c}$ can be optionally substituted,
R\textsuperscript{2,d} is independently selected at each occurrence from Ci-Csalkyl, C\textsubscript{2}-C\textsubscript{8}alkenyl, C2-Csalkynyl, (aryl)Co-C4alkyl, (aryl)C2-Csalkenyl or (aryl)C2-C8alkynyl, and each R\textsuperscript{2,d} can be optionally substituted.

**Embodiments of Formula VII**

[0365] To further illustrate the invention, various embodiments of Formula VII are provided that can be used as further described in this application. In one aspect, the disclosure includes uses, as described herein, of compounds and salts of Formula VII:

![Chemical Structure](image)

(VII), wherein:

[0366] R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{2'}, and R\textsuperscript{3} are independently selected from hydrogen, halogen, Ci-C4alkyl, C\textsubscript{1}-C4alkoxy, -Co-C\textsubscript{3}alkylNR\textsuperscript{9} \textsuperscript{10}, -Co-C4alkyl(C\textsubscript{3}-C7cycloalkyl), -0-Co-C4alkyl(C\textsubscript{3}-C7cycloalkyl), Ci-C2haloalkyl, and Ci-C\textsubscript{2}haloalkoxy;

[0367] R\textsuperscript{8} and R\textsuperscript{8'} are independently selected from hydrogen, halogen, and methyl;

[0368] R\textsuperscript{5} is hydrogen, hydroxyl, cyano, -COOH, Ci-Cealkyl, Ci-Cealkoxy, Ci-Ceaikanoyi -Co-C\textsubscript{4}alkyi(C3-C7cycloalkyl), -C(0)Co-C\textsubscript{4}alkyl(C3-C7cycloalkyl), Ci-C\textsubscript{2}haloalkyl, or Ci-C\textsubscript{2}haloalkoxy;

[0369] R\textsuperscript{6} is -C(=O)CH\textsubscript{3}, -C(0)NH\textsubscript{2}, -C(\(<<\) \(\Pi\text{ }\text{3}\)), -C(0)(cyclopropyl), or -ethyl(cyanoimino); and

[0370] R\textsuperscript{11} and R\textsuperscript{14} are independently selected from hydrogen, halogen, hydroxyl, amino, nitro, cyano, C\textsubscript{1}-C6alkyl, C2-C6alkenyl, C2-C6alkanoyl, Ci-Cealkoxy, Ci-Cethioalkyl, -Co-C\textsubscript{4}alkyl(mono- and di-Ci-Cealkylamino), -Co-C\textsubscript{4}alkyl(C3-C7cycloalkyl), -OC\textsubscript{4}alkyl(C\textsubscript{3}-C7cycloalkyl), Ci-C\textsubscript{2}hioalkyl, and Ci-C\textsubscript{2}hioalkoxy.
The use of prodrugs of any of the ether compounds provided herein is within the scope of the invention. For example, a compound of Formula I and Table 1 or a compound prepared from or consisting of the moieties in (i) Figure 1D, IE, Figure 5, Figures 6A, 6B, 6C, Figures 7 A-E and Figure 8; (ii) Figures 1, 3, 4 and 7G or (iii) Figures IB-IE, Figure 5, Figure 6E, Figures 7 A-G for the treatment of a disorder in a host, typically a human, wherein the disorder is selected from the group disclosed in the Detailed Description, Part IV, Section A are within the scope of the disclosure. Prodrugs of compounds selected from Table 2 or Table 3 or an embodiment of the active compound as described in Figure 1B, 1C, 1D, 2B, 2C, 2D, 2E, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, optionally including 4A, 4B, 4C, 4D, 4E, or 4F or a compound that is prepared from or consists of moieties in one of the following: (i) any of Figures 1B, 1C, 1D or IE; Figures 5; Figures 6A, 6B, 6C, 6D, 6E and Figure 7F (ii) Figures 1B, 1C, 1D, 1E or IF; Figure 5, Figure 61), any of Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G; and Figure 8 (iii) Figures 1A, 1B, 1C, 1D, IE, 2B, 2C, 2D or 2E, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6D, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (iv) Figures 1B, 1C, 1D, IE, 3A, 3B, 3C, 3D, 3E, 3F, 3G, 3H, 3I, 3J, 3K, 3L, 3M, 3N, 3O, 3P, 3Q, 6F, and optionally 4A, 4B, 4C, 4D, 4E, 4F, or 4G; (v) Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H; are within the scope of the disclosure, as are the use of prodrugs of compounds for the treatment of a disorder in a host, typically a human, wherein the disorder is selected from the group disclosed in the Detailed Description, Part IV, Section A and Section B, are also within the scope of the disclosure.

Non-limiting examples of compounds of the invention provided herein include the structures of Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H and their prodrugs.

III. PHARMACEUTICAL PREPARATIONS

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

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contain a compound or salt as the only active agent, or, in an alternative embodiment, the compound and at least one additional active agent.

[0374] 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.

[0375] 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.

[0376] 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, 1000 mg, 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.

[0377] The pharmaceutical composition may for example include any molar ratio of the active compound and 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.

[0378] 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, suprachoroidal, subchoroidal, choroidal, 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.

[0379] 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.

[0380] 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, U.S Patent Nos. 4,983,593, 5,013,557, 5,456,923, 5,576,025, 5,723,269, 5,858,411, 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, 9,211,261, 9,265,731, 9,358,478, and 9,387,252, incorporated by reference herein.

[0381] 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, glidants, 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 pharmacologically acceptable carriers include sugars, starches, cellulosics, 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 cyclodextrins. 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, 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.

[0382] In certain embodiments, the pharmaceutical composition for administration further includes an active compound as described herein and optionally comprises one or more of a phosphoglyceride; phosphatidylcholine; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltrimethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglyceroliscuccinate, diphasphatidyl glycerol (DPPG); hexanecanol; 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 amide; sorbitan trioleate (Span®85) glycocholate; sorbitan monolaurate (Span®20), polysorbate 20 (Tween®20); polysorbate 60 (Tweeii®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; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebroside; dicetylphosphate; dipalmitoylphosphatidyiglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyi sterate; isopropyl myristate; tyloxapol; polyethylene glycol5000-phosphatidylethanolamine; polyethylene glycol400-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 (HPMC), hydroxy cellulose (HC), methylcellulose (MC), dextran, cycloexetran, glycogen, hydroxy ethylstarch, carageenan, glycon, amylose, chitosan, N,0-carboxydimethylchitosan, algin and alginic acid, starch, chitin, inulin, konjac, glucomannan, 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. polyisocapic anhydride), polypropylfumurate, polyamide (e.g. polycaprolactam), polycetel, 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, poiyurea, polystyrene, and polyanime, polylysine, polylysine-PEG copolymer, and poly(ethyleneimine), polyethylene imine)-PEG copolymer, glycerol monolaurate, propylene glycol, Vitamin E IPGS (also known as d-a-Tocopheryi polyethylene glycol 1000 succinate), gelatin, titanium dioxide, polyvinylpyrrolidone (PVP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC), block copolyers of ethylene oxide and propylene oxide (PEO/PPO), polyethyleneglycol (PEG), sodium carboxymethylcellulose (NaCMC), hydroxypropylmethyl cellulose acetate succinate (HPMCAS).
In some embodiments, the pharmaceutical preparation may include a polymer for controlled delivery of the described compounds, including, but not limited to, a pluronic polymer, polyester (e.g., polyactic acid, poly(lactic-co-glycolic acid), polycaprolactone, polyvalerolactone, poly(l,3-dioxan-2-one)); polyanhydride (e.g., poly(sebacic anhydride)), polyether (e.g., polyethylene glycol); polyurethane; polymethacrylate; polyacrylate; and polycyanoacrylate. In some embodiments, the polymer may be modified with polyethylene glycol (PEG), with a carbohydrate, and/or with an acyclic polyacetal derived from a polysaccharide. See, e.g., Papishov, 2001, ACS Symposium Series, 786:301, incorporated by reference herein.

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.

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.

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 polyvinyl 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.

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.

Solvent removal can also be used to prepare particles of a compound that is hydrolytically unstable. In this method, the compound (or polymer matrix and one or more

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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.

[0389] 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.

[0390] 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.

[0391] 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.
[0392] 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.

[0393] 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.

[0394] Techniques for particle formation using coacervation are known in the art, for example, as described in GB-B-929 406; GB-B-929 401; 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).

[0395] 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.

[0396] 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.

[0397] 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.

[0398] 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 deliver/ systems, nanoparticles can allow targeted delivery and controlled release.

[0399] 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 to 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 drags 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.

Examples of these polyesters include poly(L-lactide-co-L-lysine) (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). Polymeric nanoparticles 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, 1000 nm, and 10,000 nm. Between 0.1 nm and 1000 nm, between 1 nm and 1000 nm, between 10 nm and 1000 nm, between 100 nm and 1000 nm, between 1 and 100 nm, between 1 and 10 nm, between 1 and 50 nm, between 100 nm and 800 nm, between 400 nm and 600 nm, or about 500 nm. In one embodiment, the nanoparticles 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, 1000 nm, and 10,000 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.

[0402] 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.

[0403] 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.

[0404] 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.

[0405] 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):318 (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.

[0406] 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 respirator' deliver' 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 deliver)' device depends on parameters, such as nature of the dmg and its formulation, the site of action, and pathophysiology of the lung.


[0408] Many methods and devices for dmg 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" (Santeii 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


hydrophilichydrophobic multiblock copolymers" (Massachusetts Institute of Technology); US2004023461, 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 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 deliver)' 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

[0412] In one aspect, 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.

Section A Disorders

[0413] In one embodiment, the invention is the use of a compound of Formula I, or a pharmaceutically acceptable salt or composition thereof, as well as the compounds of Table 1, Table 2, Table 3 or an embodiment of the active compound as described in the Figures for the treatment of a disorder as described in this Section A herein.  

[0414] 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 a compound of Formula I, Table 1, Table 2, Table 3 or an embodiment of the active compound as described in the Figures or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable
carrier. In one embodiment of the present invention, a method is provided for treating nonalcoholic steatohepatitis (NASH) in a host by administering an effective amount of a compound of Formula 1, Table 1, Table 2, Table 3 or an embodiment of the active compound as described in the Figures, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0415] In another embodiment, the active compound 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.

[0416] In one embodiment, the present invention provides a method of treating or preventing dermatomyositis by administering to a host in need thereof an effective amount of a composition comprising a compound of the current invention. In one embodiment, the present invention provides a method of treating or preventing amyotrophic lateral sclerosis by administering to a host in need thereof an effective amount of a composition comprising a compound of the current invention.

[0417] In another embodiment, a method is provided for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of biotherapeutics (e.g. CAR T-cell therapy or monoclonal antibody therapy) in a host by administering an effective amount of a compound of Formula 1, Table 1, Table 2, Table 3 or an embodiment of the active compound as described in the Figures, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. Various types of cytokine or inflammatory reactions may occur in response to 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. 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

[0418] Also contemplated herein, is the use of a compound of Formula I, Table 1, Table 2, Table 3 or an embodiment of the active compound as described in the Figures, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier 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 a!., Immuiiopharmacologic 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).

[0419] 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.

[0420] 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 vims, cytomegalovirus, Epstein-Barr virus, lichen planus, or Dengue-associated disease (e.g., hemorrhagic Dengue Fever);
(v) Masquerade syndrome, contact dermatitis, trauma induced inflammation, UYB induced inflammation, eczema, granuloma annulare, or acne.

[0421] 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.

[0422] In one embodiment, the disorder is selected from:
(i) atopic dermatitis, dermatitis, dermatomyositis, dermatomyositis bullous pemphigoid, scleroderma, sclerodermatomyositis, psoriatic arthritis, pemphigus vulgaris, cutaneous lupus, discoid lupus erythematosus, chilblain lupus erythematosus, or lupus erythematosus-lichen planus overlap syndrome;
(ii) cryoglobulinemia 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) angi oedema, 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 (IIP), drug-induced thrombocytopenia, autoimmune hemolytic anemia (AIHA), azotemia, blood vessel arid/or lymph vessel inflammation, rotational atherectomy, or delayed hemolytic transfusion reaction;

(v) British type amyloid angiopathy, Buerger's disease, bullous pemphigoid, C1q nephropathy, cancer, or catastrophic antiphospholipid syndrome.

[0423] 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), coriocobasai 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, Hailervorden-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, Othomyxoviridae, Rhabdoviridae, or Hepadnaviridae;

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

[0424] In a further embodiment, the disorder is selected from:
(viii) hyperlipidemia, hypertension, hypoalbuminemia, hypobolemic shock, hypocomplementemic urticarial vasculitis syndrome, hypophosphatasis, 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 thyroiditis, thyroiditis, Type I cryoglobulinemia, Type II mixed cryoglobulinemia, Type III mixed cryoglobulinemia, ulcerative colitis, uremia, urticaria, venous gas embolus (VGE), or Wegener's granulomatosis.

[0425] In one embodiment, a compound 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-Alttherr-Uehlinger syndrome), retroperitoneal 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, hydradenitis 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 ophthalmopathy, ligneous conjunctivitis, Mooren’s ulcer, opsoclonus myoclonus syndrome, optic neuritis, retinocochleocerebral vasculopathy (Susac’s syndrome), sympathetic ophthalmia, Tolosa-Hunt syndrome, interstitial lung disease, antisyphilitic 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), Bickerstaff’s encephalitis, chronic inflammatory demyelinating polynuropathy, idiopathic inflammatory demyelinating disease, Lambert-Eaton myasthenic 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, ischemic-reperfusion injury of the eye.

[0426] 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 a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. In one embodiment, a method for the treatment of immunothrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TIP), or idiopathic thrombocytopenic purpura (ITP) in a host is provided that includes the administration of an effective amount of a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. 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 a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. 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 a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. 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 a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. 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 a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier. In one embodiment, a method for the treatment of hemorrhagic dengue fever, in a host is provided that includes the administration of an effective amount of a compound described herein, or its salt, optionally in a pharmaceutically acceptable carrier.

Seetioo B Disorders

[0427] The compound of Table 2 or Table 3 or their pharmaceutically acceptable salts or pharmaceutical compositions are useful for treating any of the disorders described herein. In one embodiment, the compound 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 named disorder, albeit through a different mechanism.

[0428] 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.

[0429] 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, onchorceral 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.

[0430] 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-Ilarada syndrome, intermediate uveitis, birdshot retino-chorioditis, sympathetic ophthalmia, ocular dicatrical pemphigoid, ocular pemphigus, nonarteritic ischemic optic neuropathy, postoperative inflammation, and retinal vein occlusion, or uveitis (including Behcet's disease and other sub-types of uveitis).

[0431] 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.

[0432] Complement mediated disorders that may be treated or prevented by the compounds of Table 2 or Table 3 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, implants), hyperacute allograft rejection, xenograft rejection, transplantation, psoriasis, burn injury, thermal injury including burns or frostbite;

(vi) asthma, allergy, acute respiratory distress syndrome (ARBS), cystic fibrosis, adult respiratory distress syndrome, dyspnea, hemoptyisis, 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.

[0433] 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 selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0434] In another embodiment, a method for the treatment of age-related macular degeneration (AMD) is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.
[0435] In another embodiment, a method for the treatment of rheumatoid arthritis is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0436] In another embodiment, a method for the treatment of multiple sclerosis is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0437] In another embodiment, a method for the treatment of myasthenia gravis is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0438] In another embodiment, a method for the treatment of atypical hemolytic uremic syndrome (aHUS) is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0439] In another embodiment, a method for the treatment of C3 glomerulonephritis is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0440] In another embodiment, a method for the treatment of abdominal aortic aneurysm is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0441] In another embodiment, a method for the treatment of neuromyelitis optica (NMO) is provided that includes the administration of an effective amount of a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0442] 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 a compound selected from Table 2 or Table 3 of the
invention. 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 disorder, by providing an effective amount of a compound or
pharmacologically acceptable salt of a compound selected from Table 2 or Table 3 to patient with
a Factor D mediated inflammatory disorder. A compound selected from Table 2 or Table 3 may
be provided as the only active agent or may be provided together with one or more additional
active agents.

[0443] In one embodiment, a method for the treatment of a disorder associated with a
dysfunction in the complement cascade is provided that includes the administration of an effective
amount of a compound selected from Table 2 or Table 3, or a pharmacologically acceptable salt
thereof, optionally in a pharmacologically acceptable carrier. In one embodiment, a method of
inhibiting activation of the alternative complement pathway in a host is provided that includes the
administration of an effective amount of a compound selected from Table 2 or Table 3, or a
pharmacologically acceptable salt thereof, optionally in a pharmacologically acceptable carrier. In
one embodiment, a method of modulating Factor D activity in a host is provided that includes the
administration of an effective amount of a compound selected from Table 2 or Table 3, or a
pharmacologically acceptable salt thereof, optionally in a pharmacologically acceptable carrier.

[0444] In an additional alternative embodiment, the compound selected from Table 2 or
Table 3, or a pharmacologically acceptable salt thereof, optionally in a pharmacologically acceptable
carrier is used in the treatment of an autoimmune disorder.

[0445] 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 a compound of Table 2 or Table 3, or
a pharmacologically acceptable salt thereof, optionally in a pharmacologically acceptable carrier, to
a host in need thereof.

[0446] 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

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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.

[0447] Non-limiting examples of autoimmune disorders include: 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.

[0448] In one embodiment, a compound selected from Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, is used in the treatment of lupus. Non-limiting examples of lupus include lupus erythematosus, cutaneous lupus, discoid lupus erythematosus, chilblain lupus erythematosus, lupus erythematosus-lichen planus overlap syndrome.

[0449] Lupus erythematosus is a generic 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.

[0450] 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.

[0451] 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 cutis and throughout white matter. CD4+ T-cells, especially Th1, 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.

[0452] Diabetes can refer to either type 1 or type 2 diabetes. In one embodiment a compound of Table 2 or Table 3 or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, is provided at an effective dose to treat a patient with type 1 diabetes. In one embodiment a compound of Table 2 or Table 3, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, is provided at an effective dose to treat a patient with type 2 diabetes.

[0453] 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

[0454] In additional embodiments, an effective amount of 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 additional therapeutic agents for such combination therapy are provided below.

[0455] In one embodiment, an effective amount of an active compound or its salt or composition as described herein may be provided in combination or alternation with an effective amount of 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.

[0456] 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.

[0457] 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 (Erabrel).

[0458] 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).

[0459] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with an anti-IL-6 antibody, including but not limited to tocilizumab (Actemra) and siltuximab (Sylvant).

[0460] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with an IL-7 inhibitor, including but not limited to secukinumab (Cosentyx).
[0461] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with a p40 (IL12/11,23) inhibitor, including but not limited to ustekinumab (Stelara).

[0462] In an alternative embodiment, an active compound as described herein can be administered in combination or alternation with an IL23 inhibitor, including but not limited to risankizumab.

[0463] In an alternative embodiment, an active compound as described herein can be administered in combination or alteration with an anti-interferon antibody, for example but not limited to sifalimumab.

[0464] 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 tofacitinib (Xelienz). 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.

[0465] 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-PDL1 antibodies (for example, Nivolumab, Pembrolizumab, Pidilizumab and Atezolizumab) and anti-CTLA4 antibodies (Ipilimumab and Tremelimumab).

[0466] Non-limiting examples of active agents that can be used in combination with active compounds described herein are:

[0467] 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.);

[0468] Soluble complement regulators: Soluble complement receptor I (TP10) (Avant Immunotherapeutics); sCRI-sLe x/TP-20 (Avant Immunotherapeutics); MLN-2222/CAB-2 (Millenium Pharmaceuticals), Mirococept (Inflazyme Pharmaceuticals);

[0469] Therapeutic antibodies: Eculizumab/Soliris (Alexion Pharmaceuticals); Pexelizuraab (Alexion Pharmaceuticals); Ofaturauraab (Genraab A/S); TNX-234 (Tanox); TNX-558 (Tanox); TA106 (Taligen Therapeutics); Neutrazumab (G2 Therapies); Anti-properdin (Novelmed Therapeutics), HuMax-CD38 (Genmab A/S);
Complement component inhibitors: Compstatin/POT-4 (Potentia Pharmaceuticals), ARC1905 (Archemix);

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

Others: Recombinant human MBL (rhMBL; Enzon Pharmaceuticals).

Imides and glutarimide derivatives such as thalidomide, lenalidomide, pomalidomide;

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:

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Company</th>
<th>Class of Molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFG316</td>
<td>C5</td>
<td>Novartis/Morphosys</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>4(1MEW)APL-1,APL-2</td>
<td>C3/C3b</td>
<td>Apella</td>
<td>Compstatin Family</td>
</tr>
<tr>
<td>4(1MeW)POT-4</td>
<td>C3/C3b</td>
<td>Potentia</td>
<td>Compstatin Family</td>
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<td>Anti-C5 siRNA</td>
<td>C5</td>
<td>Alnylam</td>
<td>Si-RNA</td>
</tr>
<tr>
<td>Anti-FB siRNA</td>
<td>CFB</td>
<td>Alnylam</td>
<td>SiRNA</td>
</tr>
<tr>
<td>ARC1005</td>
<td>C5</td>
<td>Novo Nordisk</td>
<td>Aptamers</td>
</tr>
<tr>
<td>ATA</td>
<td>C5</td>
<td>N.A.</td>
<td>Chemical</td>
</tr>
<tr>
<td>Coversin</td>
<td>C5</td>
<td>Volution Immuno-</td>
<td>Small animal protein</td>
</tr>
<tr>
<td>CP40/AMY-101,PEG-Cp40</td>
<td>C3/C3b</td>
<td>Amyndas</td>
<td>Compstatin Family</td>
</tr>
<tr>
<td>CR1g/CFH</td>
<td>CAP C3</td>
<td>NYDAS</td>
<td>CFH-based protein</td>
</tr>
<tr>
<td>Cynryzene</td>
<td>C1n/C1s</td>
<td>ViroPharma/Baxter</td>
<td>Human purified protein</td>
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<tr>
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<td>CFD</td>
<td>Genentech/Roche</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>H17</td>
<td>C3</td>
<td>EluSys Therapeutics</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Mini-CFH</td>
<td>CAP C3</td>
<td>Amyndas</td>
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<td>CR1-based protein</td>
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<td>C5</td>
<td>Adienne</td>
<td>Monoclonal antibody</td>
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<td>C5</td>
<td>Rapharma</td>
<td>Small molecule</td>
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<tr>
<td>sCR1 (CDX-1135)</td>
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<tr>
<td>SOBI002</td>
<td>C5</td>
<td>Swedish Orphan Biovitrum</td>
<td>Affibody</td>
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<tr>
<td>SOMAmers</td>
<td>C5</td>
<td>SomaLogic</td>
<td>Aptamers</td>
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<tr>
<td>SOMAmers</td>
<td>CFB and CFD</td>
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<td>Aptamers (SELEX)</td>
</tr>
<tr>
<td>TA106</td>
<td>CFB</td>
<td>Alexion Pharmaceuticals</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>------------</td>
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<td>-------------------------</td>
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</tr>
<tr>
<td>TNT003</td>
<td>Cls</td>
<td>True North</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>TT 30 (CR2/CFH)</td>
<td>CAP C3 convertase</td>
<td>Alexion</td>
<td>CFH-based protein</td>
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<tr>
<td>TT32 (CR2./CR1)</td>
<td>CAP and CCP C3</td>
<td>Alexion</td>
<td>CR1 -based protein</td>
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<td>Nafamostat (FUT-1 75, Futhan)</td>
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<td>Torri Pharmaceuticals</td>
<td>Small molecule</td>
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<td>OMS721</td>
<td>MASP-2</td>
<td>Omeros</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>OMS906</td>
<td>MASP-3</td>
<td>Omeros</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>Bikaciomab, NM9308</td>
<td>CFB</td>
<td>Novelmed</td>
<td>Monoclonal antibody</td>
</tr>
<tr>
<td>NM9401</td>
<td>Properdin</td>
<td>Novelmed</td>
<td>Monoclonal antibody</td>
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<td>CVF, HC-1496</td>
<td>C3</td>
<td>InCode</td>
<td>Recombinant peptide</td>
</tr>
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<td>Alexion Pharmaceuticals</td>
<td>Regulator</td>
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<tr>
<td>rFH</td>
<td>C3-conv, C3b</td>
<td>Opherion</td>
<td>Regulator</td>
</tr>
<tr>
<td>5C6, AMY-301</td>
<td>CFH</td>
<td>Amydas</td>
<td>Regulator</td>
</tr>
<tr>
<td>Erdigna</td>
<td>C5</td>
<td>Adienne Pharma</td>
<td>Antibody</td>
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<td>ARC 1905</td>
<td>C5</td>
<td>Ophotech</td>
<td>Monoclonal Antibody</td>
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<td>MEDI7814</td>
<td>C5/C5a</td>
<td>MedImmune</td>
<td>Monoclonal Antibody</td>
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<td>C5a</td>
<td>Noxxon</td>
<td>Aptamer (Spiegelmer)</td>
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<td>InflaRx</td>
<td>Monoclonal Antibody</td>
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<td>C5aR</td>
<td>Cephalon, leva</td>
<td>Peptidomimetic</td>
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<td>ChemoCentryx</td>
<td>Small molecule</td>
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<td>ADC- 1004</td>
<td>C5aR</td>
<td>Alligator Bioscience</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Anti-C5aR-15L , NN8209; Anti-C5aR-215, NN8210</td>
<td>C5aR</td>
<td>NovoNordisk</td>
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<tr>
<td>lraPGG</td>
<td>CR3</td>
<td>Biothera</td>
<td>Soluble beta-glucan</td>
</tr>
</tbody>
</table>

[0475] 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.

[0476] 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.


[0478] 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, polimicin 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, acetazolamide, pilocarpine, ciprofloxacin, azithromycin, gentamycin, tobramycin, cefazolin, voriconazole, gancyclovir, cidofovir, foscarinet, diclofenac, mepafenac, ketorolac, ibuprofen, indomethacin, fluoromethaline, riraeoxione, anecortave, cyclosporine, methotrexate, tacrolimus and combinations thereof.

[0479] 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 ascoraycin, e.g. Cyclosporin A (NEORAL®), FK506 (tacrolimus), pimecroiimus, a mTQR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (RAPAMIINE®), Everolimus (Certican®), temsirolimus, zotarolimus, biolimus-7, biolimus-9, a rapalog, e.g.ridaforoiimus, azathioprine, campath 1H, a SIP receptor modulator, e.g.
fmgolimod 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 Mofetii (CELLCEPT®), OKT3 (ORTHOCLOUNE OKT3®), Prednisone, ATGAM®, THYMOMEGLOBULIN®, Brequinar Sodium, OKT4, T10B9.A-3A, 33B3.1, 15-deoxyspergualin, tresperimus, Leflunomide ARAVA®, CTLA-1g, 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), adalimuraab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, gavilimomab, antithymocyte immunoglobulin, sipilizumab, Alefacept efalizumab, pentasa, mesalaizine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, tociizumab (Actemra), siltuximab (Sylvant), secukibumab (Cosentyx), ustekinumab (Stelara), risankizumab, sifalimumab, aspirin and ibuprofen.

[0480] Examples of anti-inflammatory agents include methotrexate, dexamethasone, dexamethasone alcohol, dexamethasone sodium phosphate, fluromethalone acetate, fluromethalone alcohol, iotoprendol etabonate, medrysone, prednisolone acetate, prednisolone sodium phosphate, difluprednate, rimexolone, hydrocortisone, hydrocortisone acetate, lodoxamide tromethamine, aspirin, ibuprofen, suprofen, piroxicam, meloxicam, flubiprofen, naproxen, ketoprofen, tenoxicam, diclofenac sodium, ketotifen fumarate, diclofenac sodium, ne盼fenc, 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), saisalate (Disalcid), diflunisal (Dolobid), piroxicam (Feldene), indomethacin (Indocin), etodolac (Lodine), meloxicam (Mobic), naproxen (Naprosyn), nabumetone (Reiafen), ketorolac tromethamine (Toradol), naproxen/esomeprazole (Vimovo), and diclofenac (Voltaren), and combinations thereof.

[0481] 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 VH-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.

[0482] 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-methylpropanoic 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.

[0483] In one embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a host 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.

[0484] In one embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a host 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 host 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 host 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.

[0485] In one embodiment, the present invention provides a method of treating or preventing rheumatoid arthritis by administering to a host 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 host 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 salicylate (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 (Feidene), etodoiac
(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, Myochrysme), hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate (Rheumatrex), penicillamine (Cuprimine), and sulfasalazine (Azulfidine); biologic drugs including abatacept (Orenicia), 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.

[0486] In one embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a host 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 host 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-la), Betaseron (interferon beta-lb), Copaxone (glatiramer acetate), Extavia (interferon beta-lb), Gilenya (fingolimod), Lemtrada (alemtuzumab), Novantrone (mitoxantrone), Plergyd (peginterferon beta-la), Rebib (interferon beta-la), Tecfidera (dimethyl fumarate), Tysabri (natalizumab), Solu-Medrol (methylprednisolone), High-dose oral Deltasone (prednisone), II P. Acthar Gel (ACTH), or a combination thereof.

[0487] 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 CD 19.

[0488] 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.

[0489] 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.

[0490] 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.

[0491] 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 host in need thereof.
[0492] 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).

[0493] 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.

[0494] 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.

[0495] 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.

[0496] 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.

[0497] 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.

[0498] 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.

[0499] 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.

[0500] 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 (TIP) or aHUS.

[0501] 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 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-11, 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, siltuxiraab, secukibuniab, 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-1RA (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); Hoprost, leflunomide (anti-inflammatory and cytokine inhibiton); tranexamic acid (inhibitor of plasminogen activation); T-614 (cytokine inhibitor); prostaglandin E1; 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 and-inflammatory drug); Indomethacin (non-steroidal and-inflammatory drug); Sulfasalazine; Azathioprine; ICE inhibitor (inhibitor of the enzyme interleukin-1β 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 l; 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 oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; 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).

[0502] 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 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 biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with tociizumab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of biotherapeutics. In another embodiment, an active compound or its salt or composition as described herein may be provided in combination with etarnercept and tociizumab for the treatment or prevention of cytokine or inflammatory reactions in response to the administration of 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 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 biotherapeutics.
VI. COMBINATIONS FOR PROPHYLACTIC OR CONCOMITTANT ANTI-
BACTERIAL THERAPY

[0503] 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.

[0504] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a host 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 host has received an organ or other tissue or biological fluid transplant. In one embodiment, the host is also administered eculizumab.

[0505] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a host and, during the administration period of the compound or salt, a vaccine against a bacterial infection is administered to the host. 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.

[0506] In one aspect of the present invention, the host 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 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.

[0507] In one aspect of the present invention, an active compound or its salt or composition as described herein is administered to a host 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 host has received an organ or other tissue or biological fluid transplant. In one embodiment, the host is also administered eculizumab.

[0508] In one embodiment, the host, prior to receiving an active compound or its salt or composition as described herein, is vaccinated against a bacterial infection caused by the bacterium Neisseria meningitidis. In one embodiment, the host 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 host is vaccinated against a bacterial infection caused by Streptococcus pneumoniae. In one embodiment, the host 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 host is vaccinated against a bacterial infection caused by the bacterium Nisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae.

[0509] In other embodiments, the host is vaccinated against a bacterial infection caused by a bacterium selected from a Gram-negative bacterium. In one embodiment, the host is vaccinated against a bacterial infection caused by a bacterium selected from a Gram-positive bacterium. In one embodiment, the host 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, and one or more of, but not limited to, Bacillus anthracis, Bordetelia pertussis, Clostridium tetani, Corynebacterium diphtheria, Coxiella burnetii, Mycobacterium tuberculosis, Salmonella typhi, Vibrio cholerae, Anaplasraa phagocytophilum, Ehrlichia ewingii, Ehrlichia chaffeensis, Ehrlichia canis, Neorickettsia sennetsu, Mycobacterium leprae, Borrelia burgdorferi, Borreia mayonii, Borrelia afzelii, Borrelia garinii, Mycobacterium bovis, Staphylococcus aureus, Streptococcus pyogenes, Treponema pallidum, Franciseliea tularensis, Yersinia pestis.
[0510] In one embodiment, the host 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 conjugate group B vaccine (Bexsero, GSK; Trumenba, Pfizer), anthrax vaccine adsorbed (Biothrax, Emergent Biosolutions), tetanus toxoid (Te Anatoxal Berna, Hendricks Regional Health), Bacillus Calmette and Guerii, live, intravesical (TheraCys, Sanofi; Tice BCG, Organon), cholera vaccine, live, oral (Vachora, Sanofi; Dukorai, SBL Vaccines; ShanChol, Shantha Biotech; Micromedex, Truven Health), tetanus toxoids and diphtheria absorbed (Tdap; Decavac, Sanofi; Tenivac, Sanofi; td, Massachusetts Biological Labs), diphtheria and tetanus toxoids and pertussis (DTap; Daptacel, Sanofi, Infanrix, GSK; Tripedia, Sanofi), diphtheria and tetanus toxoids and pertussis/polio (Kinrix, GSK; Quadracel, Sanofi), diphtheria and tetanus toxoids and pertussis tetanus/hepatitis B/polio (Pediarix, GSK), diphtheria and tetanus toxoids and pertussis/ polio, haemophilus influenza type b (Pentacel, Sanofi), and/or diphtheria, and pertussis (Tdap; Boostrix, GSK; Adacel, Sanofi), or a combination thereof.

[0511] As described above, a host receiving a compound of the present invention b treat disorder is prophylactically administered an antibiotic compound in addition to a factor D inhibitor described herein. In one embodiment, the host 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), gentaraicin (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/cefoxithin (Keflin), cephalixin (Keflex), cefaclor (Distacil), cefamandole (Mandol), cefoxitin (Mefoxin), ceprozil (Cefzil), cefuroxime (Ceftin, Zinnat), cefixime (Cefspan), cefdinir (Omnicef, Cefdiel), cefditoren (Spectracef, Meiact), cefpodoxime (Claporan), cefpodoxime (Vantin) ceftazidime (Fortaz), cefitibuten (Cedar), cefditoxime (Cefzox), ceftriaxone (Treblocin), clindamycin (Cleocin), lincomycin (Lincocin), daptomycin (Cubicin), azithromycin (Zithromax, Sumamed, Xithrone), clarithromycin (Biaxin), dirithromycin (Dynabac), erythromycin (Erythocin, Ethromped), roxithromycin, troleandomycin (Tao), telithromycin (Ketek), spiramycin (Rovamycine), aztreonam (Azactam), furazolidone (Furoxone), nitrofurantoin (Macrodantin, Macrobid), iinezolid (Zyvox), posizolid, radezolid, torezolid, amoxicillin (Novamox, Amoxil), ampicillin (Principen), azlocillin, carbenicillin (Geocillin), cloxacillin (Tegopen), dicloxacillin (Dynapen), flucloxacillin (Floxacin), mezlocillin (Mezlin), methicillin (Staphemycin), 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 (Colmycin-S), polymyxin B, ciprofloxacin (Cipro, Ciproxin, Ciprobay), enoxacin (Penetrex), gatifloxacin (Tequin), gemifloxacin (Factive), levofloxacin (Levaquin), lomerloxacin (Maxaquin), moxifloxacin (Avelox), nalidixic acid (NegGram), norfloxacin (Noroxin), ofloxacin (Floxin, Ocuflox), trovafloxacin (Trovam), grepafloxacin (Raxar), sparflaxacin (Zagam), temafloxacin (Omniflox), mafenide (Suifamylon), sulfacetamide (Sulamyd, Bieph-10), sulfadiazine (Micro-Sulfon), silver sulfadiazine (Silvadene), sulfadimethoxine (Di-Methox, Albon), sulfamethizole (Tiosulf), sulfamethoxazole (Gantanol), sulfanilamide, sulfasalazine (Azulfidine), sulisloxazole (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), platen s'mycin, quinupristin/dalfopristin (Synercid), thiamphenicol, tigecycline (Tigacyl), tinidazole (Tindamax Fasigyn), trimethoprim (Proloprim, Trimpex), and/or teixobactin, or a combination thereof.

[0512] In one embodiment, the host 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.

VIL PROCESS OF PREPARATION OF ACTIVE COMPOUNDS

ABBREVTATnm

AcCl acetyl chloride
ACN acetonitrile
dba dibenzy lidenacetone
DCM dichloromethane
DIEA N,N-diisoprop y l eth y lam ine
DMA N,N-dimethyl acetamide
DMF N,N-dimethylform amide
DMSO dimethyl sulfoxide
dppf 1,1'-bi s(diphenylphosphino)ferrocene
EtOAc ethyl acetate
FA formic acid
HATU l-[bis(dimethylamino)methylene]-lII-l,2,3-triazolo[4,5-b]pyridiniuni-3-oxid hexafluorophosphate
IPA isopropyl alcohol
MeOH methanol
rt room temperature
TBAF tetra-n-butylammonium fluoride
TBDMS ieri-butyldimethylsilyl
TBDMSCI tert-butyl(dimethyl)chloride
TEA triethylamine
TFA trifluoroacetic acid
THF tetrahydrofuran
TMSBr bromotrimethylsilane
Xantphos 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

GENERAL METHODS

[0513] 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 µη
Column Temperature: 40 °C
Mobile Phase: Solvent A: H2O + 0.05% FA; Solvent B: C3fCN + 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 x 4.6 mm, 5 µη
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 rain @ 30% B, 3.4 min gradient (30-100% B), then 0.8 min @ 100% B

Detection: UV (220/254 nm)

**LC Method C**

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

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

Column Temperature: Ambient

Mobile Phase A: 0.1% TEA in water. Mobile Phase B: Acetonitrile

Flow Rate: 1.0 mL/min

Gradient:

<table>
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<tr>
<th>Time (min)</th>
<th>0.0</th>
<th>15</th>
<th>20</th>
<th>23</th>
<th>30</th>
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<tbody>
<tr>
<td>% B</td>
<td>10</td>
<td>100</td>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Detection: (210-400 nm)

**LC Method I**

Instrument: Shimadzu LC 20AD system with PDA detector

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

Column Temperature: Ambient

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

Flow Rate: 1.0 mL/min

Gradient:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0.0</th>
<th>15</th>
<th>20</th>
<th>23</th>
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<tr>
<td>% B</td>
<td>10</td>
<td>100</td>
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</table>

Detection: (210-400 nm)

**EXAMPLE 1. GENERAL ROUTE OF SYNTHESIS**

[0514] 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.

Route 1

[0515] In an alternative embodiment, central core Structure 5 is reacted with a heterocyclic or heteroaryi 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.
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.
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 X1, X2, X3 and X4 positions to generate compounds of Formula I. This chemistry is illustrated in Route 4.
Route 4

[0518] 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.

![Chemical structures and reactions](image)

Formula 1

Route 5

[0519] In an alternate embodiment, a heteroaryl compound of Structure 6-1 is protected to generate a compound of Structure 6-2, wherein PG is a protecting group. Structure 6-2 is then activated with a leaving group, LG, to generate Structure 6-3. Structure 6-3 is treated with an activated ester, Structure 6-4, to generate Structure 6-5. Structure 6-5 is deprotected and treated with an organometallic catalyst to generate Structure 6-6. In some embodiments, the organometallic catalysts are Pd(dppf)Ch, Pd2(dba)3 and Zn(CN)2 to create an ether compound having a R6 group. In some embodiments, the R6 group is cyano. Structure 6-6 is treated with an oxime to generate an amide at the R6 position, Structure 6-7. Structure 6-7 is then treated with a base, an organic solvent and LG-R2 wherein LG is a leaving group to generate structure 6-8. In some embodiments, the leaving group is a tosylate. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In one embodiment, structure 6-7 is treated with -LG(CH2)i-4P(0)R33bR33b. In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, R33b is ethoxy. In some embodiments, the
diethyl phosphonate product is hydrolyzed to a phosphonic acid. Structure 6-8 is then coupled to Structure 3 to furnish a compound described by Formula I. This chemistry is presented in Route 6.
Route 6

[0520] In an alternate embodiment, a heteroaryl compound of Structure 7-1 is protected to generate a compound of Structure 7-2, wherein PG is a protecting group. Structure 7-2 is then activated with a leaving group to generate Structure 7-3. Structure 7-3 is treated with an activated ester of Structure 7-4 to generate Structure 7-5. Structure 7-5 is deprotected and treated with a protecting group. Structure 7-2 is then activated with a leaving group to generate Structure 7-3. Structure 7-3 is treated with a base, an organic solvent and LG-R^32 wherein LG is a leaving group to generate structure 7-7. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In one embodiment, structure 7-6 is treated with -LG(CH2)i4P(O)R^2bR^3b. In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, R^2b is ethoxy. In some embodiments, the diethyl phosphonate product is hydrolyzed to a phosphonic acid. Structure 7-7 is then coupled to Structure 3 to furnish a compound described by Formula I. This chemistry is presented in Route 7.
In another embodiment, a heteroaryl compound of Structure 8-1 is acylated to form Structure 8-2. Structure 8-2 is treated with an activated ester, Structure 8-3, to generate Structure 8-4. In some embodiments, the leaving group, LG, is a halide. The protecting group is removed to generate the alcohol which is Structure 8-5. In some embodiments the protecting group is benzyl. Structure 8-5 is treated with a base to generate acid 8-6. In some embodiments, the base is lithium hydroxide. Structure 8-6 is coupled to Structure 3 of Route I to generate Structure 8-7. Structure 8-7 can be treated with various activated moieties to generate compounds within Formula I. For example, Structure 8-7 can be treated with a base, an organic solvent and LG-R$_3$ wherein LG is a leaving group to generate compounds within Formula I. This chemistry is illustrated in Route 8. In some embodiments, the leaving group is a tosylate. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In one embodiment, structure 8-7 is treated with -LG(€H$_2$)$_{1-4}$P(Q)R$_{23b}$ to generate. In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, R$_{23b}$ is ethoxy. In some embodiments, the diethyl phosphonate product is hydrolyzed to a phosphonic acid. In some embodiments, the phosphonic acid is coupled to a chlorocarbonate to generate a compound of Formula I.
In another embodiment, a heteroaryl compound of Structure 9-1 is acylated to form Structure 9-2. In an alternate embodiment, Structure 9-1 is treated with an inorganic cyanide to introduce a cyano group at the R6 position. The cyano compound can be treated with an oxinie to generate an amide at the R6 position. Structure 9-2 is treated with an activated ester, Structure 9-3, to generate Structure 9-4. In some embodiments, the leaving group, LG, is a halide. The protecting group is removed to generate the alcohol which is Structure 9-5. In some embodiments the protecting group is benzyl. Structure 9-5 is treated with a base to generate acid 9-6. In some embodiments, the base is lithium hydroxide. Structure 9-6 is coupled to Structure 3 of Route 1 to generate Structure 9-7. Structure 9-7 can be treated with various moieties to generate compounds within Formula I. For example, Structure 9-7 can be treated with a base, an organic solvent and
LG-R \(^2\) wherein LG is a leaving group to generate compounds within Formula I. This chemistry is illustrated in Route 9. In some embodiments, the leaving group is a tosylate. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In some embodiments, the base is triethylamine. In one embodiment, structure 9-7 is treated with -LG(Cl:12)i-4P(0)R \(^{23b}\). In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, R \(^{23b}\) is ethoxy. In some embodiments, the diethyl phosphonate product is hydrolyzed to a phosphonic acid. In some embodiments, the phosphonic acid is coupled to a chloro carbonate to generate a compound of Formula I.

Route 9

[0523] In another embodiment, a heteroaryl compound of Structure 10-1 is acylated to form Structure 10-2. In an alternate embodiment, Structure 10-1 is treated with an inorganic...
cyanide to introduce a cyano group at the $R^6$ position. The cyano compound can be treated with an oxime to generate an amide at the $R^5$ position. Structure 10-2 is treated with an activated ester, Structure 10-3, to generate Structure 10-4. In some embodiments, the leaving group, LG, is a halide. The protecting group is removed to generate the alcohol which is Structure 10-5. In some embodiments the protecting group is benzyl. Structure 10-5 is treated with a base to generate acid 10-6. In some embodiments, the base is lithium hydroxide. Structure 10-6 is coupled to Structure 3 of Route 1 to generate Structure 10-7. Structure 10-7 can be treated with various moieties to generate compounds within Formula I. For example, Structure 10-7 can be treated with a base, an organic solvent and $LG-R^{32}$ wherein LG is a leaving group to generate compounds within Formula I. In some embodiments, the leaving group is a tosylate. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In some embodiments, the base is triethylamine. In one embodiment, structure 10-7 is treated with $-LG(CH_2)i-4P(0)R_{23b}^{23b}$. In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, $R_{23b}^{23b}$ is ethoxy. In some embodiments, the diethyl phosphonate product is hydrolyzed to a phosphonic acid. In some embodiments, the phosphonic acid is coupled to a chloro carbonate to generate a compound of Formula I. This chemistry is illustrated in Route 10.
[0524] In another embodiment, a heteroaryi compound of Structure 11-1 is acylated to generate Structure 11-2. In an alternate embodiment, Structure 11-1 is treated with an inorganic cyanide to introduce a cyano group at the R^6 position. The cyano compound can be treated with an oxime to generate an amide at the R^6 position. Structure 11-2 is treated with an activated ester, Structure 11-3, to generate Structure 11-4. In some embodiments, the leaving group, LG, is a halide. The protecting group is removed to generate the alcohol which is Structure 11-5. In some embodiments the protecting group is benzyl. Structure 11-5 is treated with a base to generate acid 11-6. In some embodiments, the base is lithium hydroxide. Structure 11-6 is coupled to Structure 3 of Route 1 to generate Structure 11-7. Structure 11-7 can be treated with various moieties to generate compounds within Formula I. For example, Structure 11-7 can be treated with a base, an
organic solvent and LG-R\textsuperscript{12} wherein LG is a leaving group to generate compounds within Formula I. In some embodiments, the leaving group is a tosylate. In some embodiments, the leaving group is a halide. In some embodiments, the base is triethylamine. In one embodiment, structure 11-7 is treated with -LG(CH2)i4P(O)R\textsuperscript{12}R\textsuperscript{23b}. In some embodiments, LG is a leaving group. In some embodiments, LG is a tosylate. In some embodiments, R\textsuperscript{23b} is ethoxy. In some embodiments, the diethyl phosphonate product is hydrolyzed to a phosphonic acid. In some embodiments, the phosphonic acid is coupled to a chloro carbonate to generate a compound within Formula I. This chemistry is illustrated in Route 11.

Route 11
In an alternate embodiment, Structure 12-1 is coupled to an amine to generate an amide (L-B), which is Structure 12-2. Structure 12-2, is coupled to an amine to generate compounds within Formula 1. This chemistry is illustrated in Route 12.

**Example 2. Examples of Central Synthons**
[0526] In one embodiment, deuterated L-proline synthons are disclosed. Deuterated synthons include, but are not limited to, for example, the following compounds:

Z^\* is halogen.

**EXAMPLE 3. PREPARATION OF CENTRAL-L-B SYNTHONS**

Routes 1a, 1b and 1c.

[0528] In Route 1a, 5-azaspiro[2.4]heptane-4,5-dicarboxylic acid, 5-(1,1-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.

[0529] In Route 1b, (4S) 4-oxazolidinecarboxylic acid, hydrochloride is treated with an amine protecting reagent. In one embodiment, the amine protecting reagent is di-tert-butyl dicarbonate. 3,4-oxazolidinedicarboxylic acid 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-dimethylaminopyridine (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.

[0530] In Route 1c, (S)-5-(ter?-Butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylic 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.

[0531] 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.

[0532] In Route 2b, commercially available (IR, 3S, 5R)-2-[(2R,3R)-2-(2-fluorophenyl)carboxyl]-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 HATIU. 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.

[0533] In Route 2c, commercially available (2S,4R)-1-(feri-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 HATIU. 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.

[0534] In Route 2d, commercially available (S)-1-(ter t-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.

[0535] Additional starting materials that can readily be converted to Central-L-B-Synths include, but are not limited to: (S)-1-(ter t-butoxycarbonyl)-2,3-dihydro-lH-pyrrole-2-carboxylic acid, CAS 90104-21-5, available from Ark Pharm; cyclopent-1-ene-1,2-dicarboxylic acid, CAS 3128-15-2, purchased from Ark Pharm; imidazole, lH-imidazole-1,2-dicarboxylic acid, l-(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,
can be prepared according to the procedures disclosed in WO 2004/11041; (S)-Boc-5-oxopyrrolidine-2-carboxylic acid is available from the Aldrich Chemical Co.; (1S,2S,5R)-3-((R)-7-butoxycarbonyl)-3-azabicyclo[3.3.0]octahydrocyclopenta[c]pyrrole-1-carboxylic acid is available from Ark Pharm; (S)-3-Boc-thiazolidine-2-carboxylic acid is available from Alfa Aesar, (2S,4R)-1-(6-butoxycarbonyl)-4-chloropyrrolidine-2-carboxylic acid is available from Arch Bioscience; (1S,3aR,6aS)-2-(fei-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid is available from Ark Pharm; 1,2-pyrrolidinedicarboxylic acid, 3-[[phenylmethoxy]carbonyl]amino]-1-(I,I-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.


The compounds (2S,3S,4S)-4-fluoro-3-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester and (2R,3R,4R)-3-fluoro-4-methoxy-pyrrolidine-1,2-dicarboxylic acid 1-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 (2S,4R)-N-(3-CHLORO-2-FLUOROBENZYL)-4-
FLUOROPYRROLIDINE-2-CARBOXAMIDE HYDROCHLORIDE (2)

(2S,4R)-tBu 2-((3-CHLORO-2-FLUORO-BENZYL)CARBAMOYL)-4-
FLUOROPYRROLIDINE-1-CARBOXYLATE

SCHEME 1.

[0539] (2S,4R)-l-(fe rt-butoxycarbonyl)-4-fluoropyrrrolidine-2-carboxylic acid (2.33 gm, 10 mmol) was dissolved in DMF (50ml) and ¾ NEt3 (8.6 ml, 5 eq.) was added, followed by the addition of (3-chloro-2-fluorophenyl) methanamine (3.18 gm 20mmol) at 5 °C. Then HATU (8 gm, 2.1 eq) was added slowly at the same temperature. The reaction mixture was then stirred for 18 h at RT. After completion of the reaction monitored by HPLC, the reaction mixture was diluted with 1M citric acid solution (200ml + NaCl solid 20gm) and extracted with DCM (150 mL x 2), the organic layer was then washed with an aqueous solution of NaHCO3 (100 ml), water (100 ml), and brine (100 ml) and dried over Na2SO4 then concentrated under reduced pressure. The remaining residue was purified by column chromatography (eluted with DCM/EtOAc) to give (2S,4R)-tert-buty 2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (50).

(2S,4R)-N-(3-CHLORO-2-FLUOROBENZYL)-4-FLUOROPYRROLIDINE-2-CARBOXAMIDE

SCHEME 2.

(2S,4R)-N-(3-CHLORO-2-FLUOROBENZYL)-4-FLUOROPYRROLIDINE-2-CARBOXAMIDE HYDROCHLORIDE

SCHEME 2.
[0540] (2S,4R)-fer.-butyl 2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (500 mg,) was taken in 4N HCl dioxane (30ml) and resulting reaction mixture was stirred at t for 3 h. After completion of the reaction monitored by HPLC solvent was removed under reduced pressure. The residue, 52, was used for the next reaction.

EXAMPLE 5. SYNTHESES OF NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I

1-(2-((2S,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyI]-3-yl)carbamoyl)-4-fluoropyrroI-yl)-2-oxoethyl)-5-(pyrimidin-5-yloxy)-lH-indazole-3-carboxamide (31).

Scheme 3

5-((teri-Butyldimethylsilyl)oxy)-lH-indazole (31).

[0541] To a solution of lH-indazol-5-ol (50 g, 1 equiv) in DMF (500 niL) was added imidazole (63.4 g, 2.5 equiv) and TBDMS chloride (67.4 g, 1.2 eq.) at 0 °C. The reaction mixture was stirred at t for 3 h, then poured over water until a precipitated solid appeared. The solid was collected by filtration, washed with water, and dried.
5-((teri-Butyldimethylsilyl)oxy)-3-iodo-lH-indazol-1-yl)acetate

[0542] To a solution of 5-((tert-butylidimethylsilyl)oxy)-lH-indazole (45 g, 1 equiv) in THF (450 mL) were added iodine (69 g, 1.5 equiv) and potassium tert-butoxide (50.8 g, 2.5 equiv) at 0 °C. The reaction mixture was stirred at rt for 12 h. The mixture was diluted with 10% sodium thiosulfate and water, and then extracted with EtOAc. The combined organic extracts were washed with brine, and then dried. The residual crude product was purified by column chromatography.

tert-Butyl 2-(5-((teri-butyldimethylsilyl)oxy)-3-iodo-lH-indazol-1-yl)acetate

[0543] To 5-((tert-butyldimethylsilyl)oxy)-3-iodo-lH-indazole (10 g, 1 equiv) and potassium carbonate (9.2 g, 2.5 equiv) in DMF (100 mL) was added tert-butyl bromoacetate (4.3 mL, 1.1 equiv) dropwise at rt. The resulting mixture was stirred for 2 h, poured into water, and extracted with EtOAc. The combined organic extracts were concentrated under reduced pressure. The material thus obtained was used without further purification in the next step.

tert-Butyl 2-(5-hydroxy-3-iodo-lH-indazol-1-yl)acetate

[0544] To a solution of tert-butyl 2-(5-((tert-butyldimethylsilyl)oxy)-3-iodo-lH-indazol-1-yl)acetate (144 g, 1 equiv) in THF (1440 mL) was added TBAF (1M solution in THF, 324 mL, 1.1 equiv) at 0 °C and the resulting mixture was stirred at rt for 2 h. The reaction mixture was poured into ice water and extracted with EtOAc; the combined organic extracts were concentrated under reduced pressure. The residual crude product was purified by column chromatography.

tert-Butyl 2-(3-cyano-5-hydroxy-1H-indazol-1-yl)acetate

[0545] A mixture of ferf-butyl 2-(5-hydroxy-3-iodo-lH-indazol-1-yl)acetate (86 g, 1 equiv), Zn(CN)2 (29.7 g, 1.1 equiv), Pd(dppf)Ch (16.8 g, 0.1 equiv), Pd2 (dba>3 (21 g, 0.1 equiv), water (86 mL), and DMF (860 mL) was stirred at 80 °C for 3 h under nitrogen. The reaction mixture was diluted with EtOAc and then successively washed with water, sat. aq. NaHCO3, and brine. The combined organic layer was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (Hexane/EtOAc).
**tert-Butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate**

[0546] A mixture of *tert-butyl* 2-(3-cyano-5-hydroxy-1H-indazol-1-yl)acetate (49 g, 1 equiv), acetaldoxime (21.2 g, 2 equiv), Pd(OAc)\(_2\) (2 g, 0.05 equiv) and PPh\(_3\) (5 g, 0.1 equiv) in aqueous ethanol (1125 mL, H\(_2\)O/MeOH (245 mL/980 mL)) was heated to reflux for 3 h under nitrogen atmosphere. The reaction mixture was filtered through Celite\(^\text{®}\) and the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica gel (Hexane/EtOAc).

**tert-Butyl 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetate**

[0547] A mixture of 873 mg (1 equiv) of compound 7, 5-bromopyrimidine (569 mg, 1.2 equiv), cesium carbonate (1.95 g, 2 equiv), and DMF (40 mL) was purged with argon in a pressure vessel for 5 min, then tris(dibenzylideneacetone) dipalladium(O) (0.01 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.01 equiv) were added under argon. The pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The remaining residue was purified by flash column chromatography (ISCO eluted with DCM/CH\(_2\)OH) to give 60.

**2-(3-Carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetic acid**

[0548] *tert-Butyl* 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetate (100 mg) was stirred in a 1:1 mixture of CH\(_2\)Cl\(_2\)-TFA (10 mL) at rt for 4 h. The volatiles were then removed under reduced pressure. The remaining material was used directly in the next synthetic step.

**L-(2-((2S,4R)-2-((2'-Chloro-2-fluoro-[1,1]-biphenyl)-3-yl)carbamoyl)-4-fluoropyrrolidine-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yloxy)-1H-indazole-3-carboxamide** (31).

[0549] 2-(3-Carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetic acid 61 (60 mg, 0.191 mmol) from the previous step was dissolved in DMF (10 mL) and iPrNEt (0.160 mL, 5 eq.) was added, which was followed by the addition of (2S,4R)-N-(2'-chloro-2-fluoro-[1,1]-biphenyl)-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (71 mg, 1 equiv) at 5 °C. HATU (153 mg, 2.1 eq) was then added slowly at the same temperature and the reaction mixture was stirred for 5
h at rt. After completion of the reaction monitored by HPLC, the reaction mixture was added to water (50 mL + 5 g NaCl) and extracted with DCM (2 x 25 mL). The organic layer was washed successively with an aqueous solution of NaHCO₃ (20 mL), water (20 mL), and brine (20 mL), then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (ISCO eluted with DCM/CH₃OH) to give 31. ³¹NMR (400 MHz, DMSO-d₆): (major rotamer) δ 2.12-2.28 (m, 1H), 2.54-2.62 (m, 1H), 3.61-3.62 (m, 1H), 3.90-4.02 (m, 1H), 4.19-4.27 (m, 1H), 4.78 (t, J = 8 Hz, 1H), 5.48-5.76 (m, 3H), 7.07 (t, J = 8 Hz, 1H). 7.22 (t, J = 8 Hz, 1H), 7.34-7.59 (m, 7H), 7.69-7.70 (m, 1H), 7.97 (t, J = 8 Hz, 1H). 8.64 (s, 2H), 9.00 (s, 1H). 19F NMR (376 MHz, DMSO-d₆): (major rotamer) δ -126.72, -175.85. LC (method A): tR = 2.72 min. LC/MS (EI) m/z: [M + H]+ calcd for C₃₁H₂₄ClF₂N₇O₄, 631; found, 632.

(2S,4R)-N-(2'-Cloro-2'-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidin-2-carboxamide hydrochloride (62).

Scheme 4

2'-Cloro-2'-fluoro-[1,1'-biphenyl]-3-araine hydrochloride

[0550] The mixture of 63 (30 g), 64 (60 g), K₂CO₃ (91 g) and Pd(dppf)₂Cl₂ (19.25 g) in solvent (dioxane 400 mL, H₂O 100 mL) was purged with argon in a pressure vessel for 5 min and stirred for 15 h at 100 °C. The solvent was removed under reduced pressure and the remaining residue was purified by flash column chromatography. The purified material was then dissolved
in MeOH and treated with HCl/MeOH. The solvent was removed and the remaining solid was washed with IPA-heptane (1/1) to afford 65.

(2S,4R)-ferf-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate

[0551] To an ice-cold solution of 48 (530 mg) in 20 mL of CH2Cl2, 1-chloro-N,N,2-trimethylpropenylamine (0.333 mL, 1.1 equiv.) was added dropwise with stirring. The stirring was continued for 3 h at this temperature, then solid 65 (640 mg, 1.1 equiv) was added, followed by 1.12 mL of iPrNEt (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at it. After completion of the reaction monitored by HPLC, the reaction mixture was added to water (20 mL) and extracted with DCM (2 x 25 mL). The organic layer was washed successively with an aqueous solution of NaHCO3 (20 mL), water (20 mL), and brine (20 mL), then dried over Na2SO4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (ISCO eluted with Hexanes/EtOAC) to give 66.

(2S,4R)-N-(2'-Chloro-2-fluoro-[1,r-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride

[0552] (2S,4R)-ferf-Butyl 2-((2'-chloro-2-fluoro-[1,r-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate 66 (700 mg) was taken in 4N HCl dioxane (25 mL) and the resulting reaction mixture was stirred at rt for 3 h. After completion of the reaction monitored by HPLC, the solvent was removed under reduced pressure. The remaining residue 62 was used directly in the next synthetic step (preparation of 31).
EXAMPLE 6. ADDITIONAL SYNTHESES OF NON-LIMITING EXAMPLES OF COMPOUNDS OF
FORMULA I

2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetic acid

Scheme 5

To a stirring solution of 5-(benzyloxy)-1H-indole (11.08 g, 1 equiv) in DCM (200 mL) was added diethyl aluminium chloride (1 M solution in hexane; 74.6 mL, 1.5 equiv) dropwise at 0 °C. The mixture was stirred for 30 min, and then a solution of acetyl chloride (5.3 mL, 1.5 equiv) in DCM (150 mL) was added at 0 °C and stirred for 1 h at this temperature. A 5% aq citric acid solution was added at 0 °C and the reaction mixture was stirred for 15 min at rt. The precipitate was collected by filtration, washed with water, and dried in vacuo to give 1-(5-(benzyloxy)-1H-indol-3-yl)ethanone.

1-(5-(Benzyloxy)-1H-indol-3-yl)ethanone.

[0553] To a stirring solution of 5-(benzyloxy)-1H-indole (11.08 g, 1 equiv) in DCM (200 mL) was added diethyl aluminium chloride (1 M solution in hexane; 74.6 mL, 1.5 equiv) dropwise at 0 °C. The mixture was stirred for 30 min, and then a solution of acetyl chloride (5.3 mL, 1.5 equiv) in DCM (150 mL) was added at 0 °C and stirred for 1 h at this temperature. A 5% aq citric acid solution was added at 0 °C and the reaction mixture was stirred for 15 min at rt. The precipitate was collected by filtration, washed with water, and dried in vacuo to give 1-(5-(benzyloxy)-1H-indol-3-yl)ethanone.

tert-Butyl 2-(3-acetyl-5-(benzyloxy)-1H-indol-1-yl)acetate,

[0554] To a mixture of 1-(5-(benzyloxy)-1H-indol-3-yl)ethanone (6.5 g, 1 equiv) and K2CO3 (3.72 g, 1.1 equiv) in acetonitrile (50 mL) was added tert-butyl 2-bromoacetate (3.92 mL, 1.1 equiv) dropwise at rt. The resulting mixture was then heated to reflux for 18 h. After cooling to rt, the mixture was diluted with DCM (100 mL), and then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the remaining residue was purified by flash column
chromatography (silica gel, eluted with DCM/EtOAc) to give tert-butyl 2-(3-acetyl-5-(benzyloxy)-1H-indol-1-yl)acetate.

tert-Butyl 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetate (70).

[0555] To a mixture of tert-butyl 2-(3-acetyl-5-(benzyloxy)-1H-indol-1-yl)acetate (6 g) in THF (80 mL) was added Pd/C (0.05 equiv). The reaction mixture was stirred at rt for 5 h under an atmosphere of H₂ (1 atm). The reaction mixture was then filtered through a pad of Celite® and washed with DCM and MeOH. The filtrate was concentrated under reduced pressure and the remaining residue was purified by flash column chromatography (silica gel, eluted with DCM/EtOAc) to give 70.

2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (71).

[0556] tert-Butyl 2-(3-acetyl-5-hydroxy-1H-indol-1-yl) acetate (70, 814 mg, 2.8 mmol) was taken in 4 N HCl in dioxane (10 mL) and the resulting reaction mixture was stirred at rt for 48 h. The solvent was then removed under reduced pressure to give 71.

2-(3-Acetyl-6-hydroxy-1H-indol-1-yl)acetic acid (76).

Scheme 6
1-(6-(Benzyloxy)-1H-indol-3-yl)ethanone (73).

[0557] Phosphorus(III) chloride (103 mL, 1.0 equiv) was added to ice cold dimethylacetamide (31 mL, 30 equiv) with stirring and cooling in ice. 6-Benzylxoy indole (25 g, 1 equiv) was then added and the reaction mixture was stirred at rt for 12 h, then poured over ice and basified with a 4 N aqueous sodium hydroxide solution until a precipitate formed. The solid was collected by filtration, washed with water, and dried. The solid was then slurried with methanol, collected by filtration, and dried to give 1-(6-(benzyloxy)-1H-indol-3-yl)ethanone (20 g).

tert-Butyl 2-(3-acetyl-6-(benzyloxy)-1H-indol-1-yl)acetate (74).

[0558] To a mixture of 1-(6-(benzyloxy)-1H-indol-3-yl)ethanone (25 g, 1 equiv) and potassium carbonate (1.6 g, 1.1 equiv) in acetonitrile (384 mL) was added tert-butyl bromoacetate (12.4 mL, 1.1 equiv) dropwise at rt. The resulting mixture was heated to reflux for 12 h, allowed to cool to rt, poured into water, and extracted with EtOAc. The combined organic extracts were concentrated under reduced pressure. The resulting solid was slurried with MTBE, collected by filtration, and dried to give tert-butyl 2-(3-acetyl-6-(benzyloxy)-1H-indol-1-yl)acetate (26 g).

tert-Butyl 2-(3-acetyl-6-hydroxy-1H-indol-1-yl)acetate (75).

[0559] A mixture of tert-butyl 2-(3-acetyl-6-(benzyloxy)-1H-indol-1-yl)acetate (22 g, 1 equiv), DCM/MeOH (600 mL), and Pd/C (2.2 g, 10%) was stirred at rt for 12 h under an atmosphere of H₂ (3.5 kg/cm²). The reaction mixture was filtered through a pad of Celite® and washed with DCM and MeOH. The filtrate was evaporated under reduce pressure, and the remaining crude product was slurried with DCM, collected by filtration, and dried to give tert-butyl 2-(3-acetyl-6-hydroxy-1H-indol-1-yl)acetate (11.5 g).

2-(3-Acetyl-6-hydroxy-1H-indol-1-yl)acetic acid (76).

[0560] The title compound was prepared in a manner analogous to that described above for 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (71, Scheme 5).
(((3-Acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrroloidin-l-yl)-
2-oxoethyl)-lH-indol-6-yl)oxy)methyl)phosphonic add (8).

Scheme 7

(2S,4R)-l-(2-(3-Acetyl-6-hydroxy-lH-indol-l-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-
fluoropyrroloidine-2-carboxamide (77).

[0561] (2S,4R)-N-(3-Chloro-2-fluorobenzyl)-4-fluoropyrroloidine-2-carboxamide
hydrochloride 52 (2.42 g) and 2-(3-acetyl-6-hydroxy-IH-indol-l-yl)acetic acid 76 (1.61 g) were
dissolved in DMF (40 mL) and treated with HATU (3.56 g) in the presence of DIEA (4.08 mL) at
rt overnight. After the volatiles were removed under reduced pressure, the residue was purified by
column chromatography using 0-5% MeOH in DCM as eluent to give 77 (2,17 g) as a solid.

Diethyl(((3-acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrroloidin-
l-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)phosphonate (7).

[0562] (2S/4R)-I-(2-(3-Acetyl-6-hydroxy-IH-indol-l-yl)acetyl)-N-(3-chloro-2-
fluorobenzyl)-4-fluoropyrroloidine-2-carboxamide 77 (2.1 g), ((diethoxyphosphoryl)methyl) 4-
methylbenzenesulfonate (1.32 g), and CS₂CO₃ (4.2 g) in DMF (21 mL) was stirred overnight at 50 °C. The solvent was then removed under reduced pressure and the residue was purified by column chromatography using 0-15% MeOH in DCM as eluent to give 7 (1.1 g) as a solid. LC (method A): *t*ᵣ = 1.84 min. LC/MS (EI) m/z: [M + H]+ calcd for C₂₉H₃₄CIF₂N₃O₇P, 640; found, 640.

(((3-Acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)phosphonic acid (8).

[TMSBr (7 mL) was added to diethyl(((3-acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)phosphonate (7) (1.1 g) in DCM (7 mL). The mixture was stirred at rt for 3 h. Volatiles were removed under reduced pressure and the residue was co-evaporated with 10% MeOH in DCM (10 mL). The remaining solid was washed with EtOAc (10 mL) three times to give 8 (1.1 g). ^1H NMR (400 MHz, DMSO-d₆): (major rotamer) δ 2.33 (s, 3H), 3.96-4.06 (m, 4H), 4.22-4.41 (m, 2H), 5.17 (dd, J = 75.2, 16.8 Hz, 2H), 5.45 (d, J = 52 Hz, 1H), 6.82-6.83 (m, 1H), 6.93 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 2 Hz, 1H), 7.19 (t, J = 4 Hz, 1H), 7.34 (t, J = 6 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 8.04 (s, 1H), 8.54 (t, J = 3 Hz, 1H). LC (method A): *b* = 1.03 min. LC/MS (EI) m/z: [M + H]+ calcd for C₂₅H₂₆CIF₂N₃O₇P, 584; found, 584.
Diethyl(((3-acetyl-1-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (10).

Scheme 8

(2S,4R)-1-(2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (78).

[0564] (2S,4R)-N-(3-Chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride 52 (240 mg) and 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid 71 (160 mg) were dissolved in DMF (5 mL) and treated with HATU (360 mg) in the presence of DIEA (0.4 mL) at rt overnight. After volatiles were removed under reduced pressure, the residue was purified by column chromatography using 0-5% MeOH in DCM as eluent to give (2S,4R)-1-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (200 mg).
Diethyl((3-acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (10).

[0565] (2S,4R)-l-(2-(3-Acetyl-5ydroxy-lH-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxainide (100 mg), (diethoxyphosphoryl)raethyl 4-methylbenzenesulfonate (1 equiv), and CS2CO3 (200 mg) in DMF was stirred overnight at 50 °C. The solvent was removed under reduced pressure and the residue was purified by column chromatography using 0-15% MeOH in DCM as eluent to give 10 (50 mg). ¹H NMR (400 MHz, DMSO-d6): (major rotamer) δ 1.28 (t, J = 6.8 Hz, 6 H), 2.00-2.24 (m, 1H), 2.42 (s, 3H), 3.80-3.99 (m, 1H), 4.11-4.18 (in, 4H), 4.29-4.49 (m, 5 H), 5.25 (dd, J = 81, 17 Hz, 2H), 5.50 (d, J = 52.8 Hz, 1H), 6.92-6.99 (m, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.37-7.44 (m, 2H), 7.77 (d, J = 2.4 Hz, 1H), 8.21 (s, 1H), 8.58 (t, J = 5.6 Hz, 1H). LC (method A): & = 1.79 min. L(VMS (EI) m/z: [M + H]+ calcd for C39H34ClF2N7O7P, 640; found, 640.

(((3-Acetyl-I-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)(hydroxy)phosphoryl)oxy)methylisopropyl carbonate (13).

Scheme 9

[0566] To a solution of (((3-acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)phosphonic acid 8 (0.21) in DMF (2 mL), Et3N (0.16 mL) was added followed by
chloromethyl isopropyl carbonate (0.144 mL). The resulting reaction mixture was heated at 60 °C for 16 h. The solvent was removed under reduced pressure after cooling the reaction mixture to rt. The residue was purified by preparative HPLC (fractions were collected based on UV) to give 13 (50 mg) as a solid. $^1$H NMR (400 MHz, CD$_3$OD): (major rotamer) $\delta$ 1.06 (d, $J = 6.4$ Hz, 6H), 1.15-1.23 (m, 1H), 1.99-2.07 (m, 1H), 2.39 (s, 3H), 2.46-2.56 (m, 1H), 3.82-4.29 (m, 4H), 4.294.39 (m, 2H), 4.46-4.55 (m, 1H), 4.64-4.67 (m, 1H), 4.92-4.99 (m, 1H), 5.09-5.17 (m, 1H), 5.36 (d, $J = 52$ Hz, 1H), 5.55 (d, $J = 12.4$ Hz, 2H), 6.76-6.81 (m, 2H), 6.86 (d, $J = 8.8$ Hz, 1H), 6.97 (d, $J = 1.6$ Hz, 1H), 7.14-7.29 (ra, 2H), 7.92 (d, $J = 6$ Hz, 1H), 8.02 (d, $J = 8.8$ Hz, 1H); $^{31}$F NMR (376 MHz, CD$_3$OD): (major rotamer) $\delta$ -178.6, -123.4. LC (method A): $t_R = 1.38$ min. LC/MS (EI) mix: [M +H]$^+$ calcd for C$_{30}$H$_{34}$ClF$_2$N$_3$O$_{10}$P, 700; found, 700.

(2S,4R)-1-(2-(3-AcetyI-6-(N-(tert-butyl)suIfamoyl)methoxy)-lH-indol-1-yl)acetyI)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (15).

Scheme 10

[0567] A mixture of (2S,4R)-1-(2-(3-acetyI-6-hydroxy-lH-indol-1-yl)acetyI)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide 77 (0.18 g), N-fert-butyl-l-chloromethanesulfonamide (320 mg), and Cs$_2$CO$_3$ (0.8 g) in DMF (2 mL) was heated at 60 °C for 3 d. The reaction mixture was then cooled to rt and filtered. The solid was washed with DMF. The
filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (0-2% MeOH in DCM) to give 15 (60 mg) as a solid. ¹H NMR (400 MHz, CD3OD): (major rotamer) ∆₁.31 (s, 9H), 2.12-2.28 (m, 1H), 2.52 (s, 3H), 2.54-2.76 (m, 1H), 4.10-4.20 (m, 2H), 4.46 (s, 2H), 4.62 (t, J = 8 Hz), 5.12 (d, J = 11.6 Hz, 1H), 5.08-5.14 (m, 2H), 5.27 (d, J = 17.2 Hz, 1H), 5.48 (d, J = 52.4 Hz, 1H), 6.89 (t, J = 8 Hz, 1H), 7.05 (dd, J = 6.8, 2.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.26-7.32 (m, 2H), 8.09 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H); ¹³F NMR (376MHz, CD3OD): (major rotamer) ∆-178.5, -123.4. LC (method A): tᵣ = 1.83 min. LCM S (EI) m/z: [M + H]⁺ calc'd for C29H34ClF2N4O6S, 639; found, 639.

(((3-Acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)(ethyl)phosphinic Acid (16),

Scheme 11
Ethyl ethyl(hydroxymethyl)phosphinate (79).

[0568] A mixture of ethyl ethylphosphinate (2.2 g), paraformaldehyde (2.7 g), and TEA (10 mL) in DMF (10 mL) was heated at 100 °C for 3 h. Volatiles were removed under reduced pressure. The residue was treated with water and extracted with chloform. The aqueous layer was concentrated to give ethyl ethyl(hydroxymethyl)phosphinate.

(Ethoxy(ethyl)phosphoryl)methyl 4-bromobenzenesulfonate (80).

[0569] Ethyl ethyl(hydroxymethyl)phosphinate from above was mixed with 4-bromobenzenesulfonyl chloride (5 g) in DCM (30 mL) and treated with TEA (10 mL) at rt for 4 h. After aqueous workup, the solvent was removed under reduced pressure and the remaining residue was purified by column chromatography to give (ethoxy(ethyl)phosphoryl)methyl 4-bromobenzenesulfonate (385 mg).

Ethyl (((3-acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)(ethyl)phosphinate (14).

[0570] A mixture of (ethoxy(ethyl)phosphoryl)methyl 4-bromobenzenesulfonate (385 mg), (2S,4R)-1-((2-(3-acetyl-6-hydroxy-1H-indol-1-yl)acet)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide 77 (470 mg), and Cs2CO3 (1 g) in DMF (20 mL) was stirred at 50 °C overnight. The solvent was removed under reduced pressure and the remaining residue was purified by column chromatography using 5% MeOH in DCM as eluent to give 14 (427 mg). LC (method A): tR = 1.40 min. LC/MS (EI) m/z: [M + H]+ calcd for C29H34CIF2N3O6P. 624, found, 624.

(((3-Acetyl-l-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)(ethyl)phosphinic Acid (16).

[0571] Ethyl (((3-acetyl4-((2<2S,4R)-2<((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-6-yl)oxy)methyl)(ethyl)phosphinate 14 (400 mg) was dissolved in DCM (3 mL) and was treated with TMSBr (3 mL) at rt for 2 h. Volatiles were removed under reduced pressure and the residue was co-evaporated with 10% MeOH in DCM (10 mL). The remaining solid was washed with EtOAc (10 mL) three times to give 16 (300 mg). 1H NMR (400 MHz, DMSO-d6): (major rotamer) δ 2.00-2.24 (m, 1H), 2.65-2.50 (m, 7H), 2.67 (d, J
= 4.4 Hz, 1H), 3.89-4.69 (m, 7H), 5.41 (ddd, J = 84, 22, 4.4 Hz, 2H), 5.53 (d, J = 52.4 Hz, 1H), 6.83-6.88 (m, 1H), 7.20 (i, J = 7.2 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 7.88 (d, J = 84 Hz, 2H), 8.04 (d, J = 5.2 Hz, 1H), 8.30 (d, J = 84 Hz, 2H), 8.47 (s, 1H), 8.64 (f, J = 6 Hz, 1H). LC (method A): t_R = 1.18 min. LC/MS (EI) m/z: [M + H]^+ calcd for C27H30CIF2N3O6P, 596; found, 596.

(((3-Acetyl-1-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yl)oxy)methyl)phosphoryl)bis(oxy)bis(methylene) bis(2,2-dimethylpropanoate) (21).

Scheme 12

[0572] To a solution of (((3-acetyl-1-(2-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yl)oxy)methyl)phosphonic acid 8 (426 mg) in DMF (7 mL) was added TEA (0.62 mL) followed by chloromethyl pivalate (0.63 mL). After the stirred mixture was heated in a 55 °C oil bath for 24 h, additional chloromethyl pivalate (0.63 mL) and triethylamine (0.62 mL) were added. The reaction was kept at 55 °C for an additional 24 h. The volatiles were removed under reduced pressure and the remaining residue was purified by flash column chromatography on silica gel with DCM/MeOH as eluent. The desired fractions were combined, concentrated, and evaporated. The remaining residue was dissolved in acetonitrile-water and lyophilized to afford 21 (216 mg).

1H NMR (400 MHz, DMSO-d_6, V(major rotamer) δ 1.13 (s, 18H), 2.04-2.15 (m, 1H), 2.40 (s, 3H), 2.48-2.53 (m, 1H), 3.84-3.96 (m, 1H), 4.08-4.17 (m, 1H), 4.25-4.52 (m, 5H), 5.11-5.34 (m, 2H), 5.45-5.58 (m, 1H), 5.66-5.70 (m, 4H), 6.91-6.99 (m, 2H), 7.15 (s, 1H), 7.24 (t, J = 6.8 Hz, 1H),

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7.40-7.44 (m, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.14 (s, 1H), 8.62 (t, J = 6.0 Hz, 1H). $^{19}$F NMR (376 MHz, DMSO-d$_6$): (major rotamer) $\delta$ -121.74, -176.01. $^{31}$P NMR (162 MHz, DMSO-d$_6$): (major rotamer) 19.97. LC (method A): $t_R = 2.58$ min. LC/MS (EI) m/z: [M + H]$^+$ caicd for C$_{37}$H$_{46}$ClF$_2$N$_3$O$_{11}$P, 812; found, 812.

l-(2-((2$^S$, 4/Q-2-((2'-Chloro-241uoro-)
\[1,1'-biphenyl]-3-yl)-carbomoyl-4-fluoropyrrolidin-1-
yl)-2-oxoethyS-6-(sif!amoySmethoxy)-1H-indazoSe-3-carboxamide (29).

Scheme 13
6-((^-Butyldimethylsilyl)oxy)-IH-indazole (82).

[0573] To a solution of 6-hydroxy-IH-indazole (50 g) in DMF (500 mL) were added imidazole (63.4 g) and TBDMSCI (67.4 g) at 0 °C. The reaction mixture was stirred at rt for 3 h, then poured into water until a precipitate formed. The solid was collected by filtration, washed with water, and dried to give 6-((fer/-butyldimethylsilyl)oxy)-IH-indazole (80 g).

6-((^-Butyldimethylsilyl)oxy)-3-iodo-IH-indazole (83).

[0574] To a solution of 6-((tert-butyldimethylsilyl)oxy)-IH-indazole (45 g) in THF (450 mL) were added iodine (69 g) and potassium tert-hutoxide (50.8 g) at 0 °C. The reaction mixture was stirred at rt for 12 h. The mixture was diluted with 10% sodium thiosultate and water, and then extracted with EtOAc. The combined organic extracts were washed with brine, and then dried. The residual crude product was purified by column chromatography to give 6-((tert-butyldimethylsilyl)oxy)-3-iodo-IH-indazole (35 g).

tert-Butyl 2-(6-(( tert-butyldimethylsilyl)oxy)-3-iodo-IH-indazol-1-yl)acetate (84).

[0575] To a mixture of 6-((tert-butyldimethylsilyl)oxy)-3-iodo-IH-indazole (10 g) and potassium carbonate (9.2 g) in DMF (100 mL) was added tert-butyl bromoacetate (4.3 mL) dropwise at rt. The resulting mixture was stirred for 2 h, poured into water, and extracted with EtOAc. The combined organic extracts were concentrated under reduced pressure to give tert-butyl 2-(6-((fer-t-butyldimethylsilyl)oxy)-3-iodo-IH-indazol-1-yl)acetate (11 g).

tert-Butyl 2-(6-hydroxy-3-iodo-IH-indazol-1-yl)acetate (85).

[0576] To a solution of ieri-buty\ 2-6-((fer/-butyldimethylsilyl)oxy)-3-iodo-IH-indazol-1-yl)acetate (144 g) in THF (1440 mL) was added TBAF (1 M solution in THF, 324 mL) at 0 °C and the resulting mixture was stirred at rt for 2 h. The reaction mixture was poured into ice water and extracted with EtOAc; the combined organic extracts were concentrated under reduced pressure. The residual crude product was purified by column chromatography to give tert-butyl 2-(6-hydroxy-3-iodo-IH-indazol-1-yl)acetate (75 g).
**tert-Butyl 2-(3-cyano-6-hydroxy-lH-indazol-1-yl)acetate** (86).

[0577] A mixture of *tert-butyl* 2-(6-hydroxy-3-iodo-lH-indazol-1-yl)acetate (86 g), Zn(CN)2 (29.7 g), Pd (dpff)Ch (16.8 g), Pd3(dba)3 (21 g), water (86 mL), and DMF (860 mL) was stirred at 80 °C for 3 h under an atmosphere of nitrogen. The reaction mixture was diluted with EtOAc and then washed successively with water, saturated aqueous NaHCO3, and brine. The combined organic layer was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc) to give *tert-butyl* 2-(3-cyano-6-hydroxy-lH-indazol-1-yl)acetate (49 g).

**tert-Butyl 2-(3-carbamoyl-6-hydroxy-lH-indazol-1-yl)acetate** (87).

[0578] A mixture of *ier-hutyl* 2-(3-cyano-6-hydroxy-lH-indazol-1-yl)acetate (49 g), acetaldoxime (21.2 g), Pd (OAc)2 (2 g), and PPI13 (5 g) in aqueous ethanol (H2O/EtOH 245 mL/980 mL) was heated to reflux for 3 h under an atmosphere of nitrogen. The reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. The remaining crude residue was purified by column chromatography on silica gel (hexanes/EtOAc) to give *tert-butyl* 2-(3-carbamoyl-6-hydroxy-lH-indazol-1-yl)acetate (41 g).

**2-(3-Carbamoyl-6-hydroxy-lH-indazol-yl)acetic acid** (88),

[0579] **tert-Butyl** 2-(3-carbamoyl-6-hydroxy-lH-indazol-1-yl)acetate (409 mg) was dissolved in DCM (5 mL) and TFA (5 mL) was added. The reaction mixture was stirred at rt overnight and the solvent was removed under reduced pressure to give 2-(3-carbamoyl-6-hydroxy-lH-indazol-1-yl)acetic acid.

**1-(2-(2S, 4R)-2-((2-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbomoyl-4-fluoropyrroolidin-1-yl)-2-oxoethyl)-6-hydroxy-lH-indazole-3-carboxamide** (89).

[0580] 2-(3-Carbamoyl-6-hydroxy-lH-indazol-1-yl)acetic acid (228 mg) was dissolved in DMF (10 mL), and DIEA (0.51 mL) was added followed by (2S,4R)-N-(2-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrroolidine-2-carboxamide hydrochloride (428 mg). HATU (380 mg) was then added slowly and the reaction mixture was stirred for 18 h at rt. After completion of the reaction monitored by HPLC, the reaction mixture was poured into water (15 mL) and extracted with EtOAc (2 x 25 mL). The organic layer was washed successively with an aqueous solution of...
NaHCO₃ (15 mL), water (15 mL), and brine (15 mL), then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography (eluted with DCMZMeOH) to give 1-(2-((2S,4R)-2-((2′-chloro-2-fluoro-[1,1′-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-6-hydroxy-1H-indazole-3-carboxamide.

6-((N-( tert-Butyl)sulfamoyl)ethoxy)-1-(2-((2S, 4R)-2-((2′-chloro-2-fluoro-[1,1′-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide (28).

[0581] 1-(2-((2S,4R)-2-((2′-chloro-2-fluoro-[1,1′-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-6-hydroxy-1H-indazole-3-carboxamide (156 mg) was dissolved in DMF (5 mL) and CS₂CO₃ (456 mg, 5 equiv) was added followed by N-( tert-butyl)-1-chloromethanesulfonamide (260 mg). The reaction mixture was heated at 55°C for 2 d. The reaction mixture was diluted with EtOAc (10 mL) and water (4 mL). The organic layer was separated, washed with brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The remaining material was purified by preparative HPLC (ACN/water/TFA) to give 28. LC (method A); tᵣ = 2.22 min. LC/MS (El) m/z: [M + H]⁺ calcd for C₂₂H₃₃ClIF₂N₂O₆S, 703; found, 703.

i-((2-((2S, 4R)-2-((2′-Cloro-2-fluoro-[1,1′-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yI)-2-oxoethyl)-6-(sulfamoylmethoxy)-IH-indazole-3-carboxamiide (29).

[0582] 6-((N-( tert-Butyl)sulfamoyl)methoxy)-1-(2-((2S,4R)-2-((2′-chloro-2-fluoro-[1,1′-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide (28) (65 mg) was dissolved in DCM (5 mL) and then TFA (5 mL) was added. The reaction mixture was stirred for 3 d and the voiyaties were then removed under reduced pressure to give 29. ¾ NMR (400 MHz, DMSO-δ₆): (major rotamer) δ 2.12-2.29 (m, 1H), 3.88-3.92 (m, 1H), 4.16-4.21 (m, 2H), 4.75 (t, J = 7 Hz, 1H), 5.1 1-5.19 (m, 2H), 5.36-5.67 (m, 3H), 7.01-7.06 (m, 1H), 7.18-7.25 (m, 2H), 7.32-7.53 (m, 4H), 7.56-7.60 (m, 1H), 7.95-8.00 (m, 1H), 8.07 (d, J = 8.8 Hz, 1H); ¹⁹F NMR (376 MHz, DMSO-δ₆): (major rotamer) δ -126.96, -175.68. LC (method A); δ & = 1.80 min. LC/MS (El) m/z: [M + H]⁺ calcd for C₂₂H₂₀ClIF₂N₂O₆S, 647; found, 647.
(2S,4R)-1-(2-(3-Acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (30).

Scheme 14

**tert-Butyl 2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetate** (90)

[0583] A mixture of tert-butyl 2-(3-acetyl-6-hydroxy-1H-indol-1-yl)acetate 75 (290 mg), 1-bromo-pyrimidine (1.25 equiv), and K2CO3 (3 equiv) was refluxed in acetonitrile overnight. The solid was removed by filtration and washed with EtOAc (20 mL). The filtrate was concentrated and the remaining residue was purified by column chromatography to give /erf-butyl 2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetate (165 mg).

**2-(3-Acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetic acid** (91).

[0584] tert-Butyl 2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetate (158 mg) was treated with TFA (1 mL) in DCM (1 mL) overnight at rt. The sovent was removed under reduced pressure and the residue was co-evaporated with toluene (5 mL) twice. The solid was washed with EtOAc (5 mL) and dried to give 91.
(2S,4R)-l-(2-(3-Acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (30).

[0585] A mixture of 2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetic acid 91 (31 mg) and (2S,4R)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride 52 (1 equiv) in DMF was treated with HATU (1.5 equiv) and DIEA (4 equiv) at rt for 1 h. The volatiles were removed under reduced pressure. The remaining residue was treated with 10% aqueous Na2CO3 and extracted with EtOAc. The organic extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure. The residue was purified by column chromatography to give 30 (52.8 mg). 1H NMR (400 MHz, DMSO-d): (major rotamer) δ 1.96-2.07 (m, 1H), 2.36 (s, 3H), 2.42-2.50 (m, 1H), 3.74-3.87 (m, 1H), 4.02-4.08 (m, 4E), 4.18-4.27 (m, 2H), 4.34-4.37 (m, 1H), 5.05-5.30 (m, 2H), 5.34-5.47 (m, 1H), 6.92-6.98 (m, 2H), 7.1 1-7.17 (m, 2H), 7.32-7.38 (m, 2H), 8.10 (d, J = 8.8 Hz, 1H), 8.17 (s, 1H), 8.49 (t, J = 6.0 Hz, 1H), 8.55 (d, J = 4.8 Hz, 2H). 19F NMR (376 MHz, DMSO-d): (major rotamer) δ 421.28, -176.12. LC (method A): tR = 2.54 min. LC/MS (EI) m/z: [M + H]+ caicd for C28H25CIF2N5O4, 568; found, 568.

(2S,4R)-l-(2-(3-Acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (32).

Scheme 15
A mixture of 2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetic acid 9 (65.5 mg) and (2S,4R)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride 62 (78 mg) in DMF (3 mL) was treated with HATU (96 mg) and DIEA (4 equiv) at rt for 1 h. The volatiles were removed under reduced pressure. The residue was treated with 10% aqueous Na2CO3 and extracted with EtOAc. The organic extract was washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The remaining residue was purified by column chromatography to give 32 (58.1 mg). ¾ NMR (400 MHz, DMSO-d6): (major rotamer) δ 2.00-2.17 (m, 1H), 2.35 (s, 3H), 2.47-2.53 (m, 1H), 3.79-3.92 (m, 1H), 4.03-4.12 (m, 1H). 4.68 (t, J = 8.8 Hz, 1H), 5.11-5.32 (m, 2H), 5.39-5.52 (m, 1H). 6.95-7.01 (m, 2H), 7.12 (t, J = 8.0 Hz, 1H). 7.17 (t, J = 4.8 Hz, 1H), 7.30-7.41 (m, 4H). 7.50-7.52 (m, 1H), 7.86 (t, J = 7.2 Hz, 1H). 8.10 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 8.55 (d, J = 4.8 Hz, 2H), 9.91 (s, 1H). 19F NMR (376 MHz, DMSO-d6): (major rotamer) δ -126.71, -175.78. LC (method A): tR = 2.57 rain. LC/MS (EI) m/z: [M + H]+ calcd for C33H27ClF2N5O4, 630; found, 630.

(2S,4R)-l-(2-(3-Acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yi)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (33),

Scheme 16
**tert-Butyl 2-(3-acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetate (92).**

[0587] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetate 70 (700 mg), 5-bromo-2-fluoropyrimidine (1 equiv), and CS₂CO₃ (700 mg) in DMF (20 mL) was purged with argon in a pressure vessel for 5 min, then tris(dibenzylideneacetone) dipalladium(O) (0.01 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.01 equiv) were added under argon. The pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The remaining residue was purified by column chromatography (eluted with DCM/MeOH) to give tert-butyl 2-(3-acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetate (700 mg).

**2-(3-Acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetic acid (93),**

[0588] tert-Butyl 2-(3-acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetate (150 mg) was treated with TFA (10 ml) in DCM (10 mL) at rt for 3 h. The solvent was removed under reduced pressure to give 92.

**(2S,4R)-1-(2-(3-Acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (33),**

[0589] A mixture of 2-(3-acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetic acid 92 and (2S,4R)-N-(2'-chloro-2-fluoro-[1, r-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride 62 (150 mg) in DMF (10 mL) was treated with HATU (325 mg) and DIEA (4 equiv) at rt for 1 h. The reaction mixture was poured into water. The solid was collected by filtration and then purified by column chromatography using MeOH in DCM as eluent to give 33 (110 mg). H NMR (400 MHz, D₆SO-d₆): (major rotamer) δ 2.10-2.27 (m, 1H), 2.4 (s, 3H), 2.51-2.56 (m, 1H), 3.92-4.04 (m, W=4.13-4.25 (m, III), 4.78 (t, J = 8.8 Hz, 1H), 5.35 (dd, J = 69, 17, 2H), 5.06 (d, J = 56 Hz, 1H), 7.04-7.10 (m, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.37-7.51 (m, 4H), 7.57 (d, J = 6 Hz, 1H), 7.89 (d, J = 2 Hz, 1H), 7.97 (t, J = 6 Bz, 1H), 8.31 (s, 1H), 8.77 (s, 2H), 9.96 (s, 1H). LC (method A): rt = 2.45 min. LC/MS (EI) m/z: [M + H]⁺ caicd for C₃₇H₃₀BrClF₂N₅O₄, 708; found, 708.
(1R,3S,5R)-2-(2-(3-Acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (34).

Scheme 17

([0590] To an ice-cold solution of (IR,3S,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (5 mmol) in DCM (20 mL) was added l-chloro-N,N,2-triraethylpropenylamine (1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, then solid 2'-chloro-2-fluoro-[1',r-biphenyl]-3-amine hydrochloride (1.0 equiv) was added, followed by DIEA (2.5 equiv). 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 (20 mL) and extracted with DCM (2 x 25 mL). The organic layer was
washed successively with an aqueous solution of NaHCO₃ (20 mL), water (20 mL), and brine (20 mL), then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with MeOH/DCM) to give (IR,3S,5R)-fer-t-butyl 3-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate.

(IR,3S,5R)-N-(2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (96).

[0591] (IR,3S,5R)-ferf-Butyl 3-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (500 mg) was taken in 4 N HCl in dioxane (25 mL) and the resulting reaction mixture was stirred at rt for 3 h. After completion of the reaction (monitored by HPLC), the solvent was removed under reduced pressure to give (IR,3S,5R)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride.

(LR^S,5R)-2-(2-(3-Acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (34).

[0592] A mixture of 2-(3-acetyl-5-((5-bromopyrimidin-2-yl)oxy)-1H-indol-1-yl)acetic acid 93 (100 mg) and (IR,3S,5R)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (1.0 equiv) in DMF (10 mL) was treated with HATU (2.0 equiv) and DIEA (5.0 equiv) at rt for 1 h. The reaction mixture was poured into water. The solid was collected by filtration and then purified by column chromatography using 0-50% of EtOAc in DCM as eluent to give 34 (70 mg). ¾ NMR (400 MHz, DMSO-de): (major rotamer) δ 0.77-0.78 (m, 1H), 1.07-1.09 (m, 1H), 1.92 (br s, 1H), 2.42 (s, 3H), 2.51-2.56 (m, 1H), 3.81 (br s, 1H), 4.55 (t, J = 6.8 Hz, 1H), 5.36 (d, J = 17 Hz, 1H), 7.03-7.10 (m, 2H), 7.24 (t, J = 8.0 Hz, 1H), 7.37-7.45 (m, 3H), 7.51-7.58 (m, 2H), 7.89 (d, J = 2 Hz, 1H), 7.93 (t, J = 7.6 Hz, 1H), 8.37 (s, US), 8.77 (s, 2H), 9.73 (s, 1H). LC (method A): tₐ = 2.58 min. LC/MS (EI) m/z: [M + H]⁺ calcd for C₃₄H₂₇BrClFN₃O₄, 703; found, 703.
Step 1: (3R,3aR,6R,6aR)-6-(3-Methyl-4-nitrophenoxy)hexahydrofuro[3,2-b]furan-3-ol (98).

[0593] To a solution of isomannide (7.3 g, 50 mmol) in DMF (100 rtL) at 0 °C under nitrogen protection was added NaH (2.6 g, 66 mmol) portionwise. After addition, the mixture was stirred at room temperature for 30 min followed by addition of compound 1 (3.5 g 22 mmol). The mixture was stirred for another 3 h and then quenched with 2 M HCl (adjust pH to 7). The resulting mixture was extracted with ethyl acetate (250 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 1:1) to give compound 98 (2 g, yield 32%) as a yellow solid.
Step 2: \((3R^aR^6R,6aR)-6-(3-(\(E\)-2-(Dimethylamino)vinyl)-4-nitrophenoxy)hexahydrofuro[3,2-b]furan-3-ol\) (99).

[0594] To a solution of compound 98 (1.0 g, 3.56 mmol) in DMF (15 mL) at room temperature was added dimethylformamide dimethyl acetal (20 mL). The reaction mixture was heated at 150 °C for 7 h and then concentrated to afford the crude product 99 (1.0 g) as a dark red oil, which was used in the next step without purification.


[0595] To a solution of compound 99 (1.0 g, 2.98 mmol) in MeOH (20 mL) was added 10% Pd/C (100 mg). The resulting mixture was degassed twice and stirred under an atmosphere of Lb (balloon) for 2 h. After filtration, the filtrate was concentrated and purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 1:2) to give compound 100 (0.3 g, yield 39%) as a brown solid.

Step 4: \(1-(5-((3R,3aR,6R,6aR)-6-Hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indol-3-yl) ethanone\) (101).

[0596] To an ice cold solution of compound 100 (0.3 g, 1.2 mmol) in DCM (5 mL) under nitrogen was added SnCl₄ (0.65 g, 2.5 mmol) dropwise. After addition, the mixture was stirred for 30 min followed by addition of CH₃COCl (0.20 g, 2.5 mmol) dropwise. The reaction mixture was stirred for another 30 min and then quenched with aq. NaHCO₃. The resulting mixture was extracted with ethyl acetate (100 mL). The organic phase was separated, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography silica gel (eluted with petroleum ether/ethyl acetate = 1:1) to afford compound 101 (0.15 g, yield 41%) as a brown solid.

Step 5: Ethyl \(2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furii-3-yloxy)-lH-indol-1-yl)acetate\) (102).

[0597] To a mixture of compound 101 (0.15 g, 0.5 mmol) and K₂CO₃ (0.11 g, 1 mmol) in MeCN (5 mL) was added ethyl 2-chloroacetate (0.06 g, 0.5 mmol). The resulting mixture was stirred at 60 °C for 4 h. After filtration, the filtrate was concentrated and the residue was purified
Step 6: 2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (103),

[0598] To a solution of compound 102 (0.15 g, 0.39 mmol) in THF (5 mL) and H₂O (1 mL) at room temperature was added LiG₃H₂O (0.08 g, 1.93 mmol). The reaction mixture was stirred at room temperature for 2 h and then acidified with 1 M HCl (adjust pH to 5). The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered, and then concentrated to give compound 103 (0.12 g yield 85%) as a brown solid.

Step 7: (2S,4R)-1-(2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chIoro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide (104),

[0599] To a solution of compound 103 (60 mg, 0.16 mmol), compound 52 (62 mg, 0.16 mmol), and DIPEA (42 mg, 0.32 mmol) in DMF (2 mL) at room temperature was added HATU (121 mg, 0.32 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by prep-HPLC (eluted with C₄CN/water) to give compound 104 (15 mg, yield 13 %) as a white solid. ¹H-NMR: 8.10 (s, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.41-7.40 (m, 1H), 7.39-7.20 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.23 (d, J = 48 Hz, 1H), 5.13 (d, J = 1.6 Hz, 1H), 5.04 (d, J = 1.6 Hz, 1H), 4.81-4.73 (m, 2H), 4.41 (t, J = 4.0 Hz, 1H), 4.11-4.09 (m, 3H), 3.82-3.80 (m, 3H), 3.50 (t, J = 8 Hz, 1H), 2.66-2.56 (m, 1H), 2.38 (s, 3H), 2.19-2.16 (m, 1H). LC-MS: m/z 694 (M+H)⁺.

Step 8: (2S,4R)-1-(2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (106),

[0600] To a solution of compound 103 (50 mg, 0.14 mmol), compound 105 (48 mg, 0.17 mmol), and DIPEA (71 mg, 0.55 mmol) in DMF (2 mL) at room temperature was added HATU.
The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by prep-HPLC (eluted with CHsCN/water) to give compound 106 (10 mg, yield 12%) as a white solid. $^1$H-NMR: 8.26 (s, 1H), 7.95 (d, $J = 8.0$ Hz, IH), 7.91 (s, IH), 7.69 (s, IH), 7.46 (t, $J = 8.0$ Hz, IH), 7.12 (d, $J = 8.0$ Hz, IH), 7.06 (d, $J = 8.0$ Hz, IH), 6.92 (d, $J = 8.0$ Hz, IH), 5.23 (d, $J = 48$ Hz, 1H), 4.73 (t, $J = 8.0$ Hz, IH), 4.65 (t, $J = 8.0$ Hz, IH), 4.51 (t, $J = 4.0$ Hz, IH), 4.26-4.25 (m, IH), 4.17 (q, $J = 8.0$ Hz, IH), 3.92-3.78 (m, 3H), 3.68-3.55 (m, 2H), 2.70 (brs, 1H), 2.49 (s, 3H), 2.32-2.30 (m, IH). LC-MS: m/z 645 (M+H)$^+$. 

(2S,4R)-l-(2-(3-AcetyI-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(2-chloro-2-fluorobiphenyI-3-yl)-4-fluoropyrrolidin-2-carboxamide (113).

Scheme 19
Step 1: (3R,3aR,6R,6aR)-6-(3-Methyl-4-nitrophenoxy)hexahydrofuro[3,2-b]furan-3-ol (98).

[0601] To a solution of isoraannide (7.3 g, 50 mmol) in DMF (100 mL) at 0 °C under nitrogen protection was added NaH (2.6 g, 66 mmol) portionwise. After addition, the mixture was stirred at room temperature for 30 min followed by addition of compound 97 (3.5 g 22 mmol). The mixture was stirred for another 3 h and then quenched with 2 M HCl (adjust pH to 7). The resulting mixture was extracted with ethyl acetate (250 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 1:1) to give compound 98 (2 g, yield 32%) as a yellow solid.

Step 2: (3R,3aR,6R,6aR)-3-Methoxy-6-(3-methyl-4-nitrophenoxy)hexahydrofuro[3,2-b]furan (107).

[0602] To a solution of compound 98 (2 g, 7 mmol) in DMF (50 mL) at 0 °C under nitrogen was added NaH (0.84 g, 21 mmol). The reaction mixture was stirred at room temperature for 30 min followed by the addition of CH₃I (1.9 g, 21 mmol). The mixture was stirred for another 3 h and then quenched with 2 M HCl (adjust pH to 7). The resulting mixture was extracted with ethyl acetate (100 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 10:1 to 2:1) to give compound 107 (0.8 g, yield 38%) as a yellow solid.


[0603] To a solution of compound 107 (0.8 g, 2.7 mmol) in DMF (10 mL) at room temperature was added dimethylformamide dimethyl acetal (10 mL). The reaction mixture was heated at 150 °C for 7 h and then concentrated to afford the crude product 108 (0.6 g) as a dark red oil, which was used in the next step without further purification.

[0604] To a solution of compound 108 (0.6 g, 1.7 mmol) in MeOH (20 mL) was added 10% Pd/C (50 mg). The resulting mixture was degassed twice and stirred under an atmosphere of 
\( \text{H}_2 \) (balloon) for 2 h. After filtration, the filtrate was concentrated and purified by column 
chromatography on silica gel (eluted with petroleum ether/ethyl acetate = 5:1 to 1:1) to give 
compound 109 (0.4 g, yield 82%) as a brown oil.

Step 5: \( \text{l-(5-((3R,3aR,6R,6aR)-6-Methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indol-3-}
\text{yl)} \) ethanone (110),

[0605] To an ice cold solution of compound 109 (0.4 g, 1.4 mmol) in DCM (5 mL) under 
nitrogen protection, was added SnCk (0.55 g, 2.1 mmol) dropwise. After addition, the mixture was 
stirred for 30 min followed by addition of CH3COCl (0.16 g, 2.1 mmol) dropwise. The reaction 
mixture was stirred for another 30 min and then quenched with aq. NaHCO\(_3\). The resulting mixture 
was extracted with ethyl acetate (100 mL). The organic phase was separated, dried over anhydrous 
Na2SC\(_4\), filtered, and then concentrated. The residue was purified by column chromatography 
silica gel (eluted with petroleum ether/ethyl acetate = 1:1) to afford compound 110 (0.3 g, yield 
67%) as a brown solid.

Step 6: Ethyl \( \text{2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-}
\text{yloxy)-l H-indol-1-yl}) \) acetate (111),

[0606] To a mixture of compound 110 (0.3 g, 0.9 mmol) and K2CO\(_3\) (0.37 g, 2.7 mmol) in 
MeCN (5 mL) was added ethyl 2-chloroacetate (0.22 g, 1.5mmol). 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 petroleum ether/ethyl acetate = 1:1) to give 
compound 111 (0.3 g, yield 78%) as a brown oil.

Step 7: \( \text{2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-}
\text{indol-1-yl}) \) acetic acid (112),

[0607] To a solution of compound 111 (0.3 g, 0.75 mmol) in THF (5 mL) andLiO (1 mL) 
at room temperature was added LiOH·H\(_2\)O (0.1 g, 2.4 mmol). The reaction mixture was stirred at
room temperature for 4 h and then acidified with 1 M HC1 (adjust pH to 5). The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with brine and dried over anhydrous Na2SO4, filtered, and then concentrated to give compound 112 (0.1 g yield 35%) as a brown solid.

Step 8: (2S,4R)-1-(2-(3-AcetyI-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide (113).

[0608] To a solution of compound 112 (100 mg, 0.26 mmol), compound 52 (87 mg, 0.26 mmol), and DIPEA (201 mg, 1.04 mmol) in DMF (5 mL) at room temperature was added HATU (197 mg, 0.52 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by prep-HPLC (eluted with CH3CN/water) to give compound 113 (50 mg, yield 20%) as a white solid. 'H-NMR: 8.23 (s, 1H), 7.98 (t, 1H), 7.75 (d, 1H), 7.6-7.58 (m, 1H), 7.48-7.32 (m, 4H), 7.24 (m, 1H), 7.10 (m, 1H), 6.78 (m, 1H), 5.16-5.61 (m, 4H), 4.86-4.70 (m, 3H), 4.60 (t, 1H), 3.80-4.18 (m, 5H), 3.67 (t, 1H), 3.46 (t, 1H), 3.33 (s, 3H), 2.58-2.61 (m, 1H), 2.37 (s, 3H), 2.08-2.20 (m, 1H). LC-MS: m/z 694 (M+H)+.
(2S,4R)-l-(2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indol-l-yl)acetyl) -N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxanride (115).

Scheme 20


[0609] To a mixture of compound 110 (0.3 g, 0.9 mmol) and K2CO3 (0.37 g, 2.7 mmol) in MeCN (5 mL) was added ethyl 2-chloroacetate (0.22 g, 1.8 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 petroleum ether/ethyl acetate = 1:1) to give compound 7 (0.3 g, yield 78%) as a brown oil.

Step 7: 2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indol-l-yl)acetic acid (112).

[0610] To a solution of compound 114 (0.3 g, 0.75 mmol) in THF (5 mL) and H2O (1 mL) at room temperature was added LiOH·H2O (0.1 g, 2.4 mmol). The reaction mixture was stirred at...
room temperature for 4 h and then acidified with 1 M HCl (adjust pH to 5). The resulting mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered, and then concentrated to give compound 112 (0.1 g yield 35%) as a brown solid.

Step 8: (2S,4R)-1-(2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yI)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (115).

[0611] To a solution of compound 112 (100 mg, 0.26 mmol), compound 105 (84 mg, 0.26 mmol), and DiPEA (201 mg, 1.04 mmol) in DMF (5 mL) at room temperature was added HATU (197 mg, 0.52 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated. The residue was purified by prep-HPLC (eluted with CH₃CN/water) to give compound 115 (40 mg, yield 16%) as a white solid. ¹H-NMK: 8.10-8.05 (m, 2H), 7.88 (s, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 8.4 Hz, 1H), 5.42 (d, J = 12 Hz, 1H), 5.26 (d, J = 17.6 Hz, 1H), 5.13 (d, J = 15.2 Hz, 1H), 4.90-4.88 (m, 2H), 4.70-4.69 (m, 2H), 4.18-4.17 (m, 2H), 4.01-3.67 (m, 4H), 3.47 (t, J = 12 Hz, 1H), 3.33 (s, 3H), 2.70-2.65 (ra, 1H), 2.47 (s, 3H), 2.23-2.20 (m, 1H). LC-MS: m/z 645 (M+H)+.

(2S,4R)-N-Benzyl-4-fluoropyrrolidine-2-carboxamide hydrochloride

Scheme 21

[0612] To a solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added benzyl amine (1.2 equiv), HATU (1.5 equiv) and DiPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed...
with brine, dried over anhydrous $\text{Na}_2\text{SO}_4$, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford tert-butyl (2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidine-1-carboxylate. To a solution of tert-butyl (2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidine-1-carboxylate (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 (2S,4R)-N-benzyl-4-fluoropyrrolidine-2-carboxamide hydrochloride (118).
(2S,4R)-4-Fluoro-N-phenethylpyrrolidine-2-carboxamide hydrochloride

Scheme 22

[0613] To a solution of (2S,4R)-l-(ter t-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 2-phenylethan-l-amine (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/ MeOH to afford tert-butyl (2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidine-1-carboxylate. To a solution of tert-butyl (2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidine-1-carboxylate (1 equiv) in 1,4-dioxane (3 vol) at 0 °C under nitrogen atmosphere was added 4 N HQ in 1,4-dioxane (10 vol) and stirred at room temperature for 3 h. The reaction mixture was concentrated to afford (2S,4R)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide hydrochloride (121).

(2S,4R)-4-Fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamidehydrochloride (124)

Scheme 23

[0614] To a solution of (2S,4R)-l-(ter t-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 3-phenylpropan-l-amine (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at
room temperature for 3 h. After completion, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford tert-butyl (2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidine-1-carboxylate. To a solution of tert-butyl (2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidine-1-carboxylate (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 (2S,4R)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide hydrochloride.

(2S,4R)-4-Fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (127)

Scheme 24

[0615] To a solution of (2S,4R)-1-(re rrr-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen was added 4-phenylbutan-1-amine (1.2 equiv), HATU (1.5 equiv) and DPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford tert-butyl (2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidine-1-carboxylate. To a solution of tert-butyl (2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidine-1-carboxylate (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 (2S,4R)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide.
(2S,4R)-L-(2-(3-Acetyl-5-(sulfamoylmethyl)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrroldine-2-carboxamide (130).

Scheme 25

Step 1: (2S,4R)-L-(2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrroldine-2-carboxamide (128)

[0616] To a solution of 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-N-benzyl-4-fluoropyrroldine-2-carboxamide hydrochloride (1.2 equiv), STATU (1.5 equiv) and DIPEA (5 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 solid was filtered, dried to give (2S,4R)-L-(2-(3-acety1-5-hydroxy-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide.

Step 2: (2S,4R)-L-(2-(3-Acetyl-5-(N-(tert-butyl)sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrroldine-2-carboxamide (129)

[0617] To a solution of (2S,4R)-L-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrroldine-2-carboxamide (1 equiv) in ACN (10 vol) was added cesium carbonate.
(1.2 equiv) and N-(feri-butyl)-l-chloromethanesulfonamide (2 equiv). The reaction mixture was stirred at 70 °C for 2 days. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-(^tert^-butyl)sulfoamyl)methoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide. ³¹H NMR (400 MHz, CD3OD) δ 8.15 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, IH), 7.26 - 7.12 (m, 5H), 7.09 - 7.06 (m, 1H), 5.52 - 5.39 (m, 5H), 5.31 - 5.27 (m, IH), 5.15 - 5.08 (m, 3H), 4.59 (t, J = 8.4 Hz, 1H), 4.38 (s, 2H), 4.20 - 4.12 (m, 1H), 4.01 (dd, J = 12 Hz, 2.8 Hz, IH), 2.61 - 2.51 (m, IH), 2.49 (s, 3H), 2.28 - 2.15 (m, IH), 1.34 (s, 9H).

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide (130)

[0618] To a solution of (2S,4R)-4-(2<3-acetyl-5-((N-(ter^butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide (1 equiv) in DCM (10 vol) at 0 °C under nitrogen atmosphere in a sealed tube was added TFA (5 vol). The reaction mixture was heated to 40 °C for 4 h. After completion of the reaction, the reaction mixture was concentrated and purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide. ¾ NMR (400 MFIz, CD3OD) δ 8.16 (s, IH), 8.00 (s, IH), 7.40 (d, J = 7.4 Hz, IH), 7.27 - 7.24 (m, 5H), 7.11 (d, J = 8.8 Hz, IH), 5.51 - 5.25 (m, 2H), 5.15 - 5.11 (m, 3H), 4.63 - 4.61 (m, IH), 4.40 - 4.38 (m, 2H), 3.66 - 3.64 (m, 2H), 2.52 (s, 3H), 2.28 - 2.26 (m, IH), 1.69 - 1.67 (m, IH).
(2S,4R)-1-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (133)

Scheme 26

Step 1: (2S,4R)-1-(2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (131)

[0619] To a solution of 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxaraidehydrochloride (1.2 equiv), HATU (1.5 equiv) and DiPEA (5 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 solid was filtered, dried to give (2S,4R)-1-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide.
Step 2: (2S,4R)-1-(2-(3-Acetyl)-5-(N-(tert-butyl)sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (132)

[0620] To a solution of (2S,4R)-1-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (1 equiv) in ACN (10 vol) was added cesium carbonate (1.2 equiv) and N-(tert-butyl)-1-chloromethanesulfonamide (2 equiv). The reaction mixture was stirred at 70 °C for 2 days. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-((N-(fer-4-fluoro-N-phenethylpyrrolidine-2-carboxamide. ¹H NMR (400 MHz, CD3OD) δ 8.14 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, H2). 7.27 - 7.18 (m, 5H), 7.12 - 7.11 (m, 1H), 5.45 - 5.38 (m, 1H), 5.29 - 5.24 (m, 1H), 5.12 - 5.03 (m, 3H), 4.48 (d, J = 8 Hz, 1H), 4.14 (dd, J = 2, 12 Hz, 1H), 4.15 - 3.91 (m, 1H), 3.36 - 3.32 (m, 2H), 2.80 - 2.72 (m, 2H), 2.51 (s, 3H), 2.49 - 2.47 (m, 1H), 2.10 - 1.98 (m, 1H), 1.33 (s, 9H).

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (133)

[0621] To a solution of (2S,4R)-1-(2-(3-acetyl-5-((N-(terT-butyl)sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide (1 equiv) in DCM (10 vol) at 0 °C under nitrogen atmosphere in a sealed tube was added TFA (5 vol). The reaction mixture was heated to 40 °C for 4 h. After completion of the reaction, the reaction mixture was concentrated and purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide. ¹H NMR (400 MHz, CD3OD) δ 8.13 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.21 - 7.09 (m, 6H), 5.45 - 5.21 (m, 2H), 5.13 - 5.09 (m, 3H), 4.47 - 4.43 (m, 1H), 3.68 - 3.65 (m, 2H), 3.55 - 3.47 (m, 2H), 2.78 - 2.71 (m, 3H), 2.49 (s, 3H), 2.11 - 1.98 (m, 1H).
(2S,4R)-1-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (136)

Scheme 27

Step 1: (2S,4R)-1-(2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (134)

[0622] To a solution of 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide hydrochloride (1.2 equiv), HATU (1.5 equiv) and DiPEA (5 equiv). The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was quenched with water. The resulting solid was filtered, dried to give (2S,4R)-1-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide.
Step 2: (2S,4R)-1-(2-(3-Acetyl-5-(N-(t-Butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (135)

[0623] To a solution of (2S,4R)-1-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (1 equiv) in ACN (10 vol) was added cesium carbonate (1.2 equiv) and N-(t-Butyl)chloromethanesulfonamide (2 equiv). The reaction mixture was stirred at 70 °C for 2 days. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide. ³¹NMR (400 MHz, CD₃OD) δ 8.12 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 8.9 Hz, 1.6 Hz, 1H), 7.19 - 7.04 (m, 7H), 5.45 - 5.38 (m, 5H), 5.29 - 5.24 (m, 2H), 5.12 - 5.03 (m, 3H), 4.51 (t, J = 8.3 Hz, 2H), 4.14 (dd, J = 2.1 Hz, 12.4 Hz, 1H), 4.15 - 3.91 (m, 7H), 3.24 - 3.14 (m, 2H), 2.60 - 2.55 (m, 3H), 2.48 (s, 3H), 2.26 - 2.10 (m, 2H), 1.77 - 1.72 (m, 4H), 1.33 (m, 9H).

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (136)

[0624] To a solution of (2S,4R)-1-(2-(3-acetyl-5-((N-(t-Butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide (1 equiv) in DCM (10 vol) at 0 °C under nitrogen atmosphere in a sealed tube was added TFA (5 vol). The reaction mixture was heated to 40 °C for 4 h. After completion, the reaction mixture was concentrated and purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-((N-(t-Butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide. ¹H NMR (400 MHz, CD₃OD) δ 8.15 (s, 1H), 7.97 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 9 Hz, 1H), 7.19 - 7.09 (m, 6H), 5.45 - 5.38 (m, 1H), 5.29 - 5.24 (m, 2H), 5.12 - 5.03 (m, 3H), 4.55 - 4.51 (m, 2H), 4.16 (dd, J = 2.1 Hz, 12.4 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.26 - 3.15 (m, 2H), 2.60 - 2.57 (m, 3H), 2.49 (s, 3H), 2.26 - 2.10 (m, 2H), 1.77 - 1.74 (m, 4H).
Scheme 28

Step 1: (2S,4R)-l-(2-(3-Acetyl-5-((N-(4-phenylbutyl)sulfamoylamino)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (137)

[0625] To a solution of 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 127 (1.2 equiv), HATU (1.5 equiv) and DIPEA (5 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 solid was filtered, dried to give (2S,4R)-l-(2-(3-acetyl-5-((N-(4-phenylbutyl)sulfamoylamino)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide.

Step 2: (2S,4R)-l-(2-(3-Acetyl-5-((N-(4-phenylbutyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (138)

[0626] To a solution of (2S,4R)-l-(2-(3-acetyl-5-((N-(4-phenylbutyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (1 equiv) in ACN (10 vol)
vol) was added cesium carbonate (1.2 equiv) and N-(tert-butyl)-1-chioromethanesulfonamide (2 equiv). The reaction mixture was stirred at 70 °C for 2 days. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by preparative purification to give (2S,4R)-4-(2-(3-acetyl-5-(N-(feri-
butyl)sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-
carboxamide. ¾ NMR (400 MHz, CD3OD) δ 8.15 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.20 - 7.05 (m, 6H), 5.51 - 5.38 (m, 1H), 5.29 - 5.25 (m, 3H), 5.14 - 5.06 (m, 2H), 4.50 (t, J = 9 Hz, 1H), 4.15 - 4.10 (m, 1H), 4.14 (dd, J = 2.1 Hz, 12.4 Hz, 1H), 3.21 - 3.17 (m, 2H), 2.57 - 2.53 (m, 2H), 2.49 (s, 3H), 2.21 - 2.06 (m, 1H), 1.63 - 1.51 (m, 2H), 1.49 - 1.47 (m, 2H), 1.33 (s, 9H).

Step 3; (2S,4R)-1-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-
phenylbutyl)pyrrolidine -2-carboxamide (139)

[0627] To a solution of (2S,4R)-1-(2-(3-acetyl-5-((N-(tert-butyl)sulfaraoyl)methoxy)-1H-
indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (1 equiv) in DCM (10 vol) at 0 °C under nitrogen atmosphere in a sealed tube was added TFA (5 vol). The reaction mixture was heated to 40 °C for 4 h. After completion of the reaction, the reaction mixture was concentrated and purified by preparative purification to give (2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-
carboxamide. ¾ NMR (400 MHz, CD3OD) δ 8.13 (s, 1H), 7.97 (d, J = 2 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.19 - 7.05 (m, 6H), 5.50 - 5.37 (m, 1H), 5.29 - 5.22 (m, 1H), 5.13 - 5.09 (m, 3H), 4.60 - 4.59 (m, 1H), 4.49 - 4.47 (m, 1H), 4.15 - 4.13 (m, 1H), 4.00 - 3.95 (m, 1H), 3.20 - 3.17 (m, 2H), 2.60 - 2.53 (m, 2H), 2.49 (s, 3H), 2.22 - 2.19 (m, 1H), 1.62 - 1.56 (m, 2H), 1.52 - 1.45 (m, 2H).
(2S,4R)-L-(2-(3-Acetyl-5-(sulfamoylmeth)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (141)

Scheme 29

Step 1: (2S,4R)-L-(2-(3-Acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (78)

[0628] To a solution of 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (1.2 equiv), HATU (1.5 equiv) and DIPEA (5 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 solid was filtered, dried to give (2S,4R)-L-(2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide.
Step 2: (2S,4R)-l-(2-(3-Acetyl-5-((N-(tert-butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (140)

[0629] To a solution of (2S,4R)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (1 equiv) in ACN (10 vol) was added cesium carbonate (1.2 equiv) and N-(tert-butyl)-l-chloromethanesulfonamide (2 equiv). The reaction mixture was stirred at 70 °C for 2 days. After completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by preparative purification to give (2S,4R)-l-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide. 1H NMR (400 MHz, CD3OD) δ 8.14 (s, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.37 - 7.25 (m, 3H), 7.11 - 7.06 (m, 1H), 6.96 - 6.92 (m, 1H), 5.53 (s, 1H), 5.40 (s, 1H), 5.15 - 5.08 (m, 3H), 4.62 - 4.60 (m, 1H), 4.57 - 4.55 (m, 2H), 4.21 - 4.13 (m, 1H), 4.03 - 3.94 (m, 1H), 2.63 - 2.51 (m, 1H), 2.49 (s, 3H), 2.31 - 2.11 (m, 1H), 1.33 (s, 9H).

Step 3: (2S,4R)-l-(2-(3-Acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (141)

[0630] To a solution of (2S,4R)-4-(2-(3-acetyl-5-((N-(tert-butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide (1 equiv) in DCM (10 vol) at 0 °C under nitrogen atmosphere in a sealed tube was added TFA (5 vol). The reaction mixture was heated to 40 °C for 4 h. After completion of the reaction, the reaction mixture was concentrated and purified by preparative purification to give (2S,4R)-l-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide. 3/4 NMR (400 MHz, CD3OD) δ 8.13 (s, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.37 - 7.24 (m, 3H), 7.08 (dd, J = 6.4 Hz, 2.4 Hz, 1H), 6.96 - 6.92 (m, 1H), 5.52 - 5.39 (m, 1H), 5.32 - 5.28 (m, 1H), 5.13 - 5.11 (m, 3H), 4.59 - 4.57 (m, 1H), 4.44 (d, J = 3.6 Hz, 2H), 4.17 - 4.12 (m, 1H), 4.02 - 3.90 (m, 1H), 2.63 - 2.58 (m, 1H), 2.48 (s, 3H), 2.27 - 2.14 (m, 1H).
2-(3-Acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (143)

Scheme 30

Step 1: tert-Butyl 2-(3-acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetate (142)

[0631] To a solution of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetate (1 equiv) in DMF (10 vol) was added potassium carbonate (3 equiv) and (diethoxyphosphoryl)methyl 4-methylbenzenesulphonate (1.2 equiv). The reaction mixture was heated to 80 °C for 12 h. After completion of the reaction, the reaction mixture was quenched with water. The resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using Hexane/EtOAc to give compound tert-butyl 2-(3-acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetate.

Step 2: 2-(3-Acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (143)

[0632] To a solution of compound 142 (1 equiv) in DCM (10 vol) at 0 °C under nitrogen was added TFA (10 vol). The reaction mixture was heated to 50 °C for 3 h. After completion of the reaction, the reaction mixture was concentrated to give 2-(3-acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic.
(((3-Acetyl-l-(2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (145)

Scheme 31

Step-1: Diethyl (((3-acetyl-l-(2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (144)

[0633] To a solution of 2-(3-acetyl-5-((diethoxyphosphoryl)methoxy)-lH-indol-l-yl)acetic acid (1 equiv) in DME (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-N-benzyl-4-fluoropyrrolidine-2-carboxamide hydrochloride (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl (((3-acetyl-l-(2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate. ¾ NMR (400 MHz, DMSO-d6) δ 8.51 (t, J = 6 Hz, 1H), 8.21 (s, 1H), 7.77 - 7.75 (m, 1H), 7.39 (d, J = 9.2 Hz, 1H), 7.35 - 7.19 (m, 5H), 6.94 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 5.56 - 5.43 (m, 1H), 5.37 - 5.33 (m, 1H), 5.17 - 5.13 (m, 1H), 4.46 - 4.40 (m, 3H), 4.33 - 4.10 (m, 7H), 3.95 - 3.83 (m, 1H), 2.41 (s, 3H), 2.39 - 2.37 (m, 1H), 2.15 - 2.01 (m, 1H), 1.29 - 1.25 (m, 6H).
Step-2: (((3-Acetyl-1-(2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (145)

[0634] To a solution of diethyl (((3-acetyl-1-(2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (1 equiv) in DCM (35 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the resulting solid was filtered and dried. The residue was purified by preparative HPLC to give (((3-acet-1-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid. ^1H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.37 - 7.20 (m, 6H), 6.91 (d, J = 8.8 Hz, 1H), 5.50 - 5.31 (m, 2H), 5.16 - 5.11 (m, 1H), 4.45 - 4.39 (m, 2H), 4.32 - 4.26 (m, 2H), 4.24 - 3.84 (m, 5H), 2.32 (s, 3H), 2.31 - 2.29 (m, 1H), 2.15 - 1.98 (m, 6H).

(((3-Acetyl-1-2-((2S,4R)-4-fluoro-2-(phenethyicarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (147)

Scheme 32

Step-1: Diethyl (((3-acetyl-1-2-((2S,4R)-4-fluoro-2-(phenethyicarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (146)

[0635] To a solution of fert-butyl 2-(3-acetyl-5-((diethoxyphosphoryl)methoxy)-lH-indol-1-yl)acetate (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide hydrochloride (1.2 equiv), HATU (1.5 equiv) and DIEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion
of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl (((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate.  

H NMR (400 MHz, DMSO-<i>d</i>6) δ 8.20 (s, 1H), 8.11 - 8.08 (m, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.26 - 7.15 (m, 5H), 6.97 - 6.94 (m, 1H), 5.51 - 5.38 (m, 1H), 5.32 - 5.28 (m, 1H), 5.15 - 5.10 (m, 1H), 4.42 - 4.31 (m, 3H), 4.15 - 4.08 (m, 7H), 3.98 - 3.78 (m, 1H), 3.17 - 3.15 (m, 1H), 2.66 - 2.61 (m, 2H), 2.41 (s, 3H), 2.15 - 2.01 (m, 1H), 1.27 - 1.23 (m, 6H).

**Step-2:** (((3-Acetyl-1-((2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid (147)

[0636] To a solution of diethyl (((3-acetyl-1-((2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (1 equiv) in DCM (35 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the resulting solid was filtered and dried. The residue was purified by preparative HPLC to give (((3-acetyl-1-((2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid. 

H NMR (400 MHz, DMSO-<i>d</i>6) δ 8.19 (s, 1H), 8.10 - 8.08 (m, 1H), 7.72 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.26 - 7.15 (m, 5H), 6.94 - 6.92 (m, 1H), 5.56 - 5.18 (m, 2H), 5.15 - 5.13 (m, 1H), 4.38 - 4.36 (m, 1H), 4.06 - 4.04 (m, 3H), 3.89 - 3.75 (m, 1H), 3.41 - 3.38 (m, 2H), 3.20 - 3.17 (m, 2H), 2.66 - 2.63 (m, 2H), 2.40 (s, 3H), 2.39 - 2.36 (m, 1H), 1.98 - 1.88 (m, 1H).
(((3-Acetyl-1-(2-((2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid (149)

Scheme 33

Step 1: diethyl (((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (148)

[0637] To a solution of (3-acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide hydrochloride (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl (((3-acetyl-H2(2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate.

1H NMR (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 8.03 (t, J = 5.6 Hz, 1H), 7.76 (d, J = 3.6 Hz, 1H), 7.40 (d, J = 9.2 Hz, 1H), 7.21 - 7.07 (m, 5H), 6.93 - 6.90 (m, 1H), 5.55 - 5.42 (m, 1H), 5.35 - 5.30 (m, 1H), 5.16 - 5.12 (m, 1H), 4.42 - 4.33 (m, 3H), 4.16 - 4.06 (m, 1H), 3.94 - 3.81 (m, 1H), 3.07 - 2.98 (m, 2H), 2.61 - 2.58 (m, 1H), 2.41 (s, 3H), 2.12 - 2.02 (m, 1H), 1.64 - 1.60 (m, 2H), 1.28 - 1.24 (m, 6H).
Step 2: (((3-Acetyl-l-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (149)

[0638] To a solution of diethyl (((3-acetyl-l-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (1 equiv) in DCM (3 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the resulting solid was filtered and dried. The residue was purified by preparative HPLC to give (((3-acetyM-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.18 (s, 1H), 8.02 (t, J = 6 Hz, 1H), 7.72 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.22 - 7.07 (m, 5H), 6.91 - 6.88 (m, 1H), 5.56 - 5.41 (m, 1H), 5.33 - 5.29 (m, 1H), 5.14 - 5.10 (m, 1H), 4.34 (t, J = 8.4 Hz, 1H), 4.11 - 4.04 (m, 3H), 3.92 - 3.85 (m J 8.5), 3.25 - 3.17 (m, 2H), 3.09 - 2.97 (m, 2H), 2.59 - 2.56 (m, 1H), 2.39 (s, 3H), 2.11 - 1.98 (m, 1H), 1.63 - 1.60 (m, 2H).

(((3-Acetyl-l-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (151)

Scheme 34

Step 1: Diethyl (((3-acetyl-l-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (150)

[0639] To a solution of (3-acetyl-5-((diethoxyphosphoryl)methoxy)-lH-indol-l-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (2S,4R)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide (1.2 equiv), HATU (1.5 equiv) and DiPEA (3 equiv).
The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl ((3-acetyl-l-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate. ¹H NMR (400 MHz, DMSO-δ6) δ 8.19 (s, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.76 (s, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.22 - 7.05 (m, 5H), 6.95 - 6.93 (m, 1H), 5.14 - 5.10 (m, 1H), 4.47 - 4.30 (m, 2H), 4.15 - 4.07 (m, 1H), 3.96 - 3.78 (m, 1H), 3.08 - 2.96 (m, 2H), 2.40 (s, 3H), 2.39 - 2.38 (m, 1H), 2.05 - 1.98 (m, 1H), 1.51 - 1.47 (m, 3H), 1.38 - 1.33 (m, 1H), 1.26 - 1.23 (m, 6H).

Step-2: ((3-Acetyl-l-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid (151)

[0640] To a solution of diethyl ((3-acetyl-l-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (1 equiv) in DCM (35 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the resulting solid was filtered and dried. The residue was purified by preparative HPLC to give ((3-acetyl-l-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonic acid. ¾ NMR (400 MHz, DMSO-δ6) δ 11.31 (s, 1H), 8.18 (s, 1H), 7.97 - 7.96 (m, 1H), 7.73 - 7.72 (m, 1H), 7.33 - 7.32 (m, 1H), 7.20 - 7.11 (m, 4H), 6.93 - 6.92 (m, 1H), 5.52 - 5.39 (m, 1H), 5.31 - 5.27 (m, 1H), 5.13 - 5.09 (m, 1H), 4.33 - 4.32 (m, 1H), 4.05 - 3.96 (m, 1H), 3.02 - 3.01 (m, 2H), 2.40 (s, 3H), 2.39 - 2.38 (m, 1H), 2.05 - 1.98 (m, 1H), 1.36 - 1.34 (m, 2H), 1.23 - 1.22 (m, 2H).
**H-(2-((2R,4R)-4-FluoropyrroHdin-2-yI)ethyl)benzenesuifonamide** hydrochloride

**Scheme 34** (157)

Step 1: *tert*-Butyl (2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (48)

[0641] To a solution of (2S,4R)-1-((tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in THF (10 vol) at 0 °C was added borane tetrahydrofuran complex (2.1 equiv). The reaction mixture was stirred at room temperature for 2 h and then cooled at 0 °C. The resulting mixture was quenched with saturated K₂CO₃ solution and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to afford the title compound.

Step 2 and Step 3: *tert*-butyl (2R,4R)-2-(cyanomethyl)-4-fluoropyrrolidine-1-carboxylate (154)

[0642] To a solution of *tert*-butyl (2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1 equiv) in DCM (20 vol) at 0 °C was added methane sulfonyl chloride (1.5 equiv) and triethylamine (3 equiv). The reaction mixture was stirred at 0 °C for 1 h. The resulting mixture was diluted with ethyl acetate, washed with 1N HCl and saturated NaHCO₃ solution. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and then concentrated. Crude *tert*-butyl (2S,4R)-4-fluoro-2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate was dissolved in DMSO (10 vol) and sodium cyanide (3 equiv) was added. The reaction mixture was stirred at 50 °C for 15 h. The resulting mixture was cooled to room temperature and quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to give *tert*-butyl (2R,4R)-2-(cyanomethyl)-4-fluoropyrrolidine-1-carboxylate.
Step 4: **tert-Butyl (2R,4R)-2-(2-aminoethyl)-4-fluoropyrrolidine-1-carboxylate** (155)

[0643] To a solution of tert-butyl (2R,4R)-2-(cyanomethyl)-4-fluoropyrrolidine-1-carboxylate (1 equiv) in methanol (5 Vol) was added Raney Ni (1.2 equiv) and triethylamine (2 equiv). The reaction mixture was stirred at room temperature at 3.5 milli bar pressure under hydrogen atmosphere for 16 h. The resulting mixture was filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give tert-butyl (2R,4R)-2-(2-aminoethyl)-4-fluoropyrrolidine-1-carboxylate.

Step 5: **tert-Butyl (2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidine-1-carboxylate** (156)

[0644] To a solution of tert-butyl (2R,4R)-2-(2-aminoethyl)-4-fluoropyrrolidine-1-carboxylate (1 equiv) in THF (10 Vol) at 0 °C under nitrogen atmosphere was added benzene sulfonyl chloride (1.5 equiv) and triethylamine (3 equiv). The reaction mixture was stirred at room temperature for 16 h and then concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc to give tert-butyl (2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidine-1-carboxylate.

Step 6: **N-(2-((2R,4R)-4-fluoropyrrolidin-2-yl)ethyl)benzenesulfonamide hydrochloride** (157)

[0645] To a solution of tert-butyl (2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidine-1-carboxylate (1 equiv) in 1,4-dioxane (2 Vol) at 0 °C was added 4 N HCl in dioxane (10 Vol). The reaction mixture was stirred at room temperature for 4 h and then concentrated. The residue was taken in MTBE and stirred for 30 min. The resultant solid was filtered and dried to give N-(2-((2R,4R)-4-fluoropyrrolidin-2-yl)ethyl)benzenesulfonamide hydrochloride.
((3-Acetyl-1-(2-(((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrroldin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid (159)

Scheme 36

Step-1: Diethyl ((3-acetyl-1-(2-(((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrroldin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (159)

[0646] To a solution of (3-acetyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (1 equiv) in DMT (10 vol) at 0 °C under nitrogen atmosphere was added N-(2-((2R,4R)-4-fluoropyrroldin-2-yl)ethyl)benzenesulfonamide hydrochloride (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl ((3-acetyl-1-(2-(((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrroldin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate.

³¹ NMR (400 MHz, DMSO-δ6) δ 8.22 (s, 1H), 7.76 - 7.75 (m, 3H), 7.64 - 7.54 (m, 4H), 7.34 (d, J = 9.2 Hz, 1H), 6.95 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 5.43 - 5.30 (m, 1H), 5.26 - 5.21 (m, 1H), 5.11 - 5.07 (m, 1H), 4.42 (d, J = 9.6 Hz, 2H), 4.17 - 4.06 (m, 4H), 4.04 - 4.01 (m, 2H), 3.78 - 3.61 (m, 1H), 2.74 - 2.69 (m, 2H), 2.42 (s, 3H), 2.05 - 2.03 (m, 1H), 1.98 - 1.95 (m, 1H), 1.51 - 1.49 (m, 2H), 1.29 - 1.25 (m, 6H).
Step 2: (((3-Acetyl-1-(2-((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid) add (159)

[0647] To a solution of diethyl (((3-acetyl-1-(2-((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (1 equiv) in DCM (35 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the resulting solid was filtered and dried. The residue was purified by preparative HPLC to give (((3-acetyl-1-(2-((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid. ¾NMR (400 MHz, DMSO-d6) δ 8.17 (s, 1H), 7.70 - 7.54 (m, 7H), 7.26 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.41 - 5.28 (m, 1H), 5.22 - 5.18 (m, 1H), 5.09 - 5.05 (m, 1H), 4.05 - 3.97 (m, 2H), 3.85 - 3.78 (m, 3H), 2.73 - 2.70 (m, 2H), 2.40 (s, 3H), 2.05 - 2.04 (m, 1H), 1.98 - 1.95 (m, 1H), 1.48 - 1.47 (m, 2H).

(S)-N-(6-Methylpyridin-2-yl)azetidine-2-carboxamide hydrochloride (162)

Scheme 37

[0648] To a solution of (S)-1-(fer t-butoxycarbonyl)azetidine-2-carboxylic acid (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-methylpyridin-2-amine (1 equiv), DİPEA (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 (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using Hexane/ EtOAc to give compound iert-buty (S)-2-((6-methylpyridin-2-yl)carbaroaoyl)azeiidine-l-carboxylate. To a solution of compound ferf-butyl (S)-2-((6-methylpyridin-2-yl)carbamoyl)azetidine-l-carboxylate (1 equiv) in 1,4-di0xane (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 give (S)-N-(6-methylpyridin-2-yl)azetidine-2-carboxamidine hydrochloride (162).

Diethyl (S)-((3-acetyl-l-(2-(2-((6-methylpyridin-2-yl)carbamoyl)azetidin-l-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (163)

Scheme 38

[0649] To a solution of (3-acetyl-5-((diethoxyphosphoryl)methoxy)-lH-indol-1-yl)acetic acid (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added (S)-N-(6-methylpyridin-2-yl)azetidine-2-carboxamide (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give diethyl (S)-((3-acetyl-1-(2-(2-((6-methylpyridin-2-yl)carbamoyl)azetidin-1-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (163). ¾ NMR (400 MHz, DMSO-d₆) δ 10.47 (s, 1H), 8.25 - 8.21 (m, 1H), 7.91 - 7.89 (m, 1H), 7.75 - 7.67 (m, 2H), 7.45 - 7.38 (m, 1H), 7.03 - 6.97 (m, 2H), 5.21 - 4.96 (m, 3H), 4.43 - 4.40 (m, 2H), 4.29 - 4.10 (m, 5H), 3.87 - 3.86 (m, 1H), 2.50 (s, 3H), 2.42 (s, 3H), 2.30 - 2.36 (m, 2H), 1.28 - 1.25 (m, 6H).
2-(5-(N-fert-Butylsulfamoylmethoxy)-3-carbamoyl-lH-indol-l-yl)acetic acid (213)

Scheme 39

Step 1: tert-Butyl 5-(benzyloxy)-lH-indole-l-carboxylate (205)

[0650] To a solution of compound 67 (2 g, 8.98 mmol) in DCM (20 mL) at 0 °C was added EtsN (3.7 mL, 26.91 mmol) and DMAP (328 mg, 2.68 mmol), followed by addition of Boc:O (2.9 g, 13.45 mmol) in portions. After addition, the reaction was stirred at room temperature for 16 hrs. The mixture was diluted with DCM and washed with water and brine, dried over anhydrous Na₂SO₄, filtered and then concentrated to dryness. The residue was purified by column chromatography on silica gel (eluted with petroleum ether; ethyl acetate = 50:1) to give the title compound (2.5 g, 86.08% yield) as white solid. LC/MS (ESI) m/z: 268 (\textsuperscript{1}H-56+\textsuperscript{1}H)\textsuperscript{+}

Step 2: tert-Butyl 5-(benzyloxy)-3-carbamoyl-lH-indole-l-carboxylate (206)

[0651] To a solution of compound 205 (2 g, 6.19 mmol) in MeCN (40 mL) at 0 °C was drop-wise added chlorosultonyl isocyanate (0.57 mL, 6.50 mol). The reaction was stirred at room temperature overnight and then acetone (40 mL) and H₂O (5 mL) was added followed by drop-wise addition of 10% aq.KOH solution (2 mL). The mixture was stirred at room temperature for 30 min and extracted with ethyl acetate (50 mL x 2). The combined organic phases was washed with brine, dried over anhydrous NaSO₄, filtered and concentrated to dryness. The residue was
further washed with EtOAc to give the title compound (1.7 g, 75% yield) as white solid. LC/MS (ESI) m/z 311 (M-56+H)⁺

Step 3: 5-(Benzyloxy)-1H-indole-3-carboxamide (207)

[0652] To a solution of compound 206 (1.7 g, 4.64 mmol) in DCM (15 mL) was added TFA (5 mL). The reaction was stirred at 35 °C for 1 hr and then concentrated to dryness. The residue was co-evaporated with toluene twice to give the title compound (1.6 g, 100% yield) as yellow solid, which was directly used to the next reaction without further purification. LC/MS (ESI) m/z: 267 (M+H)⁺.

Step 4: tert-Butyl 2-(5-(benzyloxy)-3-carbamoyl-1H-indol-1-yl)acetate (208)

[0653] To a mixture of compound 207 (1.4 g, 5.26 mmol) and K₂CO₃ (2.18 g, 15.79 mmol) in DMF (30 mL) was added tert-butyl 2-bromoacetate (1.2 mL, 7.89 mmol). The reaction mixture was stirred at room temperature for 16 hrs. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was washed with hexanes and dried under high vacuum to give the title compound (1.3 g, 65% yield) as white solid. LC/MS (ESI) m/z: 381 (M+H)⁺.

Step 5: tert-Butyl 2-(3-carbamoyl-5-hydroxy-1H-indol-1-yl)acetate (209)

[0654] To a solution of compound 208 (1.3 g, 3.5 mmol) in THF (10 mL) was added 10% Pd/C (200 mg). The reaction was degassed under N2 atmosphere twice and stirred under a H₂ balloon for 16 hrs. The mixture was filtered and the filtrate was concentrated to dryness to give compound 209 (840 mg, 82.67 % yield) as white solid. LC/MS (ESI) m/z: 291 (M+H)⁺.

Step 6: N-ter^Butyl-l-chioromethanesulfonamide (211)

[0655] To a solution of 2-methylpropan-2-amine (0.9 mL, 8.5 mmol) in ether (20 mL) at 0 °C under nitrogen protection, was added NMM (1 mL, 8.9 mmol) and compound 210 (1.2 g, 8.05 mmol) portionwise. After addition, the mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc and washed with 1M aq. HCl and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give compound 210 (1.3 g, 87% yield) as white solid.
Step 7: \textit{tot-Butyl 2-(5-(N-ieri-butylsulfamoylmethoxy)-3-carbamaoyl-1H-indol-1-yl)acetate} (212)

[0656] To a solution of compound 211 (687 mg, 2.37 mmol) in CH3CN (20 mL) was added compound 209 (880 mg, 4.74 mmol), CS2CO3 (2.32 g, 7.11 mmol) and TBAI (438 mg, 1.18 mmol). The reaction mixture was stirred at reflux overnight. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na2SO4, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (eluted with DCM/MeOH =50:1 to 4:1) to give the title compound (230 mg, 22\% yield) as white solid. LC/MS (ESI) m/z: 440 (M+H)+.

Step 8: \textit{2-(5-(N-teri-Butylsulfamoylmethoxy)-3-carbamoyl-1H-indol-1-yl)acetic acid} (213)

[0657] To a solution of compound 212 (400 mg, 0.91 mmol) in THF/MeOH (5 mL/3 mL) was added 1 M aq.LiOH solution (3 mL). The reaction mixture was stirred at room temperature overnight. The mixture was concentrate and diluted with water and washed with diethyl ether twice. The aqueous layer was acidified by adding IN aq. HCl and extracted with DCM twice. The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated to give 213 (310 mg, 88.8\% yield) as white solid. LC/MS (ESI) m/z: 384 (M+H)+.
(R,E)-Ethyl 2-((l-phenylethyl)imino)acetate (215)

[0658] To a solution of compound 214 (15 g, 0.12 mol) in diethyl ether (200 mL) was added Na₂SO₄ (42.6 g, 0.3 mol) and ethyl glyoxalate (18.36 g, 0.12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hrs. The reaction filtered and the filtrated was concentrated under reduced pressure to give 215 (23 g, 90.6 % yield) as a colorless oil.

Step 2: (1S,3S,4R)-Ethyl 2-((R)-l-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (216)

[0659] To a solution of compound 215 (23 g, 0.11 mol) in DMF (200 mL) was added 1,3-Cycloperstadiene (18.48 g, 0.24 mmol) and trifluoroacetic acid (16 g, 0.14 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 hrs. The mixture was diluted with EtOAc and washed with 10% aq. LiCl solution and brine successively, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether; ethyl acetate =60: 1) to give the title compound (17 g, 57% yield) as a colorless oil. LC/MS (ESI) m/z: 272 [M+H]⁺.
Step 3: (1R,3S,4S)-Ethyl 2-((R)-1-phenylethyl)-2-azabicyclo[2.2.1]heptane-3-carboxylate (217)

[0660] To a solution of compound 216 (6 g, 22.1 mmol) in EtOAc (60 mL) was added Pd/C (5% wt, 0.3 g) and the mixture was degassed under N2 atmosphere for three times and stirred under Lb balloon at room temperature for 1 hr. After filtration through Celite, the filter cake was washed with EtOH. To the filtrate, conc. HCl solution (7 mL) was added and then the resulting mixture was concentrated to dryness under reduced pressure. This procedure was repeated several times until a semi-crystalline residue was formed. The residue was precipitated in Et2O/i-PrOH (50 mL, 5: 1) at 0 °C for 1 hr and filtered. The filter cake was dried under vacuum to give the title compound (5 g, 82.8% yield) as white solid, LC/MS (ESI) m/z: 274 [M+H]+.

Step 4: (1R,3S,4S)-Ethyl 2-azabicyclo[2.2.1]heptane-3-carboxylate (218)

[0661] To a solution of compound 217 (5 g, 18.3 mmol) in ethanol (10 mL) was degassed under N2 atmosphere for three times and Pd(OH)2 (500 mg, 10% wt) was added. The mixture was degassed again and stirred under H2 balloon at room temperature for 16 hrs. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (3.3 g, 98.5% yield) as a colorless oil. LC/MS (ESI) m/z: 170 [M+H]+.

Step 5: (1R,3S,4S)-2-tert-Butyl 3-ethyl 2-azabicyclo[2.2.1]heptane-2,3-dicarboxylate (219)

[0662] To a solution of compound 218 (3.3 g, 18 mmol) was in DCM (30 mL) was added triethylamine (7.5 mL, 54 mmol) and di-tert-butyl dicarbonate (7.85 g, 36 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 hrs and then diluted with DCM. The resulting mixture was washed with water and brine, dried over anhydrous Na2SO4, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate =20: 1) to give the title compound (3.6 g, 71% yield) as a colorless oil. LC/MS (ESI) m/z: 214 [M+H-56]+.

Step 6: (1R,3S,4S)-2-(tert-Butoxycarbonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic acid (220)

[0663] To a solution of compound 219 (3.6 g, 0.18 mmol) in THF (20 mL) and was added aq. NaOH solution (2 M, 27 mL, 0.54 mmol) at room temperature. The reaction mixture was stirred
at room temperature for 16 hrs and washed with ethyl acetate (20 mL x 2). The aqueous phase was acidified to pH=3 with aq. HCl (1 M) and extracted with DCM twice. The combined organic phases was dried over anhydrous Na₂SO₄, filtered and then concentrated to give the title compound (3.2 g, 99.2% yield) as white solid. LC/MS (ESI) m/z: 186 [M+H-56]+.

**Step7:**[(R,3S,4S)-tert-butyI3-((6-methyIpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (221)]

[0664] To a solution of compound 220 (2 g, 8.3 mmol) was in 1,2-Dichloroethane (20 ml) was added N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (4.1 g, 16.6 mmol) and 2-Amino-6-methylpyridine (0.9 g, 8.3 mmol) at 0 °C. The reaction mixture was stirred at 85 °C for 16 hrs and concentrated to dryness to give crude product, which was purified by column chromatography on silica gel (eluted with petroleum ether; ethyl acetate =10: 1) to give the title compound (2.1 g, 79% yield) as a white solid. LC/MS (ESI) m/z: 276 [M+H-56f.

**Step8:**[(R,3S,4S)-N-(6-Methylpyridin-2-yl)-2-azabicyclo[2.2.1]heptane-3-carboxainide (222)]

[0665] To a solution compound 221 (2.1 g, 6.5 mmol) in dioxane (15 mL) was added HCl dioxane solutions (15 mL) at 0°C. The reaction was stirred at room temperature for 3hrs and concentrated to dryness to give compound 222 (2.3 g, 99.7% yield) as yellow solid, which was directly used to the next reaction without purification. LC/MS (ESI) m/z; 232 (\(\mathrm{M}+\mathrm{H}\))\(^+\).
1-(2-((1R,3S,4S)-3-((6-Methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-5-(sulfamoylmethoxy)-1H-indole-3-carboxamide (187)

Scheme 41.

[0666] To a stirred solution of compound 213 in DMF (2 ml) was added Et3N (0.07 ml, 0.5 mmol), EDCI (67 mg, 0.35 mmol), HOBt (47 mg, 0.35 mmol) and compound 222. The reaction was stirred at room temperature overnight and then diluted with water (10 mL). The resulting mixture was extracted with DCM (5 mL x 3). The combined organic phases was washed with water and brine, dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM: MeOH = 30: 1 - 20: 1) to give compound 186. \( ^{1}H \) NMR (400 MHz, CD3OD) \( \delta \) 7.90 (s, 1H), 7.81 (dd, \( J = 10.6, 2.3 \text{ Hz, } 2\text{H} \)), 7.67 (t, \( J = 7.9 \text{ Hz, } 1\text{H} \)), 7.39 (d, \( J = 8.9 \text{ Hz, } 1\text{H} \)), 7.10 - 6.96 (m, 2H), 5.30 (d, 1H), 5.14 (d, 1H), 5.05 (d, \( J = 5.0 \text{ Hz, } 2\text{H} \)), 4.61 (s, 1H), 4.15 (s, \( 1\text{H} \)), 2.83 (s, 1H), 2.46 (d, \( J = 10.7 \text{ Hz, } 3\text{H} \)), 2.18 (d, \( J = 10.1 \text{ Hz, } 1\text{H} \)), 1.89 (t, \( J = 10.1 \text{ Hz, } 2\text{H} \)), 1.81 - 1.51 (m, 3H). LC/MS (ESI) m/z: 541 (M+H)⁻.
Scheme 42.

Step 1: (3R, 3aR, 6R, 6aR)-6-(Benzyloxy) hexahydrofuro[3, 2-b]furan-3, 6-diol (225)

To a solution of (3R, 3aR, 6R, 6aR)-hexahydrofuro[3, 2-b]furan-3, 6-diol (5.0 g, 34.25 mmol) in anhydrous DMSO (17 mL) was added LiH (272 mg, 34.25 mmol) at room temperature under N2 atmosphere, then the reaction was stirred for 30 minutes. LiCl (1.45 g, 34.25 mmol) was added into the mixture, and the mixture was stirred at 90 °C for 30 minutes. BnCl (4.34 g, 34.25 mmol) was added and the reaction mixture was stirred at 90 °C overnight. The reaction was quenched with 2M aq.HCl and the mixture was extracted with EtOAc, washed by brine, dried over anhydrous Na2SO4 and concentrated. The obtained crude product was purified by coluran chromatography on silica gel eluted with PE/EtOAc (50:1 to 5:1) to give the title compound (5.65 g, 70 % yield) as yellow solid; LC/MS (ESI) m/z: 237 (M+H)+.
Step 2: (3R, 3aR, 6R, 6aR)-3-(Benzyloxy)-6-(3-methyl-4-nitrophenoxy) hexahydrofuro [3, 2-b] furan (226)

[0668] To a solution of (3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-ol (5.6 g, 23.73 mmol) in anhydrous DMF (12 mL) was added NaH (1.42 g, 35.59 mmol, 60% dispersion in mineral oil) at 0 °C under N₂ atmosphere and the mixture was stirred for 30 minutes at room temperature. 4-fluoro-2-methyl-1-nitrobenzene (3.68 g, 23.73 mmol) was added into the mixture, and the reaction was stirred at room temperature for 3 hrs. The mixture was quenched with 2M aq. HCl and extracted with EtOAc, washed by brine, dried over anhydrous Na₂SO₄ and concentrated. The obtained crude product was purified by column chromatography on silica gel eluted with PE/ EtOAc (30:1 to 5:1) to give the title compound (3 g, 34.1% yield) as a white solid. LC/MS (ESI) m/z: 372 (M+H)+.

Step 3: 4-((3R,3aR,6R,6aR)-6-(Benzyloxy)hexahydrofuro[3,2-b]furan-3-yloxy)-2-methylaniline (227)

[0669] To a solution of (3R, 3aR, 6R, 6aR)-3-(benzyloxy)-6-(3-methyl-4-nitrophenoxy) hexahydrofuro [3, 2-b] furan (3.0 g, 8.09 mmol) in anhydrous THF (30 mL) was added Pd/C (300 mg, 10%), then the reaction was stirred for 2 h under a H₂ balloon at room temperature. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (2.68 g, 97.2% yield) as a light yellow solid. LC/MS (ESI) m/z: 342 (M+H)+.

Step 4: N-(4-((3R, 3aR, 6R, 6aR)-6-(Benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-2-methylanilinyl) acetamide (228)

[0670] To a solution of 4-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-2-methylaniline (2.68 g, 7.86 mmol) in toluene (30 mL) was added Ac₂O (882 mg, 8.65 mmol) and then the reaction was stirred for 1 hr at room temperature. The mixture was concentrated and washed by PE/ EtOAc (50:1) to give the title compound (2.83 g, 94.3% yield) as a white solid. LC/MS (ESI) m/z: 384 (M+H)+.
Step 5: 5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-1H-indazole (229)

[0671] To a solution of N-(4-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-2-raethySphenyl) acetamide (2.83 g, 7.39 mmol) in toluene (30 mL) was added Ac2O (3.77 g, 36.95 mmol) and AcOK (1.45 g, 14.78 mmol) at room temperature under N2 atmosphere and the reaction was heated to 80 °C. Isopentyl nitrite (2.59 g, 22.17 mmol) was added into the mixture, and the mixture was stirred at 80 °C overnight. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in NH3/MeOH solution (15 nil., 1M) and the mixture was stirred at room temperature for 3 hrs. LC-MS showed that the reaction was completed. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with PE/EtOAc (30: 1 to 1: 1) to give the title compound (2.0 g, 68.5 % yield) as light yellow solid. LC/MS (ESI) m/z: 353 (M+H)+.

Step 6: 5-((3R, 3aR, 6R, 6aR)-6-(Benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-3-iodo-1H-indazole (230)

[0672] To a solution of 5-((3R, 3all, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxyj-1H- indazole (1.0 g, 2.84 mmol) in DMF (8 mL) was added KOH (0.40 g, 7.10 mmol) followed by in portions addition of 12(1.08 g, 4.26 mmol) at 0 °C. The reaction was stirred at room temperature overnight. The mixture was quenched by Na2SeO3 and diluted with H2O, extracted with EtOAc, washed by brine, dried over anhydrous Na2SO4 and concentrated. The obtained crude product was purified by column chromatography on silica gel eluted with PE/ EtOAc (30: 1 to 2: 1) to give the title compound (1.0 g, 73.6 % yield) as yellow solid. LC/MS (ESI) m/z: 479 (M+H)+.

Step 7: tert - Butyl 2-(5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-3-iodo-1H- indazol-1-yl) acetate (231)

[0673] To a solution of 5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy>3- iodo-1H-indazole (1.0 g, 2.09 mmol) in MeCN (10 mL) was added K2CO3 (0.72 g, 5.23 mmol) and tert-buWyl 2-bromoacetate (0.446 g, 2.30 mmol) and the reaction was stirred at 0 °C for 3 hrs. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na2SO4 and concentrated to give the title compound (1.2 g, 96.9 % yield) as yellow solid. LC/MS (ESI) m/z: 593 (M+H)+.
Step 8: tert-Butyl 2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-IH - indazol-1-yl) acetate (232)

[0674] To a solution of tert-butyl 2-(5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-3-iodo-IH-indazol-1-yl) acetate (0.66 g, 1.11 mmol) in dry toluene (8 mL) was added tributyl (1-ethoxy vinyl) stannane (0.60 g, 1.67 mmol) and Pd(PPh$_3$)$_4$ (0.13 g, 0.11 mmol), then the reaction was stirred at 100 °C under N$_2$ atmosphere overnight. The mixture was diluted with EtOAc and washed with 10%aq. KF solution, INaq. HCl and brine successively, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography on silica gel eluted with PE/EtOAc (30:1 to 3:1) to give the title compound (0.45 g, 79.5 % yield) as yellow solid. LC/MS (ESI) m/z: 509 (M-H)$^-$. 

Step 9: tert-Butyl 2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-hydroxyhexahydrofuro [3, 2-b] furan-3-yloxy)-IH - indazol-1-yl) acetate (233)

[0675] To a solution of tert-butyl 2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-(benzyloxy) hexahydrofuro [3, 2-b] furan-3-yloxy)-IH-indazol-1-yl) acetate (0.35 g, 0.69 mmol) in MeOH (12 mL) was added 10% Pd/C (0.20 g) and the reaction was stirred under a H$_2$ balloon at room temperature overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluted with PE/EtOAc (30:1 to 1:1) to give the title compound (0.14 g, 48.6 % yield) as yellow solid. LC/MS (ESI) m/z: 419 (M+H)$^+$. 

Step 10: 2-(3-Acetyl-5-((3R, 3aR, 6R, 6aR)-6-hydroxyhexahydrofuro [3, 2-b] furan-3-yloxy)-IH-indazol-1-yl) acetic acid (234)

[0676] To a solution of tert-butyl 2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-hydroxyhexahydrofuro [3, 2-b] furan-3-yloxy)-IH-indazol-1-yl) acetate (0.13 g, 0.31 mmol) in DCM (3 mL) was added TFA (3 mL), then the reaction was stirred at room temperature for 2 hrs. The mixture was concentrated and the residue was washed with Et$_2$O to give the title compound (90 mg, 80.3 % yield) as yellow solid. LC/MS (ESI) m/z: 419 (M+H)$^+$. 

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Step 11: (2S,4R)-l - (2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indazol-1-yl)acetyl )-N-(6-bromopyridin -2-yl)-4-fluoropyrrolidine -2-carboxamide (203)

[0677] To a solution of 2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-lH-indazol-1-yl)acetic acid (80 mg, 0.22 n\text{mmol}) in DMF (2 mL) was added DIPEA (143 mg, 1.10 mmol), HATU (168 mg, 0.44 mmol) and (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide trifluoroacetate (64 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 1.5 hrs and then diluted with H2O. The mixture was extracted with EtOAc (1.5 mL x 3). The combined organic layers was washed by brine, dried over anhydrous Na2SO4 and concentrated. The residue was purified by prep-HPLC to give the title compound (30 mg, 21.6 \% yield) as white solid. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.00 (s, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.61 (dd, $J = 12.4$, 2.4 Hz, 2H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.17 (dd, $J = 8.8$, 2.0 Hz, 1H), 5.74 (d, $J = 17.2$ Hz, 1H), 5.65 - 5.44 (m, 2H), 4.94 (dd, $J = 11.6$, 6.0 Hz, 1H), 4.76 (t, $J = 4.8$ Hz, 1H), 4.65 (t, $J = 8.4$ Hz, 1H), 4.39 (t, $J = 4.8$ Hz, 1H), 4.20 (dd, $J = 22.0$, 12.4 Hz, 1H), 4.14 - 4.05 (m, 2H), 4.06-3.92 (m, 1H), 3.82 (dd, $J = 8.8$, 6.4 Hz, 1H), 3.73 (dd, $J = 8.0$, 6.8 Hz, 2H), 3.40 (t, $J = 8.4$ Hz, 1H), 2.59 (s, 3H), 2.55 (s, 1H), 2.24 - 2.05 (m, 1H); LC/MS (ESI) m/z: 632 (M+H)⁺.
2-(3-Carbamoyl-5-((diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (244)

Scheme 43,

Step 1: tert-Butyl 5-(benzoyloxyl)-1H-indole-1-carboxylate (236)

[0678] To a solution of compound 235 (2 g, 8.98 mmol) in DCM (20 mL) at 0 °C was added Et3N (3.7 mL, 26.91 mmol) and DMAP (328 mg, 2.68 mmol), followed by addition of B0C2O (2.9 g, 13.45 mmol) in portions. After addition, the reaction was stirred at room temperature for 16 hrs. The mixture was diluted with DCM and washed with water and brine, dried over anhydrous Na2SO4, filtered and then concentrated to dryness. The residue was purified by column chromatography on silica gel (eluted with petroleum ether: ethyl acetate = 50: 1) to give the title compound (2.5 g, 86.08% yield) as white solid. LC/MS (ESI) m/z: 268 (M-56+H) +
Step 2: tert-Butyl 5-(benzyloxy)-3-carbamoyl-1H-indole-1-carboxylate (237)

[0679] To a solution of compound 236 (2 g, 6.19 mmol) in MeCN (40 mL) at 0 °C was dropwise added chlorosulfonyl isocyanate (0.57 mL, 6.50 mol). The reaction was stirred at room temperature overnight and then acetone (40 mL) and H2O (5 mL) was added followed by dropwise addition of 10% aq.KOH solution (2 mL). The mixture was stirred at room temperature for 30 min and extracted with ethyl acetate (50 mL x 2). The combined organic phases was washed with brine, dried over anhydrous Na2S04, filtered and concentrated to dryness. The residue was further washed with EtOAc to give the title compound (1.7 g, 75% yield) as white solid. LC/MS (ESI) m/z: 311 (M-56+H)+

Step 3: 5-(Benzyloxy)-1H-indole-3-carboxamide (238)

[0680] To a solution of compound 237 (1.7 g, 4.64 mmol) in DCM (15 mL) was added TEA (5 mL). The reaction was stirred at 35 °C for 1 hr and then concentrated to dryness. The residue was co-evaporated with toluene twice to give the title compound (1.6 g, 100% yield) as yellow solid, which was directly used to the next reaction without further purification. LC/MS (ESI) m/z: 267 (M+H)7

Step 4: tert-Butyl 2-(5-(benzyloxy)-3-carbamoyl-1H-indol-1-yl)acetate (239)

[0681] To a mixture of compound 238 (1.4 g, 5.26 mmol) and K2CO3 (2.18 g, 15.79 mmol) in DMF (30 mL) was added isopropyl 2-bromoacetate (1.2 mL, 7.89 mmol). The reaction was stirred at room temperature for 16 hrs. The mixture was diluted with EtOAc and washed with water and brine, dried over anhydrous Na2S04 and concentrated. The residue was washed with hexane and dried under high vacuum to give the title compound (1.3 g, 65% yield) as white solid. LC/MS (ESI) m/z: 381 (M+H)7

Step 5: tert-Butyl 2-(3-carbamoyl-5-hydroxy-1H-indol-1-yl)acetate (240)

[0682] To a solution of compound 239 (1.3 g, 3.5 mmol) in THF (10 mL) was added 10% Pd/C (200 mg). The reaction was degassed under N2 atmosphere twice and stirred under H2 balloon for 16 hrs. The mixture was filtered and the filtrate was concentrated to diyness to give the title compound (840 mg, 82.67 % yield) as white solid. LC/MS (ESI) m/z: 291 (M+H)+.
Step 6: Diethoxyphosphoryl)methyl 4-chlorobenzesufonate (242)

[0683] To a solution of compound 241 (5 g, 0.03 mol) and EtsN (4.5 ml, 0.033 mol) in anhydrous ether (60 mL) was added a solution of diethyl hydroxymethylphosphonate (6.9 g, 0.033 mol) in ether at -10 °C dropwise. The reaction was stirred at 0 °C for 2 hrs and at room temperature overnight. The mixture was diluted with EtOAc and washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel (eluted with DCM/MeOH = 1: 0 to 100: 1) to afford compound (5.9 g, 60% yield) as yellow solid.

Step 7: tert-Butyl 2-(3-carbamoyl-5-(diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetate (243)

[0684] To a mixture of tert-butyl 2-(3-carbamoyl-5-hydroxy-1H-indol-1-yl)acetate (500 mg, 1.72 mmol) and C₆H₄OH (1.7 g, 5.17 mmol) in DMF (20 mL) was added compound 242 (1.3 g, 1.89 mmol). The reaction was stirred at 50 °C overnight, and then quenched with water. The resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by flash column chromatography on silica gel (eluted with DCM/MeOH = 50/ 1) to afford the title compound (900 mg, 60% yield) as yellow solid. LC/MS (ESI) m/z: 441 (M+H)⁺.

Step 8: 2-(3-Carbamoyl-5-(diethoxyphosphoryl)methoxy)-1H-indol-1-yl)acetic acid (244)

[0685] To a solution of compound 243 (450 mg, 1.02 mmol) in DCM (5 mL) was added TFA (5 mL) dropwise and the mixture was stirred at 40 °C for 2 hrs. The reaction was concentrated to dryness and washed with diethyl ether to give 244 (490 mg, 100% yield) as yellow solid, which was directly used to the next reaction without further purification. LC/MS (ESI) m/z: 385 (M+H)⁺.
diethyl 

\[(((3-\text{Carbamoyl}-1-(2-((1R,3S,4S)-3-((6-methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-IH-indol-5-yl)oxy)methyl)phosphonate\] (182)

Scheme 44.

[0686] To a solution of 2-(3-carbainoyl-5-((diethoxyphosphoryl)methoxy)-IH-indol-1-yOacetic acid (100 mg, 0.26 mmol) in DMF (2 mL) was added DIPEA (0.11 mL, 0.65 mmol), HATU (124 mg, 0.33 mmol) at room temperature. After the reaction was stirred for 10 min, N-(6-methylpyridin-2-yl)-2-azabicyclo[2.2.1]heptane-3-carboxamide (78 mg, 0.22 mmol) was added. The reaction was stirred at room temperature overnight and was then diluted with water (10 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic phases were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (eluted with DCM : MeOH = 80 : 1 – 50 : 1) to give the title compound (75 mg, 40% yield) as white solid. ¹H NMR (400 MHz, CD3OD) δ 8.34 - 8.22 (m, 1H), 7.89 (s, 1H), 7.73 (d, \(J = 2.5\) Hz, 1H), 7.46 (dd, \(J = 8.1, 4.6\) Hz, 2H), 7.39 - 7.31 (m, 1H), 7.02 - 6.91 (m, 1H), 5.38 (d, 1H), 5.15 (d, 1H), 4.69 (s, 1H), 4.43 (d, \(J = 9.8\) Hz, 2H), 4.30 - 4.17 cm, 4H), 4.13 (s, 1H), 2.91 (d, \(J = 8.9\) Hz, 1H), 2.69 (s, 3H), 2.26 (d, \(J = 10.6\) Hz, 1H), 2.03 - 1.76 (m, 3H), 1.64 (t, \(J = 13.2\) Hz, 2H), 1.42 - 1.29 (m, 6H). LC/MS (ESI) m/z: 598 (M+mH)⁺.
Scheme 45.

[0687] To a solution of diethyl (((3-carbamoyl-l-(2-((1R,3S,4S)-3-((6-methylpyridin-2-yl)carbamoyi)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-lH-indol-5-yl)oxy)methyl)phosphonate (30 mg, 0.05 mmol) in DCM (2 mL) was added TMSBr (0.6 mL) at 0 °C. After the mixture stirred at room temperature for 3 hrs, the reaction was quenched by addition of MeOH. The resulting mixture was evaporated and the residue was purified by prep-HPLC to give the titled compound (2.6 mg, 10% yield) as white solid. ¾ NMR (400 MHz, CD3OD) δ 8.34 - 8.22 (m, 1H), 7.89 (s, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.46 (dd, J = 8.1, 4.6 Hz, 2H), 7.39 - 7.31 (m, 1H), 7.02 - 6.91 (m, 1H), 5.38 (d, 1H), 5.15 (d, 1H), 4.69 (s, 1H), 4.43 (d, J = 9.8 Hz, 2H), 4.13 (s, 1H), 2.91 (d, J = 8.9 Hz, 1H), 2.69 (s, 3H), 2.26 (d, J = 10.6 Hz, 1H), 2.03 - 1.76 (m, 3H), 1.64 (t, J = 13.2 Hz, 2H). LCMS (ESI) m/z: 542 (M+H)⁺.
Diethyl(((3-acetyl-1-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (10) & ((3-acetyl-1-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid (11)

Scheme 46.

Step-1: Diethyl(((3-acetyl-1-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate (10)

[0688] To a solution of 142 (1 equiv) in DMF (10 vol) at 0 °C under nitrogen atmosphere was added 52 (1.2 equiv), HATU (1.5 equiv) and DIPEA (3 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was quenched with water (30 vol). The resulting mixture was extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and then concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH to give compound 10.

1H NMR (400 MHz, DMSO-d₆) δ 8.62 - 8.59 (m, 1H), 8.19 (s, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.23 - 7.12 (m, 2H), 6.98 - 6.90 (m, 3H), 5.59 - 5.42 (m, 1H), 5.36 - 5.32 (m, 1H), 5.16 - 5.17 (m, 1H), 4.48 - 4.23 (m, 5H), 4.16 - 4.09 (m, 5H), 3.93 - 3.84 (m, 1H), 2.44 (s, 3H), 2.43 - 2.42 (m, 1H), 2.12 - 2.00 (m, 1H), 1.28 - 1.24 (m, 6H).

Step-2: ((3-Acetyl-1-((2S,4R)-2-((3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid (11)

[0689] To a solution of compound 10 (1 equiv) in DCM (35 vol) at 0 °C under nitrogen atmosphere was added TMSBr (10 equiv). The reaction mixture was stirred at room temperature for 2 days. After completion of the reaction, the reaction mixture was quenched with water and the
resulting solid was filtered and dried. The residue was purified by preparative HPLC to give compound 11. $\frac{3}{4}$ NMR (400 MHz, DMSO-$d_{6}$) $\delta$ 8.62 - 8.59 (m, 1H), 8.19 (s, 1H), 7.74 (s, 1H), 7.44 - 7.24 (m, 3H), 6.98 - 6.88 (m, 2H), 5.55 - 5.42 (m, 1H), 5.36 - 5.32 (m, 1H), 5.19 - 5.11 (m, 1H), 4.46 - 4.07 (m, 6H), 3.93 - 3.82 (m, 1H), 2.44 (s, 3H), 2.43 - 2.42 (m, 1H), 2.12 - 2.00 (m, 1H).

$(1R,3S,5R)$-N-$(6$-Bromopyridin-2-yl)$-2$-azabicyclo[3.1.0]hexane-3-carboxamide Hydrochloride (204)

Sets erae 47

Step 1: $(1R,3S,5R)$-$i$eri-Butyl 3-$(6$-Bromopyridin-2-yl)carbamoyl]-2-azabicyclo[3.1.0]hexane-2-carboxylate

[0690] To an ice cold solution of $(IR,3S,5R)$-fc $rt$-butoxycarbonyl]-2-azabicyclo[3.1.0]hexane-2-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-trimethyl-1-propenyl amine (1.1 equiv) dropwise with stirring. Stirring was continued for 3 h at this temperature, then 6-bromopyridin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCCl, water and brine, then dried over Na2SCl4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (hexanes/EtOAc) to give compound 203.

Step 2: $(1R,3A,55$)$-$fer$-Butyl $3-$(6$-Bromopyridin-2-yl$)carbamoyl]-2$-azabicyclo[3.1.0]hexane-2-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(2S,4R)-N-(6-Bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (206)

Scheme 48

Step 1: tert-Butyl (2S,4R)-2-((6-bromopyrazin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (205)

[0692] To an ice cold solution of (2S,4R)-1-(feri-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-trimethyl-l-propenylamine (1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, and then 6-bromopyrazin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 205.

Step 2: (2S,4R)-N-(6-Bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (206)

[0693] tert-Butyl (2S,4R)-2-((6-bromopyrazin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (1 equiv) was taken in 4 N HQ in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(IR,3S,5R)-N-(6-Bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (208)

Scheme 49

![Scheme 49](image)

**Step 1:** tert-Butyl (IR,3S,5R)-3-((6-bromopyrazin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (207)

[0694] To an ice cold solution of (IR,3S,5R)-fert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-trimethyl-1-propenylamine (1.1 equiv) dropwise with stirring. The stirring continued for 3 h at this temperature, and then 6-bromopyrazin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 207.

**Step 2:** (IR,3S,5R)-N-(6-Bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (208)

[0695] tert-Butyl (IR,3S,5R)-3-((6-bromopyrazin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(2S,4R)-N-(6-Bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide
hydrochloride (210)

Scheme 50

Step 1: tert-Butyl (2S,4R)-2-((6-bromo-3-methylpyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (209)

[0696] To an ice cold solution of (2S,4R)-1-(feri-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-trimethyl-l-propenylamine (1.1 equiv) dropwise with stirring. Stirring was continued for 3 h at this temperature, and then 6-bromo-3-methylpyridin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 209.

Step 2: (2S,4R)-N-(6-Bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (210)

[0697] tert-Butyl (2S,4R)-2-((6-bromo-3-methylpyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(2S,4R)-N-(6-Bromo-4-methoxypyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (212)

Scheme 51

Step 1: tert-Butyl (2S,4R)-2-((6-bromo-4-methoxypyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (211)

[0698] To an ice-cold solution of (2S,4R)-1-(/m-butoxycarbonyl)-4-fluoropyrroldine-2-carboxylic acid (1 equiv) in DCM (10 vol) was added l-chloro-N,N,2-trimethyl-l-propenylamine (1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, and then 6-bromo-4-methoxypyridin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 211.

Step 2: (2S,4R)-N-(6-Bromo-4-methoxypyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (212)

[0699] tot-Butyl (2S,4R)-2-((6-bromo-4-methoxypyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(2S,4R)-N-(6-Bromo-5-fluoropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (214)

Scheme 52

Step 1: tert-Butyl (2S,4R)-2-((6-bromo-5-fluoropyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (213)

[0700] To an ice cold solution of (2S,4R)-l-(t-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-trimethyl-l-propenylamine (1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, and then 6-bromo-5-fluoropyridin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 213.

Step 2: (2S,4R)-N-(6-Bromo-5-fluoropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (214)

[0701] tert-Butyl (2S,4R)-2-((6-bromo-5-fluoropyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-l-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
Step 1: tert-Butyl (IR,3S,5R)-3-((6-bromo-5-fluoropyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (215)

To an ice cold solution of (IR,3S,5R)-2-(f;f-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid (1 equiv) in DCM (10 vol) was added 1-chloro-N,N,2-triethyl-1-propenylamine (1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, and then 6-bromo-5-fluoropyridin-2-amine (1.1 equiv) was added, followed by DIEA (3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water and extracted with DCM. The organic layer was washed successively with an aqueous solution of NaHCO₃, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (DCM/EtOAc) to give compound 215.

Step 2: (IR,3S,5R)-N-(6-Bromo-5-fluoropyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (216)

tert-Butyl (IR,3S,5R)-3-((6-bromo-5-fluoropyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate (1 equiv) was taken in 4 N HCl in dioxane (10 vol) and the resulting reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.
(2S,4R)-1-(2-(3-Acetyl-5-((5-fluoropyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (164)

Scheme 54

Step 1: tert-Butyl 2-(3-acetyl-5-((5-fluoropyrimidin-2-yl)oxy)-1H-indol-1-yl)acetate (218)

[0704] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indol-1-yl)acetate 70 (1 equiv), 5-bromo-2-fluoropyrimidine (1 equiv), and Cs₂CO₃ (2 equiv) in DMF (10 vol) was purged with argon in a pressure vessel for 5 min, then tris(dibenzylideneacetone) dipalladium(O) (0.01 equiv) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.01 equiv) were added under argon. The pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The residue was purified by coluran chromatography on silica gel (MeOH/DCM) to give compound 218.

Step 2: 2-(3-Acetyl-5-((5-fluoropyrimidin-2-yl)oxy)-1H-indol-1-yl)acetic acid (219)

[0705] To a solution of compound 3 (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 used directly in the next synthetic step.

**Step 3:** (2S,4R)-l-(2-(3-Acetyl-5-(5-fluoropyrimidin-2-yl)oxy)-IH-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (164)

[0706] To a solution of compound 219 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyrazin-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 164. H NMR (400 MHz, DMSO-d6) δ 2.11 - 2.30 (m, 2H), 2.42 (s, 3H), 2.60 (dt, J = 8.9, 18.6 Hz, 1H), 3.95 - 4.11 (m, 1H), 4.13 - 4.28 (m, 1H), 4.70 (dd, J = 7.5, 9.6 Hz, 1H), 5.28 (d, J = 17.3 Hz, 1H), 5.43 (d, J = 17.3 Hz, 1H), 5.57 (d, J = 52.6 Hz, 1H), 5.71 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 8.31 (s, 1H), 8.54 (s, 1H), 8.68 (s, 2H), 9.27 (s, 1H), 11.35 (s, 1H). 19F NMR (376 MHz, DMSO-d6): δ -175.66, -148.52. LC (method A): tR = 1.56 rain. LC/MS (EI) m/z: [M + H]+ 600.

(1R^S,5R)-2-(2-(3-Acetyl-5-(5-fluoropyrimidin-2-yl)oxy)-IH-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (165)

**Scheme 55**

[0707] To a solution of compound 219 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (IR,3S,5R)-N-(6-bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (1 equiv), HATU (2.1 equiv), and DIPEA
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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 165. ¹H NMR (400 MHz, DMSO-d6) δ 0.75 - 0.85 (m, 1H), 1.01 - 1.14 (m, 1H), 1.93 (tt, J = 3.6, 6.5 Hz, 1H), 2.22 - 2.40 (m, 2H), 2.43 (s, 3H), 3.77 - 3.89 (m, 1H), 4.44 - 4.55 (m, 1H), 5.32 (d, J = 17.2 Hz, 1H), 5.60 (d, J = 17.3 Hz, 1H), 7.10 (dd, J = 2.4, 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 8.38 (s, 1H), 8.54 (s, 1H), 8.69 (s, 2H), 9.27 (s, 1H), 11.13 (s, 1H). ¹⁹F NMR (376 MHz, DMSO-d6): δ -148.50. LC (method A); tᵣ = 1.7 rain. LC/MS (EI) m/z: [M + H]⁺ 594.

(2S,4R)-1-{2-(3-acetyl-5-((5-methylpyrimidin-2-yl)-4-fluoropyrrolidine-2-carboxamide (166)

**Scheme 56**

[Diagram of the reaction scheme]

**Step 1:** tert-Butyl 2-(3-acetyl-5-((5-methylpyrimidin-2-yl)-4-fluoropyrrolidine-2-carboxamide (220)

[0708] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-lH-indol-1-yl)acetate 70 (1 equiv), 2-bromo-5-methylpyrimidine (1 equiv), and Cs₂CO₃ (2 equiv) in DMF (10 vol) was purged with argon in a pressure vessel for 5 min, then tris(dibenzyldieneacetone) dipalladium(O) (0.01 equiv)
and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.01 equiv) were added under argon. The pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to it and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 220.

**Step 2:** 2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indol-1-yl)acetic acid (221)

[0709] To a solution of compound 3 (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 used directly in the next synthetic step.

**Step 3:** (2S,4R)-l-(2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (166)

[0710] To a solution of compound 221 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyrazin-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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 166. 

$$^1$$H NMR (400 MHz, DMSO-d₆) δ 2.11 - 2.32 (m, 4H), 2.42 (s, 3H), 2.54 - 2.67 (m, 1H), 3.94 - 4.11 (m, 1H), 4.19 (dd, J = 12.9, 21.9 Hz, 1H), 4.70 (t, J = 7.5, 9.6 Hz, 1H), 5.27 (d, J = 17.3 Hz, 1H), 5.43 (d, J = 17.3 Hz, 1H), 5.49 - 5.68 (m, 1H), 7.01 - 7.11 (m, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 8.30 (s, 1H), 8.43 (s, 2H), 8.54 (s, 1H), 9.27 (s, 1H), 11.35 (s, 1H). 

$$^{19}$$F NMR (376 MHz, DMSO-d₆) δ -175.66. LC (method A): tᵣ = 1.51 min. LC/MS (EI) m/z: [M + H]⁺ 596.
(2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (167)

Scheme 57
Step 1 : l-(5-Bromo-lH-indazol-3-yl)ethan-l-one (223)

[0711] To an ice cold solution of 5-bromo-lH-indazole-3-carbonitrile (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 rt and stirred for 3 h (monitored by UPLC). Then the reaction was cooled to 0 °C and the pH was adjusted to 5 using 1.5 N HCl (pH ≈ 5). Then the reaction mass was stirred at rt 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 Na2SO4, 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-lH-indazol-1-yl)acetate (224)

[0712] To l-(5-bromo-lH-indazol-3-yl)ethan-l-one (155 g, 1 equiv) and potassium carbonate (225.6 g, 2.5 equiv) in DMF (1.6 L) was added tert-butyl bromoacetate (136 mL, 1.2 equiv) dropwise at rt. 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-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yI)-lH-indazol-1-yl)acetate (225)

[0713] A mixture of tert-butyl 2-(3-acetyl-5-bromo-lH-indazol-1-yl)acetate (1 equiv), 4,4,4',5,5,5',5'-octaethyl-2,2'-bi(1,3,2dioxaborane (1.1 equiv), and potassium acetate (3 equiv) in DMF (10 vol) was purged with argon for 5 min. 1,1’-Bis(diphenylphosphino)ferrocenedichloropaliadium(II) (0.06 equiv) was then added under argon and the reaction mixture was heated at 90 °C overnight. The reaction mixture was cooled to rt and diluted with EtOAc and water. The organic layer was then separated, washed with brine, dried, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 225.
Step 4: tert-Butyl 2-(3-acetyl-5-hydroxy-lH-indazol-1-yl)acetate (226)

[0714] A mixture of tert-butyl 2-(3-acetyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-1-yl)acetate (4, 1 equiv) in Methanol (25 vol) was added H2O2 (3 equiv) The reaction mixture was stirred at room temperature for 24h, precipitated, and the solid was filtered and washed with water and methanol, filtered and dried. The obtained material was used in the next step without further purification.

Step 5: tert-Butyl 2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-lH-indazol-1-yl)acetate (227)

[0715] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-lH-indazol-1-yl)acetate (1 equiv), 2-bromo-5-methylpyrimidine (1.1 equiv), K2CO3 (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 227.

Step 6: 2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-lH-indazol-1-yl)acetic acid (228)

[0716] To a solution of compound 227 (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 used directly in the next synthetic step.

Step 7: (2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-lH-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (167)

[0717] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyrazin-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 167. ¯H NMR (400 MHz, DMSO-ε) δ 2.13 - 2.32 (m, 4H), 2.55 - 2.68 (m, 4H), 3.97 - 4.13 (m, 1H), 4.19 - 4.33 (m, 1H), 4.65 -
4.76 (m, 1H), 5.49 - 5.68 (m, 2H), 5.83 (d, J = 17.3 Hz, 1H), 7.33 (dd, J = 2.3, 9.0 Hz, 1H), 7.74 (t, J = 9.1 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 8.46 (s, 2H), 8.54 (s, 1H), 9.27 (s, 1H), 11.34 (s, 1H).

$^{19}$F NMR (376 MHz, DMSO-$d_{6}$): $\delta$ -175.73. LC (method A): $t_{R} = 1.67$ min. LC/MS (EI) m/z: [M + H]$^{+}$ 597.

$(2S,4R)$-1-(2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (169)

Scheme 58

[0718] To a solution of compound 228 (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$_2$SO$_4$, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 169. $^1$H NMR (400 MHz, DMSO-$d_{6}$) $\delta$ 2.06 - 2.27 (m, 4H), 2.54 - 2.65 (m, 4H), 3.92 - 4.14 (m, 4H), 4.17 - 4.30 (m, 4H), 4.68 (t, J = 8.5 Hz, 1H), 5.46 - 5.67 (m, 2H), 5.82 (d, J = 17.3 Hz, 1H), 7.30 - 7.36 (m, 2H), 7.65 - 7.76 (m, 2H), 7.82 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 8.46 (s, 2H), 11.00 (s, 1H). $^{19}$F NMR (376 MHz, DMSO-$d_{6}$): $\delta$ -175.68. LC (method A): $t_{R} = 1.84$ min. LC/MS (EI) m/z: [M + H]$^{+}$ 596.
To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (IR,3S,5R)-N-(6-bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 170. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 0.82 – 0.88 (m, 1H), 0.99 – 1.09 (m, 1H), 1.87 - 1.97 (m, 1H), 2.22 (s, 3H), 2.25 - 2.41 (m, 2H), 2.62 (s, 3H), 3.83 - 3.94 (m, 1H), 4.43 - 4.57 (m, 1H), 5.61 (d, \(J = 17.2\) Hz, 1H), 5.98 (d, \(J = 17.3\) Hz, 1H), 7.31 - 7.38 (m, 1H), 7.77 (d, \(J = 9.1\) Hz, 1H), 7.83 (d, \(J = 2.2\) Hz, 1H), 8.47 (s, 2H), 8.54 (s, 1H), 9.27 (s, 1H), 11.13 (s, 1H). LC (method A): \(t_R = 1.9\) min. LC/MS (EI) m/z: [M + H]\(^+\) 591.
To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (IR,3S,5R)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-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$_2$SO$_4$, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 171. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 0.79 - 0.86 (m, iH), 0.98 - 1.08 (m, 1H), 1.86 - 1.98 (m, 1H), 2.22 (s, 4 H), 2.30 - 2.40 (m, H$^2$), 2.62 (s, 3H), 3.82 - 3.95 (m, iH), 4.38 - 4.57 (m, iH), 5.60 (d, J = 17.3 Hz, 1H), 5.98 (d, J = 17.3 Hz, 1H), 7.30 - 7.38 (m, 2H), 7.67 - 7.79 (m, 2H), 7.83 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 8.2 Hz, iH), 8.47 (s, 2H), 10.76 (s, 1H). LC (method A): $t_R$ = 1.98 min. LC/MS (El) m/z: [M + H]$^+$ 590.
(2S,4R)-1-(2-(3-Acetyl-5-((5-methyipyrimidine-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (172)

Scheme 61

[0721] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromo-3-methylpyridin-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$_2$SO$_4$, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 172. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 2.02 (s, 3H), 2.11 - 2.30 (m, 4H), 2.55 - 2.72 (m, 4H), 3.94 - 4.11 (m, 1H), 4.19 - 4.33 (m, 4H), 4.62 (t, J = 8.5 Hz, 1H), 5.48 - 5.68 (m, 2H), 5.83 (d, J = 17.3 Hz, 1H), 7.31 (dd, J = 2.3, 9.0 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.68 - 7.74 (m, 1H), 7.84 (d, J = 2.2 Hz, 1H), 8.48 (s, 2H), 10.45 (s, 1H). $^{19}$F NMR (376 MHz, DMSO- d$_6$): $\delta$ -176.05. LC (method A): $\tau$ = 1.67 min. LC/MS (El) m/z: [M + H]$^+$ 610.
(IR,3S,5R)-2-(2-(3-Acetyl-5-((5-methylpyrimidine-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide \( (173) \)

**Scheme 62**

![Scheme 62](image)

[0722] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added \((IR,3S,5R)\)-N-(6-bromo-3-methylpyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-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\( \cdot \)SO\(_4\), filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 173. **\( ^{1}H\) NMR (400 MHz, DMSO-\( \text{d}_6\)) \( \delta 0.84 - 0.92 \) (m, 1H), 1.02 - 1.1 (m, 1H), 1.91 - 1.99 (m, 1H), 2.05 (s, 3H), 2.22 (s, 3H), 2.25 - 2.33 (m, 1H), 2.36 - 2.46 (m, 1H), 2.63 (s, 3H), 3.74 - 3.88 (m, 1H), 4.41 - 4.50 (m, 1H), 5.61 (d, J = 17.2 Hz, 1H), 5.93 (d, J = 17.3 Hz, 1H), 7.33 (dd, J = 2.3, 9.0 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 8.46 - 8.53 (m, 2H), 10.24 (s, 1H).**

**LC (method A):** \( t_R = 1.76 \) rain. **LC/MS (EI) m/z:** [\( \text{M} + \text{H}\)]\(^+\) 604.
(2S,4R)-1-(2-(3-Acetyl-5-((5-methyipyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-4-methoxypyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (174)

Scheme 63

[0723] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromo-4-methoxypyridin-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 174. 1H NMR (400 MHz, DMSO-d6) δ 2.04 - 2.25 (m, 4H), 2.53 - 2.59 (m, 1H), 2.61 (s, 3H), 3.81 (s, 3H), 3.92 - 4.11 (m, 1H), 4.22 (dd, J = 12, 21 Hz, 1H), 4.66 (t, J = 8.5 Hz, 1H), 5.46 - 5.65 (m, 2H), 5.81 (d, J = 17.3 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.29 - 7.34 (m, 1H), 7.64 (d, J = 1.9 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 8.46 (s, 2H), 10.94 (s, 1H). 19F NMR (376 MHz, DMSO-d6): δ -175.68. LC (method A): tr = 1.92 min. LC/MS (EI) m/z: [M + H]+ 626.
(2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-5-fluoropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide  (176)

Scheme 64

[0724] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromo-5-fluoropyridin-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 176. 1H NMR (400 MHz, DMSO-dk) δ 2.08 - 2.26 (m, 4H), 2.57 (d, J = 6.2 Hz, 1H), 2.60 (s, 3H), 3.93 - 4.13 (m, 1H), 4.22 (dd, J = 12.3, 22.1 Hz, 1H), 4.60 - 4.73 (m, 1H), 5.46 - 5.66 (m, 2H), 5.81 (d, J = 17.3 Hz, 1H), 7.26 - 7.38 (m, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.80 - 7.88 (m, 2H), 8.00 - 8.10 (m, 1H), 8.46 (s, 2H), 11.08 (s, 1H). 19F NMR (376 MHz, DMSO-d6): δ -175.68, -120.35. LC (method A): t_R = 1.92 min. LC/MS (EI) m/z: [M + H]^+ 614.
(IR,3S,5R)-2-(2-(3-Acetyl-5-((5-methylpyrimidine-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-5-fluoropyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide (177)

Scheme 65

[0725] To a solution of compound 228 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (IR,3S,5R)-N-(6-bromo-5-fluoropyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 177. \( ^1H \) NMR (400 MHz, DMSO-d_6): \( \delta \) 0.78 - 0.86 (m, 1H). 0.98 - 1.08 (m, 1H). 1.84 - 1.97 (m, 1H). 2.16 - 2.26 (m, 4H). 2.31 - 2.37 (m, 1H). 2.61 (s, 3H). 3.81 - 3.92 (s, 1H). 4.41 - 4.50 (s, 1H). 5.59 (d, J = 17.2 Hz, 1H). 5.97 (d, J = 17.3 Hz, 1H). 7.33 (dd, J = 2.3, 9.1 Hz, 1H). 7.75 (d, J = 9.0 Hz, 1H). 7.81 - 7.89 (m, 2H). 8.05 (dd, J = 3.3, 8.9 Hz, 1H). 8.46 (s, 1H). 10.84 (s, 1H). \( ^{19}F \) NMR (376 MHz, DMSO-d_6): \( \delta \) -120.94. LC (method A): \( t_R = 2.04 \) min. LC/MS (EI) m/z: [M + H]^+ 608.
(2S,4R)-l-(2-(3-Acetyl-5-((4-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide (168)

Scheme 6

Step 1: tert-Butyl 2-(3-acetyl-5-((4-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetate (230)

[0726] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), 2-bromo-4-methylpyrimidine (1.1 equiv), K2CO3 (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 230.

Step 2: 2-(3-Acetyl-5-((4-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetic acid (231)

[0727] To a solution of compound 230 (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 used directly in the next synthetic step.

Step 3: **(2S,4R)-1-(2-(3-Acetyl-5-((4-methylpyrimidin-2-yl)oxy)-IH-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrroloidine-2-carboxamide** (168)

[0728] To a solution of compound 231 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyrazin-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 168. **¹H NMR** (400 MHz, DMSO-d6) δ 2.12 - 2.30 (m, 1H), 2.39 (s, 3H), 2.54 - 2.65 (m, 4H), 3.97 - 4.15 (m, 1H), 4.18 - 4.31 (m, 1H), 4.67 - 4.75 (m, 1H), 5.49 - 5.68 (m, 2H), 5.83 (d, J = 17.3 Hz, 1H), 7.14 (d, J = 5.0 Hz, 1H), 7.33 (dd, J = 2.3, 9.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 2.2 Hz, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.54 (s, 1H), 9.27 (s, 1H), 11.34 (s, 1H). **¹⁹F NMR** (376 MHz, DMSO-d6): δ 475.73. **LC (method A); tR = 1.63 min. LC/MS (EI) ra/ž; [M + H]+ 597.**
(2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (175)

Scheme 67

Step 1: tet-Butyl 2-(3-acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetate (233)

[0729] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), 2-bromo-5-methylpyrazine (1.1 equiv), K2CO3 (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 233.

Step 2: 2-(3-Acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetic acid (234)

[0730] To a solution of compound 233 (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 used directly in the next synthetic step.

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (175)

[0731] To a solution of compound 234 (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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 175. 1H NMR (400 MHz, DMSO-d6) δ 2.06 - 2.25 (m, 1H), 2.44 (s, 3H), 2.53 - 2.64 (m, 4H), 3.95 - 4.11 (m, 1H), 4.21 (dd, J = 12.4, 22.3 Hz, 1H), 4.66 (d, J = 8.5 Hz, 1H), 5.46 - 5.66 (m, 2H), 5.81 (d, J = 17.3 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.56 - 7.77 (m, 2H), 7.83 (s, 1H), 8.00 - 8.05 (m, 2H), 8.45 (s, 1H), 10.99 (s, 1H). LC (method A): tR = 1.94 min. LC/MS (EI) m/z: [M + H]+ 596.

(2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (178)

Scheme 68

[0732] To a solution of compound 234 (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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 178. ¹H NMR (400 MHz, DMSO-d₆) δ 2.08 - 2.28 (m, 1H), 2.44 (s, 3H), 2.52 - 2.63 (m, 4H), 3.95 - 4.11 (m, 1H), 4.15 - 4.29 (m, 1H), 4.61 - 4.70 (m, 1H), 5.45 - 5.65 (m, 2H), 5.81 (d, J = 7.3 Hz, 1H), 7.30 - 7.37 (m, 1H), 7.74 - 7.80 (m, 2H), 8.00 - 8.09 (m, 2H), 8.45 (d, J = 1.3 Hz, 1H), 11.08 (s, 1H). ¹⁹F NMR (376 MHz, DMSO-d₆): δ -175.71, -120.35.

**Scheme 69**

(2S,4R)-1-(2-(3-Acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (179)

[0733] To a solution of compound 234 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromo-3-methylpyridin-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 Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 179. ¹H NMR (400 MHz, DMSO-d₆) δ 2.01 (s, 3H), 2.11 - 2.30 (m, 1H), 2.45 (s, 3H), 2.56 - 2.71 (m, 4H), 3.93 - 4.14 (m, 1H), 4.23 (dd, J = 12.5, 21.9 Hz, 1H), 4.60 (t, J = 8.5 Hz, 1H), 5.47 - 5.68 (m, 2H), 5.82 (d, J = 17.3 Hz, 1H), 7.30 (d, J = 2.3, 9.1 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.71 (d, 1H).
J = 9.0 Hz, 1H), 7.84 (d, J = 2.3 Hz, 1H), 8.06 (s, 1H), 8.46 (d, J = 1.3 Hz, 1H), 10.44 (s, 1H).\(^{19}\)F NMR (376 MHz, DMSO-de): \(\delta\) -176.05, -120.35. LC (method A): t\(_R\) = 1.77 min. LC/MS (El) m/z: [M + H\(^+\)] 610.

\((2S,4R)-1-(2-(3-Acetyl-5-((6-methylpyrimidin-4-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide\) (180)

**Scheme 70**

Step 1: *tert*-butyl 2-(3-acetyl-5-((6-methylpyrimidin-4-yl)oxy)-1H-indazol-1-yl)acetate (235)

[0734] A mixture of \(\text{tert-}\)butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), 4-bromo-6-methylpyrimidine (1.1 equiv), K\(_2\)CO\(_3\) (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 235.
Step 2: 2-(3-acetyl-5-((6-methylpyrimidin-4-yl)oxy)-1H-indazol-1-yl)acetic acid (236)

[0735] To a solution of compound 235 (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 used directly in the next synthetic step.

Step 3: (2S,4R)-1-(2-(3-acetyl-5-((6-methylpyrimidin-4-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidino-2-carboxamide (180)

[0736] To a solution of compound 236 (1 equiv) in DMF (10 vol) at 0 °C under an atmosphere of nitrogen was added (2S,4R)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidino-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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 180. 1H NMR (400 MHz, DMSO-d6) δ 2.05 - 2.28 (m, 1H), 2.44 (s, 3H), 2.53 - 2.63 (m, 4H), 3.95 - 4.11 (m, 1H), 4.22 (dd, J = 12.5, 22.2 Hz, 1H), 4.67 (t, J = 8.5 Hz, 1H), 5.46 - 5.66 (m, 2H), 5.82 (d, J = 17.3 Hz, 1H), 7.03 (s, 1H), 7.29 - 7.37 (m, 2H), 7.64 - 7.79 (m, 2H), 7.85 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 8.58 (s, 1H), 10.99 (s, 1H). 19F NMR (376 MHz, DMSO-cfc): δ -175.68. LC (method A): tR = 1.79 min. LC/MS (EI) m/z; [M + H]+ 596.
(2S,4R)-1-(2-(3-acetyl-5-((6-methylpyridazin-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (181)

Scheme 70

Step 1: tert-Butyl 2-(3-acetyl-5-((6-methylpyridazin-3-yl)oxy)-1H-indazol-1-yl)acetate [237]

[0737] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), 3-bromo-6-methylpyridazine (1.1 equiv), K2CO3 (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 237.

Step 2: 2-(3-Acetyl-5-((6-methylpyridazin-3-yl)oxy)-1H-indazol-1-yl)acetic acid (238)

[0738] To a solution of compound 237 (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 used directly in the next synthetic step.
Step 3: \((2S,4R)-\text{I}-(2-(3-Acetyl-5-((6-methylpyridazin-3-yi)oxy)-1H-indazol-1-yl)acetyi)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide\) (181)

[0739] To a solution of compound 238 (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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 181. \(^{1}H\) NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 2.06 - 2.25 (m, 1H), 2.53 - 2.58 (m, 4H), 2.60 (s, 3H), 3.96 - 4.10 (m, 1H), 4.22 (dd, \(J = 12.4, 22.2\) Hz, 1H), 4.67 (t, \(J = 8.5\) Hz, 1H), 5.45 - 5.65 (m, 2H), 5.81 (d, \(J = 17.3\) Hz, 1H), 7.31 - 7.45 (m, 3H), 7.64 - 7.79 (m, 3H), 7.84 (d, \(J = 2.3\) Hz, 1H), 8.02 (d, \(J = 8.2\) Hz, 1H), 10.99 (s, 1H). \(^{19}F\) NMR (376 MHz, DMSO-\(d_6\)) : \(\delta\) -175.67. LC (method A): \(t_R = 1.71\) rain. LC/MS (El) m/z: [M + H]+ 596.
(2S,4R)-1-(2-(3-Acetyl-5-(cyclopentyloxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (193)

Scheme 71

Step 1: tert-Butyl 2-(3-acetyl-5-(cyclopentyloxy)-1H-indazol-1-yl)acetate (239)

[0740] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), iodo-cyclopentane (1.1 equiv), K₂CO₃ (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to r and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 239.

Step 2: 2-(3-Acetyl-5-(cyclopentyloxy)-1H-indazol-1-yl)acetic acid (240)

[0741] To a solution of compound 239 (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 used directly in the next synthetic step.

Step 3: \((2S,4R)-1-(2-(3-Acetyl-5-(cyclopentyloxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidin-2-carboxamide\) (193)

[0742] To a solution of compound 240 (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\(\_2\)SO\(_4\), filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 193. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 1.55 – 1.65 (m, 2H), 1.68 - 1.79 (m, 4H), 1.86 – 2.01 (m, 2H), 2.05 - 2.25 (m, 1H), 2.53 – 2.6! (m, 3H), 3.93 - 4.10 (m, 1H), 4.19 (dd, J = 12.5, 22.2 Hz, 1H), 4.65 (t, J = 8.5 Hz, 1H), 4.80 – 4.92 (m, 1H), 5.42 - 5.62 (ra, 2H), 5.72 (d, J = 17.3 Hz, 1H), 7.07 (dd, J = 2.4, 9.1 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 10.97 (s, 1H). \(^{19}\)F NMR (376 MHz, DMSO-d): \(\delta\) -175.71. LC (method A); \(t_R\) = 2.48 min. LC/MS (EI) m/z: [M + H]\(^+\) 572.
Scheme 72

Step 1: tert-Butyl 2-(3-acetyl-5-((tetrahydrofuran-3-yl)oxy)-1H-indazol-1-yl)acetate (241)

[0743] A mixture of tert-butyl 2-(3-acetyl-5-hydroxy-1H-indazol-1-yl)acetate (1 equiv), 3-iodotetrahydrofuran (1.1 equiv), K₂CO₃ (3 equiv) and 18-Crown-6 (1 equiv) in DMF (10 vol) under argon, the pressure vessel was sealed and heated at 100 °C for 24 h. The reaction mixture was cooled to rt and diluted with water, then extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM) to give compound 241.

Step 2: 2-(3-Acetyl-5-((tetrahydrofuran-3-yl)oxy)-1H-indazol-1-yl)acetate acid (242)

[0744] To a solution of compound 241 (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 used directly in the next synthetic step.
Step 3: (2S,4R)-1-(2-(3-acetyl-5-((tetrahydrofuran-3-yl)oxy)-1H-indazoI-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide (194)

[0745] To a solution of compound 242 (1 equiv) in DMF (to 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 Na2SO4, filtered, and then concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM) to give compound 194. 1H NMR (400 MHz, DMSO-d6) δ 1.94 - 2.31 (m, 3H), 2.54 - 2.64 (m, 4H), 3.75 - 4.09 (m, 5H), 4.20 (dd, J = 12.5, 22.3 Hz, 1H), 4.66 (t, J = 8.5 Hz, 1H), 5.05 - 5.15 (m, 1H), 5.27 - 5.53 (m, 2H), 5.74 (d, J = 17.3 Hz, 1H), 7.12 (dd, J = 2.4, 9.1 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 10.98 (s, 1H). 19F NMR (376 MHz, DMSO-d6): δ -475.70. LC (method A): tR = 1.81 min. LC/MS (EI) m/z: [M + H]⁺ 574.

(lR,2S,5S)-3-(2-(3-Acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-1H-indazoI-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (185)

Scheme 73

[0746] To a mixture of 2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-hydroxyhexahydrofuro [3, 2-b] furan-3-ylene)-1H-indazoI-1-yl) acetic acid (30 mg, 0.08 mmol), (lR, 2S, 5S)-N-(6-bromo-3-methylpyridin-2-yl)-3-azabicyclo [3.1.0] hexane-2-carboxamide (24 mg, 0.08 mmol) and DIPEA (53 mg, 0.41 mmol) in DMF (2 mL) was added HATU (69 mg, 0.18 mmol) at 0 °C. The reaction was stirred at room temperature for 4 hrs. The mixture was diluted with EtOAc and washed with
10% aq. LiCl solution and brine. The organic layer was dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by prep HPLC to give the titled compound (7.9 mg, 15.4 % yield) as a white solid. 1H NMR (400 MHz, DMSO-d6): \( \delta \) 10.27 (s, 1H), 7.76 - 7.55 (m, 3H), 7.42 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 9.2, 2.4 Hz, 1H), 5.48 (q, J = 17.2 Hz, 2H), 4.94 (dd, J = 11.6, 6.4 Hz, 1H), 4.76 (t, J = 4.8 Hz, 1B), 4.57 (d, J = 5.2 Hz, 1H), 4.39 (t, J = 4.8 Hz, 1H), 4.16 - 4.04 (m, 2H), 4.00 (dd, J = 10.0, 5.6 Hz, 1H), 3.89 - 3.77 (m, 2H), 3.77 - 3.71 (m, 1H), 3.56 - 3.42 (m, 2H), 2.57 (s, 3H), 2.22 - 1.97 (m, 4H), 1.92 - 1.82 (m, 1H), 0.94 - 0.67 (m, 2H). LC/MS (ESI) ra/z: 640 (M+H)+.

\( \text{(I R,2S,5S)} - 3 - ( 2 - ( 3 - \text{Acetyl}-5 - ((3R,3aR,6R,6aR}-6\text{-hydroxyhe.-ahydrofuro[3,2-b]furan-3-yloxy)-IH-indazol-l-yl)acetyI)-N-(6-bronio-3-cyclopropylpyridin-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide (184) \)

Scheme 74
Step 1: 2-bromo-5-cyclopropylpyridine 1-oxide (245)

[0747] To a solution of 2-bromo-5-cyclopropylpyridine (2.0 g, 10.1 mmol) in CHCl₃ (10 mL) was added m-CPBA (2.62 g, 15.2 mmol). The reaction was stirred at room temperature overnight. The mixture was diluted DCM and washed with 5% aq. NaHCO₃ solution and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluted with PE/EtOAc (30: 1 to 1: 1) to give compound 245 (2.12 g, 98.6 % yield) as a white solid. LC/MS (ESI) m/z: 214 (M+H)⁺.

Step 2: 6-Bromo-N-tert-butyl-3-cyclopropylpyridin-2-amine (246)

[0748] To a mixture of 2-bromo-5-cyclopropylpyridine 1-oxide (2.12 g, 9.97 mmol) and 2-methylpropan-2-amine (5.24 g, 71.8 mmol) to toluene/DCM (30 mL, v/v = 5:2) was added a solution of 4-methylbenzenesulfonic anhydride (10.73 g, 32.9 mmol) in toluene/DCM (20 mL, v/v = 5:2) drop-wise at 0 °C. After addition was complete, the reaction was stirred at room temperature under N₂ atmosphere for 16 hrs. The mixture was diluted with DCM and washed with water and brine. The organic layer was dried and concentrated to dryness. The residue was purified by column chromatography on silica gel eluted with PE/EtOAc (50: 1 to 3: 1) to give compound 246 (1.02 g, 38.1 % yield) as a yellow solid. LC/MS (ESI) m/z: 269 (M+H)⁺.

Step 3: 6-bromo-3-cyclopropylpyridin-2-amine (247)

[0749] To a solution of 6-bromo-N-tert-butyl-3-cyclopropylpyridin-2-amine (51.1 mg, 1.90 mmol) in DCE (2 mL) was added TFA (2 mL). The reaction was stirred at 90 °C for 40 minutes in a microwave reactor. The mixture was concentrated to dryness and the residue was triturated with diethyl ether to give compound 247 (400 mg, 98.9 % yield) as a light yellow solid. LC/MS (ESI) m/z: 214 (M+H)⁺.

Step 4: (1R, 2S, 5S)-tert-butyl 2-(6-bromo-3-cyclopropypiridii-2-yicarbamoyl)-3-azabicyclo [3.1.0] hexane-3-carboxylate (249)

[0750] To a solution of 6-bromo-3-cyclopropylpyridin-2-amine (50 mg, 0.23 mmol) in DCE (1 mL) was added ethyl 2-ethoxyquinoline-l(2H)-carboxylate (EEDQ) (116 mg, 0.47 mmol), DIPEA (121 mg, 0.94 mmol) and (1R, 2S, 5S)-3-(fer t-butoxycarbonyl)-3- azabicyclo [3.1.0] hexane-2-carboxylic acid (53 mg, 0.23 mmol). The reaction was stirred at 90 °C under N₂ atmosphere overnight. The mixture was concentrated to dryness and the residue was purified by
column chromatography on silica gel eluted with PE/EtOAc (100: 1 to 30: 1) to give compound 249 (24 mg, 24.3 % yield) as a white solid. LC/MS (ESI) m/z: 422 (M+H)+.

Step 5: (1R, 2S, 5S)-N-(6-bromo-3-cyclopropylpyridin-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide TFA salt (250)

[0751] To a solution of (1R, 2S, 5S)-tert-butyl 2-(6-bromo-3-cyclopropylpyridin-2-ylcarbamoyl)-3-azabicyclo [3.1.0] hexane-3-carboxylate (24 mg, 0.06 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 1 hr. The mixture was concentrated and the residue was triturated with diethyl ether to give compound 250 (20 mg, 100% yield) as a yellow solid. LC/MS (ESI) m/z: 422 (M+H)+.

Step 6: (1R, 2S, 5S)-3-(2-(3-acetyl-5-((3R, 3aR, 6R, 6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indazol-1-yl) acetyl)-N-(6-bromo-3-cyclopropylpyridin-2-yl)-3-azabicyclo [3.1.0] hexane-2-carboxamide (184)

[0752] The title compound was prepared according to the procedure from Scheme 73 from appropriate starting materials. 1H NMR (400 MHz, DMSO-d6) δ 10.22 (s, 1H), 7.64 - 7.53 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.14 (dd, J = 9.2, 2.4 Hz, 1H), 5.48 (q, J = 16.8 Hz, 2H), 4.92 (dd, J = 13.2, 6.4 Hz, 2H), 4.76 (t, J = 4.8 Hz, 1H), 4.59 (d, J = 5.2 Hz, 1H), 4.38 (t, J = 4.8 Hz, 1H), 4.13 - 4.06 (m, 2H), 4.00 (dd, J = 9.6, 4.8 Hz, 1H), 3.87 - 3.71 (m, 4H), 2.57 (s, 3H), 2.08 - 1.96 (m, 1H), 1.94 - 1.78 (m, 2H), 0.90 - 0.71 (m, 4H), 0.58 - 0.46 (m, 2H). LC/MS (ESI) m/z: 666 ([M]+).

EXAMPLE 7. NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I

[0753] Table 1 shows illustrative compounds of Formula I with characterizing data. The assay of Example 8 was used to determine the IC50’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>
<thead>
<tr>
<th>Cmp No.</th>
<th>Structure</th>
<th>Name</th>
<th>IC₅₀</th>
<th>RT min (Method A or B)</th>
<th>MS (M+1)</th>
</tr>
</thead>
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<td>1</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-6-(cyclopropylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.14 (A)</td>
<td>544</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>3-acetyl-1-(2-(((2S,4R)-2-(3-chloro-2-fluorobenzyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yl trifluoromethanesulfonate</td>
<td>***</td>
<td>2.24 (A)</td>
<td>622</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-6-(cyclopropylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>1.46 (A)</td>
<td>538</td>
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<tr>
<td>4</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-6-(cyclopropylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-fluoro-3-(trifluoromethoxy)phenyl)pyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.66 (A)</td>
<td>580</td>
</tr>
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<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC50</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
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</tr>
<tr>
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<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-((2-(3-acetyl-6-(2-cyclopropylethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidin-2-carboxamide</td>
<td>***</td>
<td>1.70 (A)</td>
<td>558</td>
</tr>
<tr>
<td>6</td>
<td><img src="image2" alt="Structure" /></td>
<td>(2S,4R)-1-((2-(3-acetyl-6-((tricyclo[8.2.2.2^4.7]hexadeca-4,6,10,12,13,15-hexaen-5-yl)methyl)oxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidin-2-carboxamide</td>
<td>**</td>
<td>2.25 (A)</td>
<td>710</td>
</tr>
<tr>
<td>7</td>
<td><img src="image3" alt="Structure" /></td>
<td>diethyl (3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonate</td>
<td>***</td>
<td>1.84 (A)</td>
<td>640</td>
</tr>
<tr>
<td>8</td>
<td><img src="image4" alt="Structure" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.03 (A)</td>
<td>584</td>
</tr>
<tr>
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<td>Structure</td>
<td>Name</td>
<td>IC$_{50}$</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure" /></td>
<td>3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl trifluoromethanesulfonate</td>
<td>***</td>
<td>2.37 (A)</td>
<td>622</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure" /></td>
<td>diethyl (3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yloxy)methylphosphonate</td>
<td>***</td>
<td>1.79 (A)</td>
<td>640</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Structure" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.02 (A)</td>
<td>584</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Structure" /></td>
<td>(3(acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphoryl)bis(oxy)bis(methyl)isopropyl dicarbonate</td>
<td>***</td>
<td>2.16 (A)</td>
<td>816</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC50</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
<td>------------------------</td>
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</tr>
<tr>
<td>13</td>
<td>![Structure Image]</td>
<td>(((3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl)(hydroxy)phosphoryloxy)methyl(isopropyl)carbonate</td>
<td>***</td>
<td>1.38 (A)</td>
<td>700</td>
</tr>
<tr>
<td>14</td>
<td>![Structure Image]</td>
<td>ethyl ((3-acetyl-1-((2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl(ethyl)phosphinate</td>
<td>***</td>
<td>1.40 (A)</td>
<td>624</td>
</tr>
<tr>
<td>15</td>
<td>![Structure Image]</td>
<td>(2S,4R)-1-((2-((3-acetyl-6-(N-tert-butylsulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.83 (A)</td>
<td>639</td>
</tr>
<tr>
<td>16</td>
<td>![Structure Image]</td>
<td>(3-acetyl-1-((2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl(ethyl)phosphinic acid</td>
<td>***</td>
<td>1.18 (A)</td>
<td>596</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>17</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-6-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.19 (A)</td>
<td>583</td>
</tr>
<tr>
<td>18</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>diethyl (3-acetyl-1-(2-((2S,4R)-2-((R)-1-(3-chloro-2-fluorophenyl)ethylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonate</td>
<td>***</td>
<td>1.67 (A)</td>
<td>654</td>
</tr>
<tr>
<td>19</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-2-((R)-1-(3-chloro-2-fluorophenyl)ethylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>0.22 (A)</td>
<td>598</td>
</tr>
<tr>
<td>20</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>3-(hexadecyloxy)propyl hydrogen (3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonate</td>
<td>***</td>
<td>3.31 (A)</td>
<td>866</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
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<tr>
<td>21</td>
<td><img src="image" alt="Structure" /></td>
<td>(((3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl)phosphoryl)bis(oxy)bis(methylene)bis(2,2-dimethylpropanoate)</td>
<td>***</td>
<td>2.58 (A)</td>
<td>812</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Structure" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-2-((3-chloro-2-fluorophenylsulfonyl)methyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.11 (A)</td>
<td>620</td>
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<tr>
<td>23</td>
<td><img src="image" alt="Structure" /></td>
<td>1,1'-(((3-acetyl-1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl)phosphoryl)bis(oxy)bis(2-methylpropane-1,1-diyl) dipropionate</td>
<td>***</td>
<td>2.79 (A)</td>
<td>840</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC50</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>--------</td>
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<td>----------</td>
</tr>
<tr>
<td>24</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>(2S,2'S)-isopropyl 2,2'-'-(((3-acetyl-1-(2-((2S,4R)-2-((3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methyl)phosphoryl)bis(azanediyl)dipropanoate</td>
<td>***</td>
<td>2.20 (A)</td>
<td>810</td>
</tr>
<tr>
<td>25</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-4-fluoro-2-(3-fluoro-4-(trifluoromethoxy)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.46 (A)</td>
<td>620</td>
</tr>
<tr>
<td>26</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-4-fluoro-2-(3-phenoxypyphenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.51 (A)</td>
<td>610</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>---------</td>
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<td>----------------------------------------------------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>27</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>(3-acetyl-1-(2-((2S,4R)-4-fluoro-2-(2-fluoro-3-(trifluoromethoxy)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-6-yloxy)methylphosphonic acid</td>
<td>***</td>
<td>1.34 (A)</td>
<td>620</td>
</tr>
<tr>
<td>28</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>6-((N-tert-butylsulfamoylmethoxy)-1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazole-3-carboxamide</td>
<td>***</td>
<td>2.22 (A)</td>
<td>703</td>
</tr>
<tr>
<td>29</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-6-(sulfamoylmethoxy)-1H-indazole-3-carboxamide</td>
<td>***</td>
<td>1.80 (A)</td>
<td>647</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>30</td>
<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.54 (A)</td>
<td>568</td>
</tr>
<tr>
<td>31</td>
<td><img src="image2" alt="Structure" /></td>
<td>1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-((pyrimidin-5-yloxy)-1H-indazole-3-carboxamide</td>
<td>***</td>
<td>2.72 (A)</td>
<td>632</td>
</tr>
<tr>
<td>32</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-6-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.57 (A)</td>
<td>630</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>--------</td>
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<td>----------------------------------------------------------------------</td>
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<td>------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>33</td>
<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(5-bromopyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.45 (A)</td>
<td>708</td>
</tr>
<tr>
<td>34</td>
<td><img src="image2" alt="Structure" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-(5-bromopyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>2.58 (A)</td>
<td>703</td>
</tr>
<tr>
<td>35</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(5-bromopyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.04 (A)</td>
<td>660</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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<td>----------</td>
</tr>
<tr>
<td>36</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>$(2S,4R)$-1-$(2-(3-acetyl-5-(2-cyanopyrimidin-5-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.46 (A)</td>
<td>655</td>
</tr>
<tr>
<td>37</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>$(2S,4R)$-1-$(2-(3-acetyl-5-(5-fluoropyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.31 (A)</td>
<td>648</td>
</tr>
<tr>
<td>38</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>$(2S,4R)$-1-$(2-(3-acetyl-5-(pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.14 (A)</td>
<td>630</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
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<td>---------</td>
</tr>
<tr>
<td>39</td>
<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(pyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.63 (A)</td>
<td>581</td>
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<tr>
<td>40</td>
<td><img src="image2" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(5-methylpyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.26 (A)</td>
<td>644</td>
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<tr>
<td>41</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(5-methylpyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.78 (A)</td>
<td>595</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀</td>
<td>RT min (Method A or B)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>---------</td>
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<td>----------</td>
</tr>
<tr>
<td>42</td>
<td><img src="structure1.png" alt="" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(5-(trifluoromethyl)pyrimidin-2-yloxy)-1H-indol-1-yl)acetyl)-N-(2′-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.58 (A)</td>
<td>698</td>
</tr>
<tr>
<td>43</td>
<td><img src="structure2.png" alt="" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(2-chloropyrimidin-5-yloxy)-1H-indol-1-yl)acetyl)-N-(2′-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.50 (A)</td>
<td>664</td>
</tr>
</tbody>
</table>

[0754] Table 2 shows illustrative compounds of Formula I with characterizing data. The assay of Example 8 was used to determine the IC₅₀'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.

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<table>
<thead>
<tr>
<th>Cmp No.</th>
<th>Structure</th>
<th>Name</th>
<th>IC₅₀ (Method A or B)</th>
<th>RT min (Method A or B)</th>
<th>MS (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>3.52 (B)</td>
<td>680</td>
</tr>
<tr>
<td>45</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.49 (B)</td>
<td>631</td>
</tr>
<tr>
<td>46</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>3.39 (B)</td>
<td>694</td>
</tr>
</tbody>
</table>
### TABLE 3, ADDITIONAL COMPOUNDS OF THE PRESENT INVENTION

<table>
<thead>
<tr>
<th>Cmp No.</th>
<th>Structure</th>
<th>Name</th>
<th>IC₅₀ (Stars)</th>
<th>RT min (Method A, B, C or D)</th>
<th>MS (M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td><img src="image" alt="Structure" /></td>
<td>(2S,4R)-l-(2-(3-acetyl-5-((3R,3aR,6R,6aR)-6-methoxyhexahydrofuro[3,2-b]furan-3-yloxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.71 (B)</td>
<td>645</td>
</tr>
<tr>
<td>164</td>
<td><img src="image" alt="Structure" /></td>
<td>(2S,4R)-l-(2-(3-acetyl-5-((5-fluoropyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.56 (A)</td>
<td>600</td>
</tr>
<tr>
<td>165</td>
<td><img src="image" alt="Structure" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-((5-fluoropyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>1.70 (A)</td>
<td>594</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>166</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.51 (A)</td>
<td>596</td>
</tr>
<tr>
<td>167</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.67 (A)</td>
<td>598</td>
</tr>
<tr>
<td>168</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((4-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.63 (A)</td>
<td>597</td>
</tr>
<tr>
<td>169</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.84 (A)</td>
<td>596</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC$_{50}$ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>170</td>
<td><img src="image1" alt="Structure" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>1.80 (A)</td>
<td>590</td>
</tr>
<tr>
<td>171</td>
<td><img src="image2" alt="Structure" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>1.98 (A)</td>
<td>590</td>
</tr>
<tr>
<td>172</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.67 (A)</td>
<td>610</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>173</td>
<td><img src="image1" alt="Structure 173" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>1.76 (A)</td>
<td>604</td>
</tr>
<tr>
<td>174</td>
<td><img src="image2" alt="Structure 174" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-4-methoxypyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.92 (A)</td>
<td>626</td>
</tr>
<tr>
<td>175</td>
<td><img src="image3" alt="Structure 175" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.94 (A)</td>
<td>596</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC50 (Stars)</td>
<td>RT min (Method A, B, C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
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</tr>
<tr>
<td>176</td>
<td><img src="Image" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-5-fluoropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.92 (A)</td>
<td>614</td>
</tr>
<tr>
<td>177</td>
<td><img src="Image" alt="Structure" /></td>
<td>(1R,3S,5R)-2-(2-(3-acetyl-5-((5-methylpyrimidin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-5-fluoropyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide</td>
<td>***</td>
<td>2.04 (A)</td>
<td>608</td>
</tr>
<tr>
<td>178</td>
<td><img src="Image" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-5-fluoropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.01 (A)</td>
<td>614</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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</tr>
<tr>
<td>179</td>
<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((5-methylpyrazin-2-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.77 (A)</td>
<td>610</td>
</tr>
<tr>
<td>180</td>
<td><img src="image2" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((6-methylpyrimidin-4-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.79 (A)</td>
<td>597</td>
</tr>
<tr>
<td>181</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((6-methylpyridazin-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.71 (A)</td>
<td>596</td>
</tr>
<tr>
<td>145</td>
<td><img src="image4" alt="Structure" /></td>
<td>(((3-acetyl-1-2-((2S,4R)-2-(benzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)sphonic acid</td>
<td>**</td>
<td>6.44 (D)</td>
<td>532</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC_{50} (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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</tr>
<tr>
<td>147</td>
<td><img src="image1" alt="" /></td>
<td>(((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-(phenethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>9.29 (C)</td>
<td>546</td>
</tr>
<tr>
<td>149</td>
<td><img src="image2" alt="" /></td>
<td>(((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>9.78 (C)</td>
<td>560</td>
</tr>
<tr>
<td>150</td>
<td><img src="image3" alt="" /></td>
<td>diethyl (((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate</td>
<td>***</td>
<td>10.99 (D)</td>
<td>630</td>
</tr>
<tr>
<td>151</td>
<td><img src="image4" alt="" /></td>
<td>(((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-((4-phenylbutyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>10.93 (C)</td>
<td>574</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
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</tr>
<tr>
<td>144</td>
<td><img src="image1" alt="Structure" /></td>
<td>diethyl (((3-acetyl-1-(2-((2S,4R)-2-(benzyl carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate</td>
<td>***</td>
<td>11.48 (C)</td>
<td>588</td>
</tr>
<tr>
<td>146</td>
<td><img src="image2" alt="Structure" /></td>
<td>diethyl (((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-(phenethyl carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate</td>
<td>***</td>
<td>11.79 (C)</td>
<td>602</td>
</tr>
<tr>
<td>148</td>
<td><img src="image3" alt="Structure" /></td>
<td>diethyl (((3-acetyl-1-(2-((2S,4R)-4-fluoro-2-((3-phenylpropyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate</td>
<td>***</td>
<td>12.13 (C)</td>
<td>616</td>
</tr>
<tr>
<td>182</td>
<td><img src="image4" alt="Structure" /></td>
<td>diethyl (((3-carbamoyl-1-(2-((1R,3S,4S)-3-((6-methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-1H-indol-5-yl)oxy)methyl)phosphonate</td>
<td>*</td>
<td>1.64 (B)</td>
<td>598</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
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</tr>
<tr>
<td>183</td>
<td><img src="image" alt="Structure" /></td>
<td>(((3-carbamoyl-1-(2-((1R,3S,4S)-3-((6-methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-(H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>2.36 (B)</td>
<td>542</td>
</tr>
<tr>
<td>158</td>
<td><img src="image" alt="Structure" /></td>
<td>diethyl (((3-acetyl-1-(2-((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-(H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>**</td>
<td>10.37 (D)</td>
<td>638</td>
</tr>
<tr>
<td>159</td>
<td><img src="image" alt="Structure" /></td>
<td>(((3-acetyl-1-(2-((2R,4R)-4-fluoro-2-(2-(phenylsulfonamido)ethyl)pyrrolidin-1-yl)-2-oxoethyl)-(H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>9.53 (C)</td>
<td>582</td>
</tr>
<tr>
<td>163</td>
<td><img src="image" alt="Structure" /></td>
<td>(S)-diethyl (((3-acetyl-1-(2-(2-((6-methylpyridin-2-yl)carbamoyl)azetidin-1-yl)-2-oxoethyl)-(H-indol-5-yl)oxy)methyl)phosphonic acid</td>
<td>*</td>
<td>9.56 (D)</td>
<td>557</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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</tr>
<tr>
<td>184</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(1R,2S,5S)-3-(2-(3-acetyl-5-(((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-cyclopropylpyridin-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
<td>***</td>
<td>2.56 (B)</td>
<td>666</td>
</tr>
<tr>
<td>185</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(1R,2S,5S)-3-(2-(3-acetyl-5-(((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromo-3-methylpyridin-2-yl)-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
<td>***</td>
<td>2.14 (B)</td>
<td>640</td>
</tr>
<tr>
<td>186</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>5-((N-(tert-butyl)sulfamoyl)methoxy)-1-(2-(((1R,3S,4S)-3-(6-methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-1H-indole-3-carboxamide</td>
<td>*</td>
<td>2.20 (B)</td>
<td>597</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>--------</td>
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</tr>
<tr>
<td>187</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>1-(2-((1R,3S,4S)-3-((6-methylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.2.1]heptan-2-yl)-2-oxoethyl)-5-(sulfamoylmethoxy)-1H-indole-3-carboxamide</td>
<td>*</td>
<td>2.17 (B)</td>
<td>541</td>
</tr>
<tr>
<td>141</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>9.73 (D)</td>
<td>584</td>
</tr>
<tr>
<td>139</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrrolidine-2-carboxamide</td>
<td>**</td>
<td>10.34 (D)</td>
<td>608 (M-1)</td>
</tr>
<tr>
<td>130</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>8.57 (D)</td>
<td>529 (M-1)</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC$_{50}$ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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</tr>
<tr>
<td>133</td>
<td><img src="structure133.png" alt="Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrrolidine-2-carboxamide</td>
<td>**</td>
<td>10.68 (C)</td>
<td>545</td>
</tr>
<tr>
<td>136</td>
<td><img src="structure136.png" alt="Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(sulfamoylmethoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrrolidine-2-carboxamide</td>
<td>***</td>
<td>10.98 (C)</td>
<td>559</td>
</tr>
<tr>
<td>193</td>
<td><img src="structure193.png" alt="Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((tetrahydrofuran-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>1.81 (A)</td>
<td>574</td>
</tr>
<tr>
<td>194</td>
<td><img src="structure194.png" alt="Image" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(cyclopentyloxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.48 (A)</td>
<td>572</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC\textsubscript{50} (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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</tr>
<tr>
<td>138</td>
<td><img src="image1" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((N-(4-pherylbutyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-phenylbutyl)pyrroldine-2-carboxamide</td>
<td>***</td>
<td>11.67 (C)</td>
<td>629</td>
</tr>
<tr>
<td>140</td>
<td><img src="image2" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>12.65 (C)</td>
<td>639</td>
</tr>
<tr>
<td>132</td>
<td><img src="image3" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((N-(4-pherylbutyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-phenethylpyrroldine-2-carboxamide</td>
<td>***</td>
<td>10.91 (D)</td>
<td>601</td>
</tr>
<tr>
<td>135</td>
<td><img src="image4" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((N-(4-pherylbutyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-phenylpropyl)pyrroldine-2-carboxamide</td>
<td>***</td>
<td>11.31 (D)</td>
<td>615</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
<tr>
<td>---------</td>
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<td>------------------------</td>
<td>---------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>129</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-((N-(tert-butyl)sulfamoyl)methoxy)-1H-indol-1-yl)acetyl)-N-benzyl-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>10.80 (C)</td>
<td>587</td>
</tr>
<tr>
<td>200</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(((3R,3aR,6R,6aR)-6-hydroxyhexahydrofuro[3,2-b]furan-3-yl)oxy)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>2.46 (B)</td>
<td>632</td>
</tr>
<tr>
<td>201</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>(((3-acetyl-1-(2-((2S,4R)-2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-1H-indazol-6-yl)oxy)methyl)phosphonic acid</td>
<td>***</td>
<td>7.27 (D)</td>
<td>600 (M+2)</td>
</tr>
<tr>
<td>250</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>(((3-acetyl-1-(2-((1R,3S,5R)-3-((6-bromopyridin-2-yl)carbamoyl)-5-methyl-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-1H-indazol-6-yl)oxy)methyl)phosphonic acid</td>
<td>***</td>
<td>8.09 (D)</td>
<td>604 (M-1)</td>
</tr>
<tr>
<td>Cmp No.</td>
<td>Structure</td>
<td>Name</td>
<td>IC₅₀ (Stars)</td>
<td>RT min (Method A,B,C or D)</td>
<td>MS (M+1)</td>
</tr>
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<td>--------</td>
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<td>----------</td>
</tr>
<tr>
<td>251</td>
<td><img src="image1.png" alt="Structure Diagram" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(2-(3-hydroxy-2-(hydroxymethyl)-2-methylpropylsulfanyl)ethoxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>3.54 (B)</td>
<td>730</td>
</tr>
<tr>
<td>252</td>
<td><img src="image2.png" alt="Structure Diagram" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(2-((3-methyloxetan-3-yl)methylsulfanyl)ethoxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>3.61 (B)</td>
<td>712</td>
</tr>
<tr>
<td>253</td>
<td><img src="image3.png" alt="Structure Diagram" /></td>
<td>(2S,4R)-1-(2-(3-acetyl-5-(2-((3-methyloxetan-3-yl)methylsulfanyl)ethoxy)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide</td>
<td>***</td>
<td>3.60 (B)</td>
<td>728</td>
</tr>
</tbody>
</table>
### EXAMPLE 8. HUMAN FACTOR D ASSAY

[0755] 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 minutes 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 minutes 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 9. HEMOLYSIS ASSAY

[0756] 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 mM NaCl, 0.025 % NaNs, pH 7.3, Complement Technology) plus 10 mM Mg-EGTA and incubated with test compound at various concentrations for 15 minutes at 37°C. RE (Complement Technology) freshly suspended in GVB° plus 10 mM Mg-EGTA are added to a final concentration of 1 x 10⁸ cells/mL and reactions are incubated for 30 minutes 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 minutes 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 10. EFFECT OF COMBINATION THERAPY

[0757] The combinatorial efficacy of two compounds on the complement alternative pathway (CAP) is assessed by determining the effect of two compounds mixed together at various concentrations with Normal Human Serum (NHS) on the hemolysis of rabbit erythrocytes (RE) or the production of terminal complement complex (TCC). In both assays the two test compounds are prepared individually in seven-point dilution series, with an eighth sample for each containing solvent alone, and each of the 64 possible combinations is tested in duplicate or triplicate wells.

[0758] In the hemolysis assay, NHS (Complement Technology) diluted to 10% in GVB° Buffer (0.1 % gelatin, 5 mM Veronal, 145 mM NaCl, 0.025 % NaNs, pH 7.3, Complement Technology) plus 10 mM Mg-EGTA is incubated with the compounds at various concentrations for 15 minutes at 37°C. RE (Complement Technology) freshly suspended in GVB° plus 10 mM Mg-EGTA are added to a final concentration of 1 x 10⁸ cells/mL and reactions are incubated for 30 minutes at 37°C. Positive control reactions consist of GVB° plus Mg-EGTA with NHS and RE but without test compounds; negative control reactions consist of GVB° plus Mg-EGTA with RE only. Samples are centrifuged at 2000g for 3 minutes and supernatants collected. Absorbance at 405 nM (A₄₀₅) is recorded using a microplate spectrophotometer.

[0759] The assay for TCC production is conducted using the Complement system Alternative Pathway Wieslab assay kit (Euro Diagnostica). NHS diluted to 5.56% in the provided

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diluent is incubated with each compound in the wells of the provided assay plates for 60 minutes at 37°C. The wells are emptied and washed with the provided wash solution, incubated with 100 µL, enzyme-linked detection antibody at 37°C for 30 minutes, emptied and washed again, and incubated with 100 µL substrate at room temperature for 30 minutes. The provided quantitation standards are used as described by the manufacturer. Positive control reactions consist of diluent with NHS but without test compounds; negative control reactions consist of diluent only. After the 30 minute incubation, the A\textsubscript{405} of each well is recorded using a microplate spectrophotometer. TCC production is quantitated from A\textsubscript{405} by reference to the quantitation standards.

[0760] Combinatorial effect in both assays are analyzed using the three-dimensional surface-graphing method of Prichard, M.N. and C. Shipman, Jr., Antiviral Research 1990, 14: 181-205, wherein the X-axis and Y-axis indicate test compound concentrations and the Z-axis indicates the difference between measured inhibition and a theoretically determined additive inhibition. For an additive combinatorial relationship the surface graph will resemble a horizontal plane of zero height, whereas positive surface peaks indicate greater inhibition than expected and therefore synergy, and negative surface peaks indicate less inhibition than expected and therefore antagonism.

[0761] Combinatorial efficacy on the hemolysis of rabbit erythrocytes (RE) can be examined using a compound described herein and a wide variety of second active agents. For example, one non-limiting example is the peptidic complement C3 inhibitor compstatin (Tocris Bioscience). In another example, the combinatorial efficacy of a compound as described herein and a complement Factor B inhibitor can be assessed, for example, using the structure below (See compound 84 in WO2013/192345). Alternatively, the combinatorial efficacy of a compound of the present invention and a monoclonal antibody directed against complement C5 protein (anti-C5, Quidel A217, murine monoclonal antibody to human complement C5, isotype IgG1K) on the production of terminal complement complex (TCC) can be assessed. In another non-limiting example, the combinatorial efficacy of an active compound of the invention and the broad spectrum inhibitor FUT-175 (BD Biosciences) on the hemolysis of rabbit erythrocytes (RE) is assessed.
Structure of Complement Factor B Inhibitor

[0762] Synergy and antagonism volumes are the summed volumes of peaks respectively above and below the Z=0 plane on the surface graph. Volumes are determined using 95% confidence limits to assure significance. Compounds are considered additive for volumes between -25 and 25. Compounds are considered slightly synergistic for volumes between 25 and 50, moderately synergistic for volumes between 50 and 100, and strongly synergistic for volumes greater than 100. Compounds are considered slightly antagonistic for volumes between -25 and -50, moderately antagonistic for volumes between -50 and -100, and strongly antagonistic for volumes less than -100. Results are presented as means ± standard deviations from two or three independent experiments.

[0763] 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. An ether compound selected from:

\[
\begin{align*}
A & \text{ selected from a moiety of Fig. 1 (B or C);} \\
B & \text{ selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D or E) or Fig. 8;} \\
C & \text{ selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;} \\
L & \text{ is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and} \\
R^{32} & \text{ is selected from a moiety of Fig. 6 (A, B, or C).}
\end{align*}
\]

(a) A selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(b) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E);

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D, or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(d) a compound of Table 2; or

(e) a compound of Fig. 9 (A, B, C, D, E, F, G or H) wherein Z^A is R^{32} selected from a moiety of Fig. 6 (A, B or C);
or a pharmaceutically acceptable salt thereof.

2. An ether compound selected from:

\[ \begin{array}{c}
A \quad B \\
\text{C} \quad \text{L} \\
\text{A} \quad \text{O}
\end{array} \]

wherein:

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
B is selected from a moiety of Fig. 7F;
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N 0, P and Q)
or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E, F, or G); and
R\(^3\) is selected from a moiety of Fig. 6 (A, B, C, D or E);
(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 or Fig. 8,
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M, N, 0, P, or Q) or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E, F, or G); and
R\(^3\) is selected from Fig. 6D;
(c) a compound selected from Table 3; or
(d) a compound selected from Fig. 9 (A, B, C, D, E, F, G or H) wherein Z\(^{32}\) is M\(^{22}\) selected from a moiety in Fig. 6D;
or a pharmaceutically acceptable salt thereof.
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; dermatomyositis; 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 an ether compound selected from:

![Chemical structure](image)

wherein:

(a) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4F; and
   R²⁻ is selected from a moiety of Fig. 6 (A, B or C); or

(b) A compound selected from Table 1;
   or a pharmaceutically acceptable salt thereof.
4. 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 an ether compound selected from:

\[
\begin{align*}
\text{C} & \quad \text{L} \\
\text{A} & \quad \text{B}
\end{align*}
\]

wherein:

(a) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, or E); and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B or C); or

(b) A compound selected from Table 1;
   or a pharmaceutically acceptable salt thereof.
5. 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; dermatomyositis; 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 an ether compound selected from:

\[
\begin{array}{c}
  \text{A} \\
  \text{B} \\
  \text{C} \\
  \text{D} \\
  \text{E}
\end{array}
\]

wherein:

(a) A is selected from a moiety of Fig. 1 (B or C);
   B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D or E) or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F), and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B, or C);
(b) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E);
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B, or C);
(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B, or C);
(d) A is selected from a moiety of Fig. 1 (B or C);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F); and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B or C);

(e) A is selected from moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
   L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   \( R^{32} \) is selected from a moiety of Fig. 6 (A, B or C);

(f) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E);
   C is selected from a moiety of Fig. 5;
   L is selected from a bond or a moiety of Fig. 4 (A, B, C, D, E or F); and
   \( R^{32} \) is selected from Fig. 6 (A, B or C);

(g) a compound of Table 2; or

(h) a compound of Fig. 9 (A, B, C, D, E, F, G or H) wherein \( Z^{32} \) is \( R^{32} \) is a moiety selected from Fig. 6 (A, B or C);
    or a pharmaceutically acceptable salt thereof.
6. 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; dermatomyositis; 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 an ether compound selected from:

![Ether Compound Diagram]

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 7F;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M, or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   $R^{32}$ is selected from a moiety of Fig. 6 (A, B, C, D or E);

(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, E, or G), or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   $R^{32}$ is selected from a moiety of Fig. 6D;

(c) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, E or G) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   $R^{32}$ is selected from moiety Fig. 6 (D or E);

(d) A is selected from a moiety of Fig. 1 (B, C, D, or E);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 or Fig. 8;
C is selected from a moiety of Fig. 30 or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
R32 is selected from a moiety of Fig. 6 (A, B, C, D, or E);
(e) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H) and Z32 is
R32 which is selected from a moiety of Fig. 6 (D or E); or
(f) a compound selected from Table 3;
or a pharmaceutically acceptable salt thereof.

7. A method for the treatment of a host with paroxysmal nocturnal hemoglobinuria (PNH),
rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal
degeneration, an ophthalmic disease, a respiratory disease and a cardiovascular disease,
comprising administering an effective amount of a compound selected from:

\[
\begin{align*}
&\text{A} \quad \text{B} \\
&\quad \text{C} \\
&\quad \text{L} \\
&\quad \text{O} \\
&\text{A} \\
\end{align*}
\]

wherein:

(a) A is selected from a moiety of Fig. 1 (B or C);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, or E) or Fig. 8;
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
R32 is selected from a moiety of Fig. 6 (A, B, or C);
(b) A is selected from a moiety of Fig. 1 (D or E);
B is selected from a moiety of Fig. 2 (B, C, D or E);
C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or a moiety selected from Fig. 4 (B, C, D, E or F); and
R32 is a moiety selected from Fig. 6 (A, B, or C);
(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);
    B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, or E); or Fig. 8;
    C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
    L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
    R_{32} is selected from a moiety of Fig. 6 (A, B, or C);
(d) A is selected from a moiety of Fig. 1 (B or C);
    B is selected from a moiety of Fig. 7 (A, B, C, D, E, or G), or Fig. 8;
    C is selected from a moiety of Fig. 5;
    L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F);
    R_{32} is a moiety selected from Fig. 6 (A, B or C);
(e) A is selected from a moiety of Fig. 1 (D or E);
    B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;
    C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
    L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F);
    R_{32} is selected from a moiety of Fig. 6 (A, B or C);
(f) A is selected from a moiety of Fig. 1 (D or E);
    B is selected from a moiety of Fig. 2 (B, C, D or E);
    C is selected from a moiety of Fig. 5;
    L is selected from a bond or a moiety of Fig. 4 (A, B, C, D, E or F);
    R_{32} is selected from a moiety of Fig. 6 (A, B or C);
(g) a compound of Table 2; or
(h) a compound of Fig. 9 A, B, C, D, E, F, G or H wherein Z_{32} is R_{32} selected
    from Figs. 6A, B or C;
    or a pharmaceutically acceptable salt thereof.
8. A method for the treatment of a host with 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 selected from:

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E); 
B is selected from a moiety of Fig. 7F; 
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, L, J, K, L, M or N) or Fig. 5; 
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and 
R$^{32}$ is selected from a moiety of Fig. 6 (A, B, C, D or E);
(b) A is selected from a moiety of Fig. 1 (B, C, D, or E); 
B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 or Fig. 8; 
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, I, K, L, M or N) or Fig. 5; 
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and 
R$^{32}$ is selected from a moiety of Fig. 6D;
(c) A is selected from a moiety of Fig. 1 (D or E); 
B is selected from a moiety of Fig. 7 (A, B, C, D, E or G) or Fig. 8; 
C is selected from a moiety of Fig. 5; 
L is selected from a moiety of Fig. 4 (A, B, C, D, E or F); and 
R$^{32}$ is selected from a moiety of Fig. 6 D;
(d) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H) and Z$^{32}$ is 
R$^{32}$ which is selected from a moiety of 6D; or
(e) A compound selected from Table 3;
or a pharmaceutically acceptable salt thereof.
9. 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; dermatomyositis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

![Chemical structure]

wherein:

(a) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4F, and
   R32 is selected from a moiety of Fig. 6 (A, B or C); or

(b) A compound selected from Table 1;
   or a pharmaceutically acceptable salt thereof.
10. 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; dermatomyositis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

\[
\begin{align*}
    &A \quad \text{selected from a moiety of Fig. 1 (D or E);} \\
    &B \quad \text{selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;} \\
    &C \quad \text{selected from a moiety of Fig. 5;} \\
    &L \quad \text{a bond or selected from a moiety of Fig. 4 (B, C, D, or E); and} \\
    &R^{22} \quad \text{selected from a moiety of Fig. 6 (A, B or C); or} \\
\end{align*}
\]

wherein:

(a) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, or E); and
   R^{22} is selected from a moiety of Fig. 6 (A, B or C); or

(b) A compound selected from Table 1;
   or a pharmaceutically acceptable salt thereof.
11. 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; derramaomyocitis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

![Chemical structure](image)

wherein:

(a) A is selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R is selected from a moiety of Fig. 6 (A, B, or C);

(b) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E);

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R is selected from a moiety of Fig. 6 (A, B, or C);

(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D, or E) or Fig. 8;

C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R is selected from a moiety of Fig. 6 (A, B, or C);

(d) A is selected from a moiety of Fig. 1 (B or C);
B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
C is selected from a moiety of Fig. 5;
L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F), and
R_{32} is selected from a moiety of Fig. 6 (A, B or C);
(e) A is selected from moiety of Fig. 1 (D or E);
B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
R_{32} is selected from a moiety of Fig. 6 (A, B or C);
(f) A is selected from a moiety of Fig. 1 (D or E);
B is selected from a moiety of Fig. 2 (B, C, D or E);
C is selected from a moiety of Fig. 5;
L is selected from a bond or a moiety of Fig. 4 (A, B, C, I), E or F); and
R_{12} is selected from Fig. 6 (A, B or C);
(g) a compound of Table 2; or
(h) a compound of Fig. 9 (A, B, C, D, E, F, G or H) wherein Z_{32} is R_{32} is a
moiety selected from Fig. 6 (A, B or C);
or a pharmaceutically acceptable salt thereof.
12. A compound 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; dermatomyositis; amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

\[
\begin{align*}
&\text{(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);} \\
&B \text{ is selected from a moiety of Fig. 7F;} \\
&C \text{ is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M, or N) or Fig. 5;} \\
&L \text{ is a bond or selected from a moiety of Fig. 4 (B, C, D, or E); and} \\
&R^{32} \text{ is selected from a moiety of Fig. 6A, B, C, D or E;} \\
&\text{(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);} \\
&B \text{ is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, E, or G), or Fig. 8;} \\
&C \text{ is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;} \\
&L \text{ is a bond or selected from a moiety of Fig. 4 (B, C, D, or E); and} \\
&R^{32} \text{ is selected from a moiety of Fig. 6D;} \\
&\text{(c) A is selected from a moiety of Fig. 1 (D or E);} \\
&B \text{ is selected from a moiety of Fig. 7 (A, B, C, D, E or G) or Fig. 8;} \\
&C \text{ is selected from a moiety of Fig. 5;} \\
&L \text{ is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and} \\
&R^{32} \text{ is selected from moiety Fig. 6 (D or E);} \\
&\text{(d) A is selected from a moiety of Fig. 1 (B, C, D, or E);} \\
&B \text{ is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 or Fig. 8;}
\end{align*}
\]
C is selected from a moiety of Fig. 30 or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and
R^{32} is selected from a moiety of Fig. 6 (A, B, C, D, or E);
(e) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H) and Z^{32} is
R^{32} which is selected from a moiety of Fig. 6 (D or E); or
(f) a compound selected from Table 3; or
or a pharmaceutically acceptable salt thereof

13. A compound for use to treat a host with paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory disease and a cardiovascular disease, selected from:

\[
\begin{align*}
\text{A} & \rightarrow \text{B} \\
\text{C} & \rightarrow \text{L} \\
\text{L} & \rightarrow \text{O} \\
\text{O} & \rightarrow \text{A}
\end{align*}
\]

wherein:

(a) A is selected from a moiety of Fig. 1 (B or C);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, or E) or Fig. 8;
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and
R^{32} is selected from a moiety of Fig. 6 (A, B, or C),
(b) A is selected from a moiety of Fig. 1 (D or E);
B is selected from a moiety of Fig. 2 (B, C, D or E);
C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or a moiety selected from Fig. 4 (B, C, D, E or F) and
R^{32} is a moiety selected from Fig. 6 (A, B, or C),
(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(d) A is selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 7 (A, B, C, D, E, or G), or Fig. 8;

C is selected from a moiety of Fig. 5;

L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F);

R^{32} is a moiety selected from Fig. 6 (A, B or C);

(e) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F);

R^{32} is selected from a moiety of Fig. 6 (A, B or C);

(f) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E),

C is selected from a moiety of Fig. 5;

L is selected from a bond or a moiety of Fig. 4 (A, B, C, D, E or F);

R^{32} is selected from a moiety of Fig. 6 (A, B or C);

(g) a compound of Table 2; or

(h) a compound of Fig. 9 A, B, C, D, E, F, G or H wherein V^{12} is R^{32} selected

from Figs. 6A, B or C; or

a pharmaceutically acceptable salt thereof.
14. A compound for use to treat a host with 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 selected from;

![Chemical Structure](image)

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 7F,
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, L, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   R$_{32}$ is selected from a moiety of Fig. 6 (A, B, C, D or E);
(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   R$_{32}$ is selected from a moiety of Fig. 6D;
(c) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, E or G) or Fig. 8;
   C is selected from a moiety of Fig. 5:
   L is selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   R$_{32}$ is selected from a moiety of Fig. 6D;
(d) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H) and Z$_{32}$ is
   R$_{32}$ which is selected from a moiety of 6D; or
(e) A compound selected from Table 3;

or a pharmaceutically acceptable salt thereof.
15. A compound for use 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, dermatomyositis, amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

wherein:

(a) A is selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F), and

R12 is selected from a moiety of Fig. 6 (A, B, or C);

(b) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E);

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R12 is selected from a moiety of Fig. 6 (A, B, or C);

(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D, or E) or Fig. 8;

C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R12 is selected from a moiety of Fig. 6 (A, B, or C);
(d) A is selected from a moiety of Fig. 1 (B or C);
   B is selected from a moiety of Fig. 7 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F); and
   \( R_{32} \) is selected from a moiety of Fig. 6 (A, B or C);

(e) A is selected from moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);
   L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   \( R_{32} \) is selected from a moiety of Fig. 6 (A, B or C);

(f) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E);
   C is selected from a moiety of Fig. 5;
   L is selected from a bond or a moiety of Fig. 4 (A, B, C, D, E or F); and
   \( R_{32} \) is selected from Fig. 6 (A, B or C);

(g) a compound of Table 2; or

(h) a compound of Fig. 9 (A, B, C, D, E, F, G or H) wherein \( Z_{32} \) is \( R_{32} \) is a
   moiety selected from Fig. 6 (A, B or C);
   or a pharmaceutically acceptable salt thereof.
16. Use of a compound for 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, dermatomyositis, amyotrophic lateral sclerosis; cytokine or inflammatory reactions in response to biotherapeutics, or an inflammatory reaction to CAR T-cell therapy, selected from:

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 7F;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M, or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F), and
   R \textsuperscript{32} is selected from a moiety of Fig. 6 (A, B, C or D);
(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, E, or G), or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, i. j, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   R \textsuperscript{32} is selected from a moiety of Fig. 6D;
(c) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, E or G) or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   R \textsuperscript{32} is selected from moiety Fig. 6 (D or E);
(d) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 or Fig. 8,
C is selected from a moiety of Fig. 30 or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and
$R^{32}$ is selected from a moiety of Fig. 6 (A, B, C, D, or E);
(e) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H) and $Z^{32}$ is
$R^{32}$ which is selected from a moiety of Fig. 6 (D or E); or
(f) a compound selected from Table 3;
or a pharmaceutically acceptable salt thereof

17. Use of a compound in the manufacture of a medicament to treat a host with paroxysmal
nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related
macular degeneration (AMD), retinal degeneration, an ophthalmic disease, a respiratory
disease and a cardiovascular disease selected from:

![Chemical Structure](attachment:image.png)

wherein:
(a) A is selected from a moiety of Fig. 1 (B or C);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D, or E) or Fig. 8;
C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and
$R^{32}$ is selected from a moiety of Fig. 6 (A, B, or C),
(b) A is selected from a moiety of Fig. 1 (D or E);
B is selected from a moiety of Fig. 2 (B, C, D or E);
C is selected from Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
L is a bond or a moiety selected from Fig. 4 (B, C, D, E or F) and
$R^{32}$ is a moiety selected from Fig. 6 (A, B, or C),
(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);
B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^32 is selected from a moiety of Fig. 6 (A, B, or C);

(d) A is selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 7 (A, B, C, D, E, or G), or Fig. 8;

C is selected from a moiety of Fig. 5;

L is a bond or selected from a moiety of Figure 4 (A, B, C, D, E or F);

R^32 is a moiety selected from Fig. 6 (A, B or C);

(e) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (A, B, C, D, or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (A, B, C, D, E or F);

R^32 is selected from a moiety of Fig. 6 (A, B or C);

(f) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E),

C is selected from a moiety of Fig. 5;

L is selected from a bond or a moiety of Fig. 4 (A, B, C, D, E or F);

R^32 is selected from a moiety of Fig. 6 (A, B or C);

(g) a compound of Table 2; or

(h) a compound of Fig. 9 A, B, C, D, E, F, G or H wherein V^12 is R^32 selected from Figs. 6A, B or C;

or a pharmaceutically acceptable salt thereof.
18. Use of a compound in the manufacture of a medicament to treat a host with 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 selected from:

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 7F;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F) and
   R\textsuperscript{32} is selected from a moiety of Fig. 6 (A, B, C, D or E);
(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
   B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 or Fig. 8;
   C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;
   L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and
   R\textsuperscript{32} is selected from a moiety of Fig. 6D;
(c) A is selected from a moiety of Fig. 1 (D or E);
   B is selected from a moiety of Fig. 7 (A, B, C, D, E or G); or Fig. 8;
   C is selected from a moiety of Fig. 5;
   L is selected from a moiety of Fig. 4 (A, B, C, D, E or F); and
   R\textsuperscript{32} is selected from a moiety of Fig. 6 D;
(d) A compound selected from Fig. 9 (A, B, C, D, E, F, G or H); and Z\textsuperscript{32} is
   R\textsuperscript{32} which is selected from a moiety of 6D; or
(e) A compound selected from Table 3;

or a pharmaceutically acceptable salt thereof
19. A pharmaceutical composition comprising an effective amount of a compound selected from:

\[
\begin{align*}
A & \quad \text{selected from a moiety of Fig. 1 (B or C);} \\
B & \quad \text{selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D or E) or Fig. 8;}
C & \quad \text{selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;}
L & \quad \text{a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and}
R^{32} & \quad \text{is selected from a moiety of Fig. 6 (A, B, or C);}
\end{align*}
\]

wherein:

(a) A selected from a moiety of Fig. 1 (B or C);

B is selected from a moiety of Fig. 2 (B, C, D or E); Fig. 7 (A, B, C, D or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(b) A is selected from a moiety of Fig. 1 (D or E);

B is selected from a moiety of Fig. 2 (B, C, D or E);

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N) or Fig. 5;

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(c) A is selected from a moiety of Fig. 1 (B, C, D, or E);

B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 (A, B, C, D, or E) or Fig. 8;

C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N);

L is a bond or selected from a moiety of Fig. 4 (B, C, D, E or F); and

R^{32} is selected from a moiety of Fig. 6 (A, B, or C);

(d) a compound of Table 2; or

(e) a compound of Fig. 9 (A, B, C, D, E, F, G or H) wherein Z^{32} is R^{32} selected from a moiety of Fig. 6 (A, B or C);

or a pharmaceutically acceptable salt thereof.
20. A pharmaceutical composition comprising an effective amount of a compound selected from:

wherein:

(a) A is selected from a moiety of Fig. 1 (B, C, D, or E);
    B is selected from a moiety of Fig. 7F;
    C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M or N 0, P and Q);
    or Fig. 5;
    L is a bond or selected from a moiety of Fig. 4 (B, C, D, E, F, or G); and
    R^{32} is selected from a moiety of Fig. 6 (A, B, C, D or E);

(b) A is selected from a moiety of Fig. 1 (B, C, D, or E);
    B is selected from a moiety of Fig. 2 (B, C, D or E), Fig. 7 or Fig. 8;
    C is selected from a moiety of Fig. 3 (B, C, D, E, F, G, H, I, J, K, L, M, N, 0, P, or Q) or Fig. 5;
    L is a bond or selected from a moiety of Fig. 4 (B, C, D, E, F, or G); and
    R^{32} is selected from Fig. 6D;

(c) a compound selected from Table 3; or

(d) a compound selected from Fig. 9 (A, B, C, D, E, F, G or H) wherein Z^{32} is M^{72}
    selected from a moiety in Fig. 6D;
    or a pharmaceutically acceptable salt thereof.

21. The methods of claims 3, 4, 5, 6, 7, or 8 wherein the host is a human.

22. The compounds of claims 9, 10, 11, 12, 13, or 14 used for the treatment of a human.

23. Use of the compounds of claims 15, 16, 17, or 18 in the manufacture of a medicament for a human.
FIG. 3H
FIG. 3Q
FIG. 4A

[Chemical structure diagram]
FIG. 4E
FIG. 4F
FIG. 6B
FIG. 6C
FIG. 7G
FIG. 8

Chemical structures are shown in the figure.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20 16/048701

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)

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)

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) (keyword delimited)

Electronic data base consulted during the international search (name of database and, where practicable, search terms used)

PatBase, STN, PubMed, Google Patents, Google Scholar

Search terms used: indole carboxamide pyrroline cyclopentyl fatty liver

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

Date of the actual completion of the international search
05 December 2016

Date of mailing of the international search report
10 JAN 2017

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Authorized officer
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PCT OSP: 571-272-7774

Form PCT/ISA/2 10 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

**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. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III**  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, 5, 7, 11, 13, 15, 17, 19, and 21-23 have been analyzed subject to the restriction that the claims read on an ether compound having the formula of the instant invention wherein: A is the first shown moiety in Fig. 1B; B is the first shown moiety of Fig. 2B; C is the first shown moiety in Fig. 3B; L is a bond; R32 is the first shown moiety in Fig. 6A.

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, 5, 7, 11, 13, 15, 17, 19, 21-23

**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 fees 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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)
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 1-23 are drawn to compounds having the formula of the instant invention, methods for the treatment of a host with a disorder, compounds for use to treat a host with a disorder, compounds for use in the manufacture of a medicament to treat a host with a disorder, and pharmaceutical compositions.

The first invention of Group I is restricted to an ether compound having the formula of the instant invention: wherein: A is the first shown moiety of Fig. 1B; B is the first shown moiety of Fig. 2B; C is the first shown moiety in Fig. 3B; L is a bond; R32 is the first shown moiety in Fig. 6A; methods for the treatment of a host with a disorder; compounds for use to treat a host with a disorder; compounds for use in the manufacture of a medicament to treat a host with a disorder; and pharmaceutical compositions. It is believed that claims 1, 5, 7, 11, 13, 15, 17, 19, and 21-23 read on this first named invention and 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 having the formula of the instant invention: wherein: A is the second shown moiety of Fig. 1B; B is the first shown moiety of Fig. 2B; C is the first shown moiety in Fig. 3B; L is the first shown moiety of Fig. 4B; R32 is the first shown moiety in Fig. 6A; methods for the treatment of a host with a disorder; compounds for use to treat a host with a disorder; compounds for use in the manufacture of a medicament to treat a host with a disorder; and pharmaceutical compositions. 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 indicated above under this group. Failure to clearly define 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, and B.

The Groups I share the technical features of a compound having the core structure of the instant invention; 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 sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; a method for the treatment of a host with paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic 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 paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; a compound for use 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; dermatomicytis; 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 compound for use to treat a host with paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; a compound for use 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; dermatomicytis; 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 compound for use in the manufacture of a medicament to treat a host with paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; a compound for use in the manufacture of a medicament to treat a host with paroxysmal nocturnal hemoglobinuria (PNH), rheumatoid arthritis, multiple sclerosis, age-related macular degeneration (AMD), rhematoid arthritis, anaphylactic disease, a respiratory disease or a cardiovascular disease, comprising administering an effective amount of a compound; and a pharmaceutical composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2012/0295684 A1 to Altmann et al. teach a compound having the core structure of the instant invention (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...lipid 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]), comprising administering an effective amount of a compound (Claims 20 and 22; Para. [0017]; Para. [0859]); 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); and a pharmaceutical composition (Abstract; Claim 18; Para. [0015]) comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof (Abstract; Claim 18; Para. [0015]).

The inventions listed in Groups I therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.