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(54) **Titre : COMPOSES ARYLE, HETEROARYLE ET HETEROCYCLIQUES POUR LE TRAITEMENT DE TROUBLES INDUITS PAR UN COMPLEMENT**

(54) **Title: ARYL, HETEROARYL, AND HETEROCYCLIC COMPOUNDS FOR TREATMENT OF COMPLEMENT MEDIATED DISORDERS**

(57) **Abrégé/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^{12} or R^{13} on the A group is an aryl, heteroaryl or heterocycle (R^{32}) are provided. The inhibitors described herein target factor D and inhibit or regulate the complement cascade at an early and essential point in the alternative complement pathway, and reduce factor D's ability to modulate the classical and lectin complement pathways. The inhibitors of factor D described herein are capable of reducing the excessive activation of complement, which has been linked to certain autoimmune, inflammatory, and neurodegenerative diseases, as well as ischemia-reperfusion injury and cancer.

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ARYL, HETEROARYL, AND HETEROCYCLIC COMPOUNDS FOR TREATMENT OF COMPLEMENT MEDIATED DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional U.S. Application No. 61/944,189, filed February 25, 2014, provisional U.S. Application No. 62/022,916, filed July 10, 2014, and provisional U.S. Application 62/046,783, filed September 5, 2014. The entirety of each of these applications is hereby incorporated by reference for all purposes.

BACKGROUND

[0002] The complement system is a part of the innate immune system which does not adapt to changes over the course of the host's life, but is recruited and used by the adaptive immune system. For example, it assists, or complements, the ability of antibodies and phagocytic cells to clear pathogens. This sophisticated regulatory pathway allows rapid reaction to pathogenic organisms while protecting host cells from destruction. Over thirty proteins and protein fragments make up the complement system. These proteins act through opsonization (enhancing phaogytosis of antigens), chemotaxis (attracting macrophages and neutrophils), cell lysis (rupturing membranes of foreign cells) and agglutination (clustering and binding of pathogens together).

[0003] The complement system has three pathways: classical, alternative and lectin. Complement factor D plays an early and central role in activation of the alternative pathway of the complement cascade. Activation of the alternative complement pathway is initiated by spontaneous hydrolysis of a thioester bond within C3 to produce C3(H_2O), which associates with factor B to form the C3(H_2O)B complex. Complement factor D acts to cleave factor B within the C3(H_2O)B complex to form Ba and Bb. The Bb fragment remains associated with C3(H_2O) to form the alternative pathway C3 convertase C3(H_2O)Bb. Additionally, C3b generated by any of the C3 convertases also associates with factor B to form C3bB, which factor D cleaves to generate the later stage alternative pathway C3 convertase C3bBb. This latter form of the alternative pathway C3 convertase may provide important downstream amplification within all three of the defined complement pathways, leading ultimately to the recruitment and assembly of additional factors in the complement cascade pathway, including the cleavage of C5 to C5a and

C5b. C5b acts in the assembly of factors C6, C7, C8, and C9 into the membrane attack complex, which can destroy pathogenic cells by lysing the cell.

[0004] 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.

[0005] Age-related macular degeneration (AMD) is a leading cause of vision loss in industrialized countries. Based on a number of genetic studies, there is evidence of the link between the complement cascade and macular degeneration. Individuals with mutations in the gene encoding complement factor H have a fivefold increased risk of macular degeneration and individuals with mutations in other complement factor genes also have an increased risk of AMD. Individuals with mutant factor H also have increased levels of C-reactive protein, a marker of inflammation. Without adequate functioning factor H, the alternative pathway of the complement cascade is overly activated leading to cellular damage. Inhibition of the alternative pathway is thus desired.

[0006] Paroxysmal nocturnal hemoglobinuria (PNH) is a non-malignant, hematological disorder characterized by the expansion of hematopoietic stem cells and progeny mature blood cells which are deficient in some surface proteins. PNH erythrocytes are not capable of modulating their surface complement activation, which leads to the typical hallmark of PNH – the chronic activation of complement mediated intravascular anemia. Currently, only one product, the anti-C5 monoclonal antibody eculizumab, has been approved in the U.S. for treatment of PNH. However, many of the patients treated with eculizumab remain anemic, and many patients continue to require blood transfusions. In addition, treatment with eculizumab requires life-long intravenous injections. Thus, there is an unmet need to develop novel inhibitors of the complement pathway.

[0007] 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.

[0008] 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.

[0009] Biocryst Pharmaceuticals US Pat. No. 6653340 titled "Compounds useful in the complement, coagulat and kallikrein pathways and method for their preparation" describes fused bicyclic ring compounds that are potent inhibitors of factor D. Development of the factor D inhibitor BCX1470 was discontinued due to lack of specificity and short half-life of the compound.

[0010] Novartis PCT patent publication WO2012/093101 titled "Indole compounds or analogues thereof useful for the treatment of age-related macular degeneration" describes certain factor D inhibitors.

[0011] Novartis PCT patent publications WO2014/002057 titled "Pyrrolidine derivatives and their use as complement pathway modulators" and WO2014/009833 titled "Complement pathway modulators and uses thereof" describe additional factor D inhibitors with heterocyclic substituents. Additional factor D inhibitors are described in Novartis PCT patent publications WO2014/002051, WO2014/002052, WO2014/002053, WO2014/002054, WO2014/002058, WO2014/002059, and WO2014/005150.

[0012] 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.

[0013] Japan Tobacco Inc. PCT patent publication WO1999/048492 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.

[0014] Ferring B.V. and Yamanouchi Pharmaceutical Co. lTD. PCT patent publication

WO1993/020099 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.

[0015] Alexion Pharmaceuticals PCT patent publication WO1995/029697 titled "Methods and compositions for the treatment of glomerulonephritis and other inflammatory diseases" discloses antibodies directed to C5 of the complement pathway for the treatment of glomerulonephritis and inflammatory conditions involving pathologic activation of the complement system. Alexion Pharmaceutical's anti-C5 antibody eculizumab (Soliris®) is currently the only complement-specific antibody on the market, and is the first and only approved treatment for paroxysmal nocturnal hemoglobinuria (PNH).

[0016] Compounds which mediate the complement pathway, and for example, act as factor D inhibitors are needed for treatment of disorders in a host, including a human, associated with misregulation of the complement cascade.

SUMMARY

[0017] It has been discovered that a compound of Formula I, or a pharmaceutically acceptable salt or composition thereof, wherein R^{12} or R^{13} on the A group is an aryl, heteroaryl or heterocycle, is a superior inhibitor of complement factor D.

[0018] In one embodiment, a method for the treatment of a disorder associated with a dysfunction, including increased activity, of the complement pathway is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, as described in more detail below.

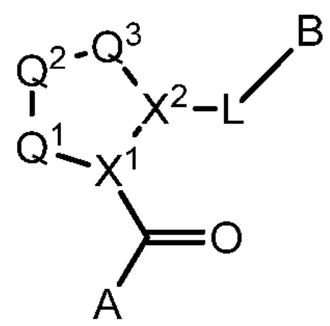
[0019] In one embodiment, the disorder is associated with the alternative complement cascade pathway. In yet another embodiment, the disorder is associated with the complement classical pathway. In a further embodiment, the disorder is associated with the complement lectin pathway. The factor D inhibitors provided herein can thus 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.

[0020] Specific embodiments of this invention are directed to certain disease indications. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of rheumatoid arthritis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of multiple sclerosis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0021] In other embodiments of the invention, an active compound provided herein can be used to treat or prevent a disorder in a host mediated by complement factor D, or by an excessive or detrimental amount of the C3 amplification loop of the complement pathway. As examples, the invention includes methods to treat or prevent complement associated disorders that are induced by antibody-antigen interactions, a component of an immune or autoimmune disorder or by ischemic injury. The invention also provides methods to decrease inflammation or an immune response, including an autoimmune response, where mediated or affected by factor D.

[0022] The disclosure provides compounds of Formula I



(I)

and the pharmaceutically acceptable salts and compositions thereof, wherein:

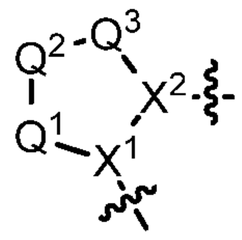
[0023] Q^1 is $N(R^1)$ or $C(R^1R^{1'})$;

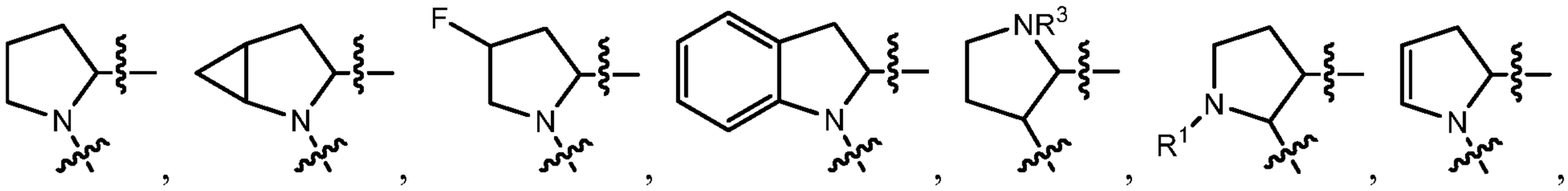
[0024] Q^2 is $C(R^2R^{2'})$, $C(R^2R^{2'})$-$C(R^2R^{2'})$, S, O, $N(R^2)$ or $C(R^2R^{2'})O$;

[0025] Q^3 is $N(R^3)$, S, or $C(R^3R^{3'})$;

[0026] X^1 and X^2 are independently N, CH, or CZ, or X^1 and X^2 together are C=C; and

[0027] wherein Q^1, Q^2, Q^3, X^1, and X^2 are selected such that a stable compound results.

[0028] Non-limiting examples of the  ring are illustrated below (any of which can be otherwise substituted with R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$) as described in more detail below.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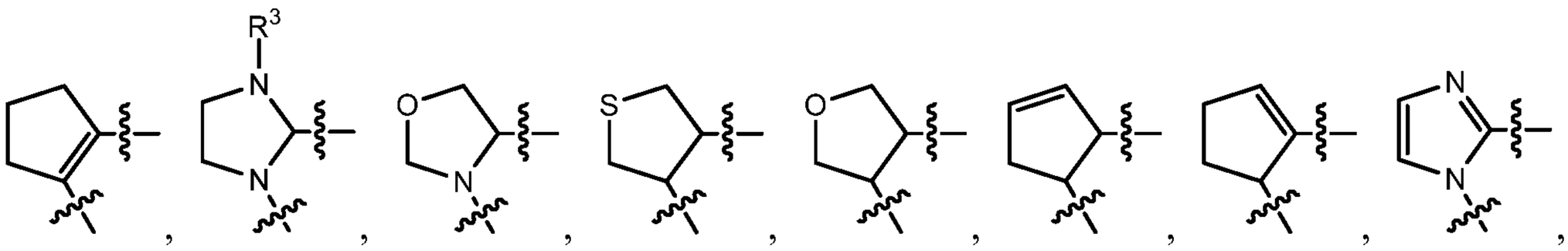
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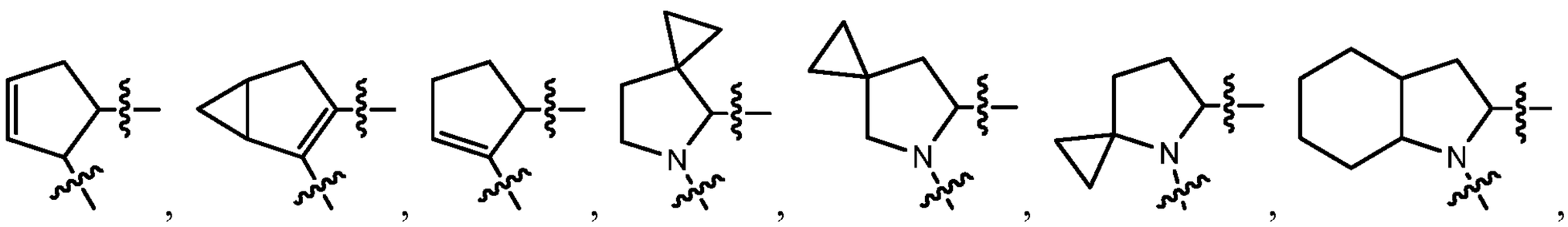
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[0029] R and R' are independently chosen from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl wherein each group can be optionally substituted or any other substituent group herein that provides the desired properties. In some embodiments, the ring includes one or more chiral carbon atoms. The invention includes embodiments in which the chiral carbon can be provided as an enantiomer, or mixtrues 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.

[0030] Z is F, Cl, NH_2, CH_3, CH_2D, CHD_2, or CD_3.

[0031] R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently chosen at each occurrence, as appropriate, and only where a stable compound results, from hydrogen, halogen, hydroxyl, nitro, cyano, amino, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_2-C_6alkynyl, C_2-C_6alkanoyl, C_1-C_6thioalkyl, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, -C_0-C_4alkylNR^9R^{10}, -$C(O)OR^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -$OC(O)NR^9R^{10}$, -$NR^9C(O)OR^{10}$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, where R^9 and R^{10} are independently chosen at each occurrence from hydrogen, C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), and -O-C_0-C_4alkyl(C_3-C_7cycloalkyl).

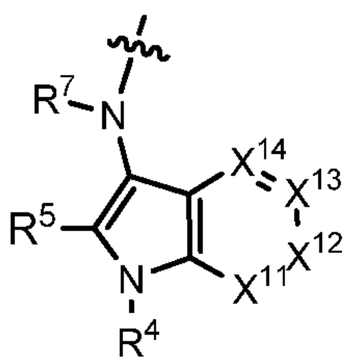
[0032] In alternative embodiments, R^1 and $R^{1'}$ or R^3 and $R^{3'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently chosen from N, O, or S; R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring; or R^2 and $R^{2'}$may be taken together to form a 3- to 6-membered heterocyclic spiro ring; each of which spiro ring each of which ring may be unsubstituted or substituted with 1 or more substituents independently chosen from halogen (and in particular F), hydroxyl, cyano, -COOH, C_1-C_4alkyl (including in particular methyl), C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, hydroxyC_1-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0033] In alternative embodiments, R^1 and R^2 may be taken together to form a 3-membered carbocyclic ring; R^1 and R^2 may be taken together to form a 4- to 6-membered carbocyclic or aryl ring or a 4- to 6-membered heterocyclic or heteroaryl ring containing 1 or 2 heteroatoms independently chosen from N, O, and S; or R^2 and R^3, if bound to adjacent carbon

atoms, may be taken together to form a 3- to 6-membered carbocyclic or aryl ring or a 3- to 6-membered heterocyclic or heteroaryl ring; each of which ring may be unsubstituted or substituted with 1 or more substituents independently chosen from halogen (and in particular F), hydroxyl, cyano, -COOH, C_1-C_4alkyl (including in particular methyl), C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, hydroxyC_1-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0034] In alternative embodiments, R^1 and $R^{1'}$, R^2 and $R^{2'}$, or R^3 and $R^{3'}$ can be taken together to form a carbonyl group. In alternative embodiments, R^1 and R^2 or R^2 and R^3 can be taken together to form a carbon-carbon double bond.

[0035] A is a group chosen from: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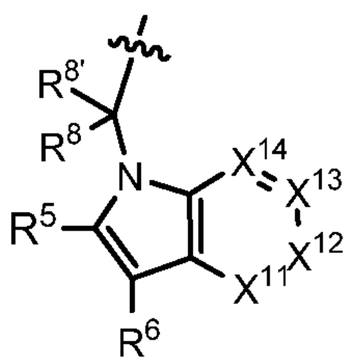
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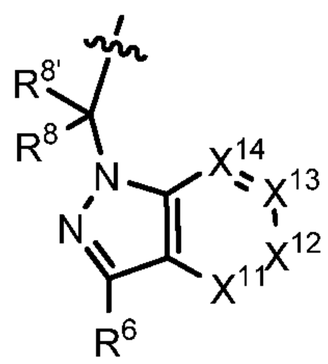
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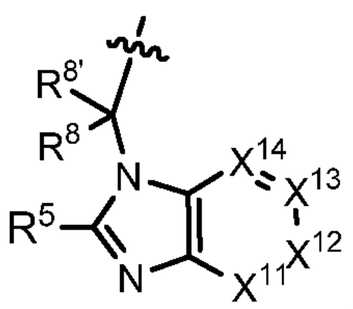
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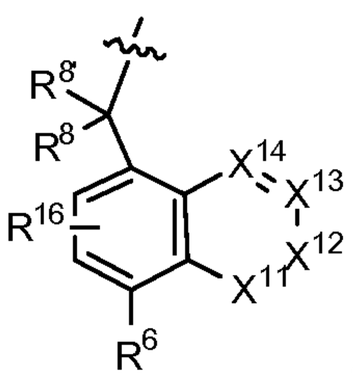
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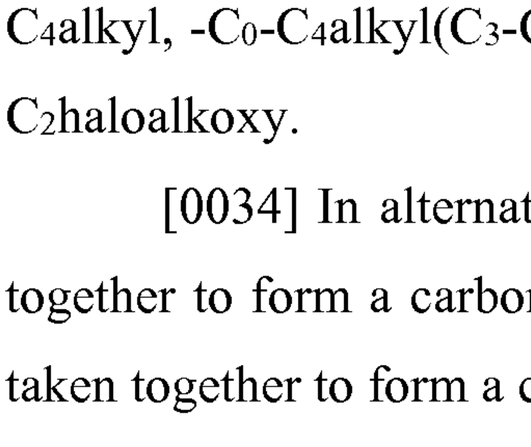
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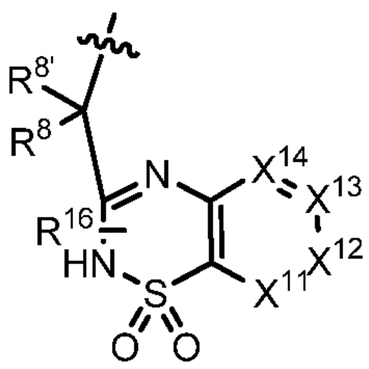
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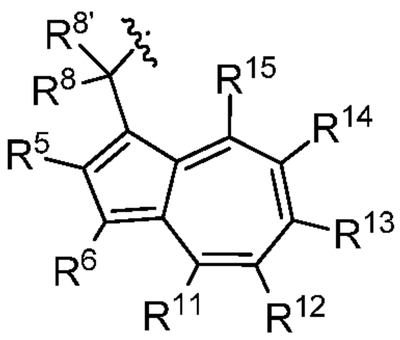
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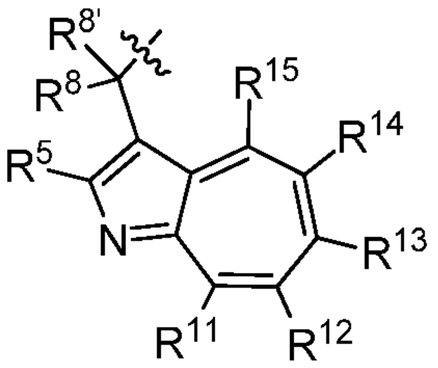
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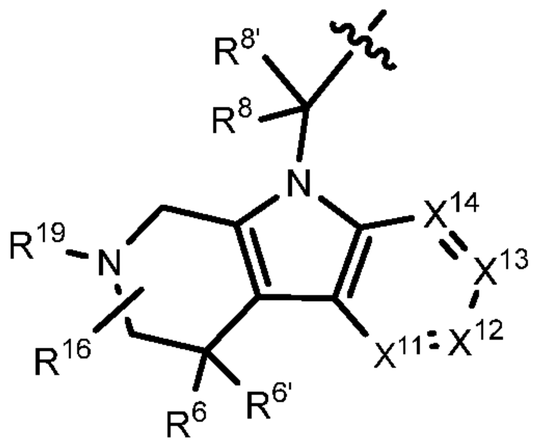
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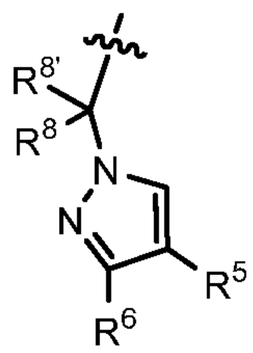
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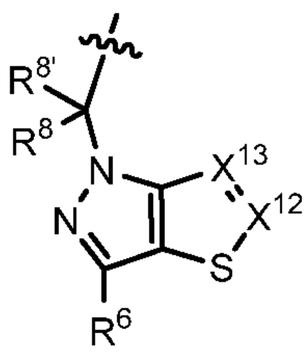
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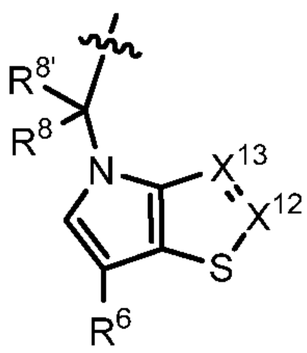
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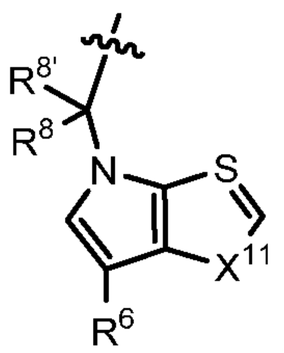
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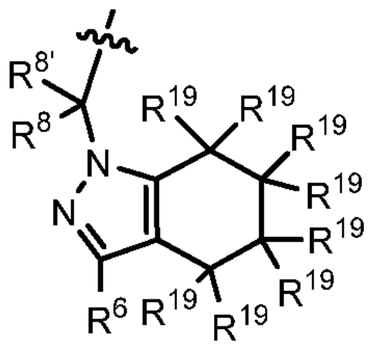
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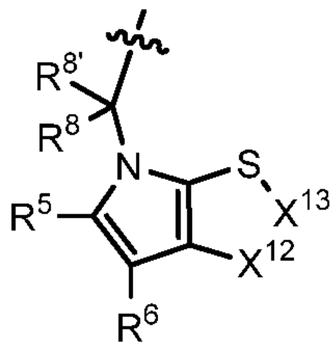
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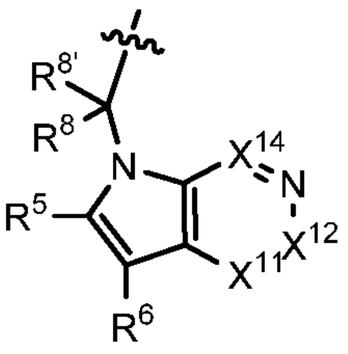
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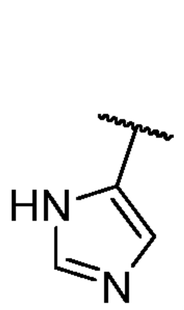
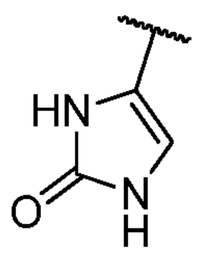
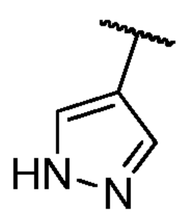
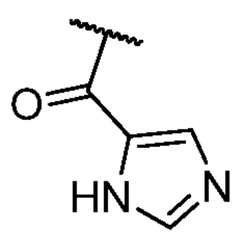
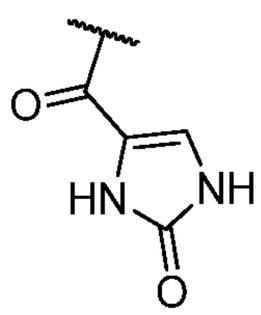
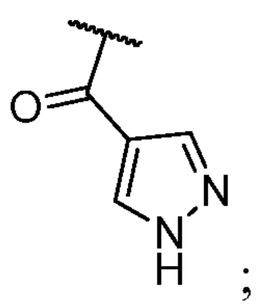
[0036] R^4 is chosen from -CHO, -$CONH_2$, C_2-C_6alkanoyl, hydrogen, -SO_2NH_2, -$C(CH_2)_2F$, -$CH(CF_3)NH_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_2alkyl(C_3-C_7cycloalkyl),


, 
, 
, 
, 
, or 
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each of which R^4 other than hydrogen, -CHO, and –$CONH_2$, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_2alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0037] R^5 and R^6 are independently chosen from –CHO, -$C(O)NH_2$, -$C(O)NH(CH_3)$, C_2-C_6alkanoyl, hydrogen, hydroxyl, halogen, cyano, nitro, -COOH, -SO_2NH_2, vinyl, C_1-C_6alkyl (including methyl), C_2-C_6alkenyl, C_1-C_6alkoxy, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_4alkyl(C_3-C_7cycloalkyl), -$P(O)(OR^9)_2$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)N(CH_2CH_2R^9)(R^{10})$, -$NR^9C(O)R^{10}$, phenyl, or 5- to 6-membered heteroaryl.

[0038] Each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH is unsubstituted or optionally substituted. For example, R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH may be substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, imino, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_4alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0039] $R^{6'}$ is hydrogen, halogen, hydroxyl, C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or C_1-C_4alkoxy; or R^6 and $R^{6'}$ may be taken together to form an oxo, vinyl, or imino group.

[0040] R^7 is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl).

[0041] R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, and (C_1-C_4alkylamino)C_0-C_2alkyl; or R^8 and $R^{8'}$ are taken together to form an oxo group; or R^8 and $R^{8'}$ can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring.

[0042] R^{16} is absent or may include one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0043] R^{19} is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -SO_2C_1-C_6alkyl, (mono- and di-C_1-C_6alkylamino)C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkyl(C_3-C_7heterocycloalkyl), -C_0-C_4alkyl(aryl), C_0-C_4alkyl(heteroaryl), and wherein R^{19} other than hydrogen is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, -COOH, and –C(O)OC_1-C_4alkyl.

[0044] X^{11} is N or CR^{11}.

[0045] X^{12} is N or CR^{12}.

[0046] X^{13} is N or CR^{13}.

[0047] X^{14} is N or CR^{14}.

[0048] No more than 2 of X^{11}, X^{12}, X^{13}, and X^{14} are N.

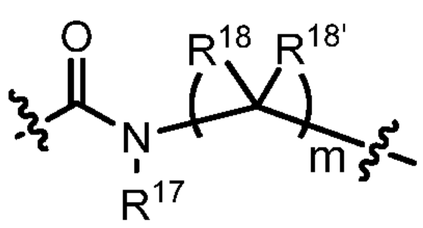
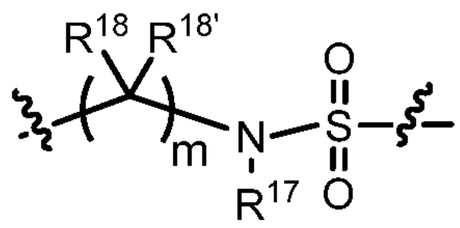
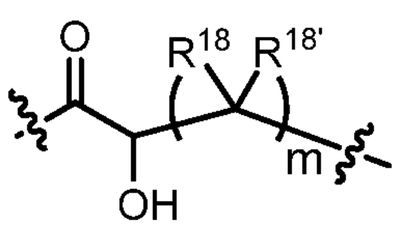
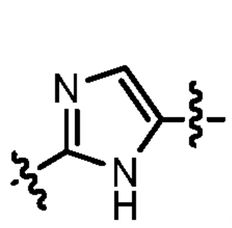
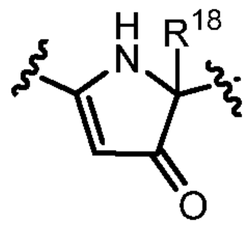
[0049] One of R^{12} and R^{13} is chosen from R^{31} and the other of R^{12} and R^{13} is chosen from R^{32}. In an alternative embodiment, R^{12} and R^{13} are each independently selected from an R^{32} moiety.

[0050] R^{31} is chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_2-C_6alkenyloxy, -C(O)OR^9, C_1-C_6thioalkyl, -C_0-C_4alkylNR^9R^{10}, -C(O)NR^9R^{10}, -SO_2R^9, -$SO_2NR^9R^{10}$, -OC(O)R^9, and -C(NR^9)NR^9R^{10}, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent chosen from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl)(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0051] R^{32} is selected from aryl; saturated or unsaturated heterocycle (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the heterocycle is bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{12} or R^{13} position; and heteroaryl (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the aryl, heterocycle or heteroaryl

ring can be optionally substituted.

[0052] R^{11}, R^{14}, and R^{15} are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -O(PO)(OR^9)$_2$, -(PO)(OR^9)$_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-C_6alkenyl(aryl), C_2-C_6alkenyl(cycloalkyl), C_2-C_6alkenyl(heterocycle), C_2-C_6alkenyl(heteroaryl), C_2-C_6alkynyl, C_2-C_6alkynyl(aryl), C_2-C_6alkynyl(cycloalkyl), C_2-C_6alkynyl(heterocycle), C_2-C_6alkynyl(heteroaryl), C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkoxy(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0053] L is a bond or is chosen from the formulas  ,  ,  ,  and  , where R^{17} is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl) and R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3.

[0054] 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_2-C_6alkenyl; C_2-C_6alkynyl; –(C_0-C_4alkyl)(aryl); –(C_0-C_4alkyl)(heteroaryl); or –(C_0-C_4alkyl)(biphenyl).

[0055] Each of which B is unsubstituted or substituted with one or more substituents independently chosen from R^{33} and R^{34}, and 0 or 1 substituents chosen from R^{35} and R^{36}.

[0056] R^{33} is independently chosen from halogen, hydroxyl, -COOH, cyano, C_1-C_6alkyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkylNR^9R^{10}, -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0057] R^{34} is independently chosen from nitro, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6thioalkyl, -JC_3-C_7cycloalkyl, -B(OH)$_2$, -JC(O)NR^9R^{23},-JOSO_2OR^{21}, -C(O)$(CH_2)_{1\text{-}4}$S(O)R^{21}, -O$(CH_2)_{1\text{-}4}$S(O)$NR^{21}R^{22}$, -JOP(O)(OR^{21})(OR^{22}), -JP(O)(OR^{21})(OR^{22}), -JOP(O)(OR^{21})R^{22}, -JP(O)(OR^{21})R^{22}, -JOP(O)$R^{21}R^{22}$, -JP(O)$R^{21}R^{22}$, -JSP(O)(OR^{21})(OR^{22}), -JSP(O)(OR^{21})(R^{22}), -JSP(O)(R^{21})(R^{22}), -JNR^9P(O)(NHR^{21})(NHR^{22}), -JNR^9P(O)(OR^{21})(NHR^{22}), -JNR^9P(O)(OR^{21})(OR^{22}), -JC(S)R^{21}, -J$NR^{21}SO_2R^{22}$, -JNR^9S(O)$NR^{10}R^{22}$, -J$NR^9SO_2NR^{10}R^{22}$, -J$SO_2NR^9COR^{22}$, -J$SO_2NR^9CONR^{21}R^{22}$, -J$NR^{21}SO_2R^{22}$, -JC(O)$NR^{21}SO_2R^{22}$, -JC(NH_2)NR^{22},

-$JC(NH_2)NR^9S(O)_2R^{22}$, -$JOC(O)NR^{21}R^{22}$, -$JNR^{21}C(O)OR^{22}$, -$JNR^{21}OC(O)R^{22}$, -$(CH_2)_{1-4}C(O)NR^{21}R^{22}$, -$JC(O)R^{24}R^{25}$, -$JNR^9C(O)R^{21}$, -$JC(O)R^{21}$, -$JNR^9C(O)NR^{10}R^{22}$, -$CCR^{21}$, -$(CH_2)_{1-4}OC(O)R^{21}$, and -$JC(O)OR^{23}$; each of which R^{34} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0058] R^{35} is independently chosen from naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl containing 1 or 2 heteroatoms chosen from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R^{35} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0059] R^{36} is independently chosen from tetrazolyl, (phenyl)C_0-C_2alkyl, (phenyl)C_1-C_2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently chosen from N, O, B, and S, each of which R^{36} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, -$OSi(CH_3)_2C(CH_3)_3$, –$Si(CH_3)_2C(CH_3)_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0060] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, -C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{21} and R^{22} can be optionally substituted.

[0061] R^{23} is independently chosen at each occurrence from C_1-C_6alkyl, C_1-C_6haloalkyl, (aryl)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered

heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{23} can be optionally substituted.

[0062] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyl group, or a 6- to 10- membered bicyclic heterocyclic group having fused, spiro, or bridged rings, and each R^{24} and R^{25} can be optionally substituted.

[0063] J is independently chosen at each occurrence from a covalent bond, C_1-C_4alkylene, -OC_1-C_4alkylene, C_2-C_4alkenylene, and C_2-C_4alkynylene.

[0064] Pharmaceutical compositions comprising a compound or salt of Formula I together with a pharmaceutically acceptable carrier are also disclosed.

[0065] Methods of treating or preventing disorders mediated by complement cascade factor D, including but not limited to age-related macular degeneration (AMD), retinal degeneration, other ophthalmic diseases (e.g., geographic atrophy), paroxysymal nocturnal hemoglobinuria (PNH), multiple sclerosis (MS), arthritis including rheumatoid arthritis (RA), a respiratory disease or a cardiovascular disease, are provided, comprising administering a therapeutically effective amount of a compound or salt of Formula I to a host, including a human, in need of such treatment are also disclosed.

[0066] In another embodiment, an effective amount of an active factor D inhibiting compound is provided to treat an inflammatory or immune disorder, including an autoimmune disorder, that is meadited or affected by factor D. In an alternative embodiment, the compound of Formula I can be used to treat a disorder mediated by the complement pathway, regardless whether it is acting through Factor D.

[0067] The present invention includes at least the following features:

(a) a compound of Formula I as described herein, and pharmaceutically acceptable salts and prodrugs thereof (each of which and all subgenuses and species thereof considered individually and specifically described);

(b) Formula I 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, including age-related macular degeneration (AMD), retinal

degeneration, paroxysymal nocturnal hemoglobinuria (PNH), multiple sclerosis (MS), and rheumatoid arthritis (RA) and other disorders described further herein;

(c) use of Formula I, and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for use in treating or preventing disorders mediated by complement cascade factor D, including age-related macular degeneration (AMD), retinal degeneration, paroxysymal nocturnal hemoglobinuria (PNH), multiple sclerosis (MS), and rheumatoid arthritis (RA) and other disorders described further herein;

(d) a process for manufacturing a medicament intended for the therapeutic use for treating or preventing treating or preventing disorders mediated by complement cascade factor D, including age-related macular degeneration (AMD), retinal degeneration, paroxysymal nocturnal hemoglobinuria (PNH), multiple sclerosis (MS), and rheumatoid arthritis (RA) and other disorders described further herein characterized in that Formula I as described herein is used in the manufacture;

(e) a pharmaceutical formulation comprising an effective host-treating amount of the Formula I or a pharmaceutically acceptable salt or prodrug thereof together with a pharmaceutically acceptable carrier or diluent;

(f) Formula I as described herein in substantially pure form, including substantially isolated from other chemical entities (e.g., at least 90 or 95%);

(g) processes for the manufacture of the compounds of Formula I and salts, compositions, dosage forms thereof; and

(h) processes for the preparation of therapeutic products that contain an effective amount of Formula I, as described herein.

DETAILED DESCRIPTION

I. TERMINOLOGY

[0068] 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.

[0069] The compounds in any of the Formulas described herein include enantiomers, mixtures of enantiomers, diastereomers, tautomers, racemates and other isomers, such as rotamers, as if each is specifically described. "Formula I" includes all subgeneric groups of

Formula I, such as Formula IA and Formula IB 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 IC - ID, and Formulas II – XXX, and also includes pharmaceutically acceptable salts of all subgeneric groups of Formula I, such as Formulas IA - ID, and Formulas II – XXX, unless contraindicated by the context in which this phrase is used.

[0070] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0071] The present invention includes compounds of Formula I and the use of compounds with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons.

[0072] Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}CI, ^{125}I respectively. The invention includes isotopically modified compounds of Formula I. 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.

[0073] By way of general example and without limitation, isotopes of hydrogen, for example, deuterium (^{2}H) and tritium (^{3}H) may be used anywhere in described structures that achieves the desired result. Alternatively or in addition, isotopes of carbon, e.g., ^{13}C and ^{14}C, may be used. In one embodiment, the isotopic substitution is deuterium for hydrogen at one or more locations on the molecule to improve the performance of the drug, for example, the pharmacodynamics, pharmacokinetics, biodistribution, half-life, stability, AUC, Tmax, Cmax, etc. For example, the deuterium can be bound to carbon in a location of bond breakage during metabolism (an α-deuterium kinetic isotope effect) or next to or near the site of bond breakage (a β-deuterium kinetic isotope effect).

[0074] Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is 90, 95 or 99% or more enriched in an isotope at any location of interest. In one embodiments deuterium is 90, 95 or 99% enriched at a desired location. Unless otherwise stated, the enrichment at any point is above natural abundance and enough to alter a detectable property of the drug in a human.

[0075] In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group substituent on the L-B moiety region. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group selected from any of R^{18}, $R^{18'}$, R^{33}, R^{34}, R^{35}, and/or R^{36}. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group substituent within the A-carbonyl moiety region. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs at $R^{4,}$ R^{5}, R^{6}, $R^{6'}$, R^{7}, R^{8}, $R^{8'}$, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{19}, R^{21}, R^{22}, R^{23}, R^{31}, and R^{32}. In other embodiments, certain substituents on the proline ring are selectively deuterated. For example, in one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs at R, $R^{'}$, R^{1}, $R^{1'}$, R^{2}, $R^{2'}$, R^{3}, and/or $R^{3'}$. In one embodiment, for example, when any of the R substituents of the proline ring are methyl or methoxy, the alkyl residue is optionally deuterated, e.g., CD_3 or

OCD_3. In certain other embodiments, when two substituents of the proline ring are combined to form a cyclopropyl ring, the unsubstituted methylene carbon is deuterated.

[0076] 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 (e.g., CD_3). For example, when any of R groups are, or contain for example through substitution, methyl or ethyl, the alkyl residue is typically deuterated, e.g., CD_3, CH_2CD_3 or CD_2CD_3.

[0077] The compound of the present invention may form a solvate with solvents (including water). Therefore, in one embodiment, the invention includes a solvated form of the active compound. The term "solvate" refers to a molecular complex of a compound of the present invention (including salts thereof) with one or more solvent molecules. 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.* D_2O, d_6-acetone, d_6-DMSO. A solvate can be in a liquid or solid form.

[0078] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-(C=O)NH_2$ is attached through carbon of the keto (C=O) group.

[0079] 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. For example, when the substituent is oxo (i.e., =O) then two hydrogens on the atom are replaced. When an oxo group replaces two hydrogens in an aromatic moiety, the corresponding partially unsaturated ring replaces the aromatic ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates.

[0080] A stable compound or stable structure refers to a compound leading to a compound that can be isolated and can be formulated into a dosage form with a shelf life of at least one month.

[0081] Any suitable group may be present on a "substituted" or "optionally substituted" position that forms a stable molecule and advances 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 C_2-C_6 alkanoyl group); carboxamide; alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy such as phenoxy; alkylthio including those having one or more thioether linkages; alkylsulfinyl; alkylsulfonyl groups including those having one or more sulfonyl linkages; aminoalkyl groups including groups having one or more N atoms; aryl (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having for example, 1 to 3 separate or fused rings and from 6 to about 14 or 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy, for example, having 1 to 3 separate or fused rings with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen and amino. In certain embodiments "optionally substituted" includes one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, -$CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, -C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, hydoxyC_1-C_6alkyl, ester, carbamate, urea, sulfonamide,-C_1-C_6alkyl(heterocyclo), C_1-C_6alkyl(heteroaryl), -C_1-C_6alkyl(C_3-C_7cycloalkyl), O-C_1-C_6alkyl(C_3-C_7cycloalkyl), $B(OH)_2$, phosphate, phosphonate and C_1-C_2haloalkoxy.

[0082] "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 C_1-C_2, C_1-C_3, or C_1-C_6. The specified ranges as used herein indicate an alkyl group having each member of the range described as an independent species. For example, the term C_1-C_6 alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C_1-

C_4alkyl 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 C_0-C_n alkyl is used herein in conjunction with another group, for example, (C_3-C_7cycloalkyl)C_0-C_4 alkyl, or –C_0-C_4alkyl(C_3-C_7cycloalkyl), the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond (C_0alkyl), 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-C_0-C_4alkyl(C_3-C_7cycloalkyl). 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 and 2,3-dimethylbutane. In one embodiment, the alkyl group is optionally substituted as described above.

[0083] "Alkenyl" is a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds that may occur at a stable point along the chain. Nonlimiting examples are C_2-C_8alkenyl, C_2-C_6alkenyl and C_2-C_4alkenyl. 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.

[0084] "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, C_2-C_8alkynyl or C_2-C_6alkynyl. The specified ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. In one embodiment, the alkynyl group is optionally substituted as described above.

[0085] "Alkylene"is a bivalent saturated hydrocarbon. Alkylenes, for example, can be a 1 to 8 carbon moiety, 1 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_1-C_4alkylene, C_1-C_3alkylene, or C_1-C_2alkylene.

[0086] "Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_2-C_4alkenylene.

[0087] "Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_2-C_4alkynylene.

[0088] "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-methylpentoxy. Similarly an "alkylthio" or a "thioalkyl" group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a sulfur bridge (-S-). In one embodiment, the alkoxy group is optionally substituted as described above.

[0089] "Alkenyloxy" is an alkenyl group as defined covalently bound to the group it substitutes by an oxygen bridge (-O-).

[0090] "Alkanoyl" 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 C_2alkanoyl is a CH_3(C=O)- group. In one embodiment, the alkanoyl group is optionally substituted as described above.

[0091] "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.

[0092] "Amide" or "carboxamide" is $-C(O)NR^aR^b$ wherein R^a and R^b are each independently selected from hydrogen, alkyl, for example, C_1-C_6alkyl, alkenyl, for example, C_2-C_6alkenyl, alkynyl, for example, C_2-C_6alkynyl, –C_0-C_4alkyl(C_3-C_7cycloalkyl), –C_0-C_4alkyl(C_3-C_7heterocycloalkyl), –C_0-C_4alkyl(aryl), and –C_0-C_4alkyl(heteroaryl); or together with the nitrogen to which they are bonded, R^a and R^b can form a C_3-C_7heterocyclic ring. In one embodiment, the R^a and R^b groups are each independently optionally substituted as described above.

[0093] "Carbocyclic group", "carbocyclic ring", or "cycloalkyl" is a saturated or partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. A carbocyclic group

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

[0094] "Carbocyclic-oxy group" is a monocyclic carbocyclic ring or a mono- or bi-cyclic carbocyclic group as defined above attached to the group it substitutes via an oxygen, -O-, linker.

[0095] "Haloalkyl" indicates both branched and straight-chain alkyl groups substituted with 1 or more halogen atoms, up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, monofluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0096] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0097] "Hydroxyalkyl" is an alkyl group as previously described, substituted with at least one hydroxyl subsitutuent.

[0098] "Aminoalkyl" is an alkyl group as previously described, substituted with at least one amino subsitutuent.

[0099] "Halo" or "halogen" indicates independently any of fluoro, chloro, bromo, and iodo.

[0100] "Aryl" indicates aromatic groups 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 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and 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.

[0101] 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 radical 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 oxygen. 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. Chem. Soc. (1960) 82:5566. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, piperidonyl, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, pyrazolidinylimidazolinyl, imidazolidinyl, 2-oxa-5-azabicyclo[2.2.2]octane, 3-oxa-8-azabicyclo[3.2.1]octane, 8-oxa-3-azabicyclo[3.2.1]octane, 6-oxa-3-azabicyclo[3.1.1]heptane, 2-oxa-5-azabicyclo[2.2.1]heptane, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl, quinolizinyl, N-pyridyl ureas, and pyrrolopyrimidine. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 1 or 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle

groups herein are optionally substituted independently with one or more substituents described herein.

[0102] "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.

[0103] "Heteroaryl" indicates a stable monocyclic aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 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 O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. In one embodiment, the total number of S and O atoms in the heteroaryl group is not more than 2. In another embodiment, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, tetrahydrofuranyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein. "Heteroaryloxy" is a heteroaryl group as described bound to the group it substituted via an oxygen, -O-, linker.

[0104] "Heterocycloalkyl" is a saturated ring group. It may have, for example, 1, 2, 3, or 4 heteroatoms independently chosen from N, S, and O, with remaining ring atoms being carbon.

In a typical embodiment, nitrogen is the heteroatm. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

[0105] The term "mono- and/ or di-alkylamino" indicates secondary or tertiary alkylamino groups, wherein the alkyl groups are independently chosen 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.

[0106] 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.

[0107] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt of Formula I, 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.

[0108] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds 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, ethanol, isopropanol, or acetonitrile are typical, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0109] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include

the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. 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).

[0110] 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.

[0111] 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, and includes, in one embodiment, an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

[0112] A "patient" or "host" or "subject" is a human or non-human animal in need of modulation of the complement factor D pathway. Typically the host is a human. A "patient" or "host" or "subject" also refers to for example, mammals, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like.

[0113] 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 that are useful to treat any of the disorders described herein, or to control or improve the underlying cause or symptoms associated with any physiological or pathological disorder described herein in a host, typically a human. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent. Prodrug strategies exist which provide choices in modulating the conditions for *in vivo* generation of the parent drug, all of which are deemed included herein. Nonlimiting examples of prodrug strategies include

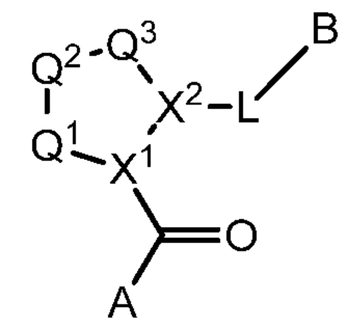
covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylation, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others.

[0114] "Providing a compound of Formula I with at least one additional active agent" means the compound of Formula I 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 separated by some amount of time that is within the time in which both the compound of Formula I and the at least one additional active agent are within the blood stream of a patient. In certain embodiments the compound of Formula I 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 of Formula I 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 or topical contact.

[0115] A "therapeutically effective amount" of a pharmaceutical composition/combination of this invention means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of a macular degeneration. 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

[0116] According to the present invention, a compound of Formula I is provided:



(I)

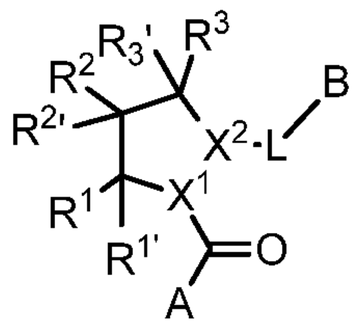
as well as the pharmaceutically acceptable salts and compositions thereof. Formula I can be considered to have a central core, an L-B substituent, and a (C=O)A substituent. It has been

discovered that a compound of Formula I, or a pharmaceutically acceptable salt or composition thereof, wherein R^{12} or R^{13} on the A group is an aryl, heteroaryl or heterocycle, is a superior inhibitor of complement factor D, and therefore can be used as an effective amount to treat a host in need of complement factor D modulation.

[0117] Non-limiting examples of compounds falling within Formula I with variations in the variables e.g., A, B, R^1-$R^{3'}$, and L, are illustrated below. The disclosure includes all combinations of these definitions so long as a stable compound results.

Formulas II - XXX

[0118] In one aspect, the disclosure includes compounds and salts 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 which are within the scope of Formula I. 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.



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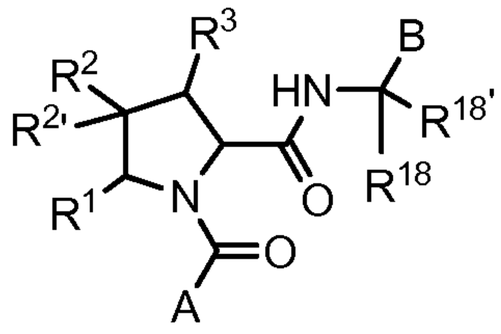

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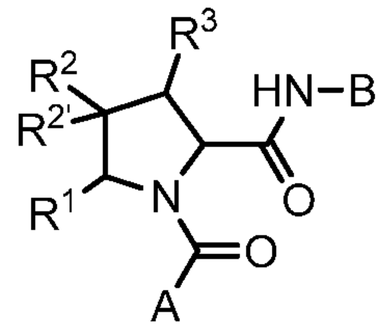

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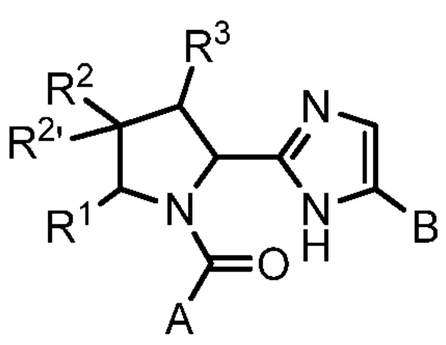

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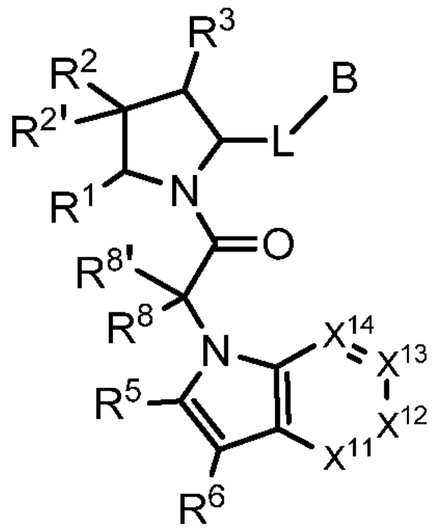

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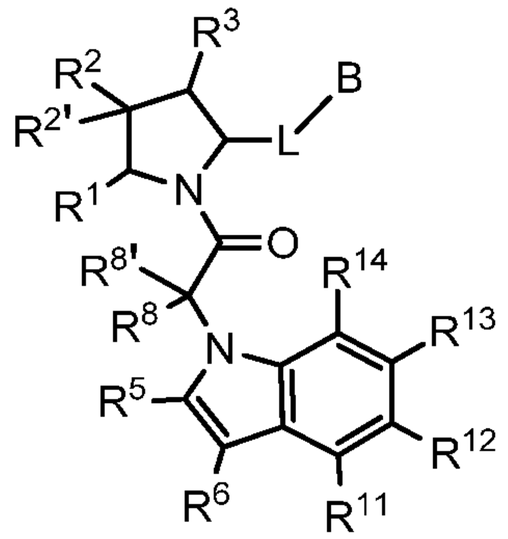

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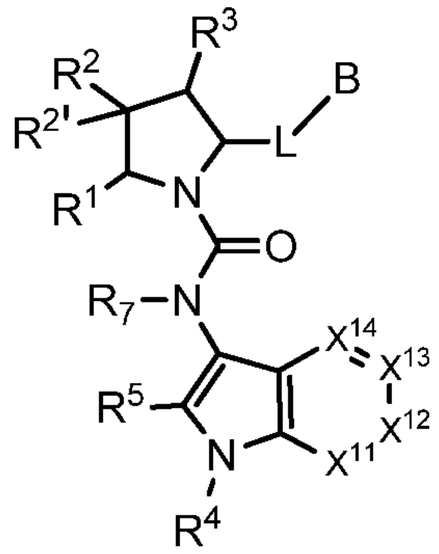

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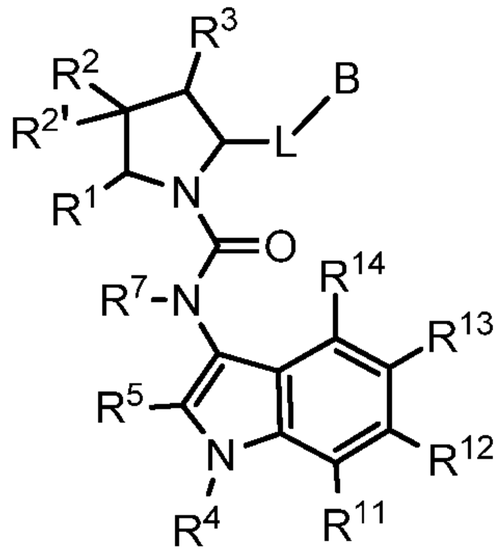

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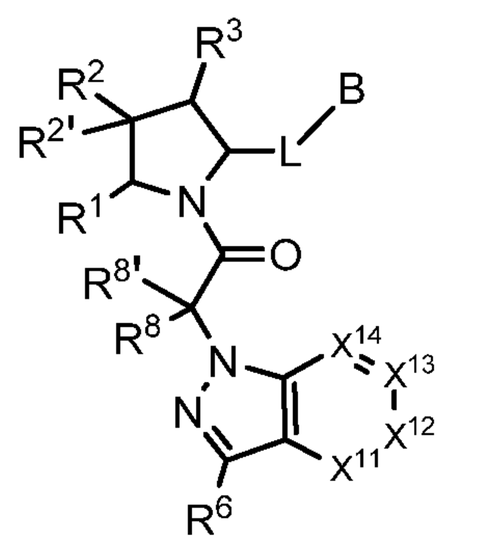

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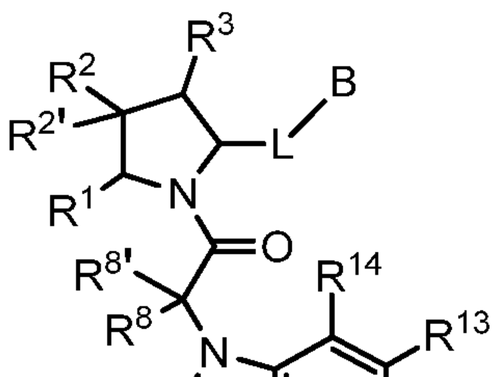

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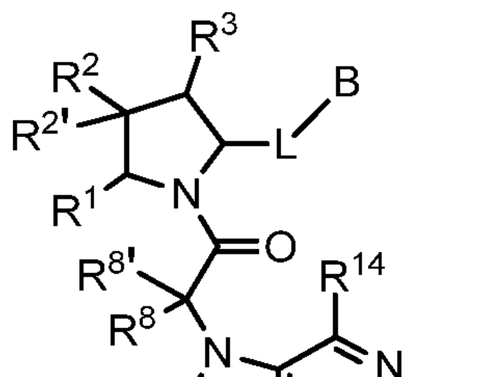

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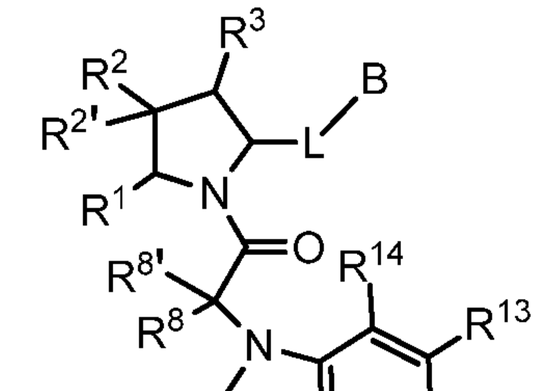

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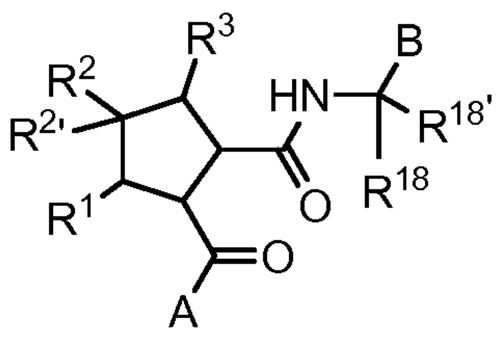

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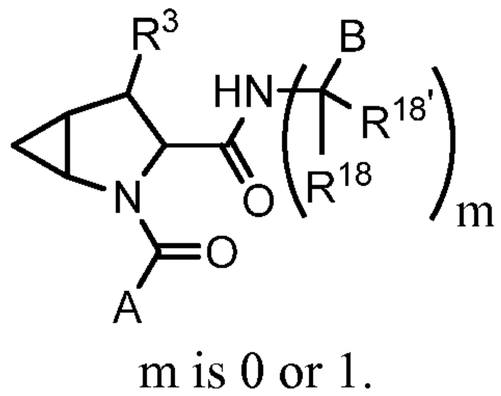
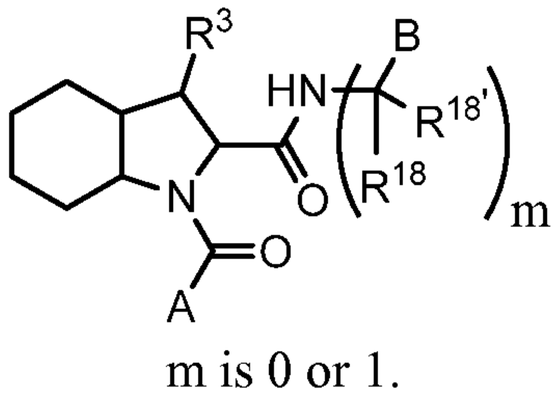


m is 0 or 1.

Formula XV



m is 0 or 1.

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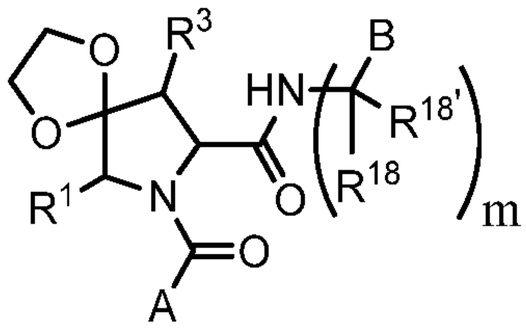

m is 0 or 1.

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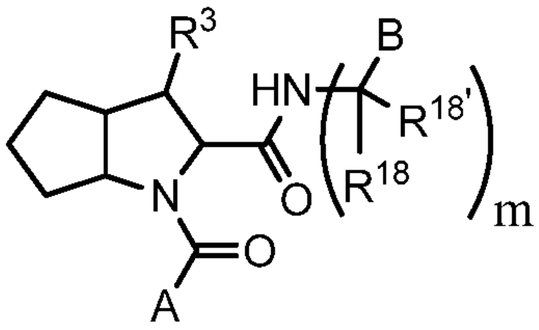

m is 0 or 1.

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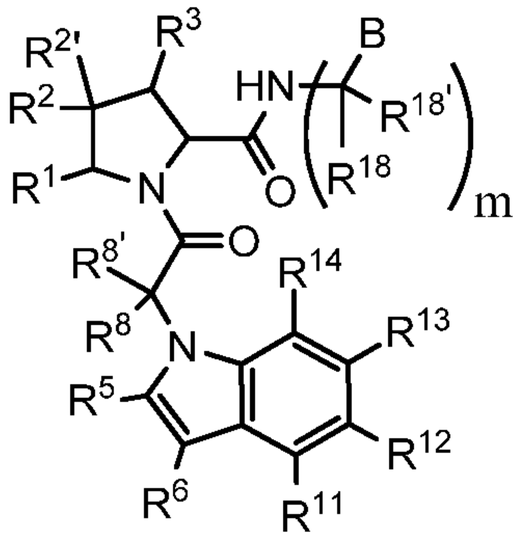

m is 0 or 1.

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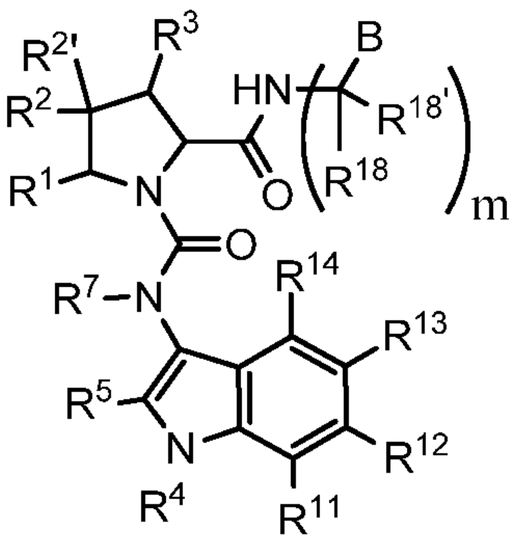
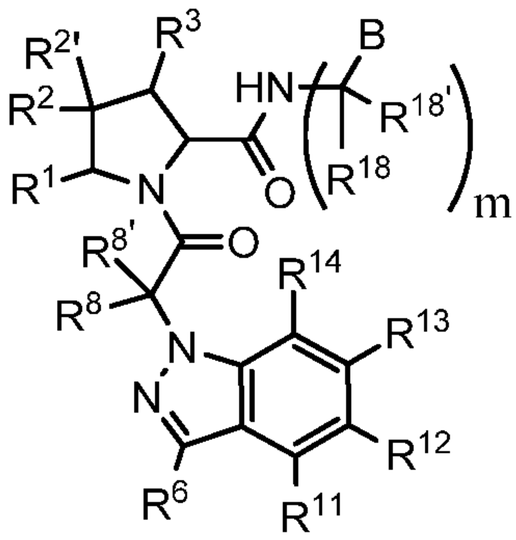


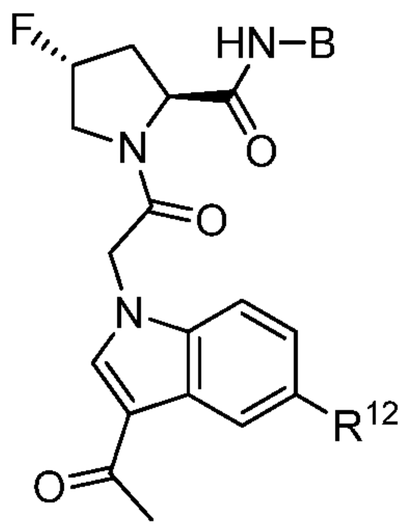
m is 0 or 1.

Formula XX



m is 0 or 1.

Formula XXI



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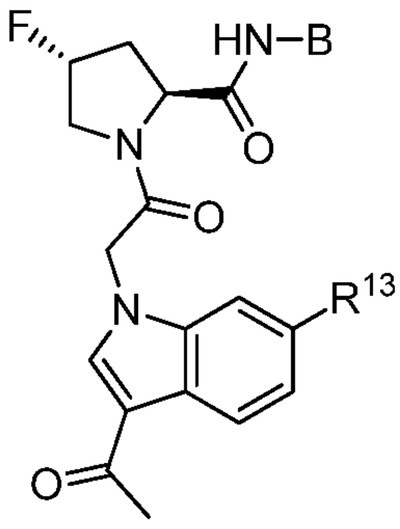

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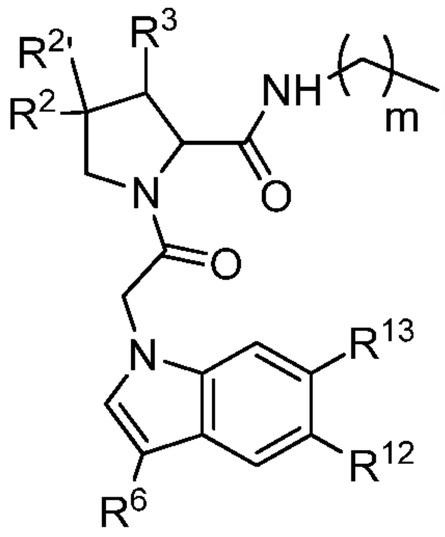

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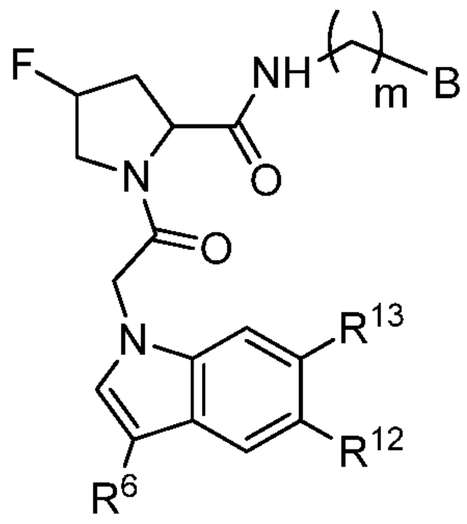

m is 0 or 1.

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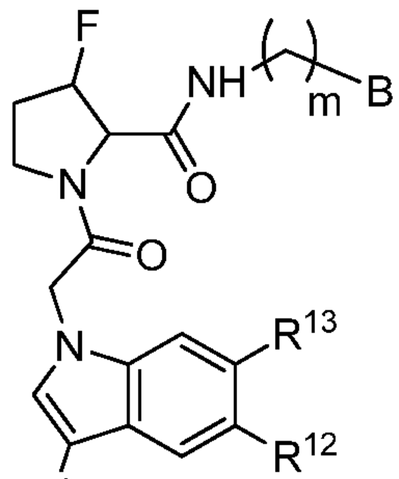

m is 0 or 1.

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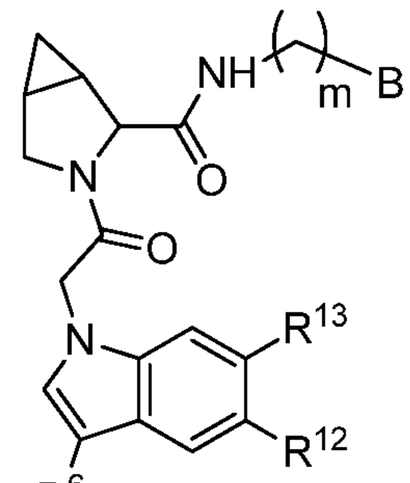

m is 0 or 1.

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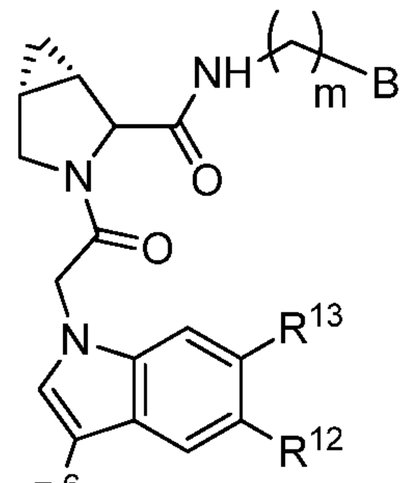
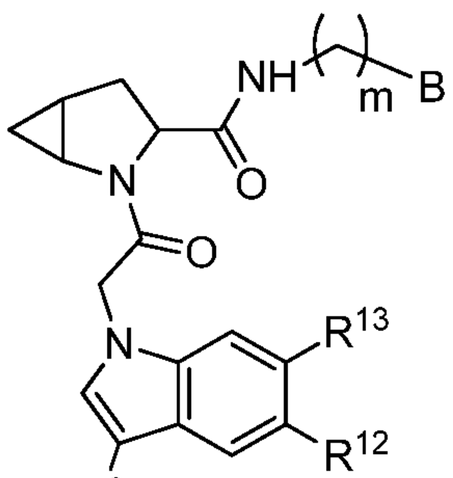


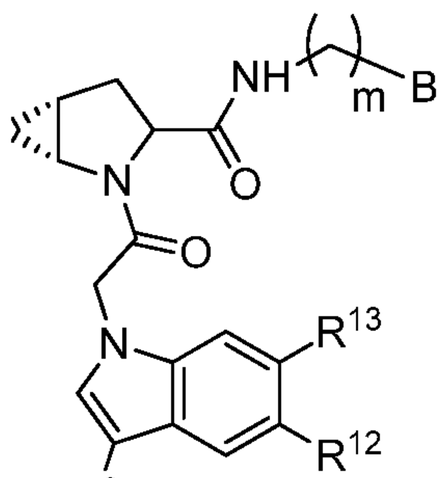
m is 0 or 1.

Formula XXVIII



m is 0 or 1.

Formula XXIX



m is 0 or 1.

Formula XXX

[0119] In these embodiments, it should be understood that where R^1 or R^3 is attached to a carbon, there can be two independent attachments as in $R^2/R^{2'}$ and these formulas should be considered to include all such variations.

[0120] Additionally, the disclosure includes compounds and salts of Formula I and pharmaceutically acceptable compositions thereof, and any of its subformulae (II-XXX) in which at least one of the following conditions is met in the embodiments described below.

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

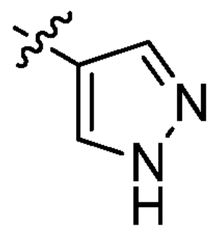
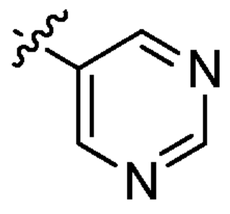
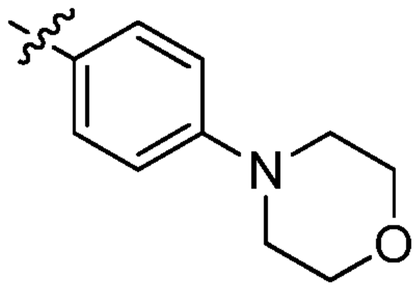
[0121] It has been surprisingly discovered that a compound of Formula I, a pharmaceutically acceptable salt or composition thereof, wherein R^{12} or R^{13} on the A group is an aryl, heteroaryl, or heterocycle, is a superior inhibitor of Complement Factor D.

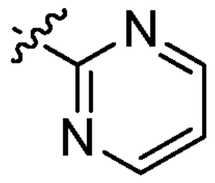
[0122] One of R^{12} and R^{13} is chosen from R^{31} and the other of R^{12} and R^{13} is chosen from R^{32}. In another embodiment, each of R^{12} and R^{13} can be independently selected from R^{32}.

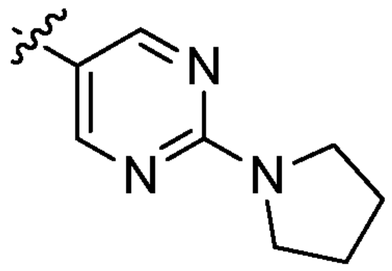
[0123] R^{31} is chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_2-C_6alkenyloxy, -$C(O)OR^9$, C_1-C_6thioalkyl, -C_0-C_4alkylNR^9R^{10}, -$C(O)NR^9R^{10}$, -SO_2R^9, -$SO_2NR^9R^{10}$, -$OC(O)R^9$, and -$C(NR^9)NR^9R^{10}$, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent chosen from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl)(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

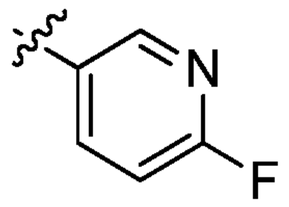
[0124] R^{32} is selected from from aryl; saturated or unsaturated heterocycle (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the heterocycle is bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{12} or R^{13} position; and heteroaryl (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the aryl, heterocycle or heteroaryl ring can be optionally substituted.

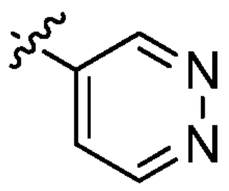
[0125] Nonlimiting examples of R^{32} are

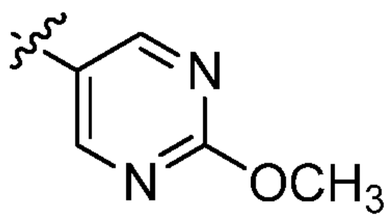




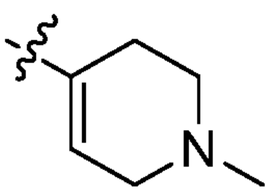


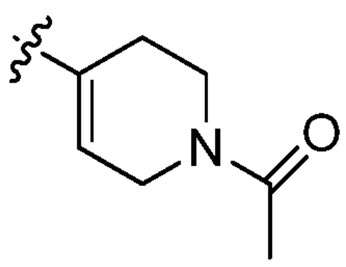


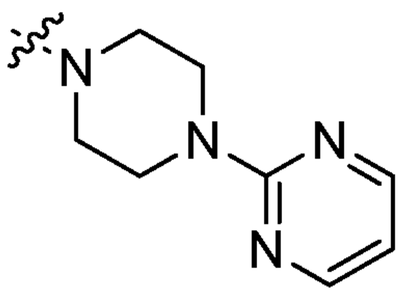


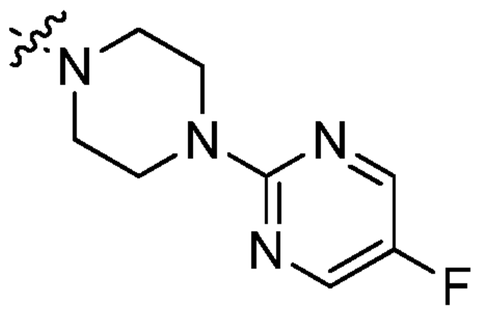


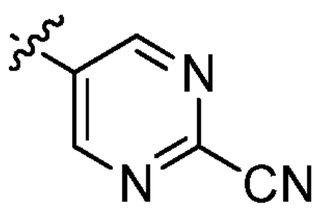


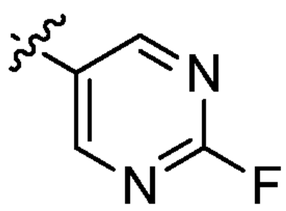


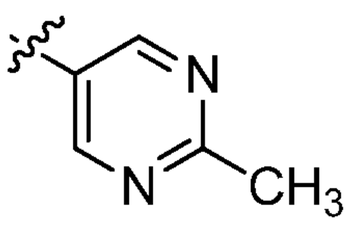


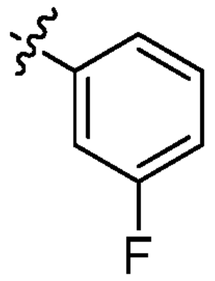


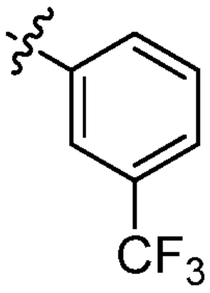


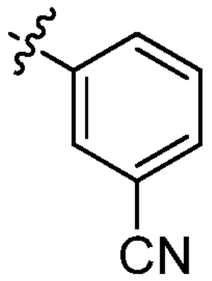


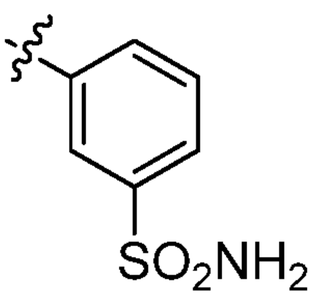


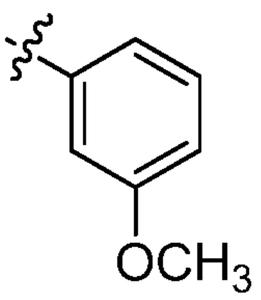


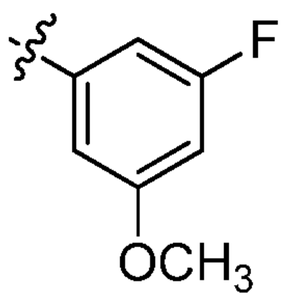


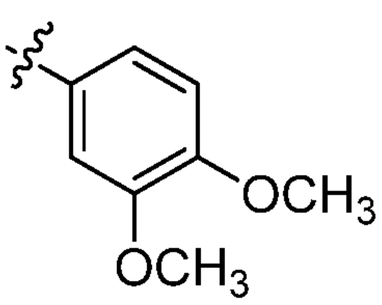


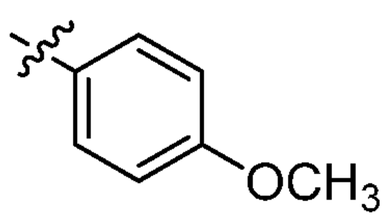


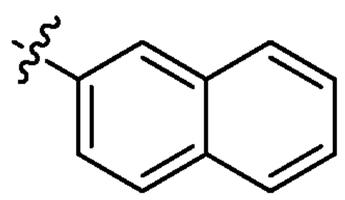


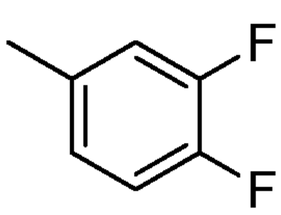


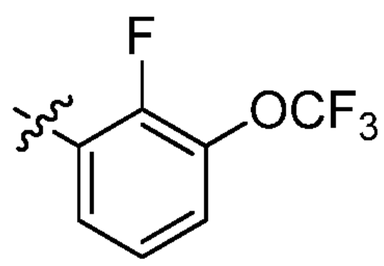


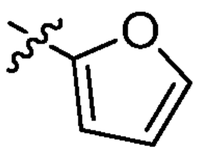


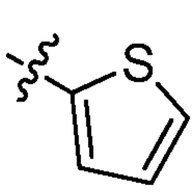
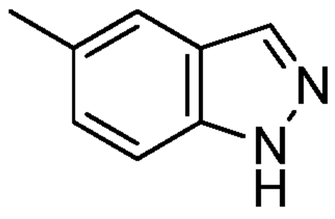
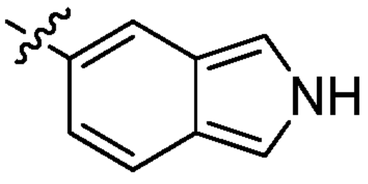
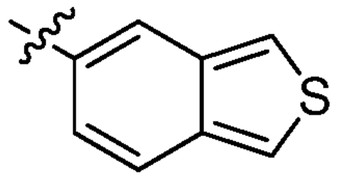
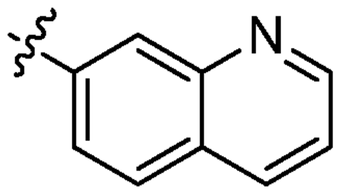
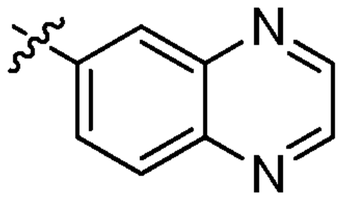
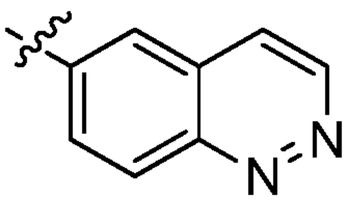
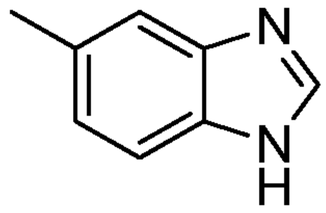
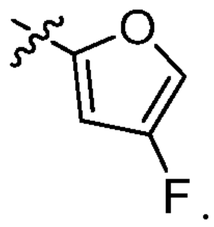


















and  .

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

[0126] In one embodiment, R^{12} is R^{32}.

[0127] In one embodiment, R^{13} is R^{32}.

[0128] In one embodiment, R^{12} is R^{32}, which is aryl.

[0129] In one embodiment, R^{12} is optionally substituted aryl.

[0130] In one embodiment, R^{12} is an optionally substituted saturated or unsaturated heterocycle bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{12} position.

[0131] In one embodiment, R^{12} is an optionally substituted heteroaryl.

[0132] In one embodiment, R^{13} is an optionally substituted aryl.

[0133] In one embodiment, R^{13} is an optionally substituted saturated or unsaturated heterocycle bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{13} position.

[0134] In one embodiment, R^{13} is optionally substituted heteroaryl.

[0135] In one embodiment, R^{12} is R^{32}, which is (5- or 6- membered unsaturated or aromatic heterocycle), having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (5- or 6- membered unsaturated heterocycle) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}.

[0136] In one embodiment, R^{12} is R^{32}, which is (4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (4- to 7-membered heterocycloalkyl) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}.

[0137] In one embodiment, R^{13} is R^{32}, which is aryl.

[0138] In one embodiment, R^{13} is R^{32}, which is (5- or 6- membered unsaturated or aromatic heterocycle), having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (5- or 6- membered unsaturated heterocycle) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}.

[0139] In one embodiment, R^{13} is R^{32}, which is (4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (4- to 7-membered heterocycloalkyl) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}.

[0140] In one embodiment, the disclosure provides compounds of Formula I, wherein;

[0141] one of R^{12} and R^{13} is H and the other of R^{12} and R^{13} is R^{32},where

[0142] R^{32} is chosen from aryl, which can be optionally substituted; (5- or 6- membered unsaturated or aromatic heterocycle), having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (5- or 6- membered unsaturated heterocycle) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}, wherein the (5- or 6- membered unsaturated or aromatic heterocycle) can be optionally substituted; and (4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (4- to 7-membered heterocycloalkyl) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}, and the (4- to 7-membered heterocycloalkyl) can be optionally substituted.

[0143] In another embodiment, the disclosure provides compounds of Formula I, wherein;

[0144] R^1, $R^{1'}$, R^2, and $R^{3'}$are all hydrogen;

[0145] R^2 is fluoro and R^3 is hydrogen, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl);

[0146] R^5 is hydrogen, halogen, or C_1-C_2alkyl;

[0147] R^{11}, R^{13}, R^{14}, and R^{15} if present, are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, amino, C_1-C_4alkyl, C_1-C_4alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_2alkylamino), trifluoromethyl, and trifluoromethoxy;

[0148] X^{12} is CR^{12}; and

[0149] R^{12} is chosen from aryl, which can be optionally substituted; (5- or 6- membered unsaturated or aromatic heterocycle), having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (5- or 6- membered unsaturated heterocycle) is bonded through a

carbon atom to a carbon of CR^{12} or CR^{13}, wherein the (5- or 6- membered unsaturated or aromatic heterocycle) can be optionally substituted; and (4- to 7-membered heterocycloalkyl) having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, wherein the (4- to 7-membered heterocycloalkyl) is bonded through a carbon atom to a carbon of CR^{12} or CR^{13}, and the (4- to 7-membered heterocycloalkyl) can be optionally substituted.

[0150] In one embodiment, the disclosure provides compounds of Formula I, wherein;

[0151] m is 0 or 1;

[0152] R^2 is halogen, $R^{2'}$ is hydrogen or halogen, and R^3 is hydrogen, halogen, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl);

[0153] R^6 is –C(O)C_1-C_4alkyl, -C(O)NH_2, -C(O)CF_3, -C(O)(C_3-C_7cycloalkyl), or -ethyl(cyanoimino);

[0154] one of R^{12} and R^{13} is selected from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, trifluoromethyl, and trifluoromethoxy; the other of R^{12} and R^{13} is R^{32}, where

[0155] R^{32} is selected from from aryl; saturated or unsaturated heterocycle (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the heterocycle is bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{12} or R^{13} position; and heteroaryl (for example a 5-6 membered ring having 1, 2, or 3 heteroatoms independently chosen from N, O, and S), wherein the aryl, heterocycle or heteroaryl ring can be optionally substituted.

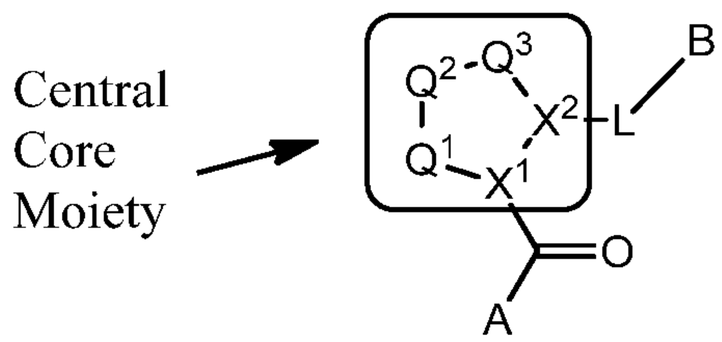
[0156] In one embodiment, the disclosure provides compounds of Formula I, wherein one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; and the other of R^{12} and R^{13} is R^{32}, where

[0157] R^{32} is chosen from aryl, heteroaryl or heterocycle bonded to the A ring through a heterocyclic carbon atom;

[0158] In one embodiment, R^{32} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -P(O)$(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

Central Core Moiety

[0159] The central core moiety in Formula I is illustrated below:



wherein:

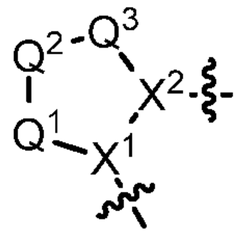
[0160] Q^1 is $N(R^1)$ or $C(R^1R^{1'})$;

[0161] Q^2 is $C(R^2R^{2'})$, $C(R^2R^{2'})$-$C(R^2R^{2'})$, S, O, $N(R^2)$ or $C(R^2R^{2'})O$;

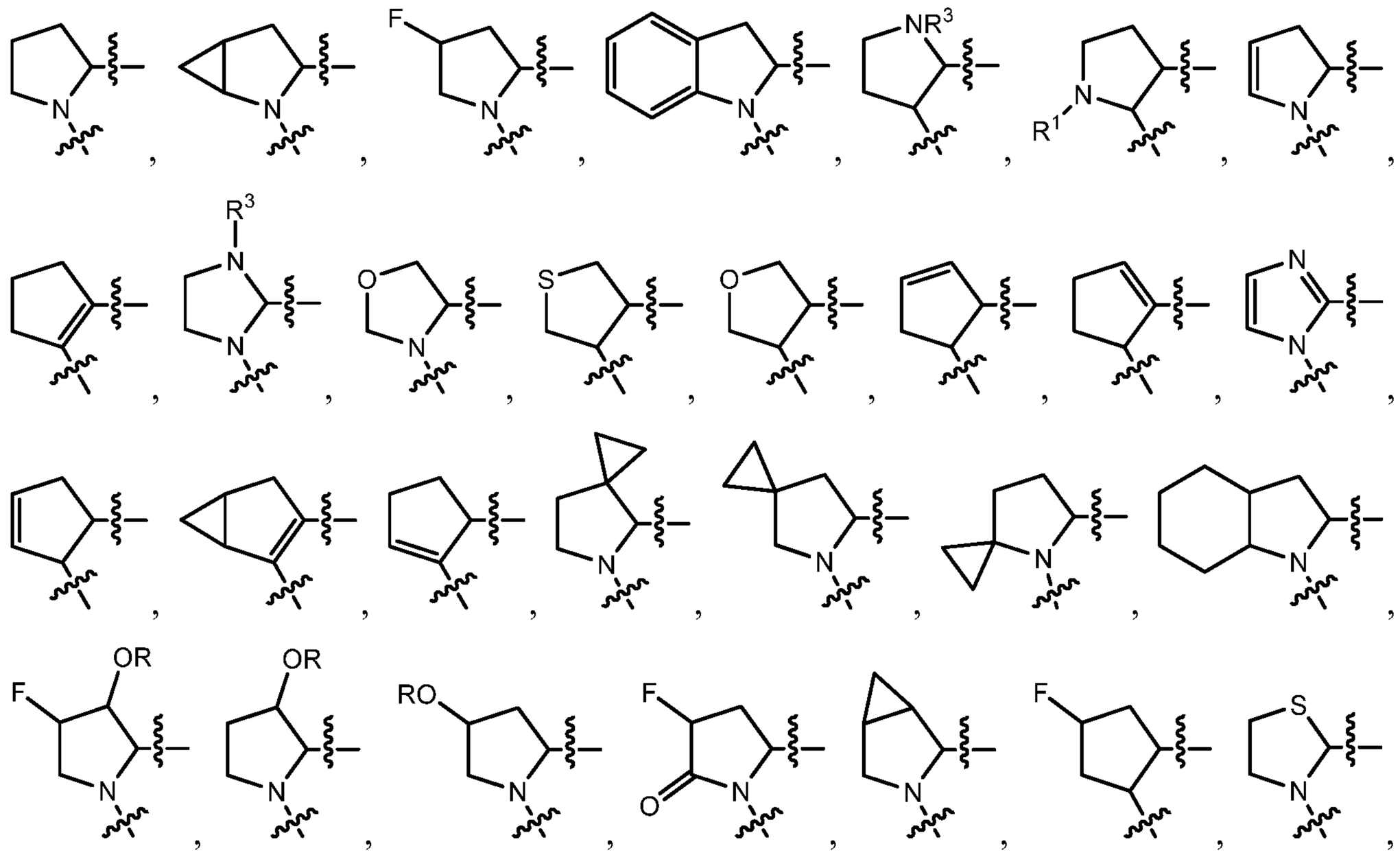
[0162] Q^3 is $N(R^3)$, S, or $C(R^3R^{3'})$;

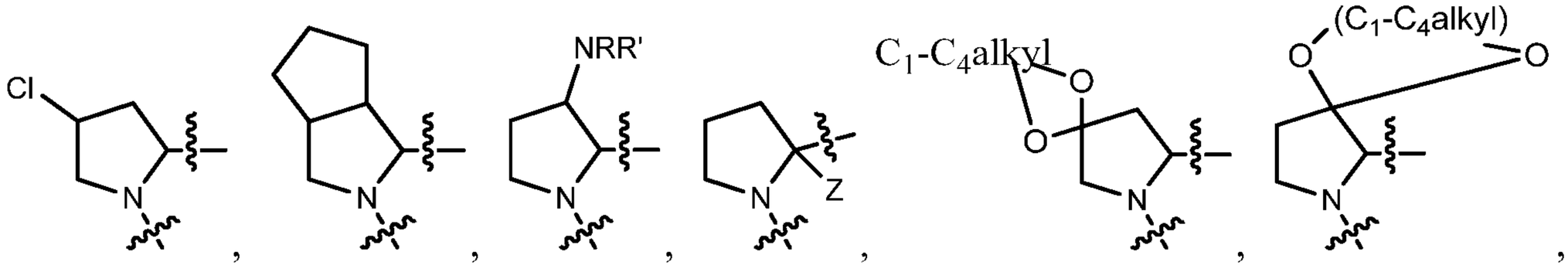
[0163] X^1 and X^2 are independently N, CH, or CZ, or X^1 and X^2 together are C=C; and

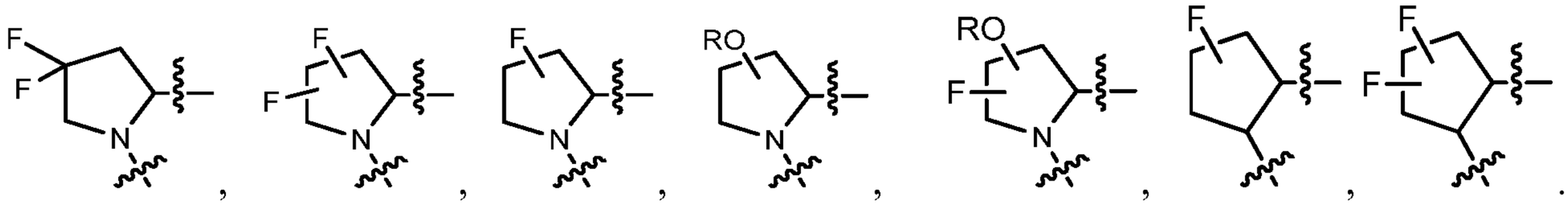
[0164] wherein Q^1, Q^2, Q^3, X^1, and X^2 are selected such that a stable compound results.

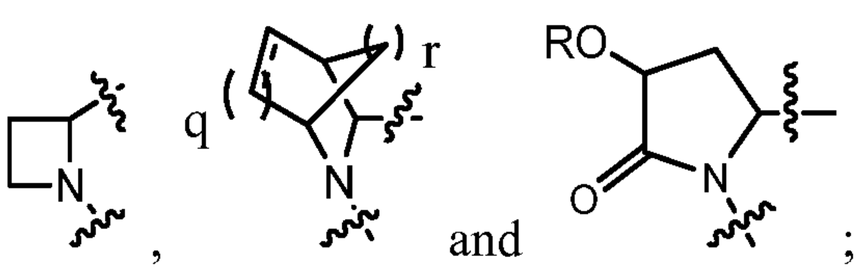


[0165] Non-limiting examples of the ring are illustrated below (any of which can be otherwise substituted with R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$) as described in more detail below.









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

[0166] R and R' are independently chosen from H, alkyl, cycloalkyl, cycloalkylalkyl, 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 embodiments in which the chiral carbon can be provided as an enantiomer, or mixtrues 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.

[0167] Z is F, Cl, NH_2, CH_3, CH_2D, CHD_2, or CD_3.

[0168] R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently chosen at each occurrence, as appropriate, and only where a stable compound results, from hydrogen, halogen, hydroxyl, nitro, cyano, amino, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_2-C_6alkynyl, C_2-C_6alkanoyl, C_1-C_6thioalkyl, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, -C_0-C_4alkylNR^9R^{10}, -$C(O)OR^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -$OC(O)NR^9R^{10}$, -$NR^9C(O)OR^{10}$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, where R^9 and R^{10} are independently chosen at each occurrence from hydrogen, C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), and -O-C_0-C_4alkyl(C_3-C_7cycloalkyl).

Non-limiting Central Core Embodiments

[0169] In alternative embodiments, R^1 and $R^{1'}$ or R^3 and $R^{3'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently chosen 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;

[0170] each of which ring may be unsubstituted or substituted with 1 or more substituents independently chosen from halogen (and in particular F), hydroxyl, cyano, -COOH, C_1-C_4alkyl (including in particular methyl), C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, hydroxyC_1-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0171] In alternative embodiments, R^1 and R^2 may be taken together to form a 3-membered carbocyclic ring; R^1 and R^2 may be taken together to form a 4- to 6-membered carbocyclic or aryl ring or a 4- to 6-membered heterocyclic or heteroaryl ring containing 1 or 2 heteroatoms independently chosen from N, O, and S; or R^2 and R^3, if bound to adjacent carbon atoms, may be taken together to form a 3- to 6-membered carbocyclic or aryl ring or a 3- to 6-membered heterocyclic or heteroaryl ring;

[0172] each of which ring may be unsubstituted or substituted with 1 or more substituents independently chosen from halogen (and in particular F), hydroxyl, cyano, -COOH, C_1-C_4alkyl (including in particular methyl), C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, hydroxyC_1-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0173] In one embodiment, the central core moiety is proline.

[0174] In one embodiment, the central core moiety is 4-fluoroproline.

[0175] In one embodiment, R^1, $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro.

[0176] In one embodiment, R^1, $R^{1'}$, $R^{2'}$, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro and R^3 is -C_0-C_4alkyl(C_3-C_7cycloalkyl) or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl).

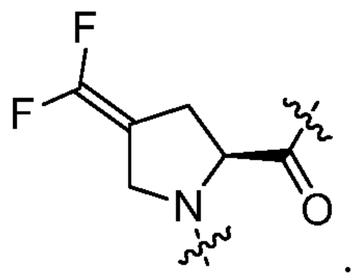
[0177] In one embodiment, R^1 and R^2 are taken together to form a 3- to 6-membered cycloalkyl group, and $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, where present, are all hydrogen.

[0178] In one embodiment, R^1, $R^{1'}$, R^3, and $R^{3'}$, if present, are all hydrogen, and R^2 and $R^{2'}$ are taken together to form a 5- or 6-membered heterocycloalkyl group having 1 or 2 oxygen atoms.

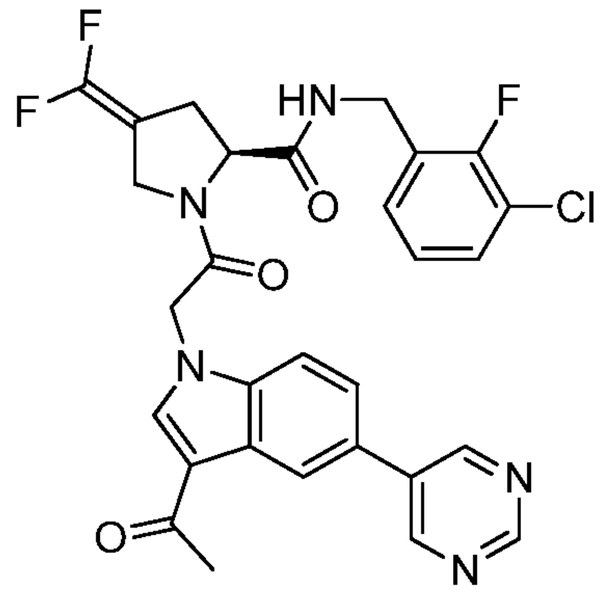
[0179] In one embodiment, R^1 is hydrogen and R^2 is fluoro.

[0180] In one embodiment, R^1 and R^2 are joined to form a 3 membered ring.

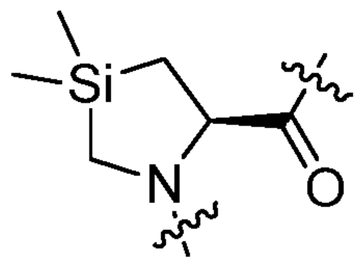
[0181] The disclosure includes compounds of Formula I in which the central pyrrolidine is vinyl substituted, for example:



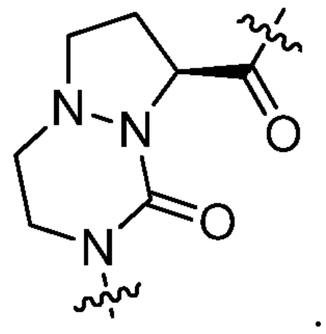
[0182] In one embodiment, the compound of Formula I has the structure:



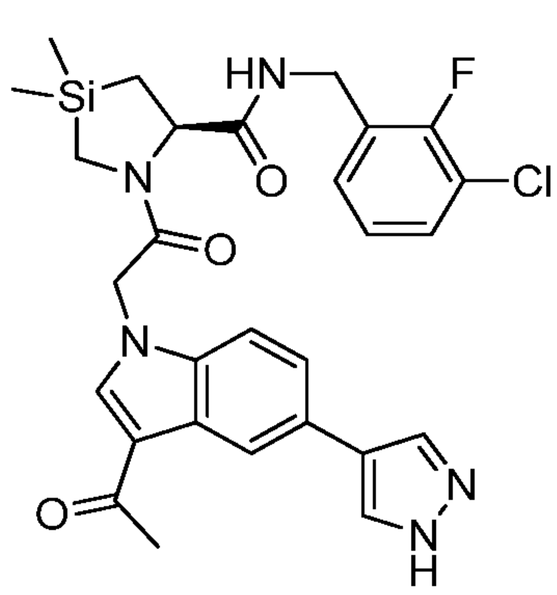
[0183] In one embodiment, the central pyrrolidine is modified by addition of a second heteroatom to a pyrrolidine ring, such as N, O, S, or Si, for example:

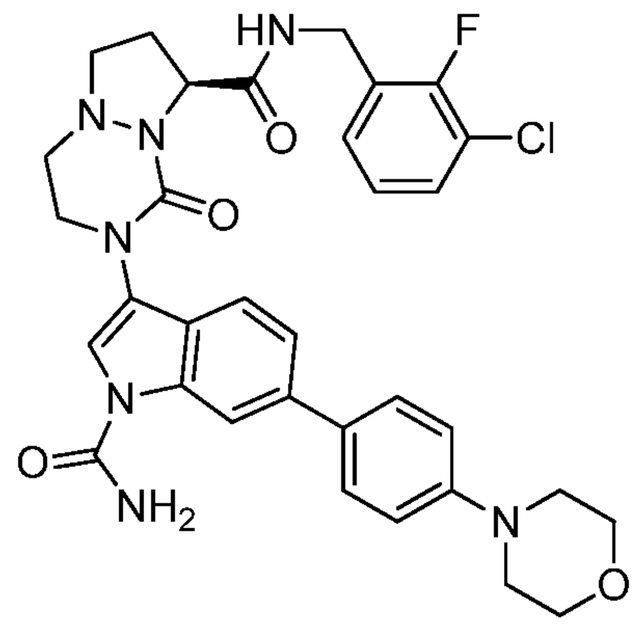


[0184] Another modification within the scope of the disclosure is joining a substituent on the central pyrrolidine ring to R^7 or R^8 to form a 5- to 6- membered heterocyclic ring, for example:



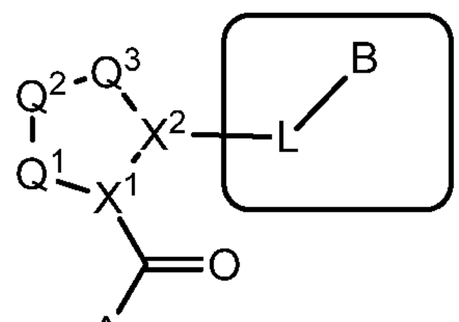
[0185] Example compounds having the modifications disclosed above include:





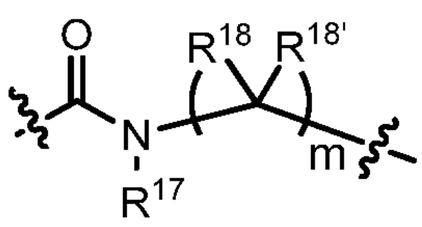
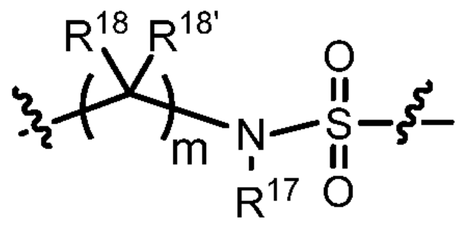
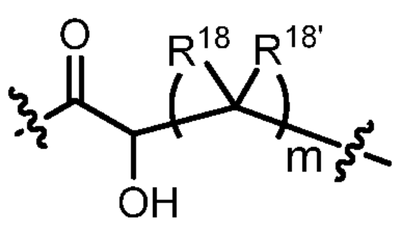
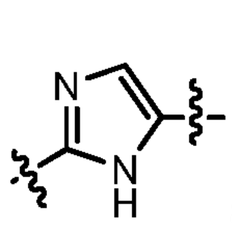
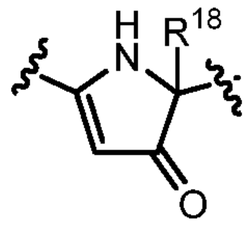
Central Core L-B Substituents

[0186] The central core **L-B substituents** in Formula I are illustrated below:



A .

[0187] L is a bond or is chosen from the formulas:


, 
, 
, 
and 
,

where R^{17} is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl) and R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3.

[0188] 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_2-C_6alkenyl; C_2-C_6alkynyl; –(C_0-C_4alkyl)(aryl); –(C_0-C_4alkyl)(heteroaryl); or –(C_0-C_4alkyl)(biphenyl).

[0189] Each of which B is unsubstituted or substituted with one or more substituents independently chosen from R^{33} and R^{34}, and 0 or 1 substituents chosen from R^{35} and R^{36}:

[0190] R^{33} is independently chosen from halogen, hydroxyl, -COOH, cyano, C_1-C_6alkyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkylNR^9R^{10}, -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

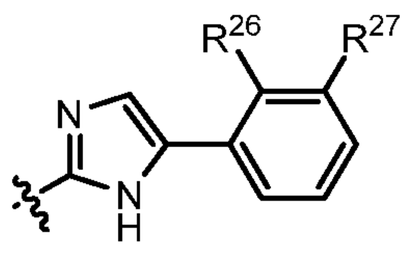
[0191] R^{34} is independently chosen from nitro, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6thioalkyl, -JC_3-C_7cycloalkyl, -$B(OH)_2$, -J$C(O)NR^9R^{23}$,-JOSO_2OR^{21}, -$C(O)(CH_2)_{1-4}S(O)R^{21}$, -$O(CH_2)_{1-4}S(O)NR^{21}R^{22}$, -J$OP(O)(OR^{21})(OR^{22})$, -J$P(O)(OR^{21})(OR^{22})$, -J$OP(O)(OR^{21})R^{22}$, -J$P(O)(OR^{21})R^{22}$, -J$OP(O)R^{21}R^{22}$, -J$P(O)R^{21}R^{22}$, -J$SP(O)(OR^{21})(OR^{22})$, -J$SP(O)(OR^{21})(R^{22})$, -J$SP(O)(R^{21})(R^{22})$, -J$NR^9P(O)(NHR^{21})(NHR^{22})$, -J$NR^9P(O)(OR^{21})(NHR^{22})$, -J$NR^9P(O)(OR^{21})(OR^{22})$, -J$C(S)R^{21}$, -J$NR^{21}SO_2R^{22}$, -J$NR^9S(O)NR^{10}R^{22}$, -J$NR^9SO_2NR^{10}R^{22}$, -J$SO_2NR^9COR^{22}$, -J$SO_2NR^9CONR^{21}R^{22}$, -J$NR^{21}SO_2R^{22}$, -J$C(O)NR^{21}SO_2R^{22}$, -J$C(NH_2)NR^{22}$, -J$C(NH_2)NR^9S(O)_2R^{22}$, -J$OC(O)NR^{21}R^{22}$, -J$NR^{21}C(O)OR^{22}$, -J$NR^{21}OC(O)R^{22}$, -$(CH_2)_{1-4}C(O)NR^{21}R^{22}$, -J$C(O)R^{24}R^{25}$, -J$NR^9C(O)R^{21}$, -J$C(O)R^{21}$, -J$NR^9C(O)NR^{10}R^{22}$, -J$CCR^{21}$, -$(CH_2)_{1-4}OC(O)R^{21}$, and -J$C(O)OR^{23}$; each of which R^{34} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0192] R^{35} is independently chosen from naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl containing 1 or 2 heteroatoms chosen from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R^{35} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

[0193] R^{36} is independently chosen from tetrazolyl, (phenyl)C_0-C_2alkyl, (phenyl)C_1-C_2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently chosen from N, O, B, and S, each of which R^{36} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, -$OSi(CH_3)_2C(CH_3)_3$, –$Si(CH_3)_2C(CH_3)_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0194] J is independently chosen at each occurrence from a covalent bond, C_1-C_4alkylene, -OC_1-C_4alkylene, C_2-C_4alkenylene, and C_2-C_4alkynylene.

[0195] In one embodiment, –L-B- is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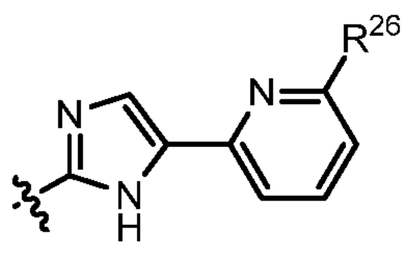
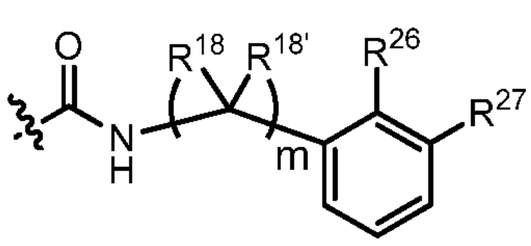

, where

R^{26} and R^{27} are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkoxy(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, C_1-C_2haloalkoxy, and C_1-C_2haloalkylthio.

Non-Limiting L-B Embodiments

[0196] In another embodiment, –L-B- is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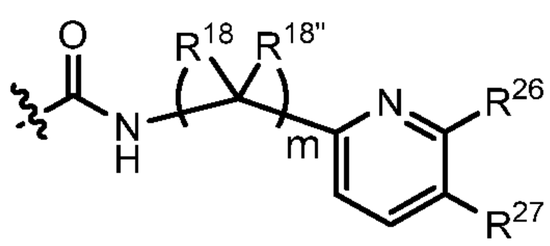
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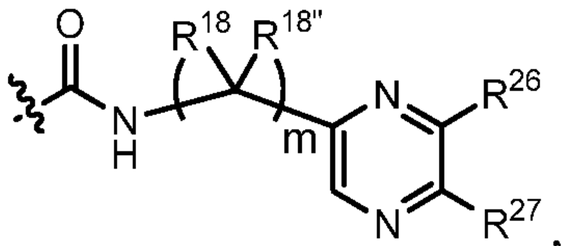
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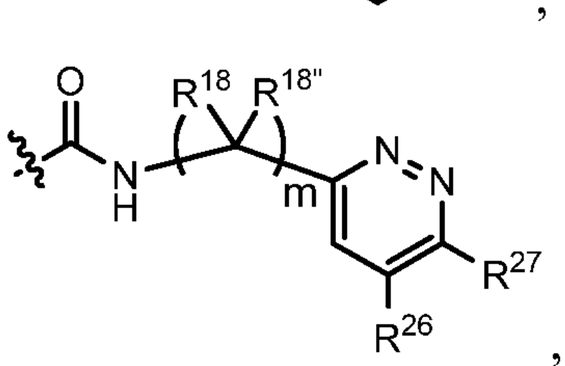
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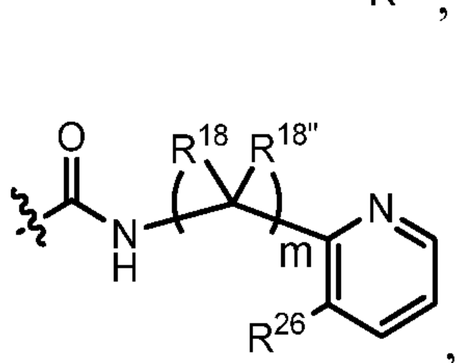
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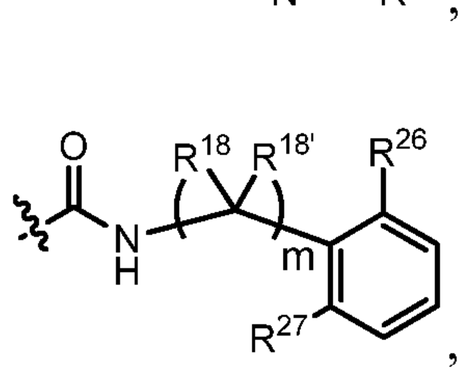
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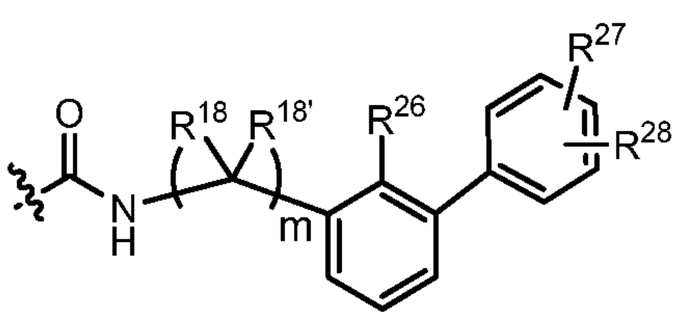
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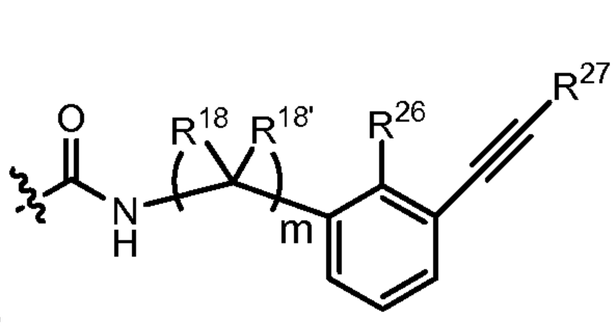
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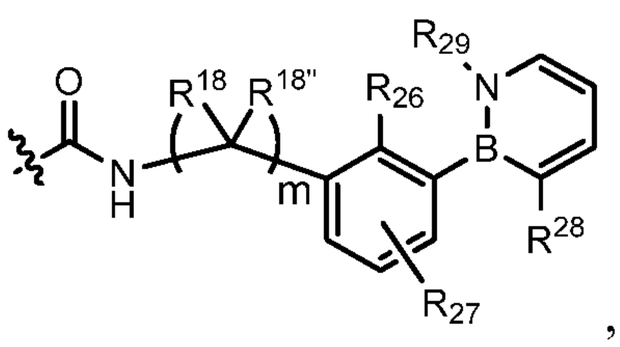
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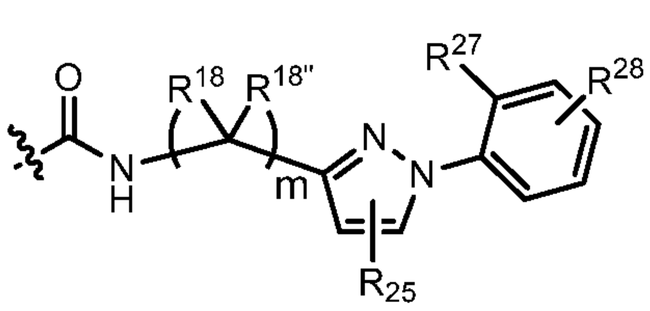
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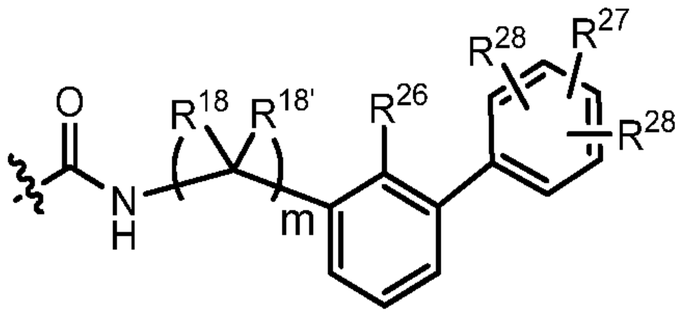

; wherein

[0197] R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0 or 1; and

[0198] R^{26}, R^{27}, and R^{28} are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (aryl)C_0-C_4alkyl-, (heteroaryl)C_0-C_4alkyl-, and -C_0-C_4alkoxy(C_3-C_7cycloalkyl); each of which R^{26}, R^{27}, and R^{28} other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, C_1-C_2alkoxy, C_1-C_2haloalkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl-, and C_1-C_2haloalkoxy; and

[0199] R^{29} is hydrogen, C_1-C_2alkyl, C_1C_2haloalkyl or $–Si(CH_3)_2C(CH_3)_3$.

[0200] In one embodiment, m is 0.

[0201] In one embodiment, the disclosure further includes compounds and salts of Formula I in which B is 2-fluoro-3-chlorophenyl. In another embodiment, another carbocyclic, aryl, heterocyclic, or heteroaryl group such as 2-bromo-pyridin-6-yl, 1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl, 2,2-dichlorocyclopropylmethyl, or 2-fluoro-3-trimethylsilylphenyl is used.

[0202] In another embodiment, B is phenyl, pyridyl, or indanyl each of which is unsubstituted or substituted with one or more substituents independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, -C_0-C_4alkoxy(C_3-C_7cycloalkyl), (phenyl)C_0-C_2alkyl, (pyridyl)C_0-C_2alkyl; each of which substituents other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, C_1-C_2alkyl, C_1-C_2alkoxy, $–OSi(CH_3)_2C(CH_3)_3$, $–Si(CH_3)_2C(CH_3)_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0203] In another embodiment, B is phenyl or pyridyl substituted with 1, 2, or 3 substituents chosen from chloro, bromo, hydroxyl, -SCF_3, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, phenyl and trifluoromethoxy each of which substituents other than chloro, bromo, hydroxyl, -SCF_3, can be optionally substitued.

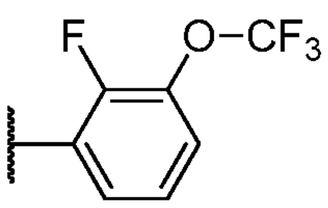
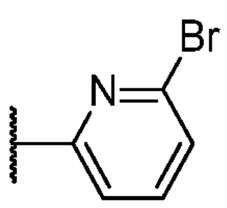
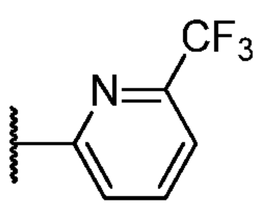
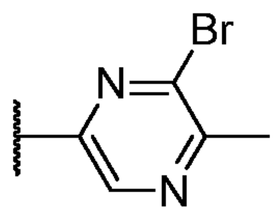
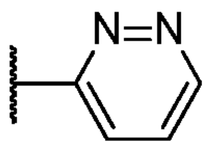
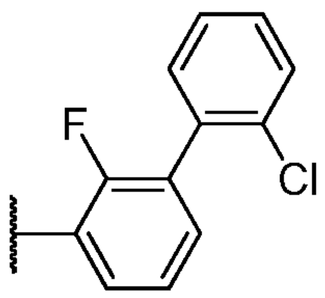
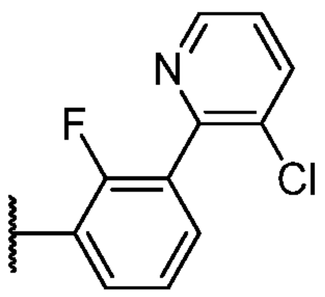
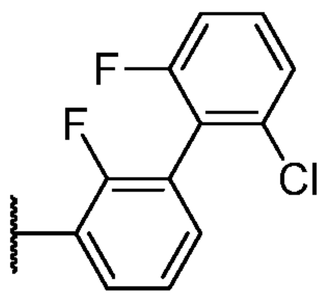
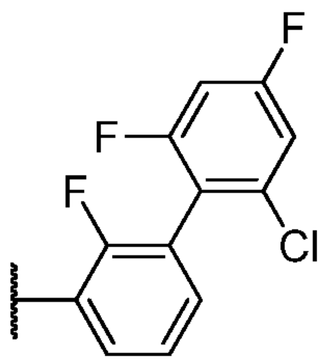
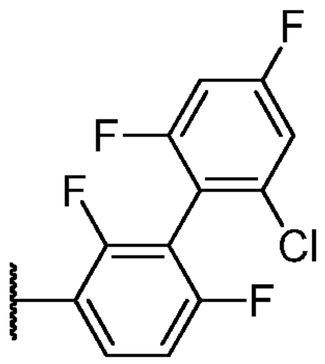
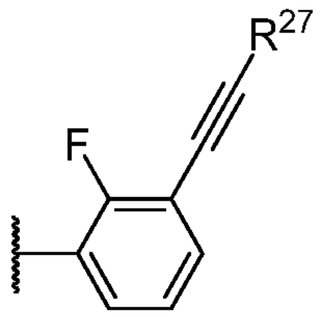
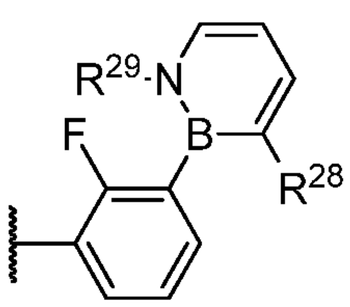
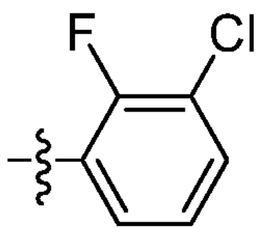
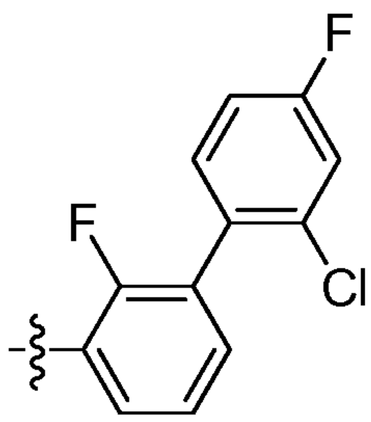
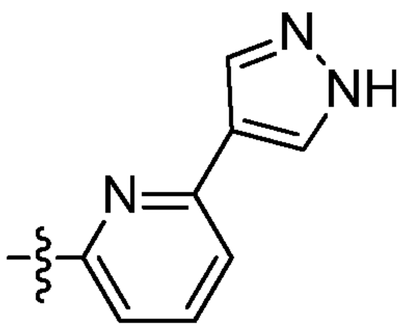
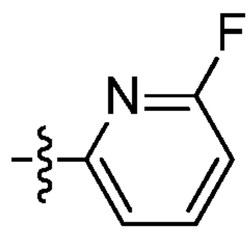
[0204] In certain embodiments, B is a 2-fluoro-3-chlorophenyl or a 2-fluoro-3-trifluoromethoxyphenyl group.

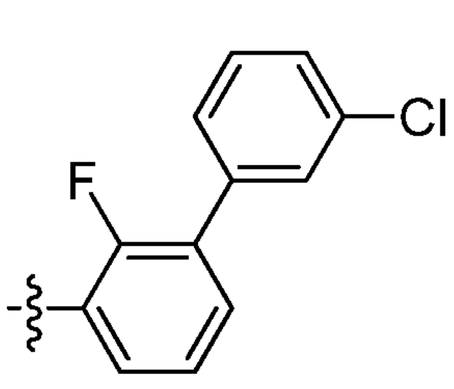
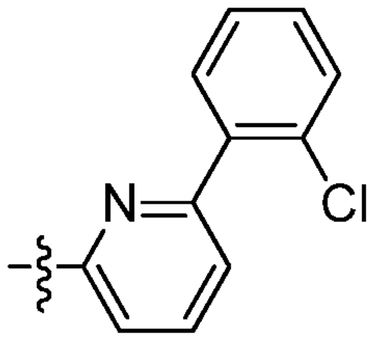
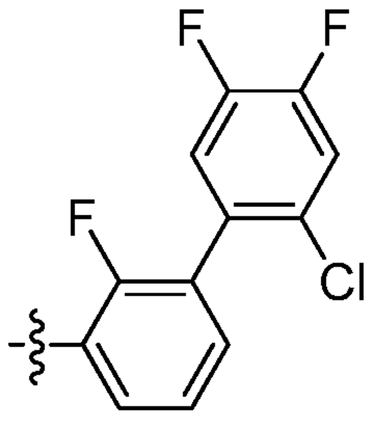
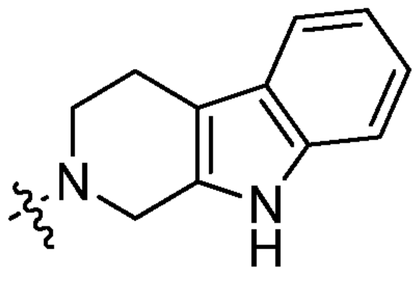
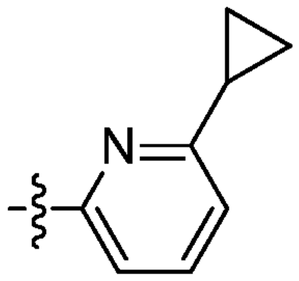
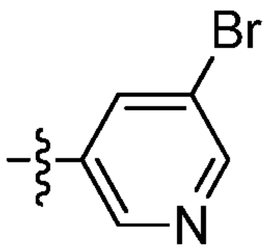
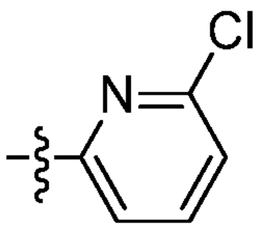
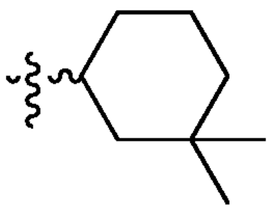
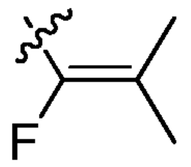
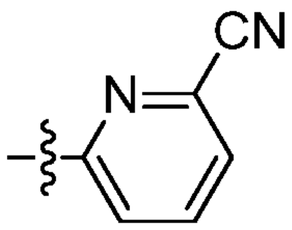
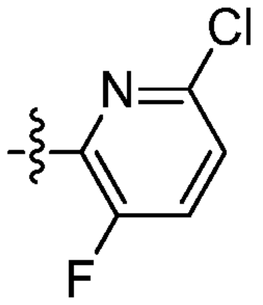
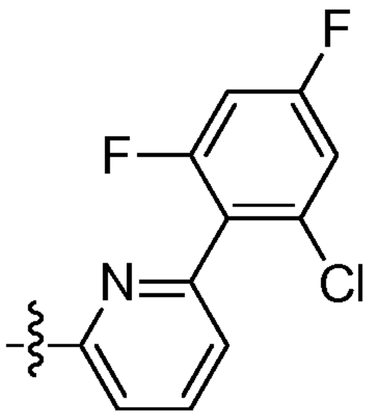
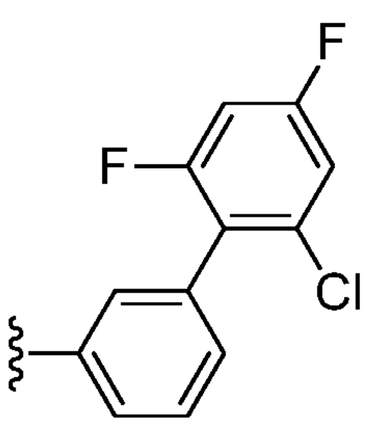
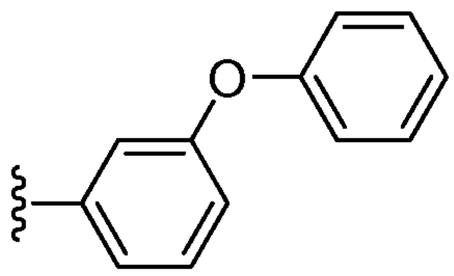
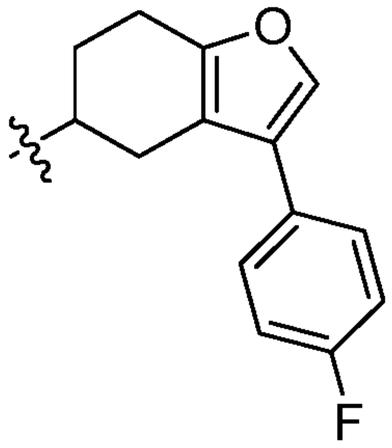
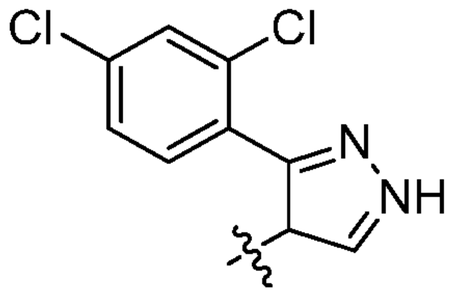
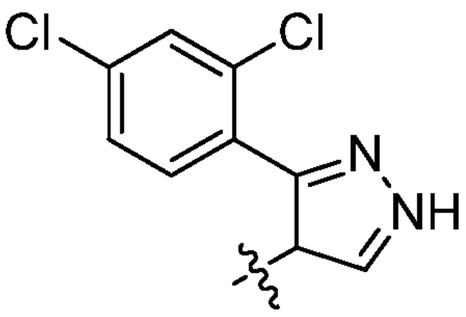
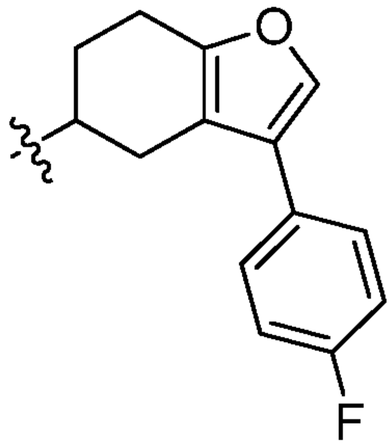
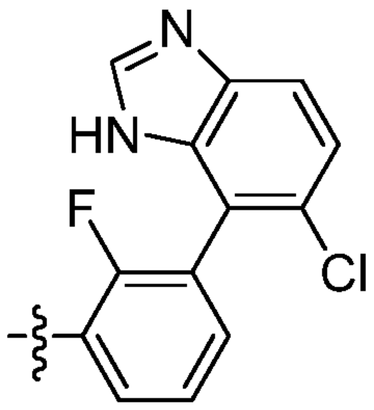
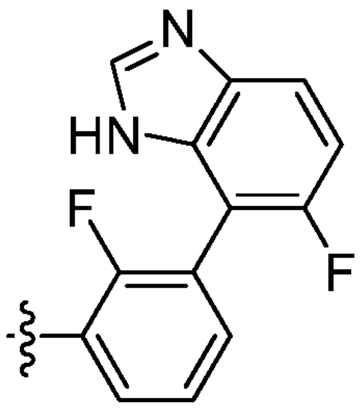
[0205] In one embodiment, B is pyridyl, optionally substituted with halogen, C_1-C_2alkoxy, and trifluoromethyl.

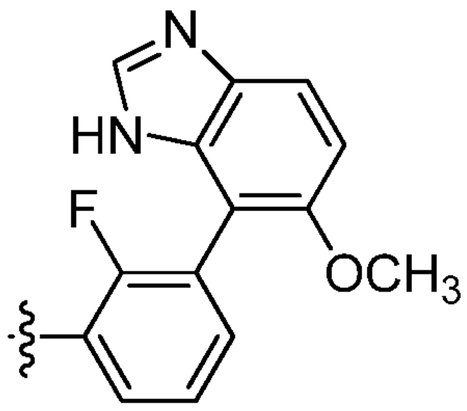
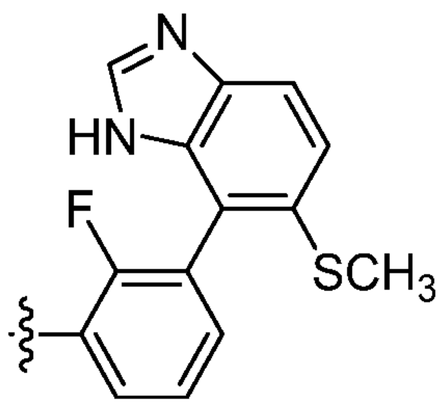
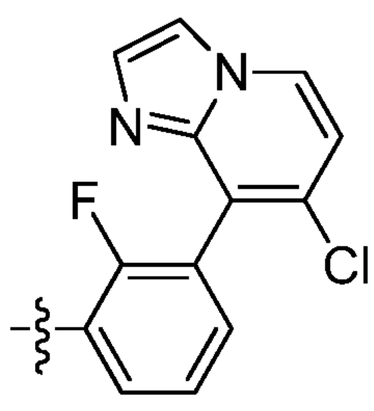
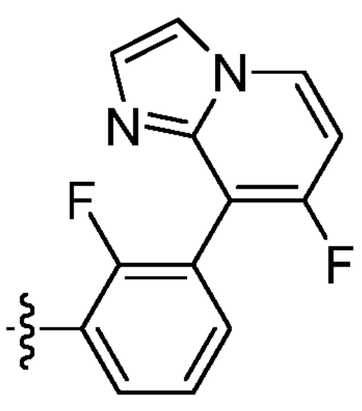
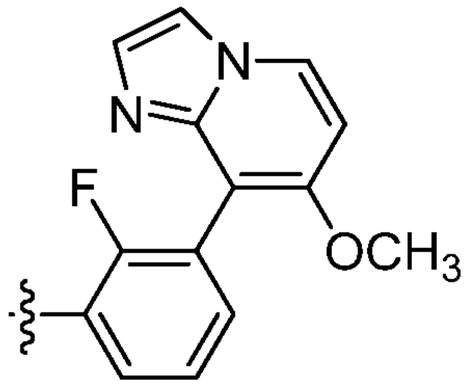
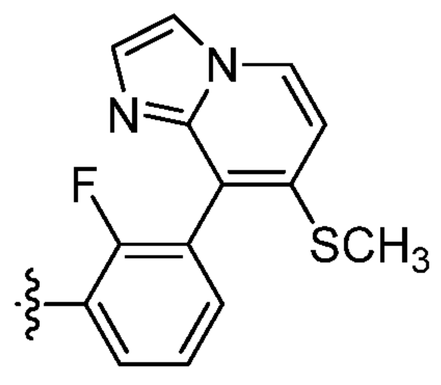
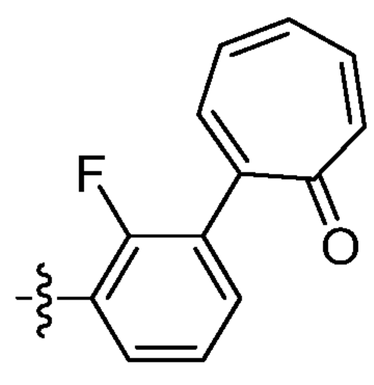
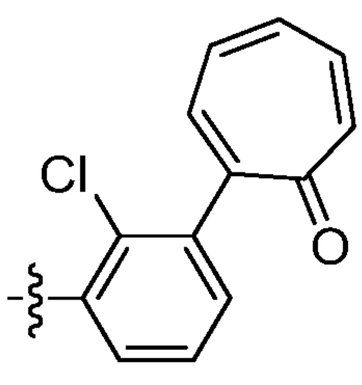
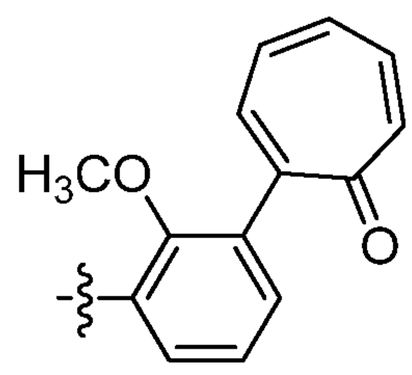
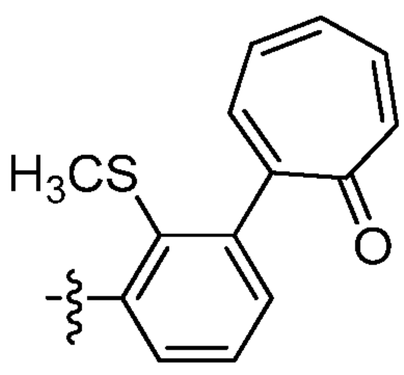
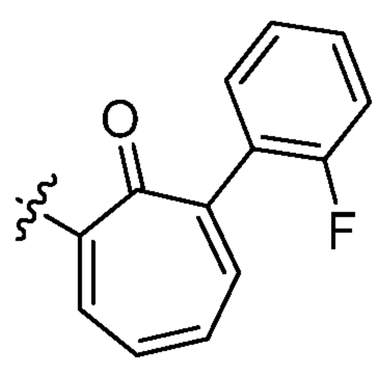
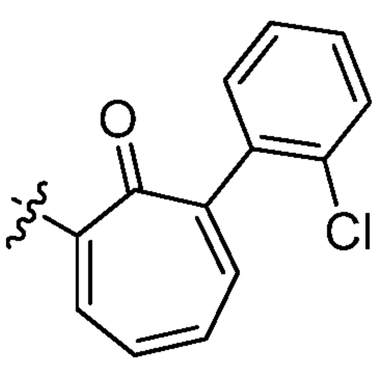
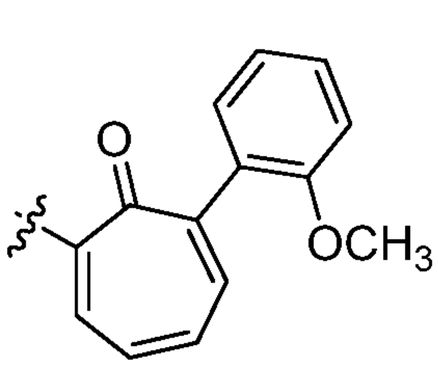
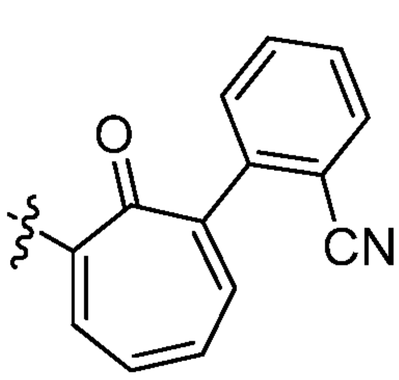
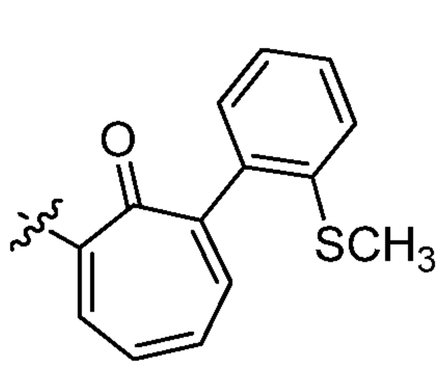
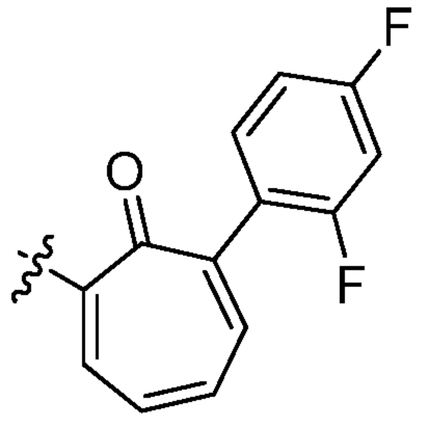
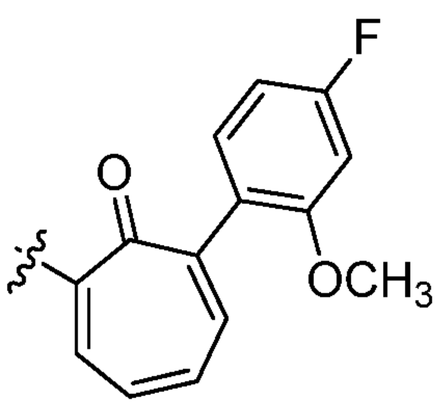
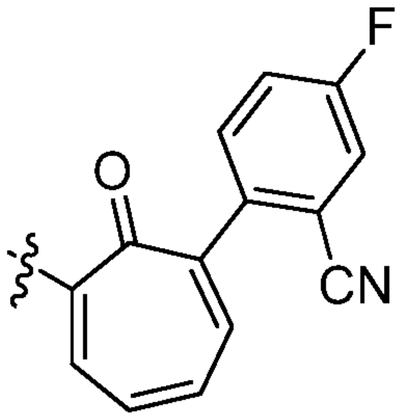
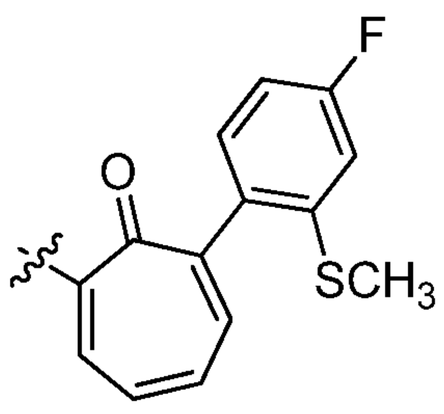
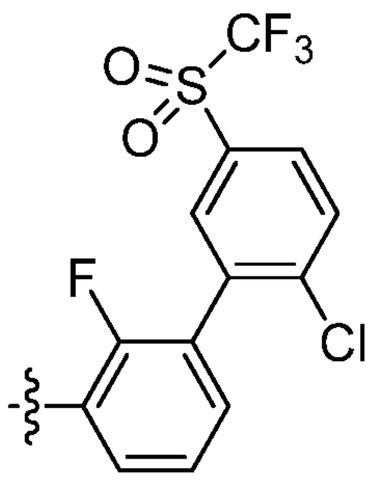
[0206] In one embodiment, B is phenyl, substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, and optionally substituted phenyl.

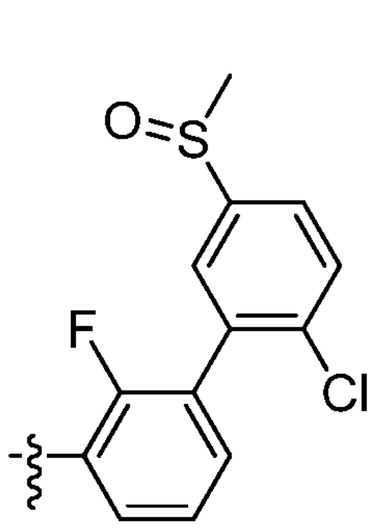
[0207] In one embodiment, R^{23} is independently chosen at each occurrence from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S.

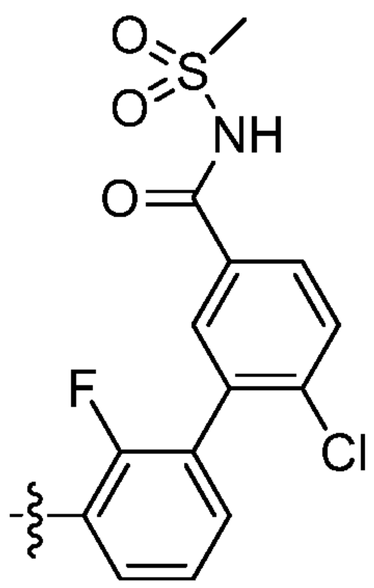
[0208] In one embodiment, B is selected from

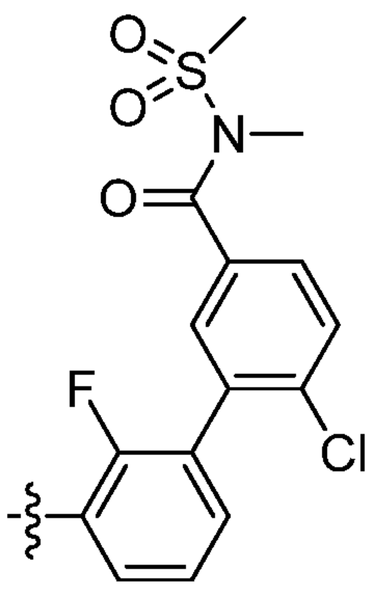

















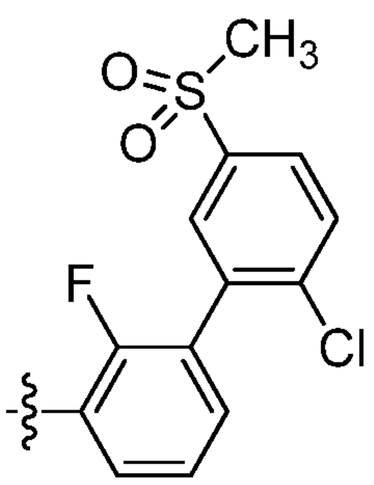





















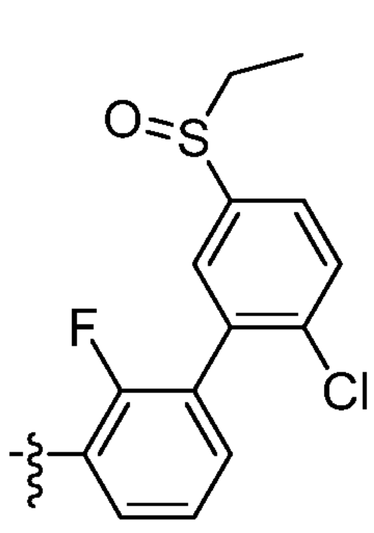





















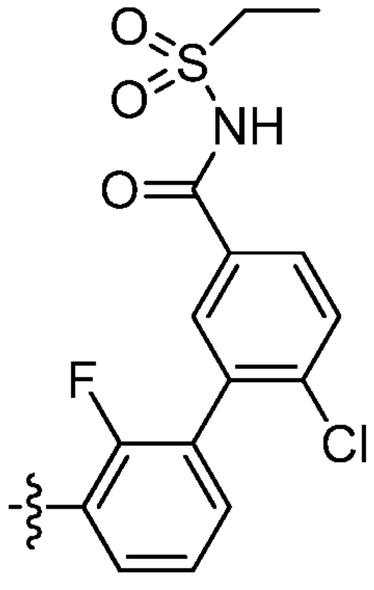


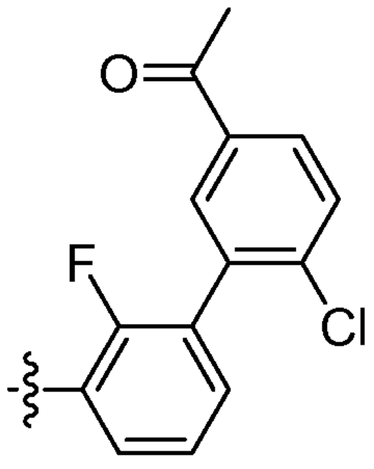


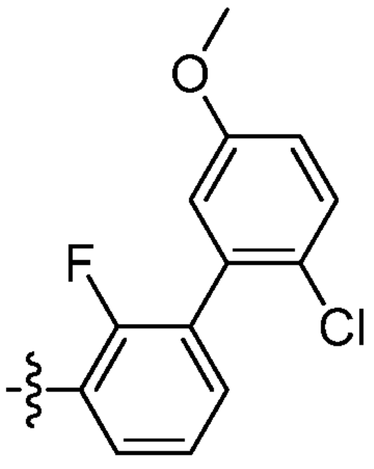


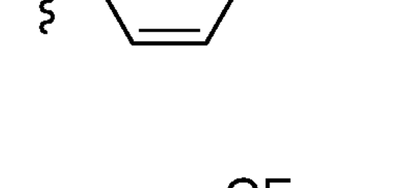


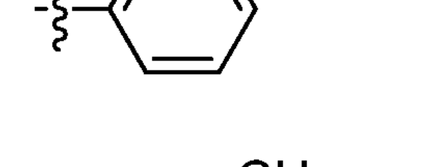


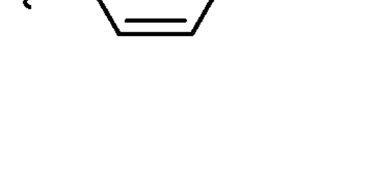


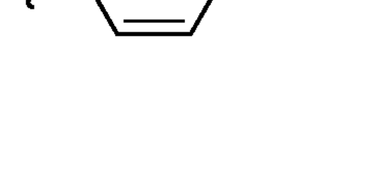


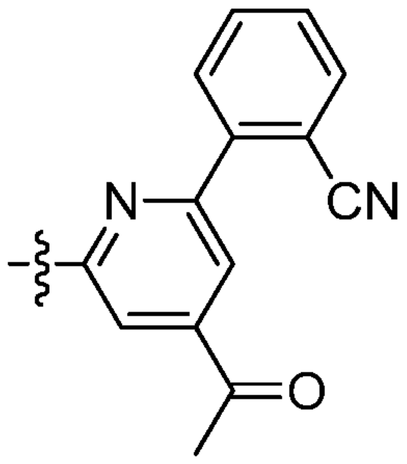


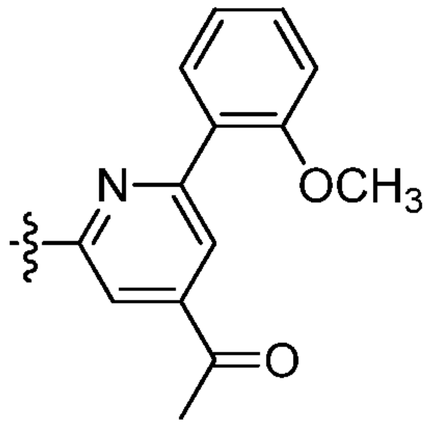


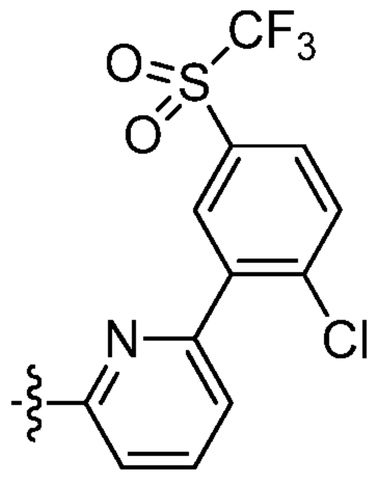


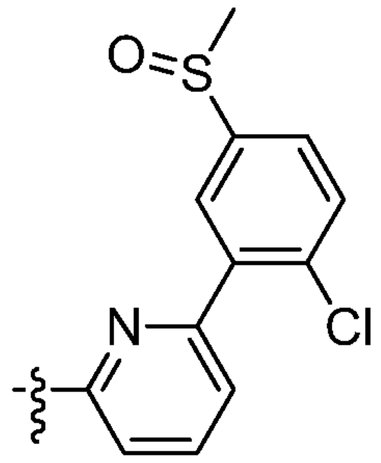


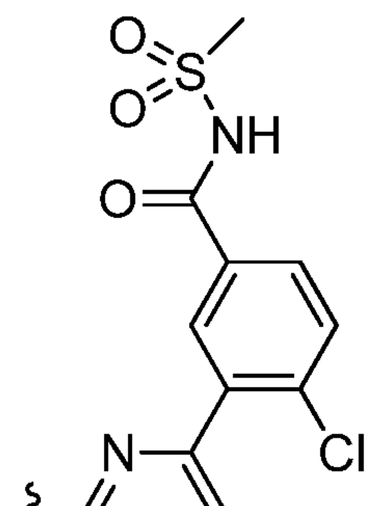


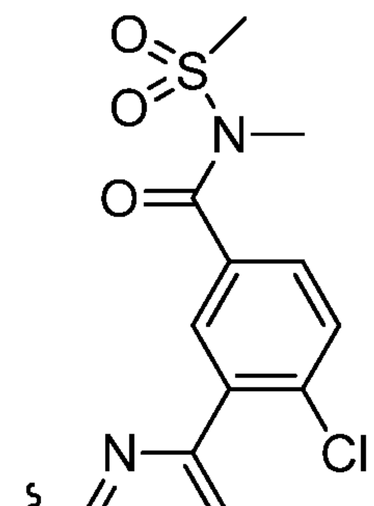


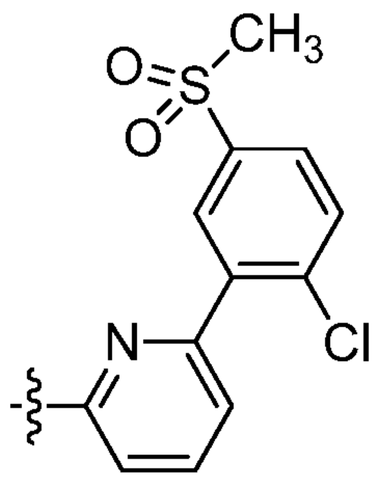


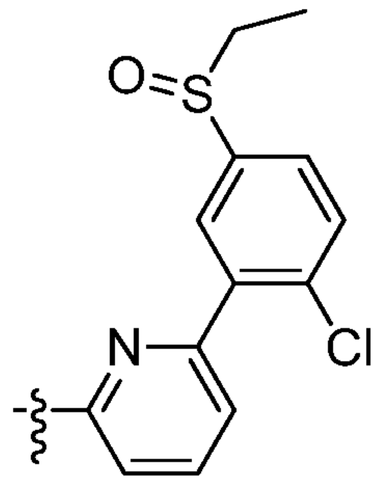


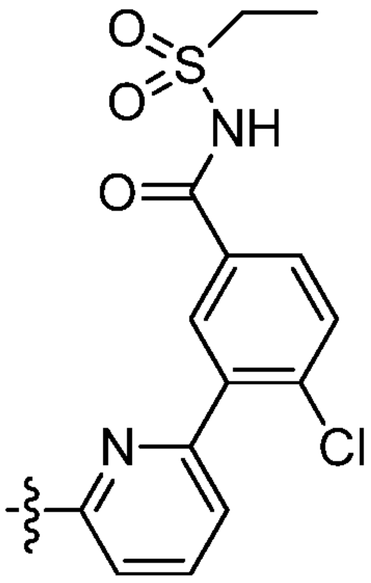


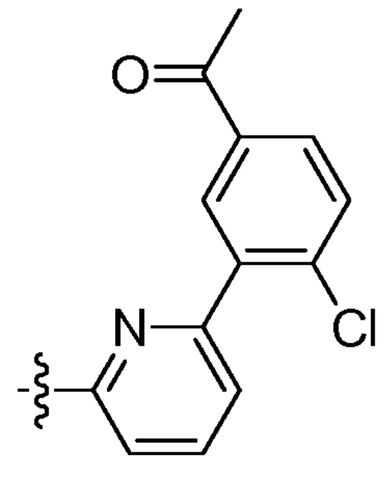


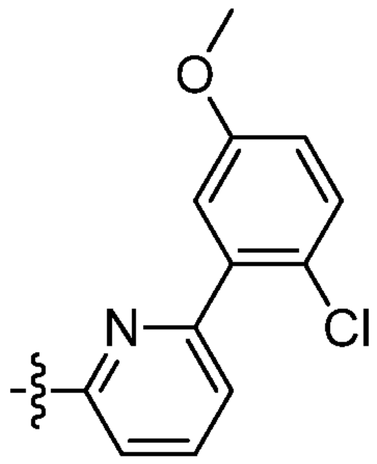


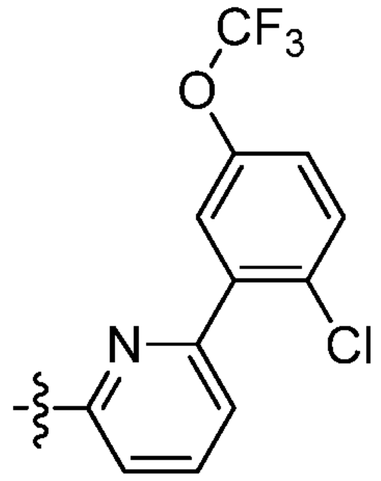


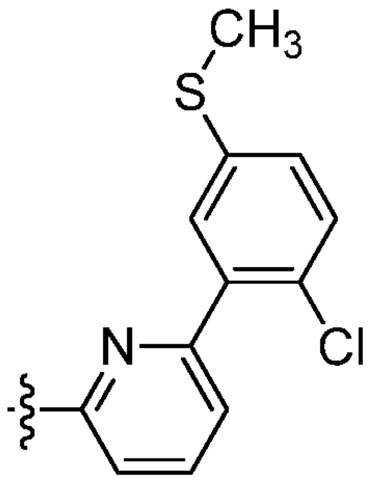


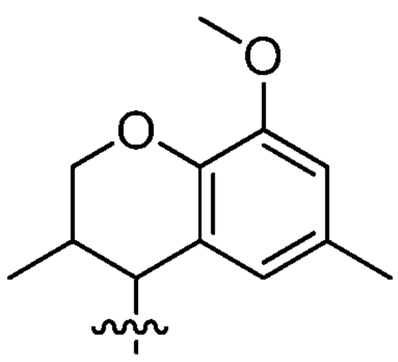


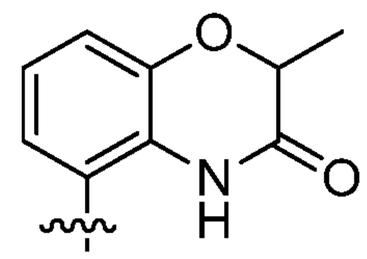


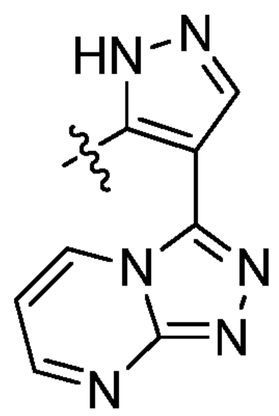


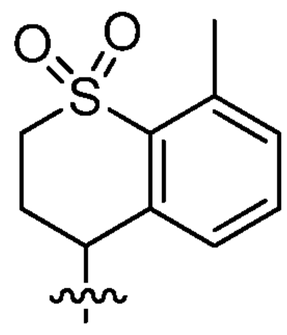


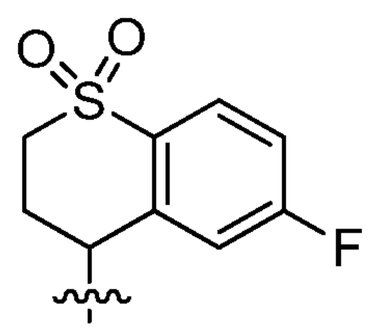


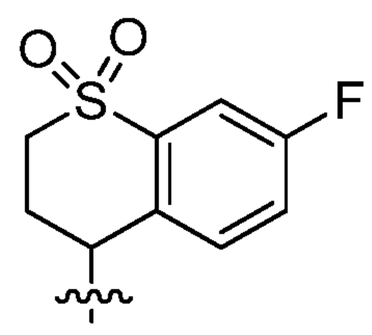


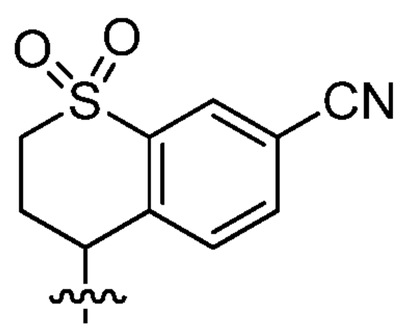


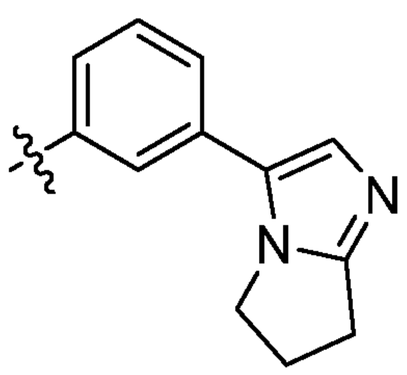
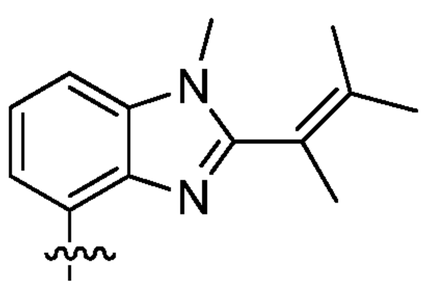
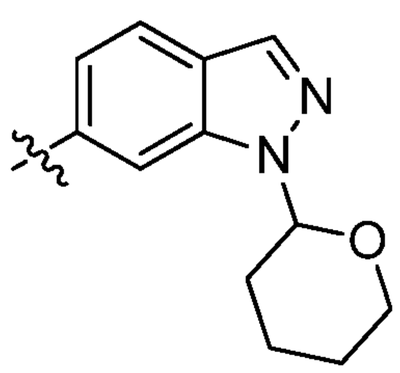
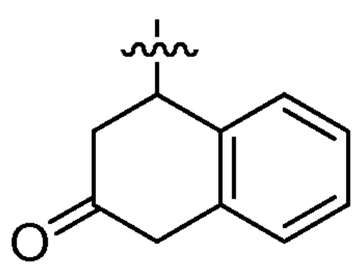
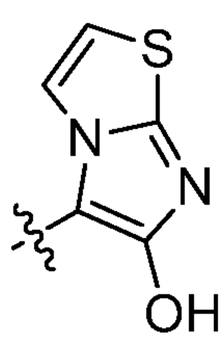
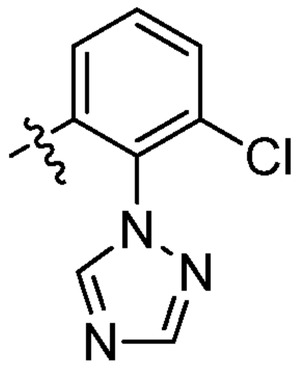
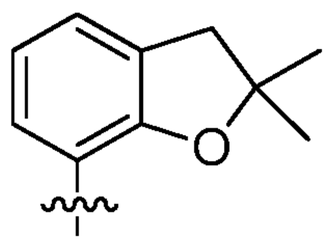


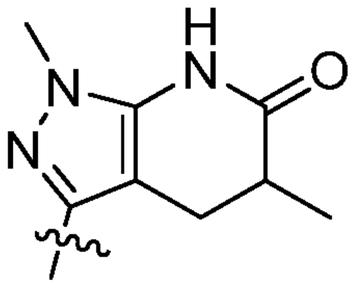
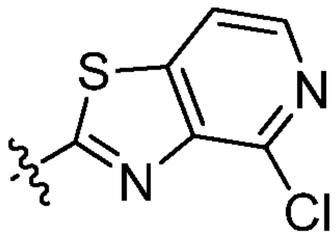
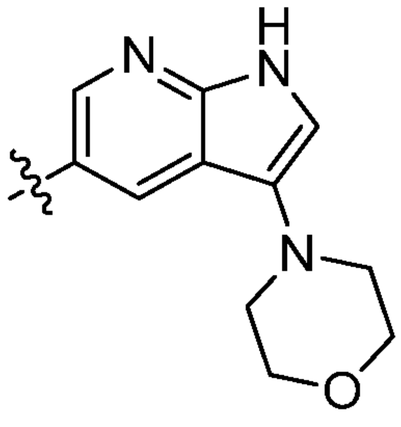
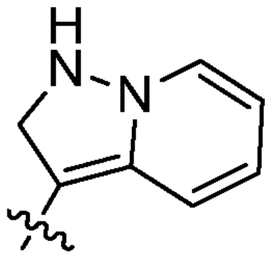
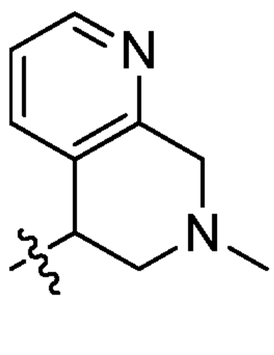
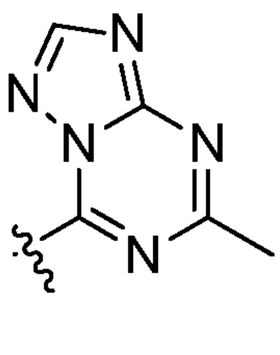
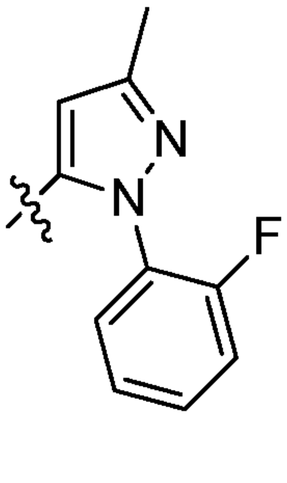
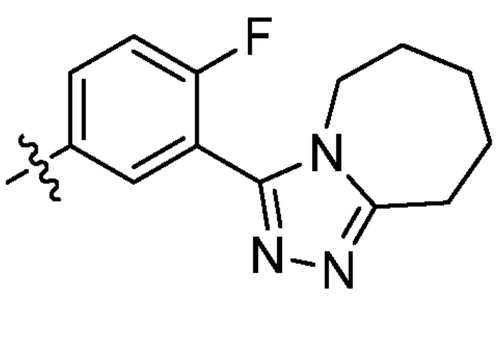
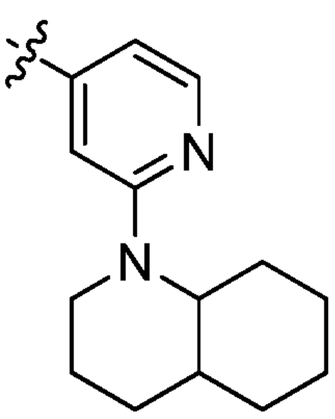
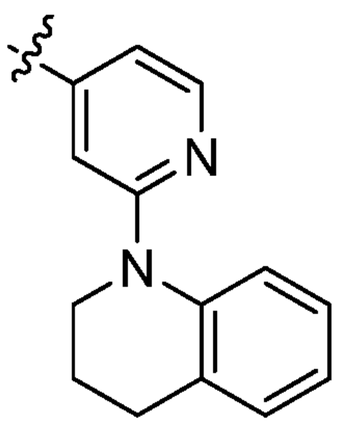
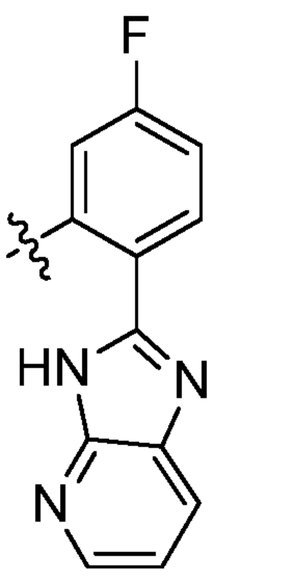
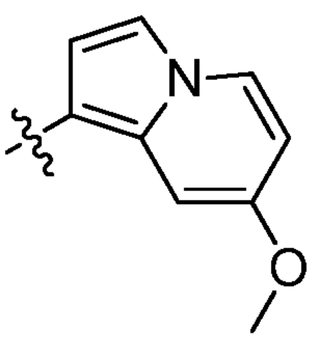


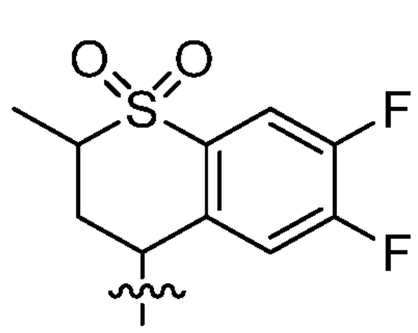


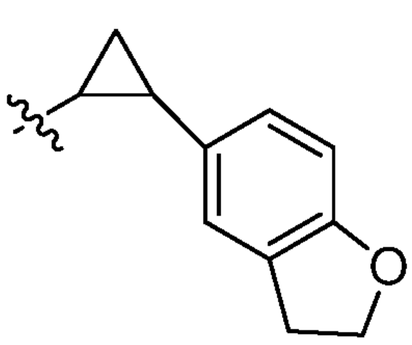


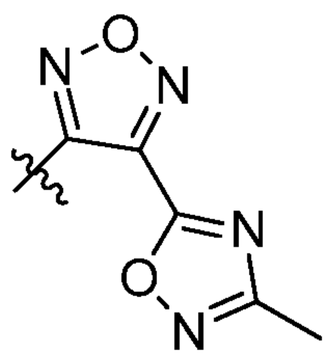


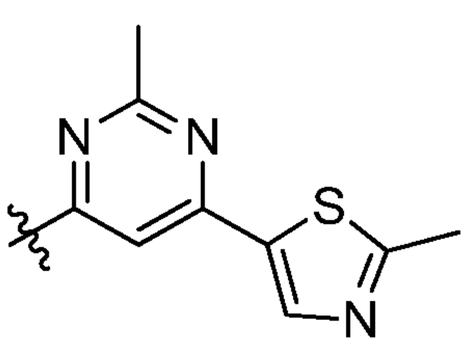
















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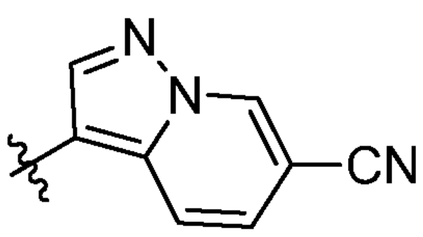
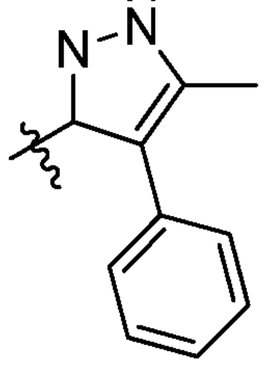
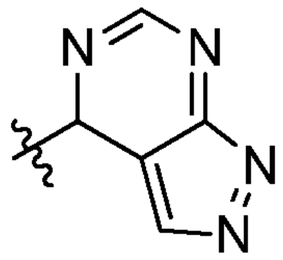
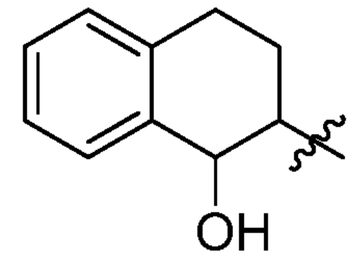
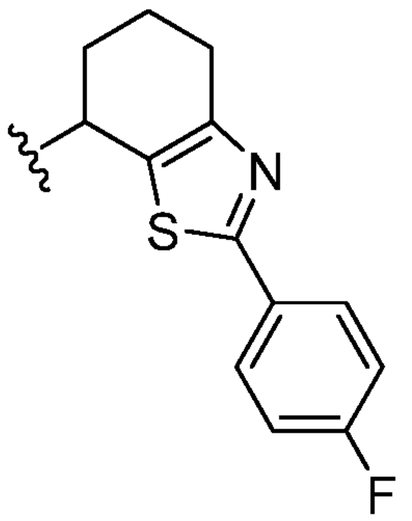
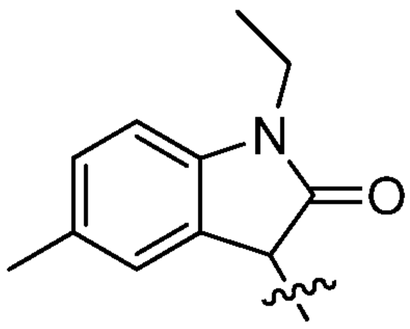


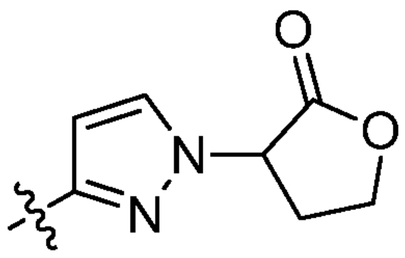


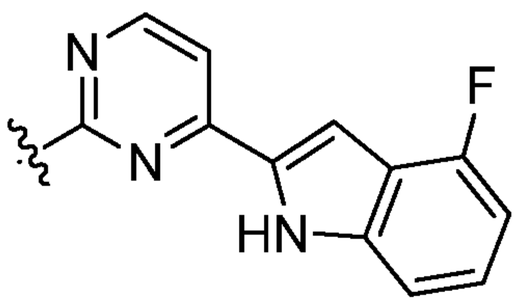


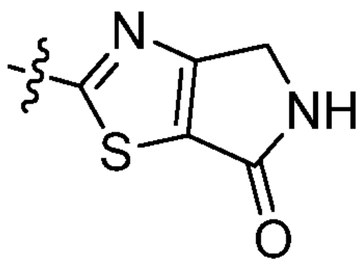


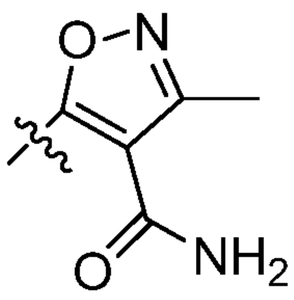


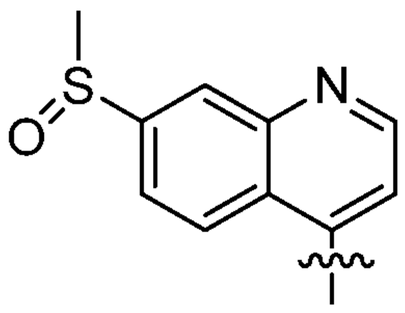


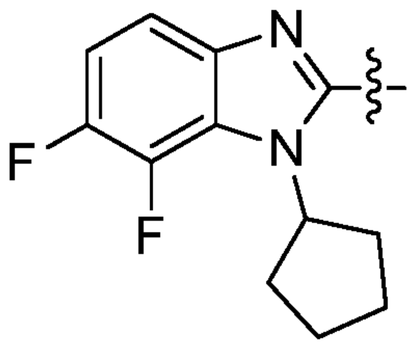


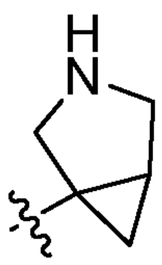


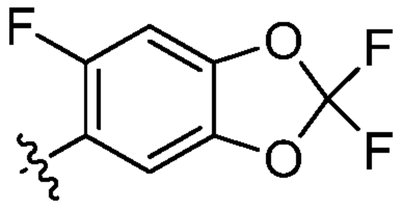


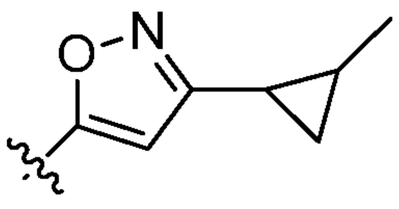


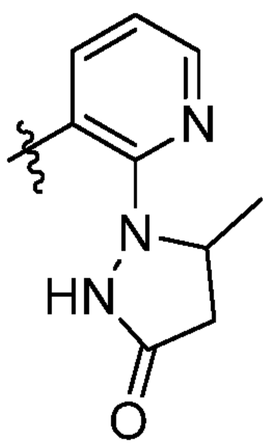








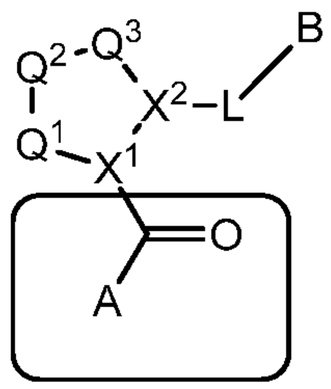




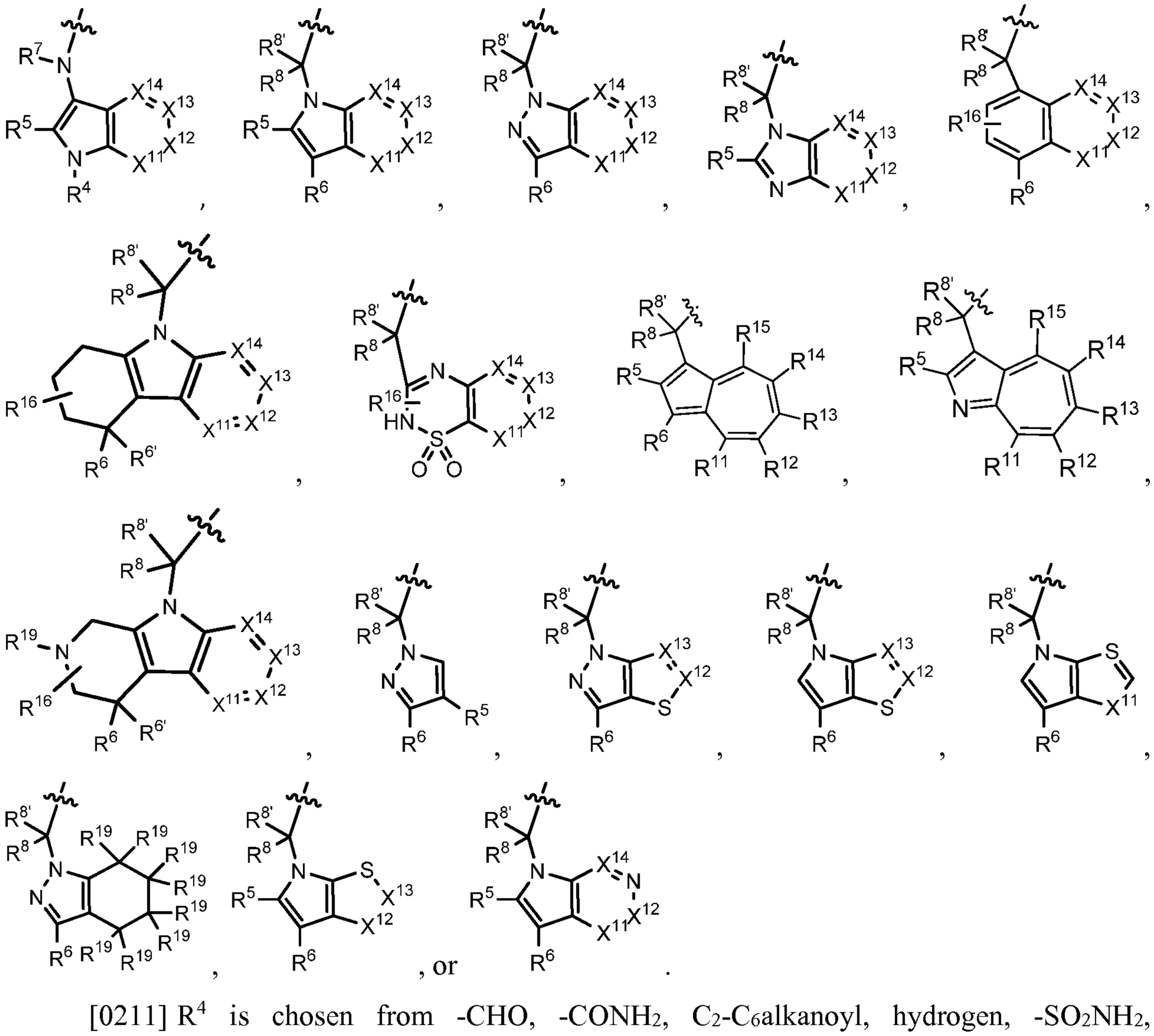
where R^{27} is hydrogen, methyl, or trifluoromethyl; R^{28} is hydrogen or halogen; and R^{29} is hydrogen, methyl, trifluoromethyl, or $-Si(CH_3)_2C(CH_3)_3$.

Central Core (C=O)A Substituent

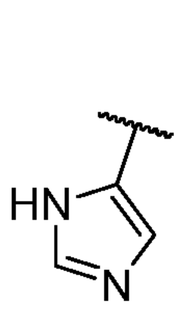
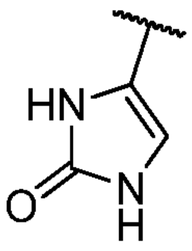
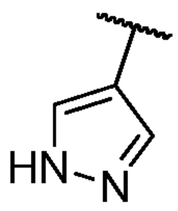
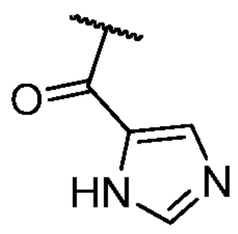
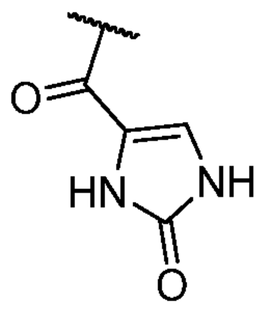
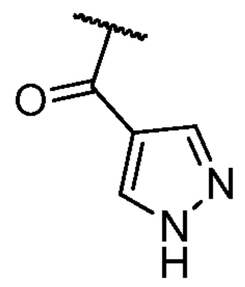
[0209] The central core (C=O)A substituent in Formula I is illustrated below:



[0210] A is a group chosen from:



[0211] R^4 is chosen from -CHO, -$CONH_2$, C_2-C_6alkanoyl, hydrogen, -SO_2NH_2, -$C(CH_2)_2F$, -$CH(CF_3)NH_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_2alkyl(C_3-C_7cycloalkyl),


, 
, 
, 
, 
, or 
;

each of which R^4 other than hydrogen, -CHO, and $–CONH_2$, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_2alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0212] R^5 and R^6 are independently chosen from –CHO, -$C(O)NH_2$, -$C(O)NH(CH_3)$, C_2-C_6alkanoyl, hydrogen, hydroxyl, halogen, cyano, nitro, -COOH, -SO_2NH_2, vinyl, C_1-C_6alkyl (including methyl), C_2-C_6alkenyl, C_1-C_6alkoxy, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_4alkyl(C_3-C_7cycloalkyl), -$P(O)(OR^9)_2$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)N(CH_2CH_2R^9)(R^{10})$, -$NR^9C(O)R^{10}$, phenyl, or 5- to 6-membered heteroaryl.

[0213] Each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH is unsubstituted or optionally substituted. For example, R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH may be substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, imino, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_4alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0214] $R^{6'}$ is hydrogen, halogen, hydroxyl, C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or C_1-C_4alkoxy; or R^6 and $R^{6'}$ may be taken together to form an oxo, vinyl, or imino group.

[0215] R^7 is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl).

[0216] R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, and (C_1-C_4alkylamino)C_0-C_2alkyl; or R^8 and $R^{8'}$ are taken together to form an oxo group; or R^8 and $R^{8'}$ can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring.

[0217] R^{16} is absent or may include one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0218] R^{19} is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -SO_2C_1-C_6alkyl, (mono- and di-C_1-C_6alkylamino)C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkyl(C_3-C_7heterocycloalkyl), -C_0-C_4alkyl(aryl), C_0-C_4alkyl(heteroaryl), and wherein R^{19} other than

hydrogen is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, -COOH, and –C(O)OC$_1$-C$_4$alkyl.

[0219] X^{11} is N or CR^{11}.

[0220] X^{12} is N or CR^{12}.

[0221] X^{13} is N or CR^{13}.

[0222] X^{14} is N or CR^{14}.

[0223] No more than 2 of X^{11}, X^{12}, X^{13}, and X^{14} are N.

[0224] R^{11}, R^{14}, and R^{15} are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -O(PO)$(OR^9)_2$, -(PO)$(OR^9)_2$, C$_1$-C$_6$alkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, C$_2$-C$_6$alkenyl(aryl), C$_2$-C$_6$alkenyl(cycloalkyl), C$_2$-C$_6$alkenyl(heterocycle), C$_2$-C$_6$alkenyl(heteroaryl), C$_2$-C$_6$alkynyl, C$_2$-C$_6$alkynyl(aryl), C$_2$-C$_6$alkynyl(cycloalkyl), C$_2$-C$_6$alkynyl(heterocycle), C$_2$-C$_6$alkynyl(heteroaryl), C$_2$-C$_6$alkanoyl, C$_1$-C$_6$alkoxy, C$_1$-C$_6$thioalkyl, -C$_0$-C$_4$alkyl(mono- and di-C$_1$-C$_6$alkylamino), -C$_0$-C$_4$alkyl(C$_3$-C$_7$cycloalkyl), -C$_0$-C$_4$alkoxy(C$_3$-C$_7$cycloalkyl), C$_1$-C$_2$haloalkyl, and C$_1$-C$_2$haloalkoxy.

[0225] In one embodiment, R^5 and R^6 are independently chosen from –CHO, -C(O)NH$_2$, -C(O)NH(CH$_3$), C$_2$-C$_6$alkanoyl, and hydrogen.

[0226] In one embodiment, each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, imino, cyano, cyanoimino, C$_1$-C$_2$alkyl, C$_1$-C$_4$alkoxy, -C$_0$-C$_2$alkyl(mono- and di-C$_1$-C$_4$alkylamino), C$_1$-C$_2$haloalkyl, and C$_1$-C$_2$haloalkoxy.

[0227] In one embodiment, R^8 and $R^{8'}$ are independently hydrogen or methyl.

[0228] In one embodiment, R^8 and $R^{8'}$ are hydrogen.

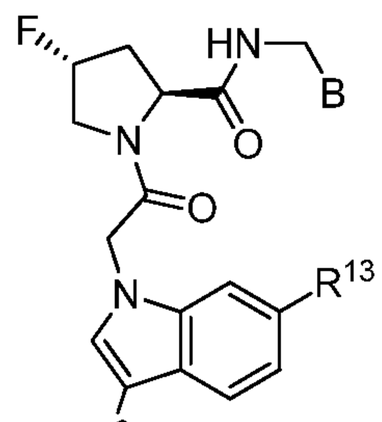
[0229] In one embodiment, R^7 is hydrogen or methyl.

[0230] In one embodiment, R^7 is hydrogen.

Embodiments of Formulas IA, IB, IC, and ID

[0231] To further illustrate the invention, various embodiments of Formula IA, IB, IC and ID are provided. These are presented by way of example to show some of the variations among presented compounds within the invention and can be applied to any of the Formulas I-XXX.

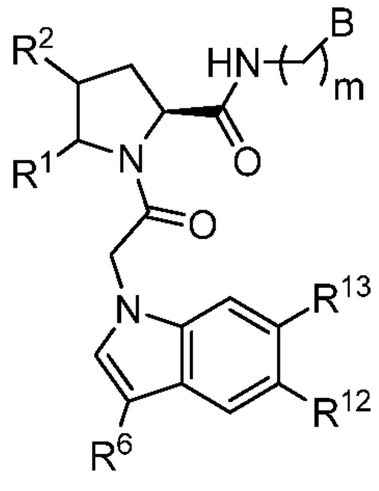
[0232] In one aspect, this disclosure includes compounds and salts of Formula IA:



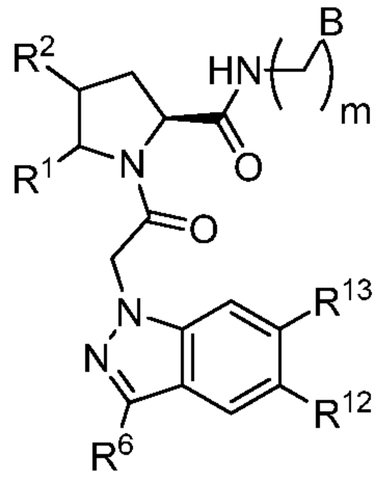
(IA) where

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

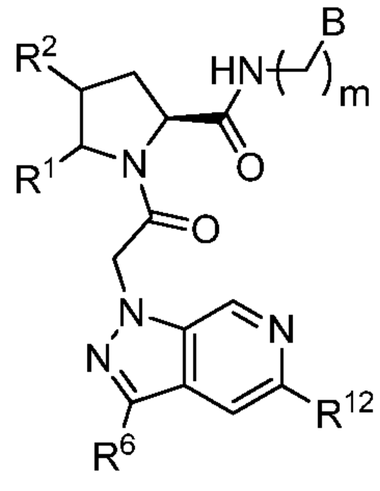
[0233] In another aspect, this disclosure includes compounds and salts of Formula IB, IC, and ID.



IB



IC



ID.

[0234] 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.

[0235] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0236] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0237] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0238] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0239] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0240] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0241] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0242] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0243] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0244] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0245] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0246] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0247] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

[0248] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

[0249] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 is H, R^2 is F, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

[0250] In some embodiments, structures are provided including Formulas IB and IC, wherein m=0, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

[0251] In some embodiments, 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 R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0252] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0253] In some embodiments, 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 R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0254] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is heteroaryl.

[0255] In some embodiments, 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 heteroaryl, and B is heteroaryl.

[0256] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0257] In some embodiments, 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 heteroaryl, and B is heteroaryl.

[0258] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is heteroaryl.

[0259] In some embodiments, 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 R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0260] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0261] In some embodiments, 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 R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0262] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is R^{32}, R^{32} is heteroaryl, R^{13} is H, and B is phenyl.

[0263] In some embodiments, 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 heteroaryl, and B is phenyl.

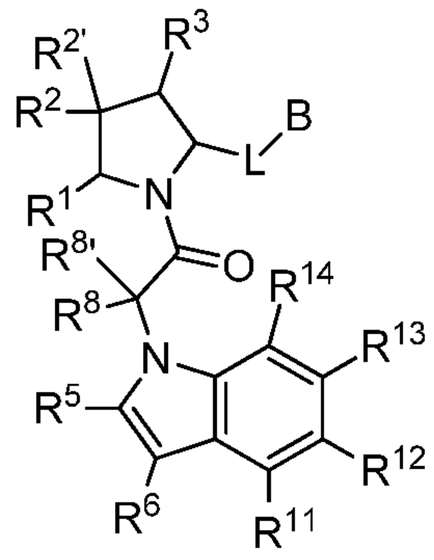
[0264] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is alkanoyl, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

[0265] In some embodiments, 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 heteroaryl, and B is phenyl.

[0266] In some embodiments, structures are provided including Formulas IB and IC, wherein m=1, R^1 and R^2 are joined to form a 3 membered ring, R^6 is amide, R^{12} is H, R^{13} is R^{32}, R^{32} is heteroaryl, and B is phenyl.

Embodiments of Formula VII

[0267] To further illustrate the invention, various embodiments of Formula VII. In one aspect, the disclosure includes compounds and salts of Formula VII:



(VII), wherein:

[0268] R^1, R^2, $R^{2'}$, and R^3 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, -C_0-C_2alkylNR^9R^{10}, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0269] R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, and methyl;

[0270] R^5 is hydrogen, hydroxyl, cyano, -COOH, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_6alkanoyl -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C(O)C_0-C_4alkyl(C_3-C_7cycloalkyl, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy;

[0271] R^6 is –C(O)CH_3, -C(O)NH_2, -C(O)CF_3, -C(O)(cyclopropyl), or -ethyl(cyanoimino); and

[0272] R^{11} and R^{14} are independently chosen from hydrogen, halogen, hydroxyl, amino, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -OC_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0273] Prodrugs of Formula I are also within the scope of the disclosure.

III. PHARMACEUTICAL PREPARATIONS

[0274] Compounds disclosed herein can be administered as the neat chemical, but can also administered as a pharmaceutical composition, that includes an effective amount for a host in need of treatment of the selected compound of Formula I, as described herein. Accordingly, the disclosure provides pharmaceutical compositions comprising an effective amount of compound or pharmaceutically acceptable salt of Formula I, together with at least one

pharmaceutically acceptable carrier. The pharmaceutical composition may contain a compound or salt of Formula I as the only active agent, or, in an alternative embodiment, Formula I and at least one additional active agent. 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 a compound of Formula I 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 25, 50, 100, 200, 250, 300, 400, 500, 600, 700, or 750 mg of active compound, or its salt. The pharmaceutical composition may also include a molar ratio of a compound of Formula I and an additional active agent. 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 another anti-inflammatory agent.

[0275] Compounds disclosed 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, intraveneous, intra-aortal, intracranial, or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers. The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a pill, a capsule, a tablet, a syrup, a transdermal patch, or an ophthalmic solution. 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.

[0276] Carriers include excipients and diluents and 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.

[0277] Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidents, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a

diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin; talc, and vegetable oils. Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0278] The pharmaceutical compositions/combinations can be formulated for oral administration. These compositions can contain any amount of active compound for Formula I that achieves the desired result, for example between 0.1 and 99 weight % (wt.%) of a compound of Formula I and usually at least about 5 wt.% of a compound of Formula I. Some embodiments contain from about 25 wt.% to about 50 wt. % or from about 5 wt.% to about 75 wt.% of the compound of Formula I.

[0279] The complement factor D inhibitors of the present invention can be administered, for example, either systemically or locally. Systemic administration includes, for example, oral, transdermal, subdermal, intraperitioneal, subcutaneous, transnasal, sublingual, or rectal. Local administration for ocular administration includes: topical, intravitreal, periocular, transscleral, retrobulbar, juxtascleral, sub-tenon, or via an intraocular device. The inhibitors may be delivered via a sustained delivery device implanted intravitreally or transsclerally, or by other known means of local ocular delivery.

IV. METHODS OF TREATMENT

[0280] The compounds and pharmaceutical compositions disclosed herein are 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 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. Complement mediated disorders that may be treated or prevented by the compounds and compositions of this disclosure include, but are not limited to, inflammatory effects of sepsis, systemic inflammatory response syndrome (SIRS), ischemia/ reperfusion injury (I/R injury), psoriasis, myasthenia gravis, system lupus erythematosus (SLE), paroxysmal nocturnal hemoglobinuria (PNH), hereditary angioedema, multiple sclerosis, trauma, burn injury, capillary leak syndrome, obesity, diabetes, Alzheimer's dementia, stroke, schizophrenia, epilepsy, age-related macular degeneration, glaucoma, diabetic retinopathy, asthma, allergy, acute respiratory distress

syndrome (ARDS), atypical hemolytic uremic syndrome (aHUS), hemolytic uremic syndrome (HUS), cystic fibrosis, myocardial infarction, lupus nephritides, Crohn's disease, rheumatoid arthritis, atherosclerosis, transplant rejection, prevention of fetal loss, biomaterial reactions (e.g. in hemodialysis, inplants), C3 glomerulonephritis, abdominal aortic aneurysm, neuromyelitis optica (NMO), vasculitis, neurological disorders, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during I L-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, adult respiratory distress syndrome, thermal injury including burns or frostbite, myocarditis, post-ischemic reperfusion conditions, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, immune complex disorders and autoimmune diseases, SLE nephritis, proliferative nephritis, liver fibrosis, hemolytic anemia, tissue regeneration and neural regeneration. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (e.g., silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gases and chemicals, e.g., chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (e.g., burn, freeze), bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, Pauci-immune vasculitis, immune complex- associated inflammation, uveitis (including Behcet's disease and other sub-types of uveitis), antiphospholipid syndrome, arthritis, autoimmune heart disease, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, transplantation, diseases of the central nervous system and other neurodegenerative conditions, glomerulonephritis (including membrane proliferative glomerulonephritis), blistering cutaneous diseases (including bullous pemphigoid, pemphigus, and epidermolysis bullosa), ocular cicatrical pemphigoid, MPGN II, uveitis, adult macular degeneration, diabetic retinopathy, retinitis pigmentosa, macular edema, Behcet's uveitis, multifocal choroiditis, Vogt-Koyangi-Harada syndrome, imtermediate uveitis, birdshot retino-

chorioditis, sympathetic ophthalmia, ocular dicatricial pemphigoid, ocular pemphigus, nonartertic ischemic optic neuropathy, postoperative inflammation, and retinal vein occlusion.

[0281] 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.

[0282] 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of rheumatoid arthritis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of multiple sclerosis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of myasthenia gravis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In another embodiment, a method for the treatment of C3 glomerulonephritis is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0283] 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 of Formula I 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 disease, by providing an effective amount of a compound or pharmaceutically acceptable salt of Formula I to patient with a factor D mediated inflammatory disorder. A compound or salt of Formula I may be provided as the only active agent or may be provided together with one or more additional active agents.

[0284] 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 of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In one embodiment, a method of inhibiting activation of the alternative complement pathway in a subject is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier. In one embodiment, a method of modulating factor D activity in a subject is provided that includes the administration of an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier.

[0285] "Prevention" as used in this disclosure means decreasing the likelihood of the appearance of symptoms in a patient administered the compound prophylactically as compared to the likelihood of the appearance of symptoms in patients not administered the compound or decreasing the severity of symptoms in a patient administered the compound prophylactically as compared to the severity of symptoms experienced by patients with the disorder or condition who were not administered the compound. In an alternative embodiment, an effective amount of

a compound of Formula I is used to prevent or prophylaxis of a complement factor D related disorder.

[0286] An effective amount of a pharmaceutical composition/ combination of the invention may be 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 disease; (b) cause a regression of an inflammatory, immune, including an autoimmune, disorder or complement factor D related disease; or (c) cause a cure of an inflammatory, immune, including an autoimmune, disorder or complement factor D related disease.

[0287] An effective amount of a compound or pharmaceutical composition described herein will also provide a sufficient amount of the active agent when administered to a patient to provide a clinical benefit. Such an amount may be ascertained experimentally, for example by assaying blood concentration of the agent, or theoretically, by calculating bioavailability.

V. COMBINATION THERAPY

[0288] In one embodiment, a compound or salt of Formula I may be provided in combination or alternation with at least one additional inhibitor of the complement system or a second active compound with a different biological mechanism of action. In one embodiment, a compound or salt of Formula I may be provided in combination with a complement C5 inhibitor or C5 convertase inhibitor. In another embodiment, a compound or salt of Formula I may be provided in combination with eculizumab. In one embodiment, a compound or salt of Formula I may be provided in combination with additional inhibitors of factor D.

[0289] In one embodiment, a compound or salt of Formula I may be provided together with a compound that inhibits an enzyme that metabolizes protease inhibitors. In one embodiment, a compound or salt of Formula I may be provided together with ritonavir.

[0290] In nonlimiting embodiments, a compound or salt of Formula I may be provided together with a protease inhibitor, a soluble complement regulator, a therapeutic antibody (monoclonal or polyclonal), complement component inhibitors, receptor agonists, or siRNAs.

[0291] Nonlimiting examples of active agents in these categories are:

[0292] Protease inhibitors: plasma-derived C1-INH concentrates, for example Cetor® (Sanquin), Berinert-P® (CSL Behring, Lev Pharma), and Cinryze®; and recombinant human C1-inhibitors, for example Rhucin®;

[0293] Soluble complement regulators: Soluble complement receptor 1 (TP10) (Avant Immunotherapeutics); sCR1-sLe^X/TP-20 (Avant Immunotherapeutics); MLN-2222 /CAB-2 (Millenium Pharmaceuticals); Mirococept (Inflazyme Pharmaceuticals);

[0294] Therapeutic antibodies: Eculizumab/Soliris (Alexion Pharmaceuticals); Pexelizumab (Alexion Pharmaceuticals); Ofatumumab (Genmab A/S); TNX-234 (Tanox); TNX-558 (Tanox); TA106 (Taligen Therapeutics); Neutrazumab (G2 Therapies); Anti-properdin (Novelmed Therapeutics); HuMax-CD38 (Genmab A/S);

[0295] Complement component inhibitors: Compstatin/POT-4 (Potentia Pharmaceuticals); ARC1905 (Archemix);

[0296] Receptor agonists: PMX-53 (Peptech Ltd.); JPE-137 (Jerini); JSM-7717 (Jerini);

[0297] Others: Recombinant human MBL (rhMBL; Enzon Pharmaceuticals).

[0298] In an embodiment, the present invention provides a method of treating or preventing age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention. In one embodiment, the compositions of the present invention are administered in combination with an anti-VEGF agent. Nonlimiting 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.

[0299] In another embodiment, a compound of Formula I can be combined with a second agent in order to treat a disorder of the eye.

[0300] Examples of types of therapeutic agents that can be used in combination for ocular applications include anti-inflammatory drugs, antimicrobial agents, anti-angiogenesis agents, immunosuppressants, antibodies, steroids, ocular antihypertensive drugs and combinations thereof. Examples of therapeutic agents include amikacin, anecortane acetate, anthracenedione, anthracycline, an azole, amphotericin B, bevacizumab, camptothecin, cefuroxime, chloramphenicol, chlorhexidine, chlorhexidine digluconate, clortrimazole, a

clotrimazole cephalosporin, corticosteroids, dexamethasone, desamethazone, econazole, eftazidime, epipodophyllotoxin, fluconazole, flucytosine, fluoropyrimidines, fluoroquinolines, gatifloxacin, glycopeptides, imidazoles, itraconazole, ivermectin, ketoconazole, levofloxacin, macrolides, miconazole, miconazole nitrate, moxifloxacin, natamycin, neomycin, nystatin, ofloxacin, polyhexamethylene biguanide, prednisolone, prednisolone acetate, pegaptanib, platinum analogues, polymicin B, propamidine isethionate, pyrimidine nucleoside, ranibizumab, squalamine lactate, sulfonamides, triamcinolone, triamcinolone acetonide, triazoles, vancomycin, anti-vascular endothelial growth factor (VEGF) agents, VEGF antibodies, VEGF antibody fragments, vinca alkaloid, timolol, betaxolol, travoprost, latanoprost, bimatoprost, brimonidine, dorzolamide, acetazolamide, pilocarpine, ciprofloxacin, azithromycin, gentamycin, tobramycin, cefazolin, voriconazole, gancyclovir, cidofovir, foscarnet, diclofenac, nepafenac, ketorolac, ibuprofen, indomethacin, fluoromethalone, rimexolone, anecortave, cyclosporine, methotrexate, tacrolimus and combinations thereof. Examples of eye disorders that may be treated according to the compositions and methods disclosed herein include amoebic keratitis, fungal keratitis, bacterial keratitis, viral keratitis, onchorcercal keratitis, bacterial keratoconjunctivitis, viral keratoconjunctivitis, corneal dystrophic diseases, Fuchs' endothelial dystrophy, Sjogren's syndrome, Stevens-Johnson syndrome, autoimmune dry eye diseases, environmental dry eye diseases, corneal neovascularization diseases, post-corneal transplant rejection prophylaxis and treatment, autoimmune uveitis, infectious uveitis, anterior uveitis, posterior uveitis (including toxoplasmosis), pan-uveitis, an inflammatory disease of the vitreous or retina, endophthalmitis prophylaxis and treatment, macular edema, macular degeneration, age related macular degeneration, proliferative and non-proliferative diabetic retinopathy, hypertensive retinopathy, an autoimmune disease of the retina, primary and metastatic intraocular melanoma, other intraocular metastatic tumors, open angle glaucoma, closed angle glaucoma, pigmentary glaucoma and combinations thereof.

[0301] A compound of Formula I, or a combination of Formula I and another active agent, can be administered into an eye compartment of via injection into the vitreous chamber, subretinal space, subchoroidal space, the episclera, the conjunctiva, the sclera, the anterior chamber, and the cornea and compartments therein (e.g., subepithelial, intrastromal, endothelial).

[0302] In an alternative embodiment, a compound of Formula I, or a combination of Formula I and another active agent, can be administered into an eye compartment via binding to

a mucosal penetrating particle to treat a condition located in the vitreous chamber, subretinal space, subchoroidal space, the episclera, the conjunctiva, the sclera or the anterior chamber, and the cornea and compartments therein (e.g., subepithelial, intrastromal, endothelial). Mucosal penetrating particles are known in the art, and are described in, for example, PCT published application WO 2013166436 to Kala Pharmaceuticals, incorporated in its entirety herein.

[0303] In other embodiments, a composition comprising compound of Formula I suitable for topical administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising a compound of Formula I, wherein Formula I constitutes at least about 80 wt% of the core particle, and a coating comprising one or more surface-altering agents, wherein the one or more surface-altering agents comprise at least one of a poloxamer, a poly(vinyl alcohol), or a polysorbate. The one or more surface-altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm. The one or more surface-altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[0304] It will be appreciated by one of ordinary skill in the art that particles suitable for use with the presently disclosed methods can exist in a variety of shapes, including, but not limited to, spheroids, rods, disks, pyramids, cubes, cylinders, nanohelixes, nanosprings, nanorings, rod- shaped particles, arrow-shaped particles, teardrop-shaped particles, tetrapod-shaped particles, prism-shaped particles, and a plurality of other geometric and non-geometric shapes. In some embodiments, the presently disclosed particles have a spherical shape.

[0305] In one embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention. In one embodiment, the present invention provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with additional inhibitors of the complement system or another active compound with a different biological mechanism of action. In another embodiment, the present invention

provides a method of treating or preventing paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with eculizumab.

[0306] In one embodiment, the present invention provides a method of treating or preventing rheumatoid arthritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention. In one embodiment, the present invention provides a method of treating or preventing rheumatoid arthritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with an additional inhibitor of the complement system. In another embodiment, the present invention provides a method of treating or preventing rheumatoid arthritis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with methotrexate.

[0307] In certain embodiments, a compound of Formula I is administered in combination or alternation with at least one anti-rhuematoid arthritis drug selected from: salicylates including aspirin (Anacin, Ascriptin, Bayer Aspirin, Ecotrin) and salsalate (Mono-Gesic, Salgesic); nonsteroidal anti-inflammatory drugs (NSAIDs); nonselective inhibitors of the cyclo-oxygenase (COX-1 and COX-2) enzymes, including diclofenac (Cataflam, Voltaren), ibuprofen (Advil, Motrin), ketoprofen (Orudis), naproxen (Aleve, Naprosyn), piroxicam (Feldene), etodolac (Lodine), indomethacin, oxaprozin (Daypro), nabumetone (Relafen), and meloxicam (Mobic); selective cyclo-oxygenase-2 (COX-2) inhibitors including Celecoxib (Celebrex); disease-modifying antirheumatic drugs (DMARDs), including azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold salts (Ridaura, Solganal, Aurolate, Myochrysine), hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate (Rheumatrex), penicillamine (Cuprimine), and sulfasalazine (Azulfidine); biologic drugs including abatacept (Orencia), etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), and anakinra (Kineret); corticosteroids including betamethasone (Celestone Soluspan), cortisone (Cortone), dexamethasone (Decadron), methylprednisolone (SoluMedrol, DepoMedrol), prednisolone (Delta-Cortef), prednisone (Deltasone, Orasone), and triamcinolone (Aristocort); gold salts, including Auranofin (Ridaura); Aurothioglucose (Solganal); Aurolate; Myochrysine; or any combination thereof.

[0308] In one embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention. In one embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with additional inhibitors of the complement system. In another embodiment, the present invention provides a method of treating or preventing multiple sclerosis by administering to a subject in need thereof an effective amount of a composition comprising a compound of the current invention in combination or alternation with a corticosteroid. Examples of corticosteroids include, but are not limited to, prednisone, dexamethasone, solumedrol, and methylprednisolone.

[0309] In one embodiment, a compound of Formula I is combined with at least one anti-multiple sclerosis drug selected from: Aubagio (teriflunomide), Avonex (interferon beta-1a), Betaseron (interferon beta-1b), Copaxone (glatiramer acetate), Extavia (interferon beta-1b), Gilenya (fingolimod), Lemtrada (alemtuzumab), Novantrone (mitoxantrone), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a), Tecfidera (dimethyl fumarate), Tysabri (natalizumab), Solu-Medrol (methylprednisolone), High-dose oral Deltasone (prednisone), H.P. Acthar Gel (ACTH), and combinations thereof.

[0310] In one aspect, a compound or salt of Formula I may be provided in combination or alternation with an immunosuppressive agent or an anti-inflammatory agent.

[0311] In one embodiment of the present invention, a compound described herein can be administered in combination or alternation with at least one immunosuppressive agent. The immunosuppressive agent as nonlimiting examples, may be a calcineurin inhibitor, e.g. a cyclosporin or an ascomycin, e.g. Cyclosporin A (NEORAL®), FK506 (tacrolimus), pimecrolimus, a mTOR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (RAPAMUNE®), Everolimus (Certican®), temsirolimus, zotarolimus, biolimus-7, biolimus-9, a rapalog, e.g.ridaforolimus, azathioprine, campath 1H, a S1P receptor modulator, e.g. fingolimod or an analogue thereof, an anti IL-8 antibody, mycophenolic acid or a salt thereof, e.g. sodium salt, or a prodrug thereof, e.g. Mycophenolate Mofetil (CELLCEPT®), OKT3 (ORTHOCLONE OKT3®), Prednisone, ATGAM®, THYMOGLOBULIN®, Brequinar Sodium, OKT4, T10B9.A-3A, 33B3.1, 15-deoxyspergualin, tresperimus, Leflunomide ARAVA®, CTLAI-Ig,

anti-CD25, anti-IL2R, Basiliximab (SIMULECT®), Daclizumab (ZENAPAX®), mizorbine, methotrexate, dexamethasone, ISAtx-247, SDZ ASM 981 (pimecrolimus, Elidel®), CTLA4lg (Abatacept), belatacept, LFA3lg, etanercept (sold as Enbrel® by Immunex), adalimumab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, gavilimomab, antithymocyte immunoglobulin, siplizumab, Alefacept efalizumab, pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

[0312] Examples of anti-inflammatory agents include methotrexate, dexamethasone, dexamethasone alcohol, dexamethasone sodium phosphate, fluromethalone acetate, fluromethalone alcohol, lotoprendol etabonate, medrysone, prednisolone acetate, prednisolone sodium phosphate, difluprednate, rimexolone, hydrocortisone, hydrocortisone acetate, lodoxamide tromethamine, aspirin, ibuprofen, suprofen, piroxicam, meloxicam, flubiprofen, naproxan, ketoprofen, tenoxicam, diclofenac sodium, ketotifen fumarate, diclofenac sodium, nepafenac, bromfenac, flurbiprofen sodium, suprofen, celecoxib, naproxen, rofecoxib, glucocorticoids, diclofenac, and any combination thereof. In one embodiment, a compound of Formula I is combined with one or more non-steroidal anti-inflammatory drugs (NSAIDs) selected from naproxen sodium (Anaprox), celecoxib (Celebrex), sulindac (Clinoril), oxaprozin (Daypro), salsalate (Disalcid), diflunisal (Dolobid), piroxicam (Feldene), indomethacin (Indocin), etodolac (Lodine), meloxicam (Mobic), naproxen (Naprosyn), nabumetone (Relafen), ketorolac tromethamine (Toradol), naproxen/esomeprazole (Vimovo), and diclofenac (Voltaren), and combinations thereof.

VI. PROCESS OF PREPARATION OF COMPOUNDS OF FORMULA I

ABBREVIATIONS

$(Boc)_2O$	di-tert-butyl dicarbonate
ACN	Acetonitrile
AcOEt, EtOAc	ethyl acetate
CH_3OH, MeOH	Methanol
CsF	Cesium fluoride
CuI	Cuprous iodide
DCM, CH_2Cl_2	Dichloromethane

DIEA, DIPEA	N,N-diisopropylethylamine
DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphoryl azide
Et_3N, TEA	Triethylamine
EtOAc	Ethylacetate
EtOH	Ethanol
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HCl	Hydrochloric acid
$^{i}Pr_2NEt$	N,N-diisopropylethylamine
K_2CO_3	Potassium carbonate
LiOH	Lithium hydroxide
MTBE	Methyl ^{t}butylether
Na_2SO_4	Sodium sulfate
NaCl	Sodium chloride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NEt_3	Trimethylamine
Pd (OAc) 2	Palaldium acetate
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino) ferrocene]dichloropalladium(II)
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd_2 (dba) 3	Tris(dibenzylideneacetone)dipalladium(0)
PPh_3	Triphenylphosphine
RT	Room temperature
tBuOK	potassium tert-butoxide
TEA	Trimethylamine
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid

THF	Tetrahydrofuran
TMSBr	Bromotrimethylsilane
t_R	Retention time
Zn $(CN)_2$	Zinc cyanide

General Methods

[0313] 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 × 50 mm, 1.7 μm

Column Temperature: 40 °C

Mobile Phase: Solvent A: H_2O + 0.05% FA; Solvent B: CH_3CN + 0.05% FA

Flow Rate: 0.8 mL/min

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

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

LC Method B

Instrument: Shimadzu LC-2010A HT

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

Column Temperature: 40 °C

Mobile Phase: Solvent A: H_2O/CH_3OH/FA = 90/10/0.1; Solvent B: H_2O/CH_3OH/FA = 10/90/0.1

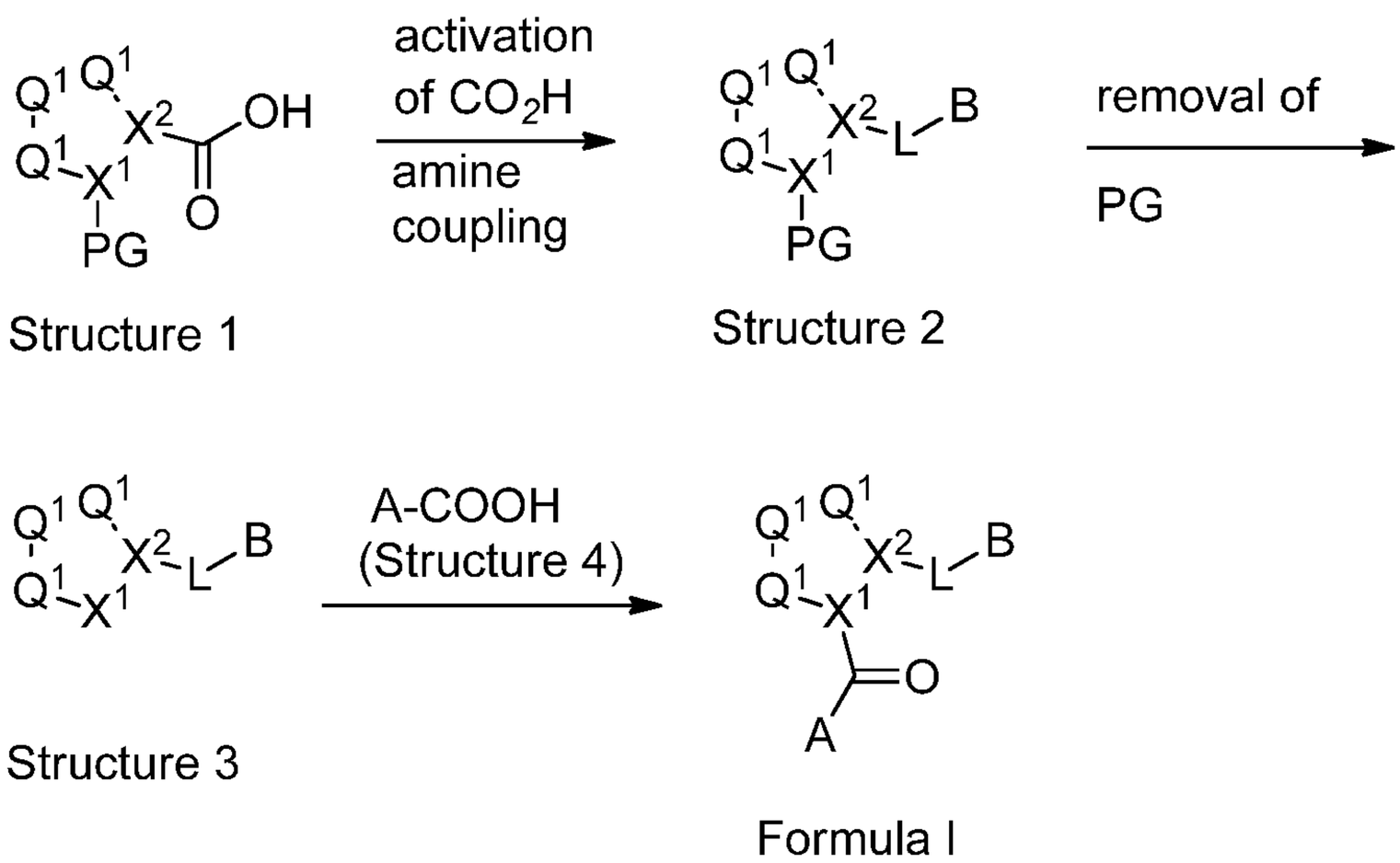
Flow Rate: 3 mL/min

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

Detection: UV (220/254 nm)

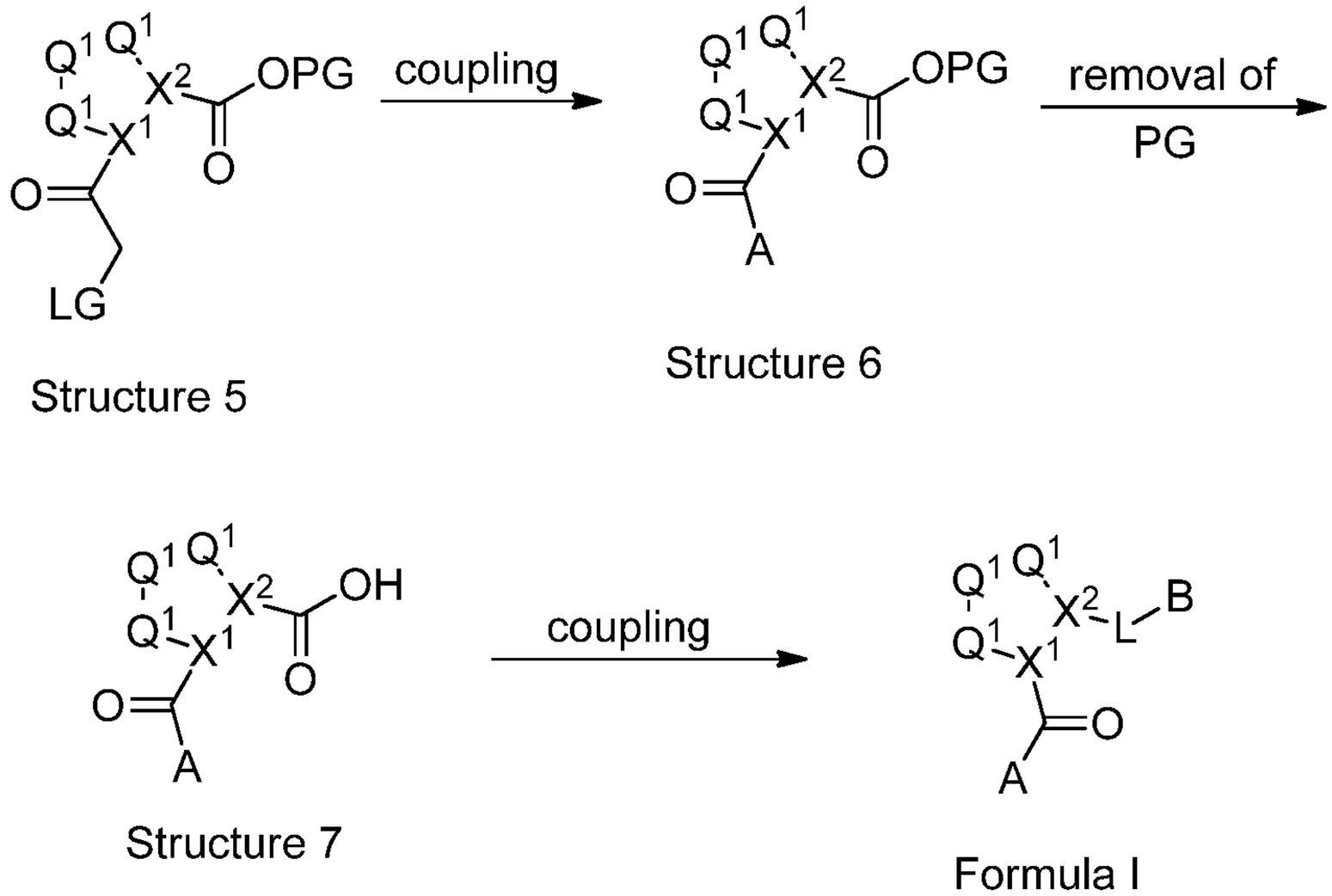
EXAMPLE 1. GENERAL ROUTE OF SYNTHESIS

[0314] 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(O)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.



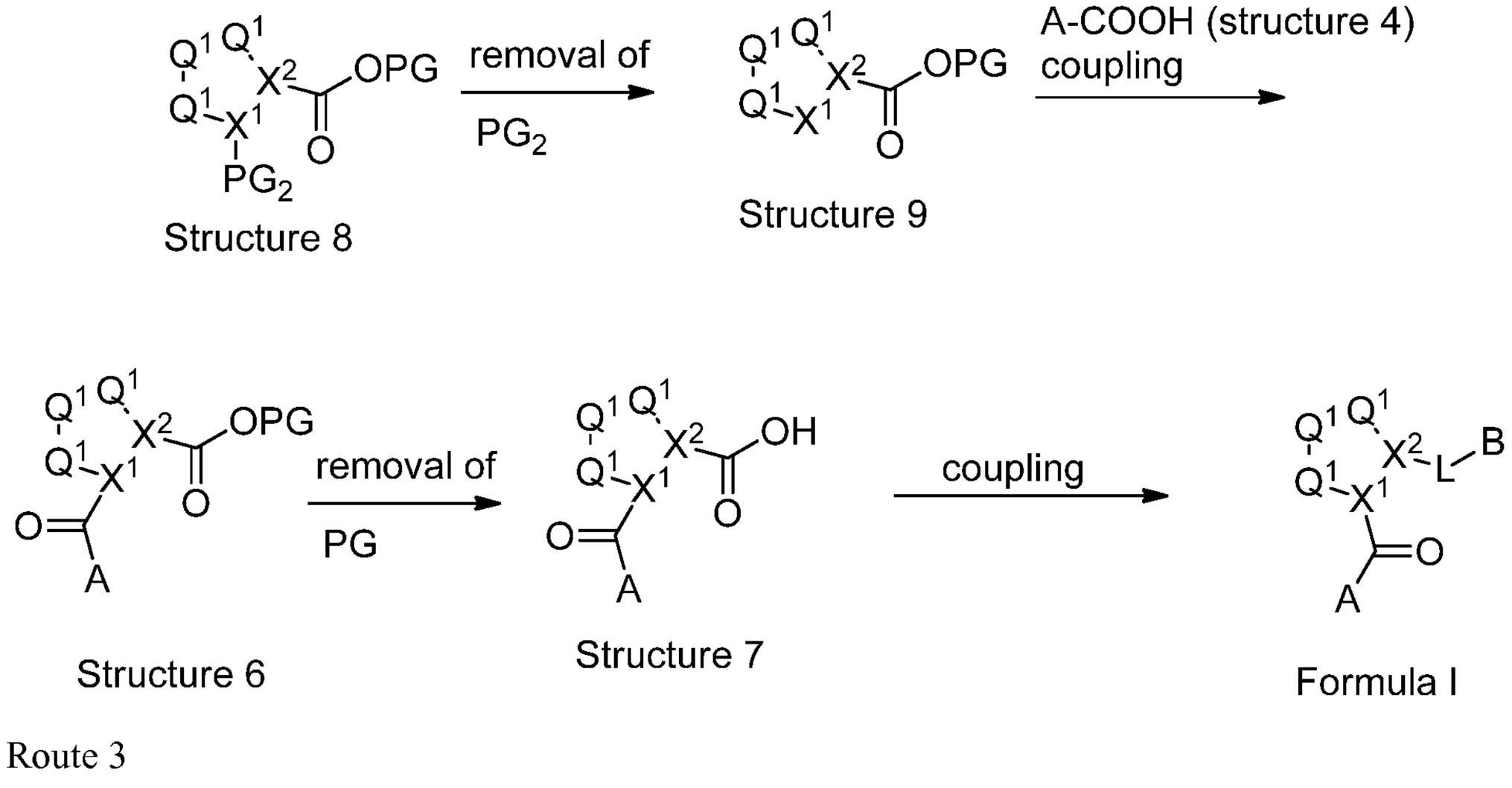
Route 1

[0315] In an alternative embodiment, central core Structure 5 is reacted with a heterocyclic or heteroaryl compound to generate a compound of Structure 6. In one embodiment, Structure 6 is deprotected to generate a carboxylic acid, Structure 7. In one embodiment, Structure 7 is coupled to an amine to generate a compound of Formula I. This chemistry is illustrated in Route 2.



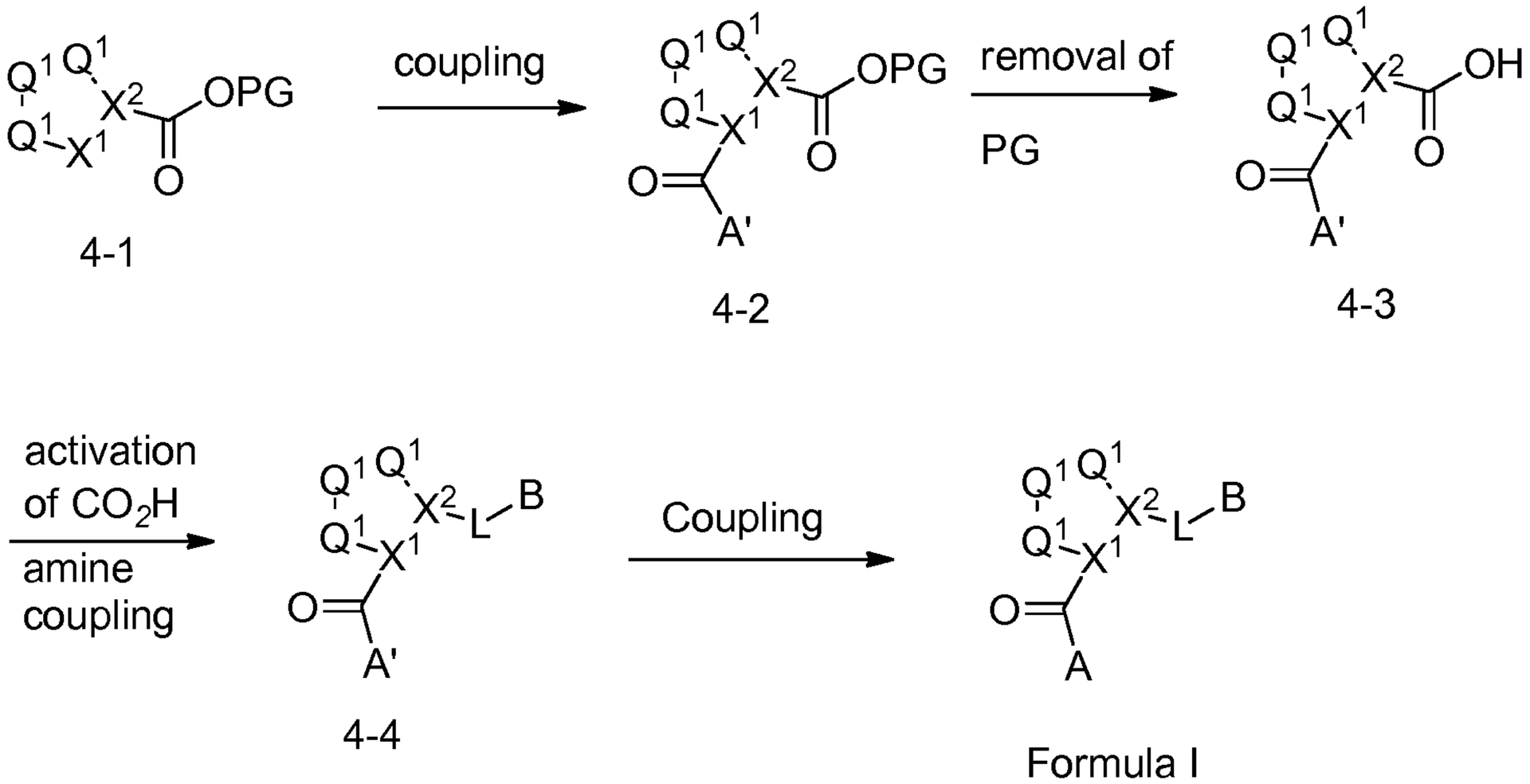
Route 2

[0316] 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.



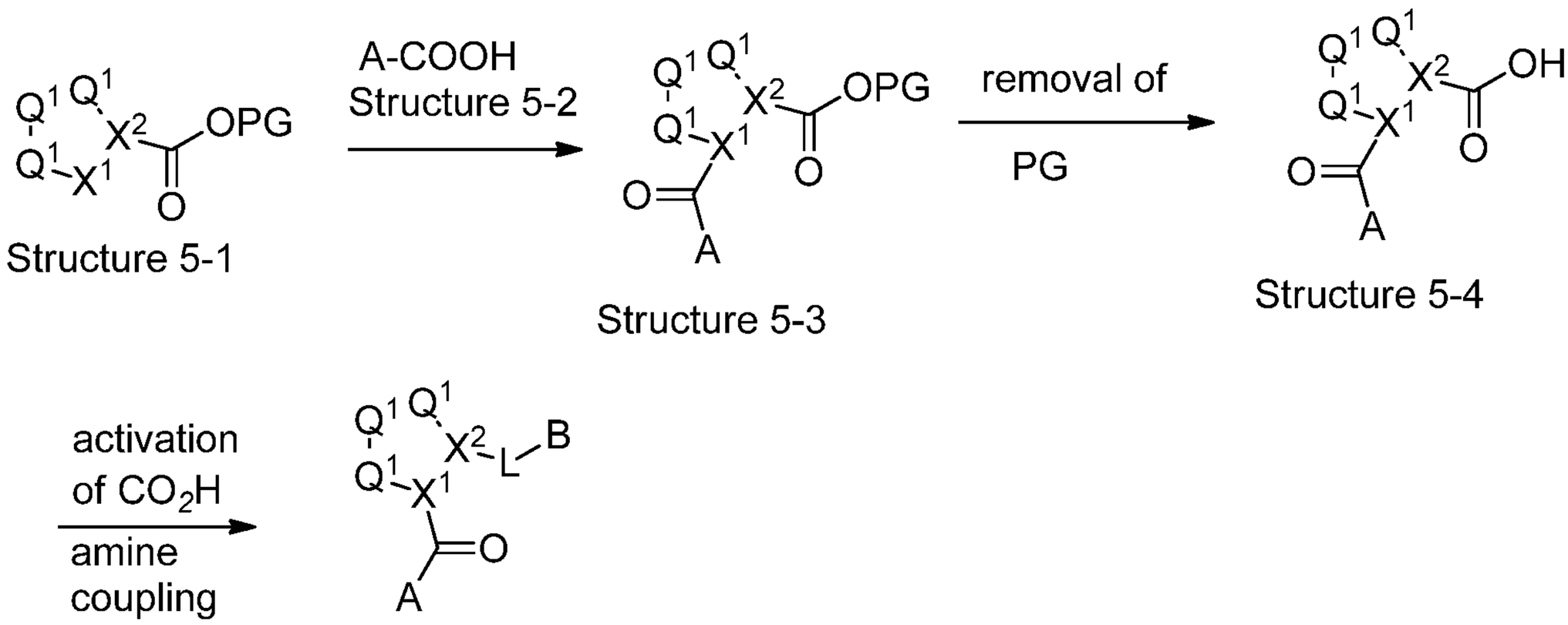
Route 3

[0317] In an alternate embodiment, a heteroaryl or aryl moiety, 4-1, is coupled to a central core to generate 4-2. The protected acid, 4-2 is deblocked to form the carboxylic acid, 4-3. The carboxylic acid is then coupled to form an amide (L-B) which is 4-4 . The heteroaryl or aryl moiety, A', can then be further derivitized to add substituents at the X^{11}, X^{12}, X^{13} and X^{14} positions to generate compounds of Formula I. This chemistry is illustrated in Route 4.



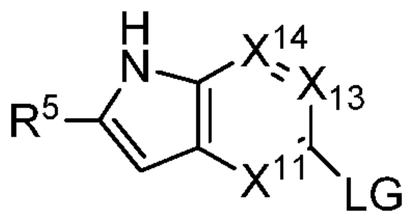
Route 4

[0318] 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.

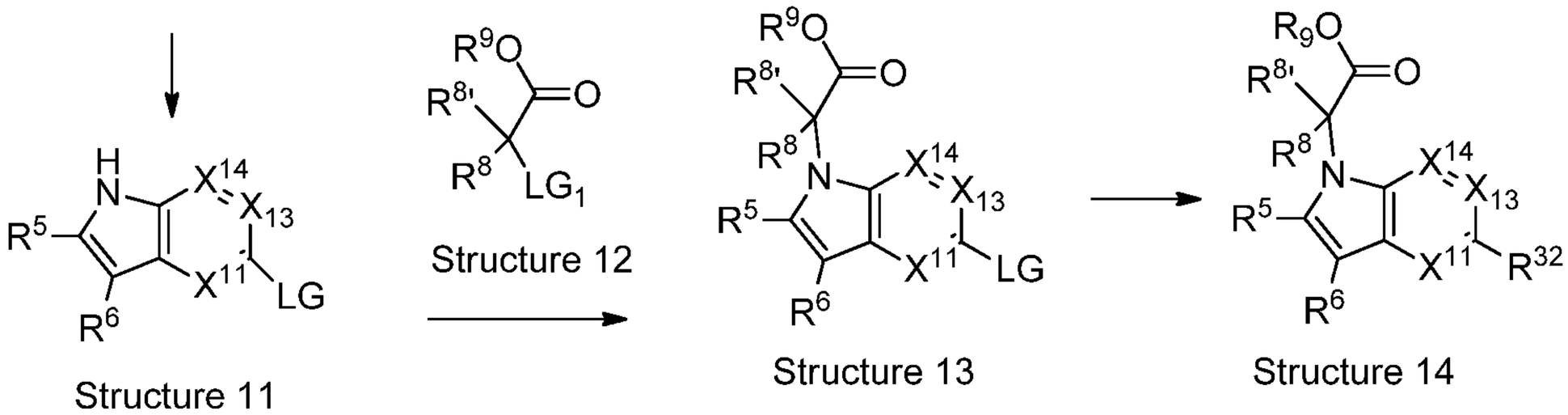


Route 5

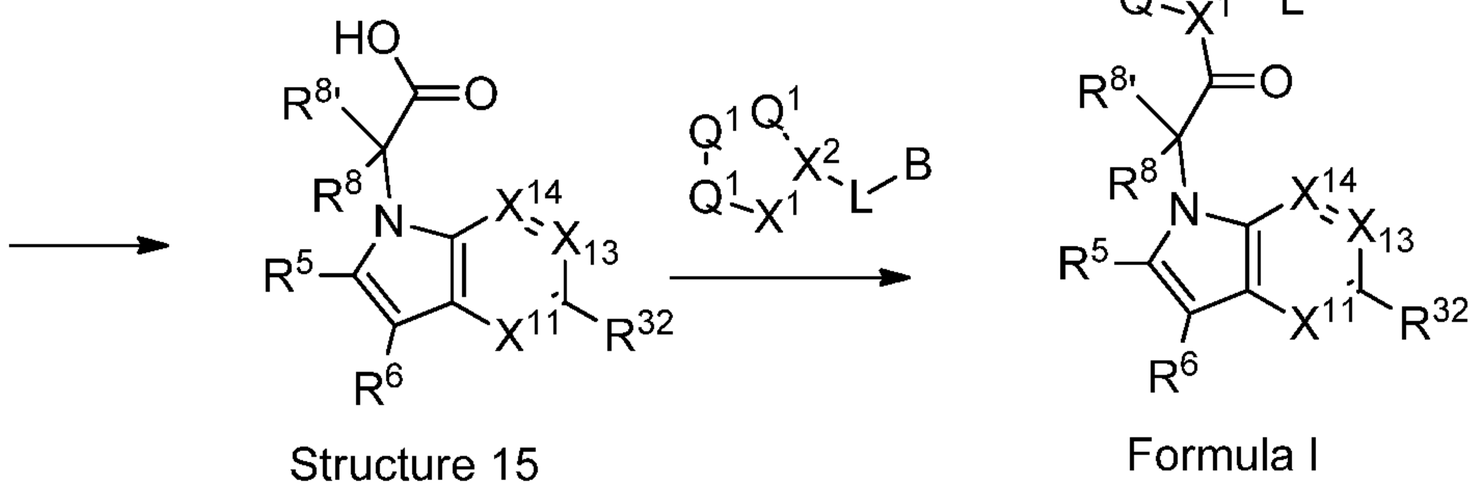
[0319] In an alternate embodiment, a heteroaryl compound of Structure 10 is acylated to generate a compound of Structure 11, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 11 is coupled to Structure 12 to generate Structure 13. In some embodiments, LG_1 is a leaving group. In some embodiments, the LG_1 is a halide. Structure 13 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 14. In some embodiments, Structure 13 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 14 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure 15. Structure 15 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 6.



Structure 10



Structure 11 Structure 12 Structure 13 Structure 14



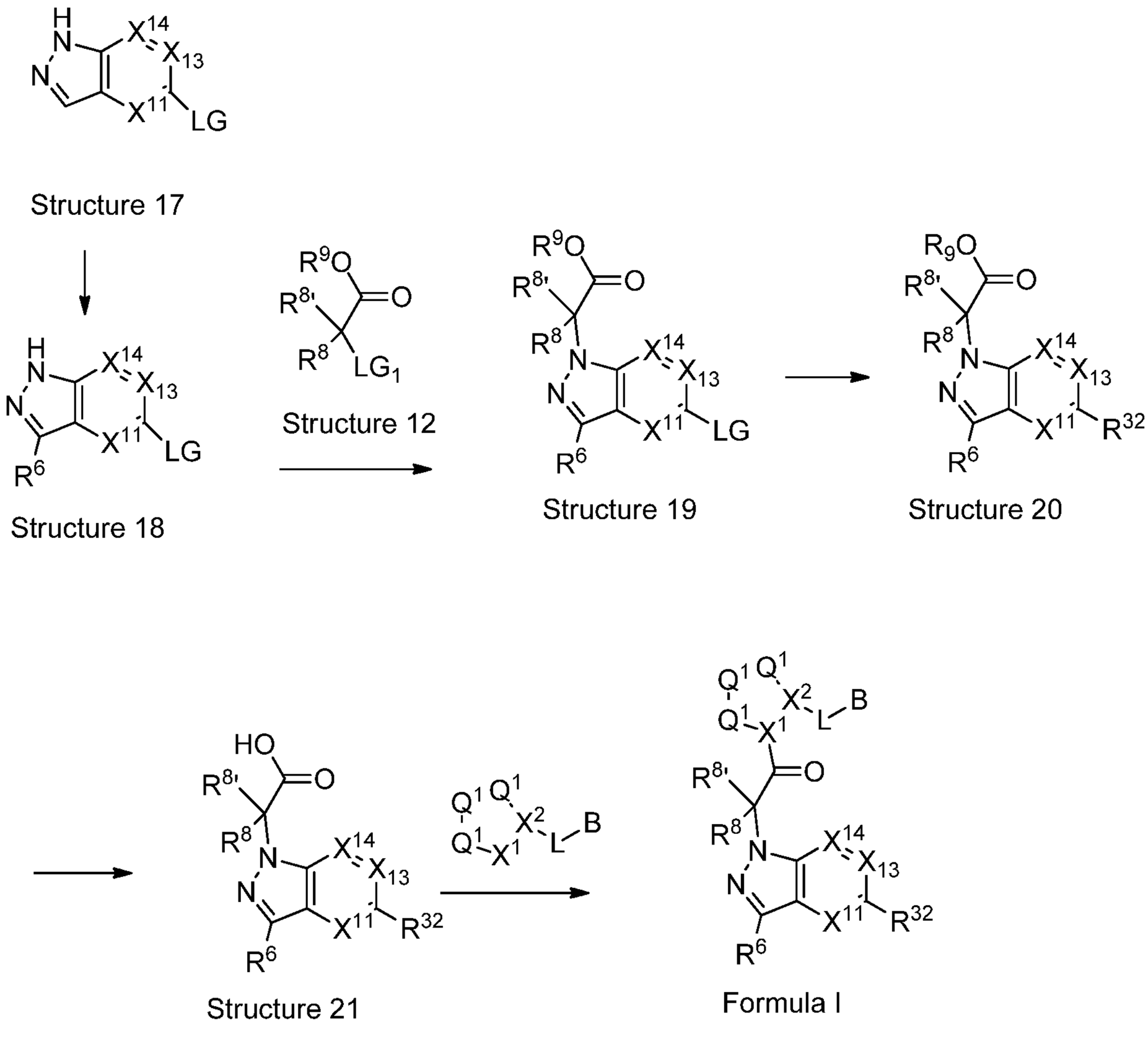
Structure 15 Formula I

Route 6

[0320] In an alternate embodiment, a heteroaryl compound of Structure 17 is acylated to generate a compound of Structure 18, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 18 is coupled to an activated ester, Structure 12 from Route 6, wherein LG_1 can be a halogen to generate Structure 19.

[0321] Structure 19 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 20. In some embodiments, Structure 19 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 20 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to

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

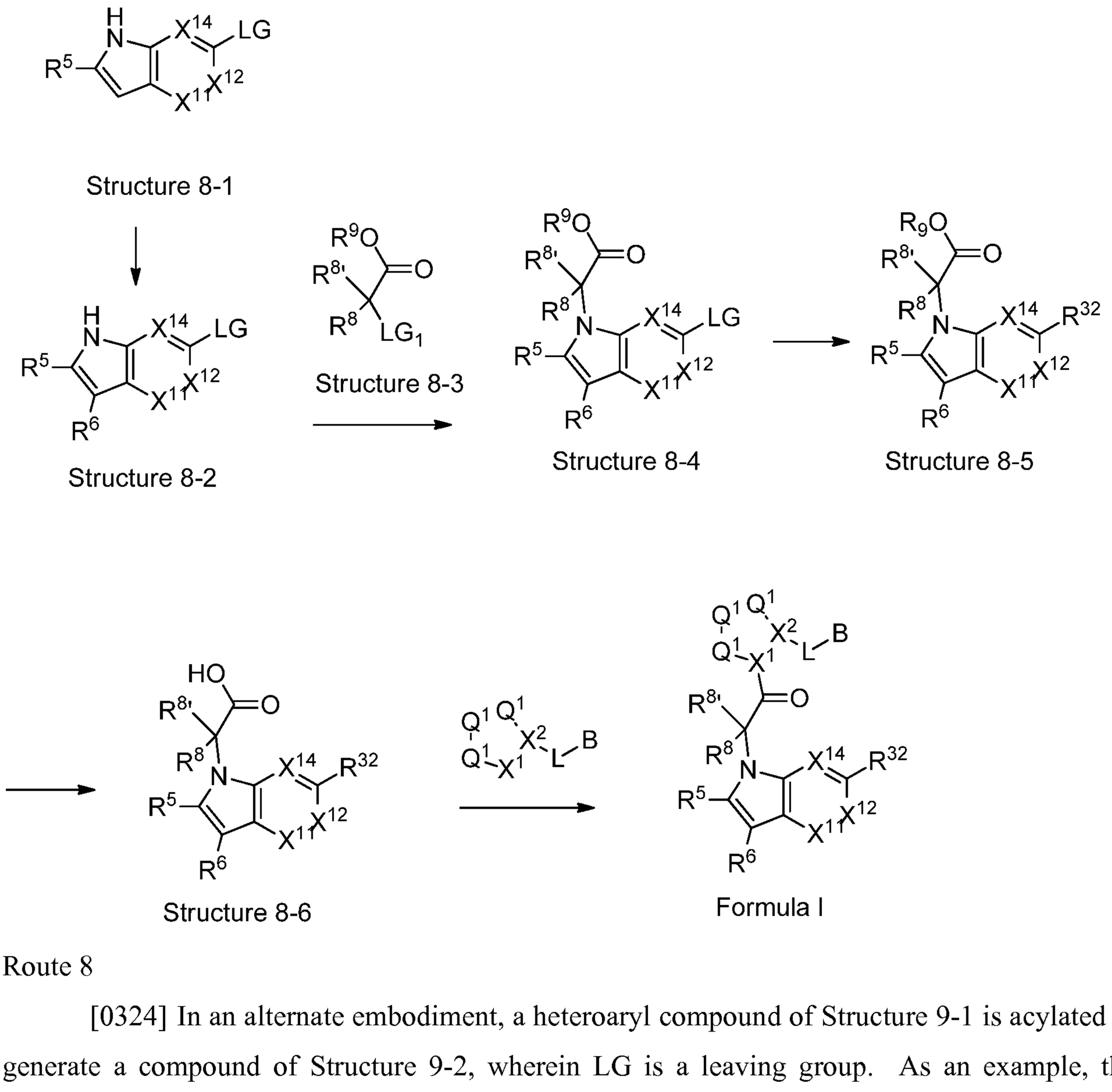


Route 7

[0322] In an alternate embodiment, a heteroaryl compound of Structure 8-1 is acylated to generate a compound of Structure 8-2, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 8-2 is coupled to Structure 8-3 to generate Structure 8-4. In some embodiments, LG_1 is a leaving group. In some embodiments, the LG_1 is a halide.

[0323] Structure 8-4 is coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 8-5. In some embodiments, Structure 8-4 is treated with an aryl, heteroaryl or

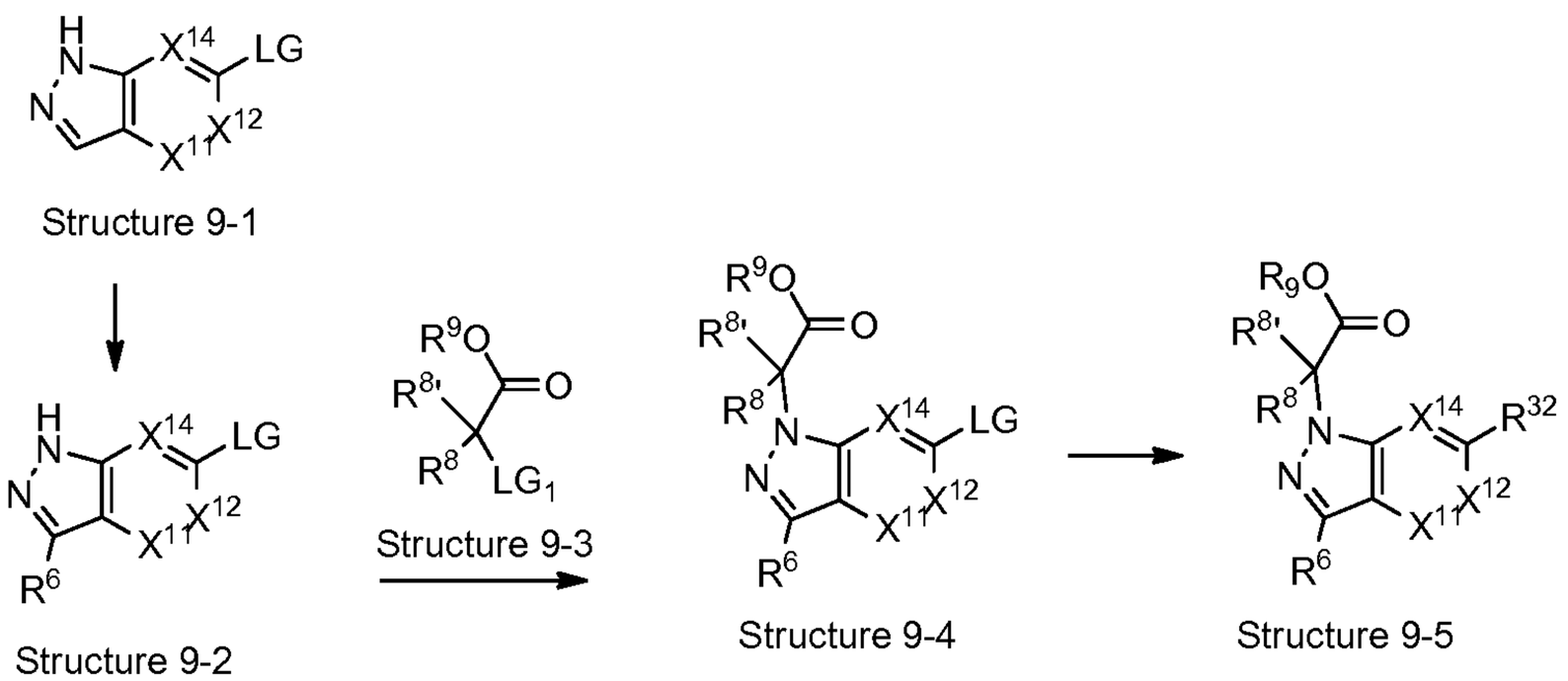
heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 8-5 is treated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

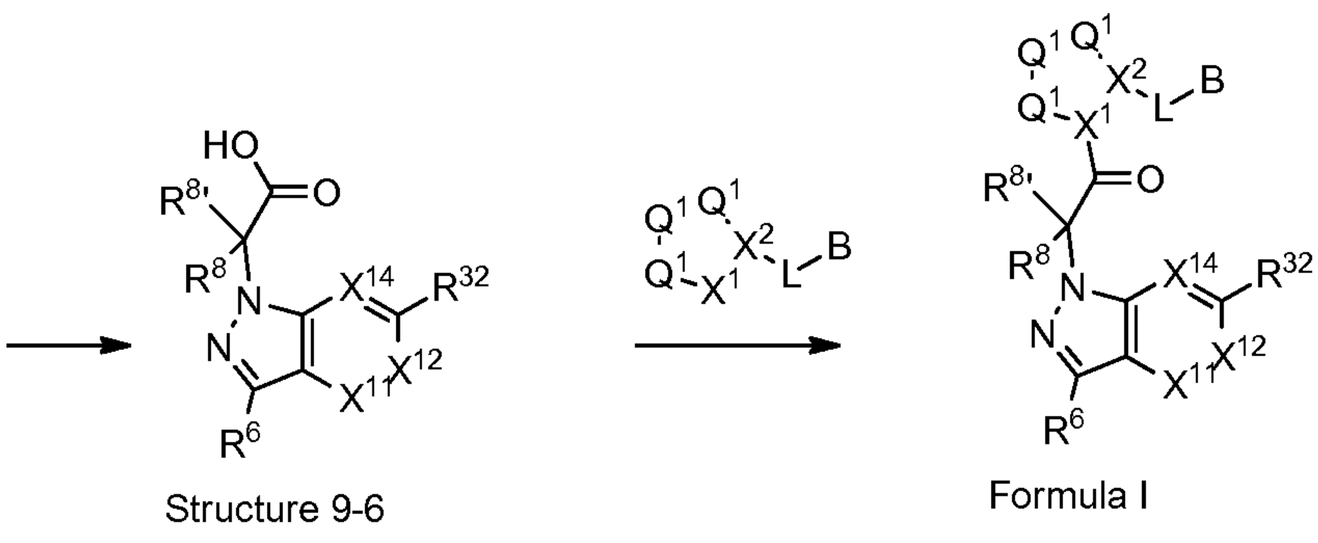


Route 8

[0324] In an alternate embodiment, a heteroaryl compound of Structure 9-1 is acylated to generate a compound of Structure 9-2, wherein LG is a leaving group. As an example, the leaving group can be a halide, for example bromide. Structure 9-2 is coupled to an activated ester, Structure 9-3, wherein LG_1 can be a halide to generate Structure 9-4. Structure 9-4 is

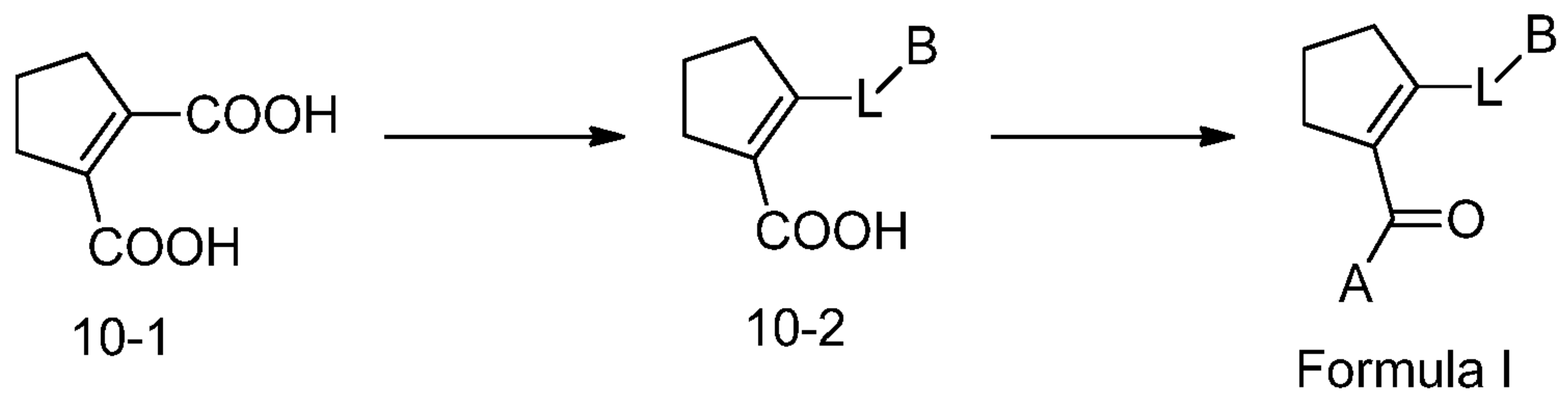
coupled to an aryl, heteroaryl or heterocylic compound to generate Structure 9-5. In some embodiments, Structure 9-4 is treated with an aryl, heteroaryl or heterocylic boronic acid, an organometallic catalyst, a base and an organic solvent. In some embodiments, the organometallic catalyst is tetrakis(triphenylphosphine)palladium (0). In some embodiments, the base is cesium carbonate. In some embodiments, the organic solvent is DMF. Structure 9-5 is treated with an organic acid such as, but not limited to, trifluoroacetic acid to generate Structure 9-6. Structure 9-6 is coupled to Structure 3 from Route 1 to generate a compound within Formula I. This chemistry is illustrated in Route 9.





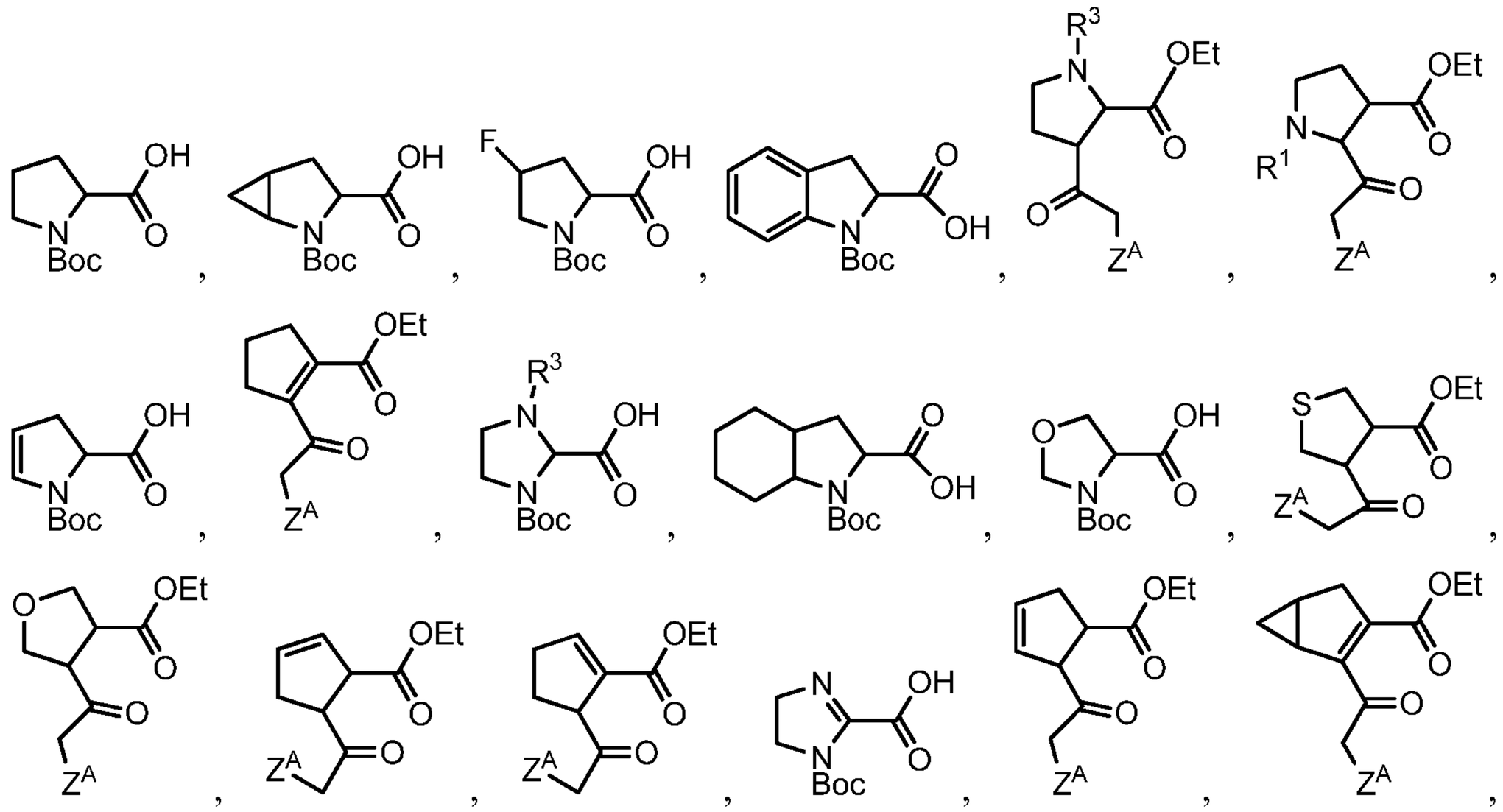
Route 9

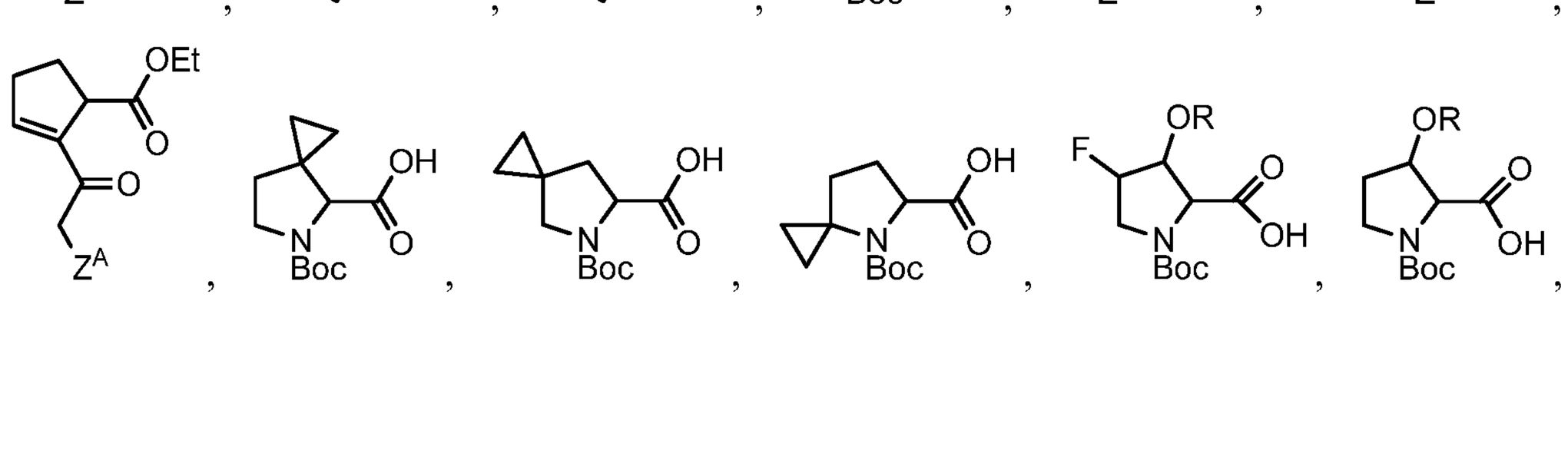
In an alternate embodiment, Structure 10-1 is coupled to an amine to generate an amide (L-B), and Structure 10-2. Structure 10-2, is coupled to an amine to generate compounds within Formula I. This chemistry is illustrated in Route 10.

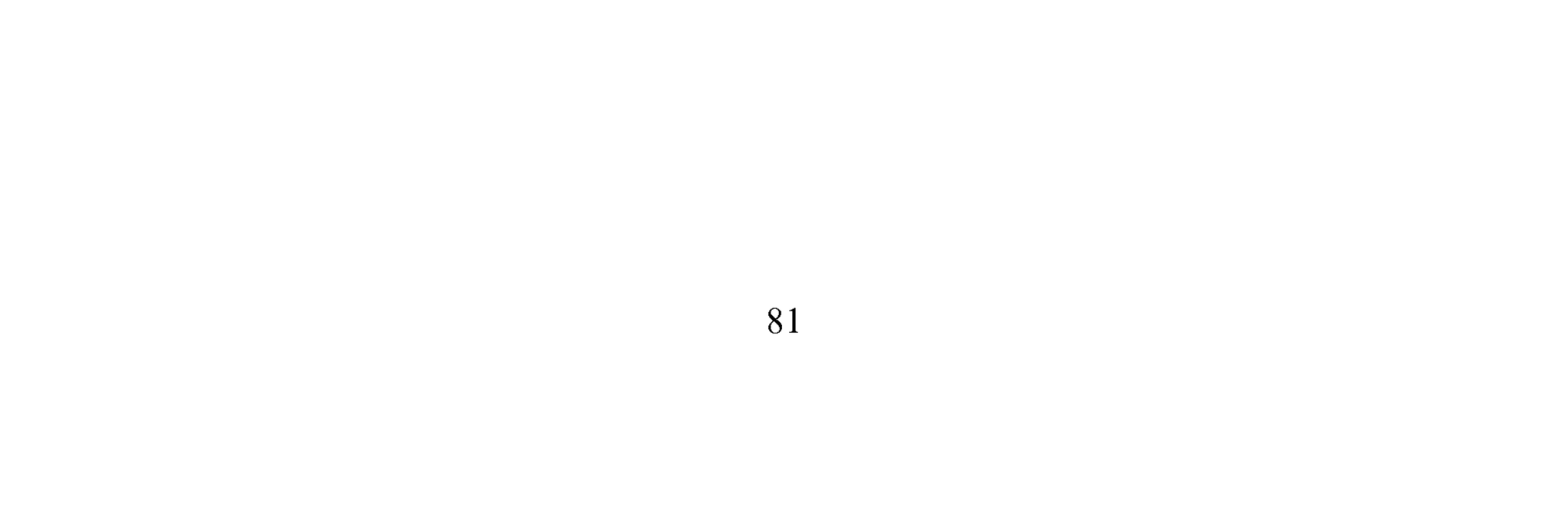


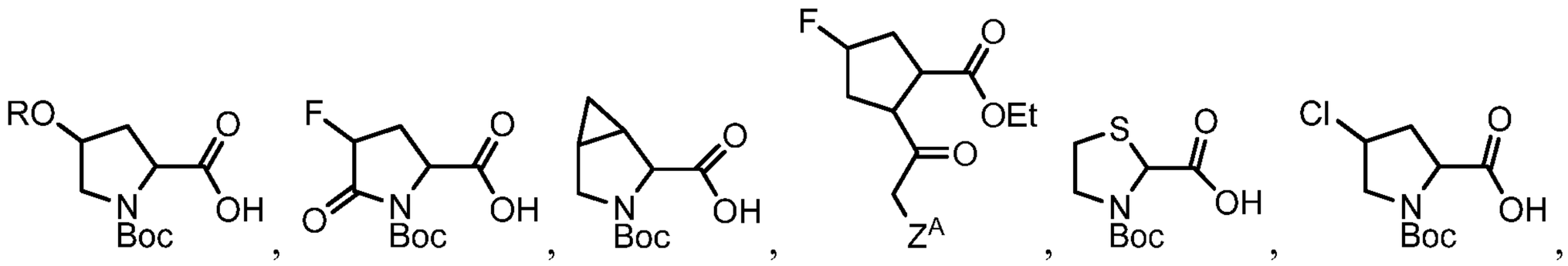
Route 10

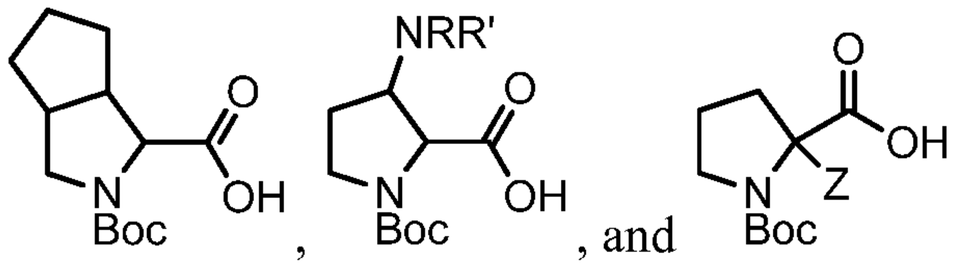
EXAMPLE 2. EXAMPLES OF CENTRAL SYNTHONS







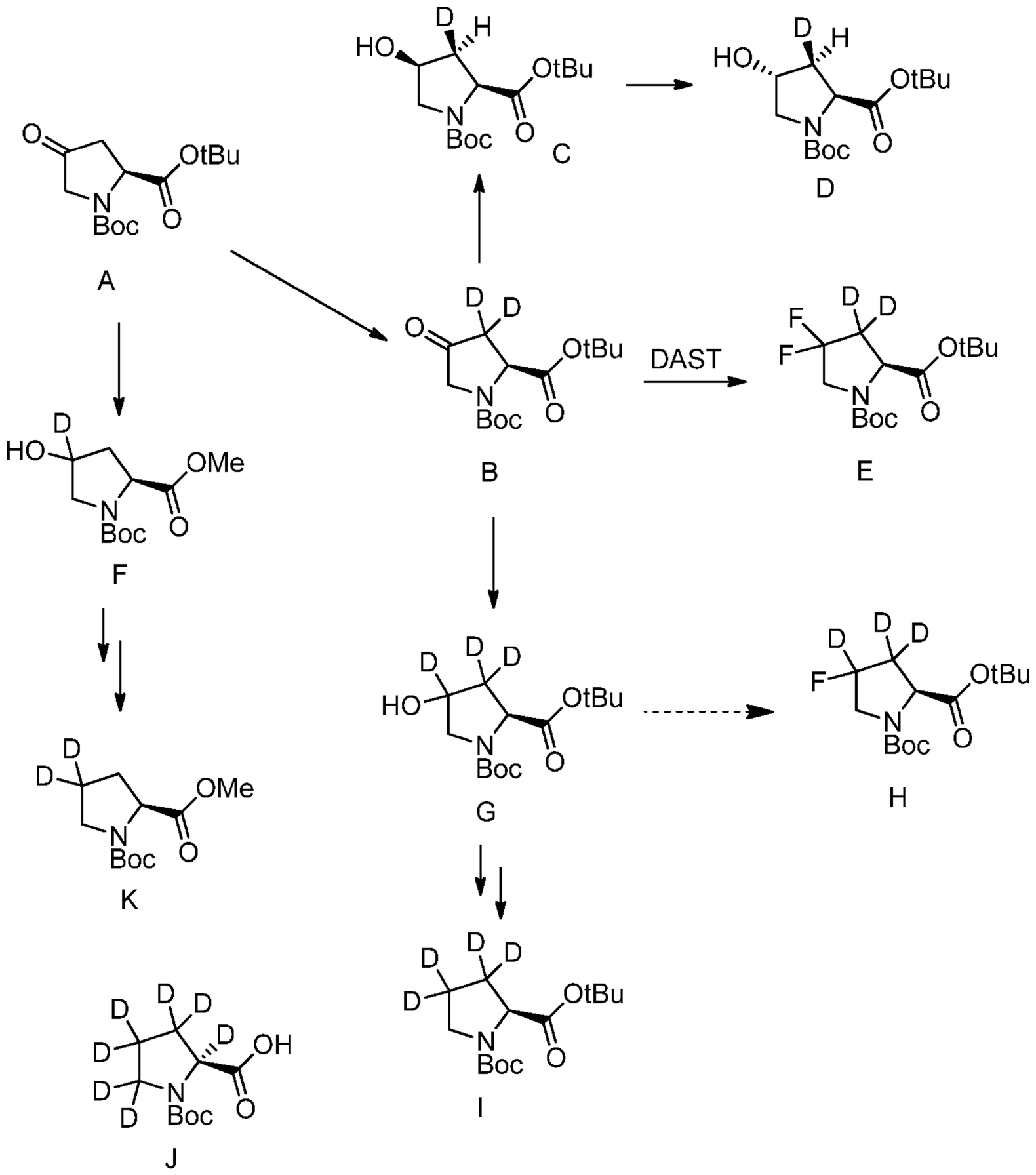




, and .

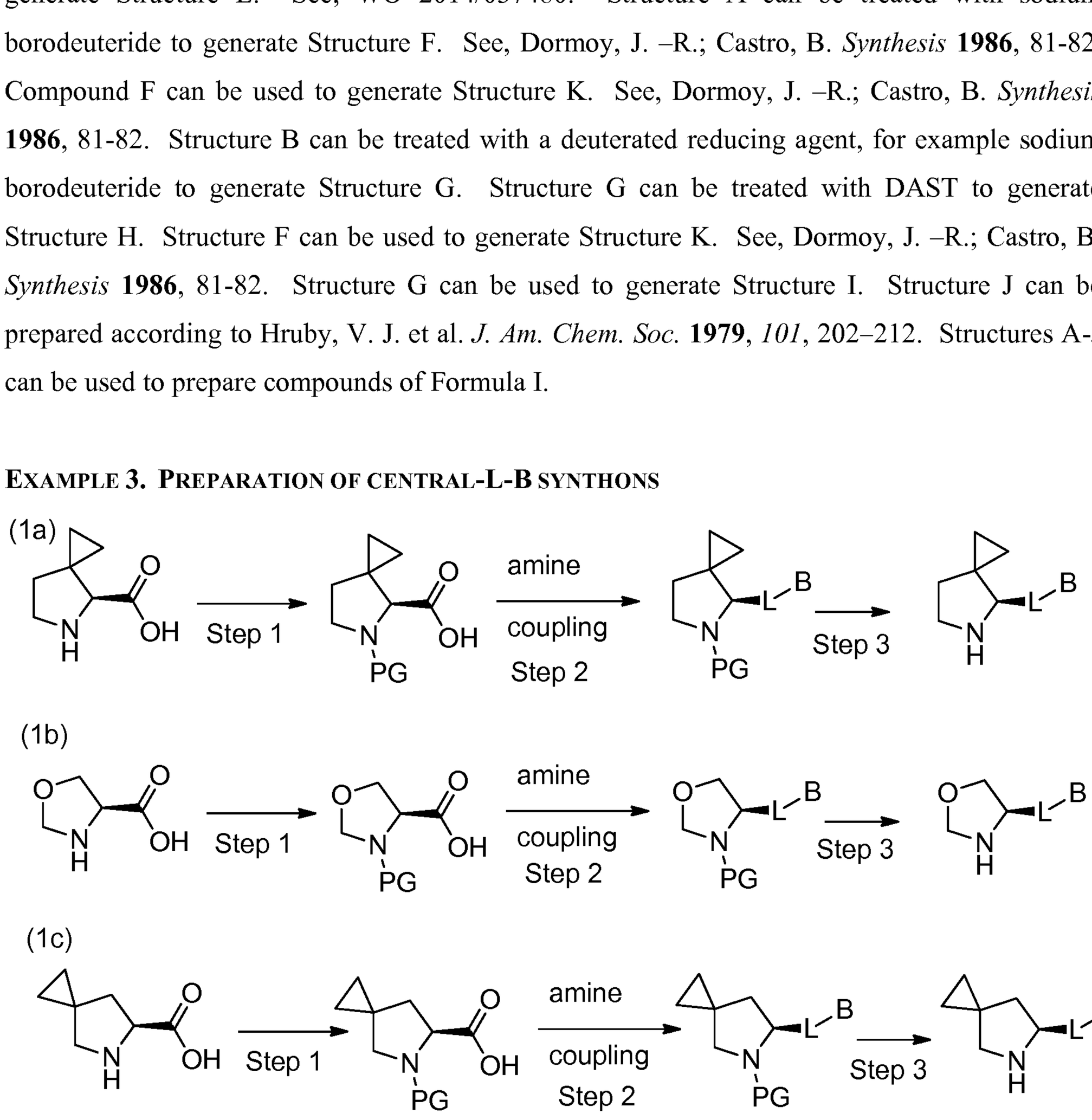
Z^A is halogen.

[0325] In one embodiment, deuterated L-proline synthons are disclosed. Deuterated synthons include, but are not limited to, for example, the following compounds:



[0326] Structure A can be treated with deuterium oxide to generate Structure B. See, Barraclough, P. et al. Tetrahedron Lett. **2005**, 46, 4653–4655; Barraclough, P. et al. Org. Biomol. Chem. **2006**, 4, 1483–1491 and WO 2014/037480 (p.103). Structure B can be reduced to generate Structure C. See, Barraclough, P. et al. Tetrahedron Lett. **2005**, 46, 4653–4655; Barraclough, P. et al. Org. Biomol. Chem. **2006**, 4, 1483–1491. Structure C can be treated with Mitsunobu reaction conditions to generate Structure D. Structure B can be treated with DAST to generate Structure E. See, WO 2014/037480. Structure A can be treated with sodium borodeuteride to generate Structure F. See, Dormoy, J. –R.; Castro, B. *Synthesis* **1986**, 81-82. Compound F can be used to generate Structure K. See, Dormoy, J. –R.; Castro, B. *Synthesis* **1986**, 81-82. Structure B can be treated with a deuterated reducing agent, for example sodium borodeuteride to generate Structure G. Structure G can be treated with DAST to generate Structure H. Structure F can be used to generate Structure K. See, Dormoy, J. –R.; Castro, B. *Synthesis* **1986**, 81-82. Structure G can be used to generate Structure I. Structure J can be prepared according to Hruby, V. J. et al. *J. Am. Chem. Soc.* **1979**, *101*, 202–212. Structures A-J can be used to prepare compounds of Formula I.

EXAMPLE 3. PREPARATION OF CENTRAL-L-B SYNTHONS



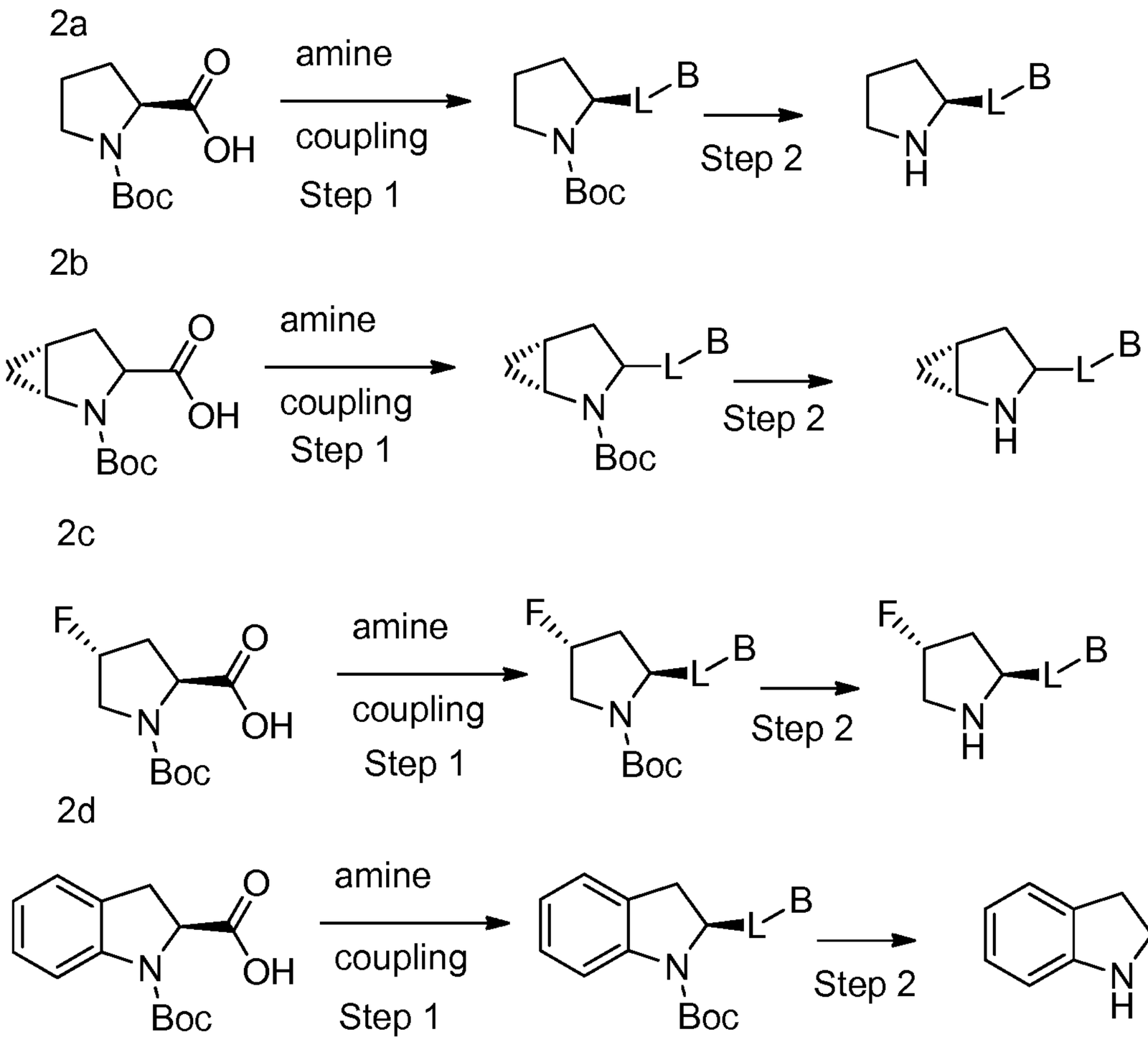
Routes 1a, 1b and 1c.

[0327] In Route 1a, 5-azaspiro[2.4]heptane-4,5-dicarboxylic acid, 5-(1,1-dimethylethyl) ester, (4*S*)-, CAS 209269-08-9, can be prepared as described in Tandon, M. et al. Bioorg. Med. Chem. Lett. 1998, 8, 1139-1144. 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.

[0328] 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. In another embodiment, 3,4-oxazolidinedicarboxylic acid, 3-(1,1-dimethylethyl) ester, (4S)-, is commercially available from JPM2 Pharmaceuticals. In one embodiment the reaction is carried out in an organic solvent in the presence of a base. In one embodiment, the organic solvent is acetonitrile. In one embodiment, the base is 4-dimentylaminopyridine (DMAP). In Step 2, the protected 4-oxazolidinecarboxylic acid is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 3, the protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0329] In Route 1c, (S)-5-(tert-Butoxycarbonyl)-5-azaspiro[2.4]heptane-6-caboxylic acid, CAS 1129634-44-1, is commercially available from Ark Pharm. In Step 2, the carboxylic acid is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 3, the protecting group is removed. In one embodiment, the starting material is

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



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

[0330] 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.

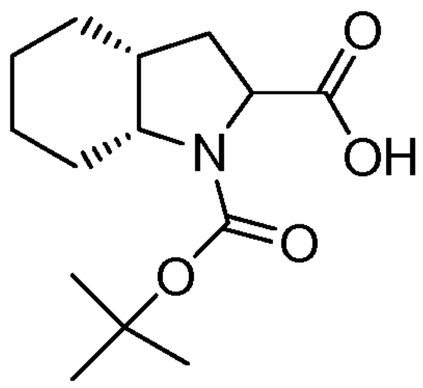
[0331] In Route 2b, commercially available (1R, 3S, 5R)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[3.1.0]hexane-3-carboxylic acid, from Enamine, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B

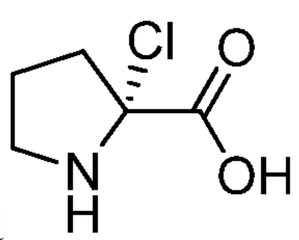
moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0332] In Route 2c, commercially available (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid, from Manchester Organics, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane.

[0333] In Route 2d, commercially available (S)-1-(tert-butoxycarbonyl)indoline-2-carboxylic acid, from Chem-Impex, is coupled to an amine in the presence of an organic solvent, a base and a coupling reagent to generate an amide bond; the L-B moiety. In one embodiment, the amine is (3-chloro-2-fluorophenyl) methanamine. In one embodiment, the organic solvent is DMF. In one embodiment, the base is diisopropylethylamine. In one embodiment, the coupling reagent is HATU. In Step 2, the Boc protecting group is removed. In one embodiment, the starting material is reacted with an acid in the presence of an organic solvent. In one embodiment, the acid is 4N hydrochloric acid. In one embodiment, the organic solvent is dioxane. This chemistry is illustrated in Scheme 2.

[0334] Additional starting materials that can readily be converted to Central-L-B-Synthons include, but are not limited to: (S)-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-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, 1H-imidazole-1,2-dicarboxylic acid, 1-(1,1-dimethylethyl) 2-ethyl ester, CAS 553650-00-3, commercially available from FCH Group; Boc-L-octahydroindole-2-carboxylic acid can be purchased from Chem Impex. The compound,

[0335]  can be prepared according to the procedures disclosed in WO 2004/111041; (S)-Boc-5-oxopyrrolidine-2-carboxylic acid is available from the Aldrich Chemical Co.; (1S,2S,5R)-3-(tert-butoxycarbonyl)-3-azabicyclo[3.3.0]hexane-2-carboxylic acid is available from Ark Pharm; (S)-3-Boc-thiazolidine-2-carboxylic acid is available from Alfa Aesar; (2S,4R)-1-(tert-butoxycarbonyl)-4-chloropyrrolidine-2-carboxylic acid is available from Arch Bioscience; (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid is available from Ark Pharm; 1,2-pyrrolidinedicarboxylic acid, 3-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-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.

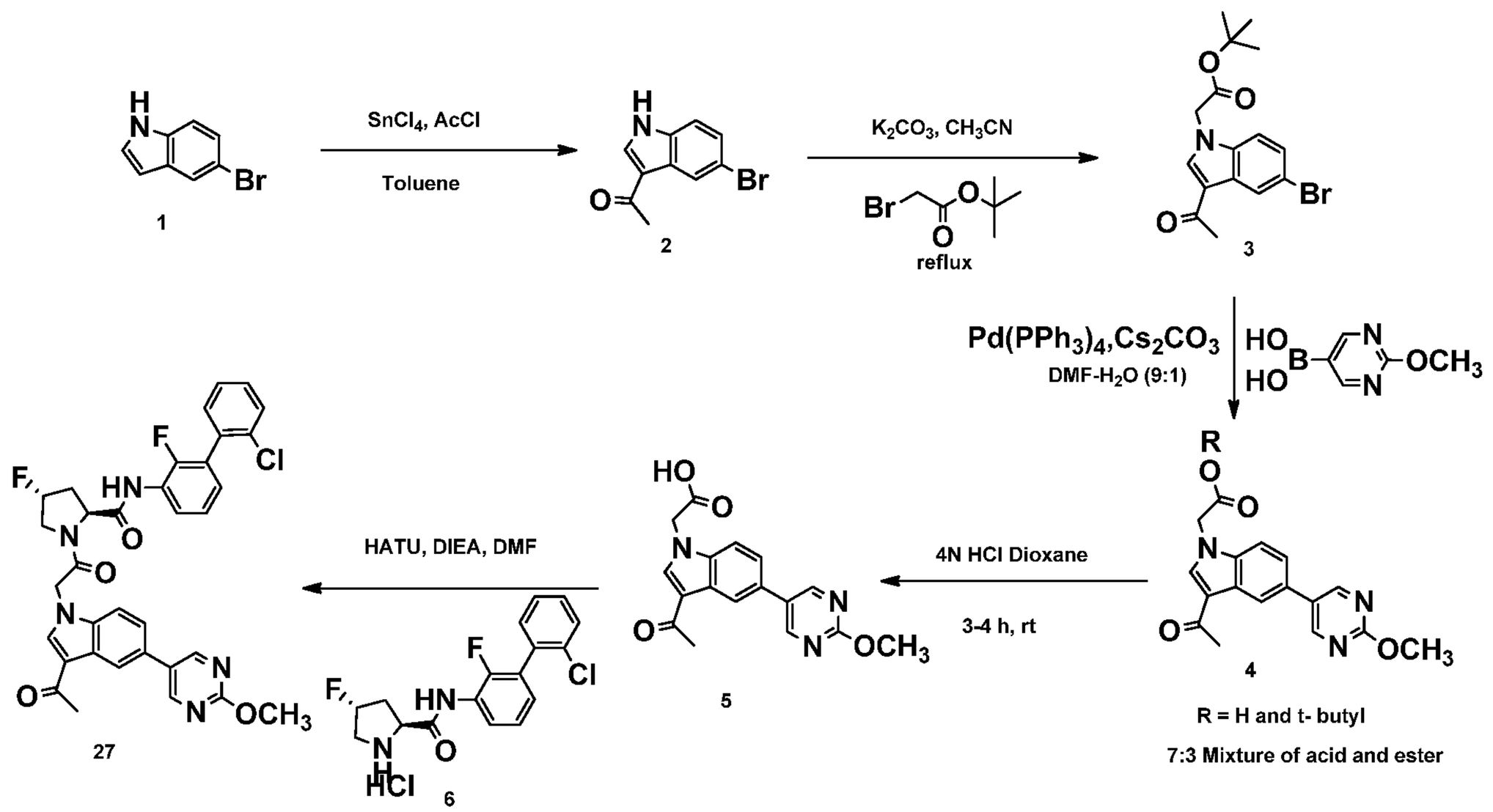
[0336] The compound  can be prepared as disclosed by Braun, J.V.; Heymons, Albrecht Berichte der Deutschen Chemischen Gesellschaft [Abteilung] B: Abhandlungen (1930) 63B, 502-7.

[0337] 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 ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I

SYNTHESIS OF (2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (27).

Scheme 1



[0338] 1-(5-Bromo-1*H*-indol-3-yl)ethanone (**2**) was prepared from 5-bromoindole according to the procedure of MacKay *et al.* (MacKay, J. A.; Bishop, R.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421-3424.)

tert-Butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate (3).

[0339] A mixture of 3.9 g (16.4 mmol) of 1-(5-bromo-1H-indol-3-yl)ethanone, 2.63 mL (18.02 mmol) of *tert*-butyl bromoacetate and 2.50 g (18.02 mmol) potassium carbonate in anhydrous acetonitrile (80 mL) was refluxed for 5 h. The reaction mixture was then cooled to rt and the solvent was removed under reduced pressure. The residue was taken in a 1:1 mixture of CH_2Cl_2 and water (100 mL:100 mL). The two layers were separated and the organic layer was washed with water (2 × 100 mL). Finally, the organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was stirred with 50 mL of heptane for 30 min, cooled in an ice bath and filtered, washing the solid with cold heptane (10 mL). This cream colored solid was dried under high vacuum to give 5.6 g of *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate.

tert-butyl 2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetate (4).

[0340] A mixture of 351 mg (1 equiv) of **3**, (2-methoxypyrimidin-5-yl)boronic acid (230 mg. 1.5 equiv), cesium carbonate (650 mg, 2 equiv) in DMF (15 mL) and water (1.5 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (57

mg, 0.05 equiv) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product (7:3 mixture of acid and ester) was used directly in the next synthetic step.

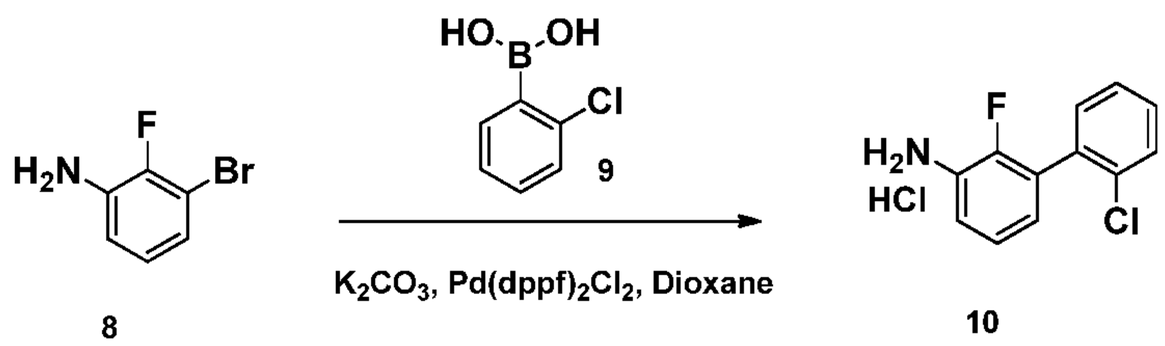
2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetic acid (5).

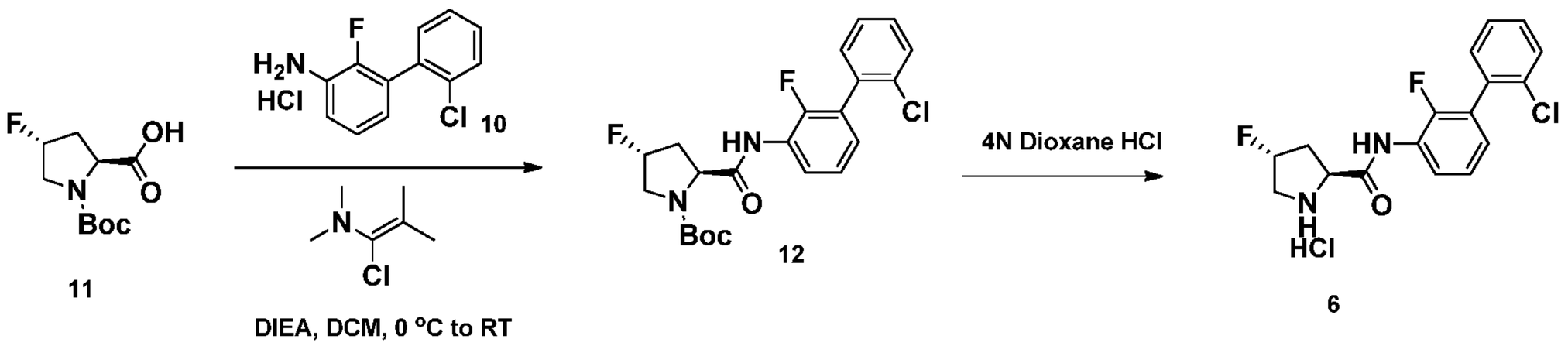
[0341] tert-Butyl 2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetate (crude from above reaction), was taken in 4N HCl dioxane (20 mL) and the resulting reaction mixture was stirred at rt for 4 h .After completion of the reaction, the solvent was removed under reduced pressure. The remaining material was used directly in the next synthetic step.

(2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (27).

[0342] Compound **5** (100 mg, 1 equiv) from the previous step was dissolved in DMF (10 mL) and iPr_2NEt (0.269 mL, 5 equiv) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (111 mg, 1 equiv) at 5 °C. HATU (263 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. After completion of the reaction monitored by HPLC, the reaction mixture was added to water (50 mL + 10 g NaCl) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (ISCO eluted with DCM/CH3OH) to give **7**. ^1H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.13-2.3 (m, 1H), 2.45 (s, 3H), 2.68-2.70 (m, 1H), 3.95-4.05 (m, 4H), 4.16-4.24 (m, 1 H), 4.78 (t, J = 8 Hz, 1H), 5.28 (d, J = 20 Hz, 1H), 5.45 (d, J = 20 Hz, 1H), 5.50-5.63 (m, 1H), 7.04-7.08 (m, 1H), 7.20-7.24 (m, 1H), 7.37-7.61 (m, 7H), 7.75-7.78 (m, 1H), 7.94-7.98 (m, 1H), 8.31 (s, 1H), 8.88 (s 1H), 8.97 (s 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -126.64, -175.79. LC (method A): tR = 2.16 min. LC/MS (EI) m/z: [M + H]+ calcd for $C_{34}H_{28}ClF_2N_5O_4$, 643; found, 644.

Scheme 2





2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-amine hydrochloride (10).

[0343] A mixture of **8** (30 g), **9** (60 g), K_2CO_3 (91 g) and $Pd(dppf)_2Cl_2$ (19.25 g) in solvent (dioxane 400 mL, H_2O 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 **10.**

(2S,4R)-tert-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (12).

[0344] To an ice-cold solution of **11** (530 mg) in 20 mL of CH_2Cl_2, 1-chloro-N,N,2-trimethyl-1-propenylamine (0.333 mL, 1.1 equiv) was added dropwise with stirring. The stirring was continued for 3 h at this temperature, then solid **10** (640 mg, 1.1 equiv) was added, followed by 1.12 mL of iPr_2NEt (3 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 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining

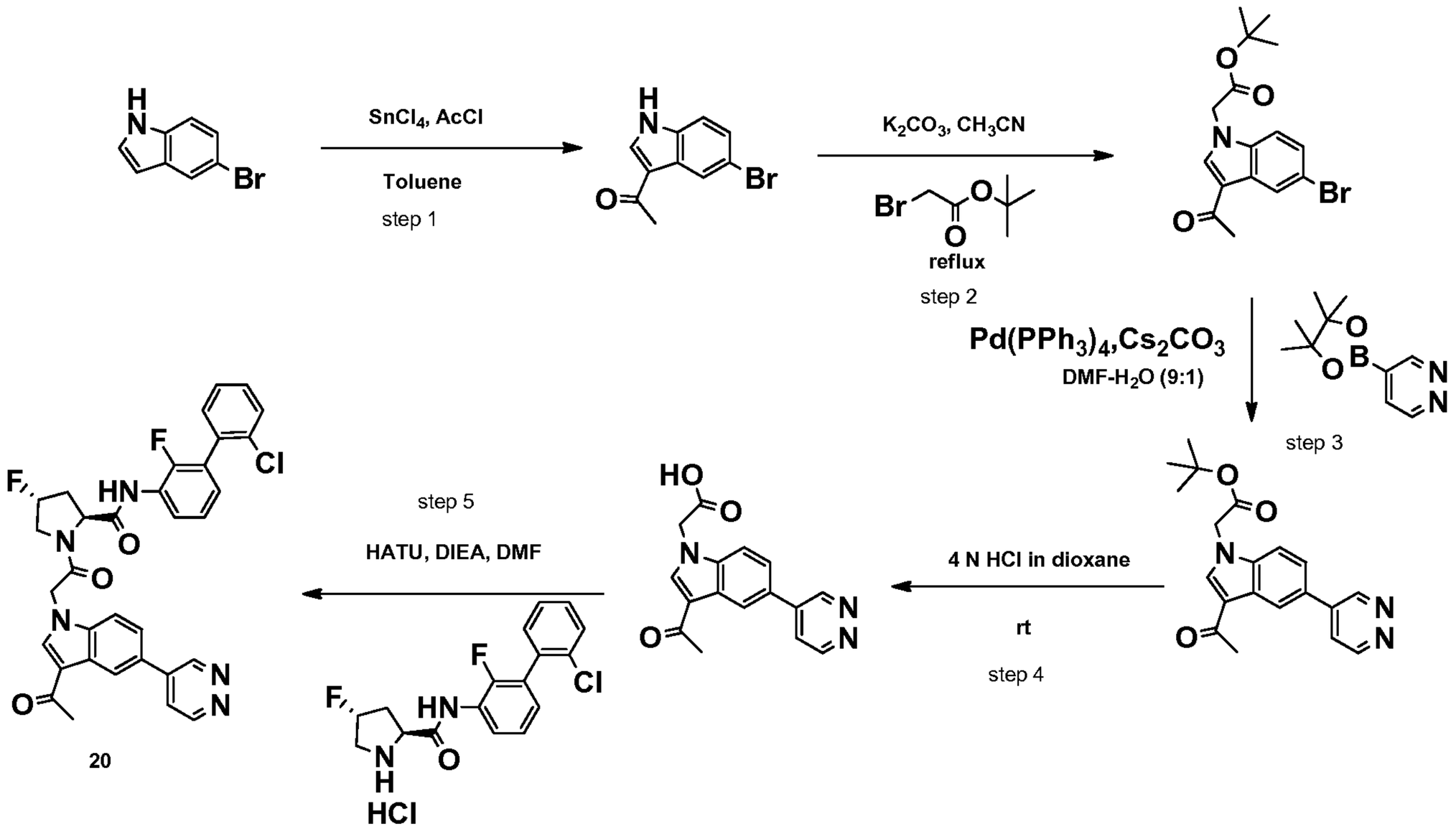
residue was purified by flash column chromatography (ISCO eluted with Hexanes/EtOAC) to give **12**.

(2S,4R)-N-(2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (6).

[0345] (2S,4R)-tert-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate **12** (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 **6** was used directly in the next synthetic step (preparation of **7**).

EXAMPLE 5. ADDITIONAL SYNTHESES OF ARYL, HETROARYL, AND HETEROCYCLIC COMPOUNDS OF FORMULA I

Scheme 1



Step 1: 1-(5-Bromo-1H-indol-3-yl)ethanone.

[0346] The title compound was prepared was prepared from 5-bromoindole according to the procedure of MacKay *et al.* (MacKay, J. A.; Bishop, R.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421-3424.)

Step 2: tert-Butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate.

[0347] A mixture of 1-(5-bromo-1H-indol-3-yl)ethanone (3.9 g, 16.4 mmol), tert-butyl bromoacetate (2.63 mL, 18.02 mmol), and potassium carbonate (2.50 g, 18.02 mmol) in anhydrous acetonitrile (80 mL) was refluxed for 5 h. The reaction mixture was then cooled to rt and the solvent was removed under reduced pressure. The residue was taken in a 1:1 mixture of DCM and water (100 mL:100 mL). The two layers were separated and the organic layer was washed with water (2 × 100 mL). Finally, the organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was stirred with 50 mL of heptane for 30 min, cooled in an ice bath and filtered, washing the solid with cold heptane (10 mL). This cream colored solid was dried under high vacuum to give 5.6 g of *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate.

Step 3: tert-butyl 2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetate.

[0348] A mixture of tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (351 mg, 1 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine (250 mg, 1.5 equiv), cesium carbonate (700 mg, 2 equiv), DMF (15 mL), and water (1.5 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (57 mg, 0.05 equiv) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

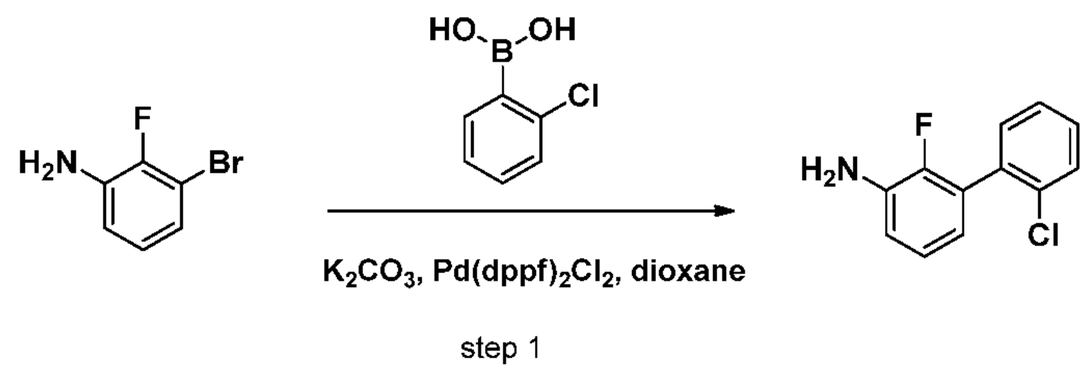
Step 4: 2-(3-Acetyl-5-(pyridazin-4-yl)-1*H*-indol-1-yl)acetic acid.

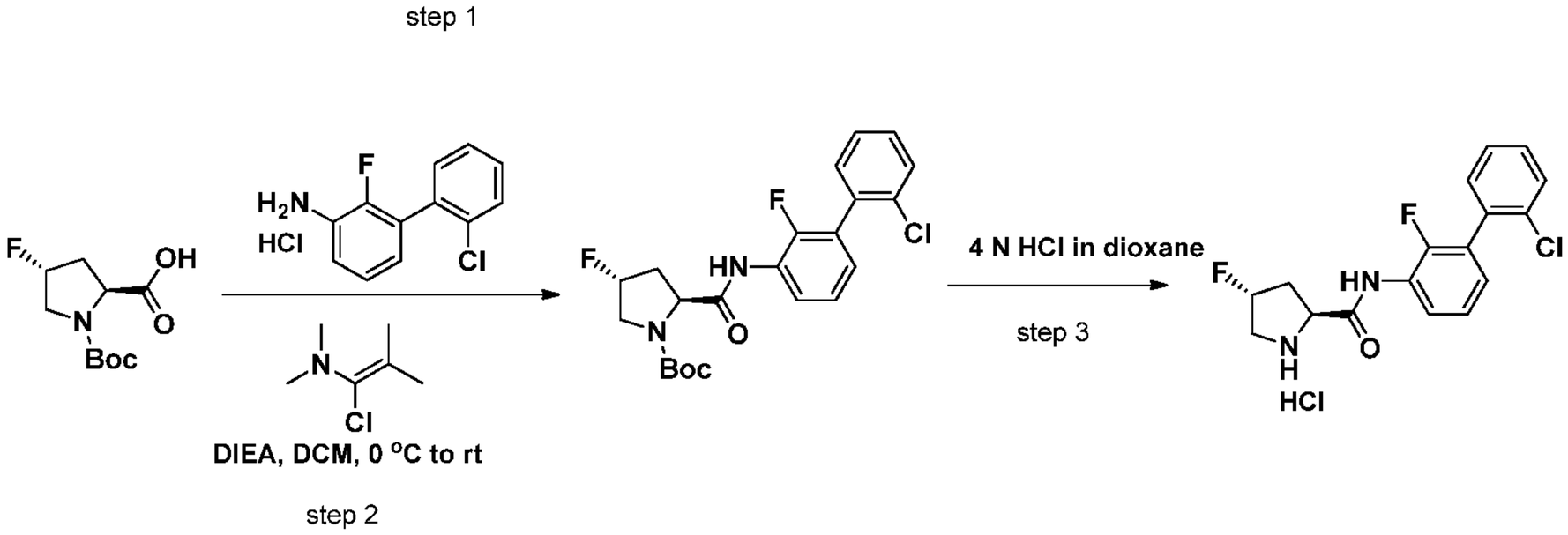
[0349] tert-Butyl 2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (20 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 5: (2*S*,4R)-1-(2-(3-Acetyl-5-(pyridazin-4-yl)-1*H*-indol-1-yl)acetyl)-*N*-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (20).

[0350] 2-(3-Acetyl-5-(pyridazin-4-yl)-1*H*-indol-1-yl)acetic acid (100 mg, 1 equiv) was dissolved in DMF (10 mL) and DIEA (0.269 mL, 5 equiv) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (111 mg, 1 equiv) at 5 °C. HATU (263 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **20**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.13-2.30 (m, 1H), 2.45 (s, 3H), 2.58-2.68 (m, 1H), 3.95-4.05 (m, 1H), 4.13-4.22 (m, 1 H), 4.75 (t, J = 8 Hz, 1H), 5.28 (d, J = 20 Hz, 1H), 5.45 (d, J = 20 Hz, 1H), 5.50-5.63 (m, 1H), 7.06-7.10 (m, 1H), 7.31-7.49 (m, 4H), 7.51-7.61 (m, 1H), 7.65-7.80 (m, 1H), 7.92-8.03 (m, 2H), 8.35 (s, 1H), 8.61 (s 1H), 9.23 (d, 1H), 9.61 (s, 1H), 9.97 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -126.74, -175.78. LC (method A): t_R = 2.58 min. LC/MS (EI) m/z: $[M + H]^+$ 614.

Scheme 2





Step1: 2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-amine hydrochloride.

[0351] A mixture of 3-bromo-2-fluoroaniline (30 g), (2-chlorophenyl) boronic acid (60 g), K_2CO_3 (91 g), and $Pd(dppf)_2Cl_2$ (19.25 g) in solvent (dioxane 400 mL, H_2O 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 the title compound.

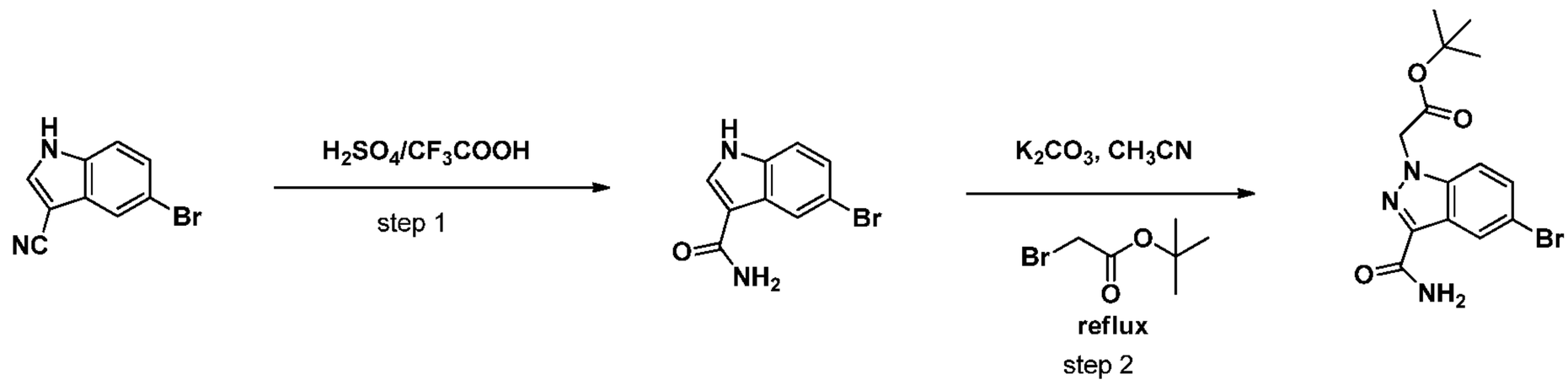
Step 2: (2S,4R)-tert-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate.

[0352] To an ice-cold solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (530 mg) in DCM (20 mL) was added 1-chloro-N,N,2-trimethyl-1-propenylamine (0.333 mL, 1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, then solid of 2'-chloro-2-fluoro-[1,1'-biphenyl]-3-amine hydrochloride (640 mg, 1.1 equiv) was added, followed by DIEA (1.12 mL, 3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water (20 mL) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with hexanes/EtOAc) to give (2S,4R)-tert-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate.

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

[0353] (2*S*, 4*R*)-*tert*-Butyl 2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (700 mg) was taken in 4 N HCl in dioxane (25 mL) 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.

Scheme 3



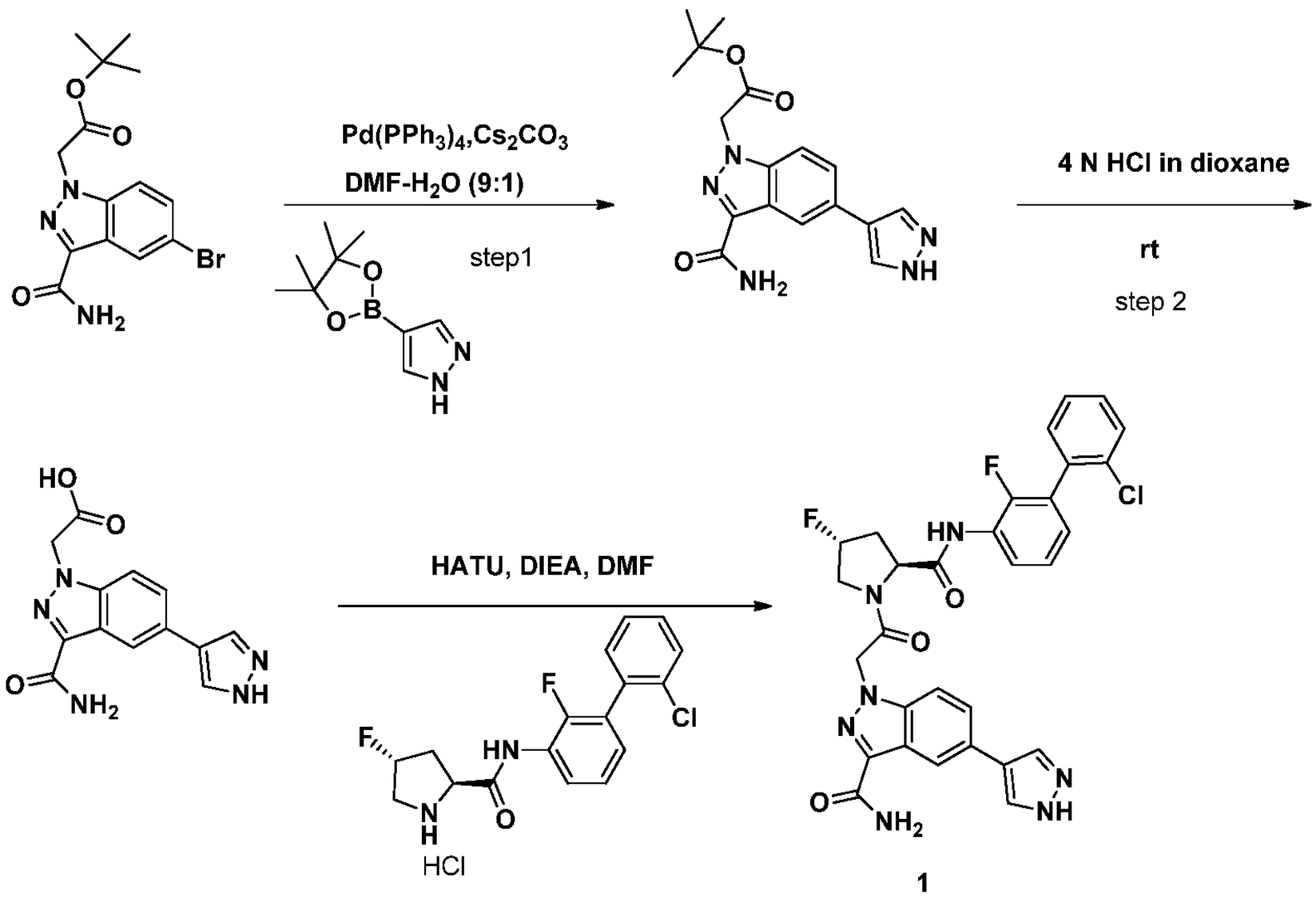
Step 1: 5-Bromo-1*H*-indole-3-carboxamide.

[0354] A mixture of 5-bromo-1H-indole-3-carbonitrile (10 g) in TFA (160 mL) and sulfuric acid (40 mL) was stirred at rt for 4 h. The reaction mixture was then poured into ice, and the precipitated solid was collected by filtration, washed with water, and dried in vacuo to give 5-bromo-1H-indole-3-carboxamide.

Step 2: *tert*-Butyl 2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate.

[0355] A mixture of 5-bromo-1H-indole-3-carboxamide (9.8 g, 41.66 mmol), *tert*-butyl bromoacetate (6.67 mL, 1.1 equiv), and potassium carbonate (6.32 g, 1.1 equiv) in anhydrous acetonitrile (100 mL) was refluxed for 5 h. The reaction mixture was then cooled to rt and the solvent was removed under reduced pressure. The residue was taken in a mixture of DCM and water. The two layers were separated and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give tert-butyl 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetate.

Scheme 4



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(1*H*-pyrazol-4-yl)-1*H*-indazol-1-yl)acetate.

[0356] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (211 mg, 1 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (140 mg), cesium carbonate (391 mg, 2 equiv), DMF (10 mL), and water (1.0 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (35 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

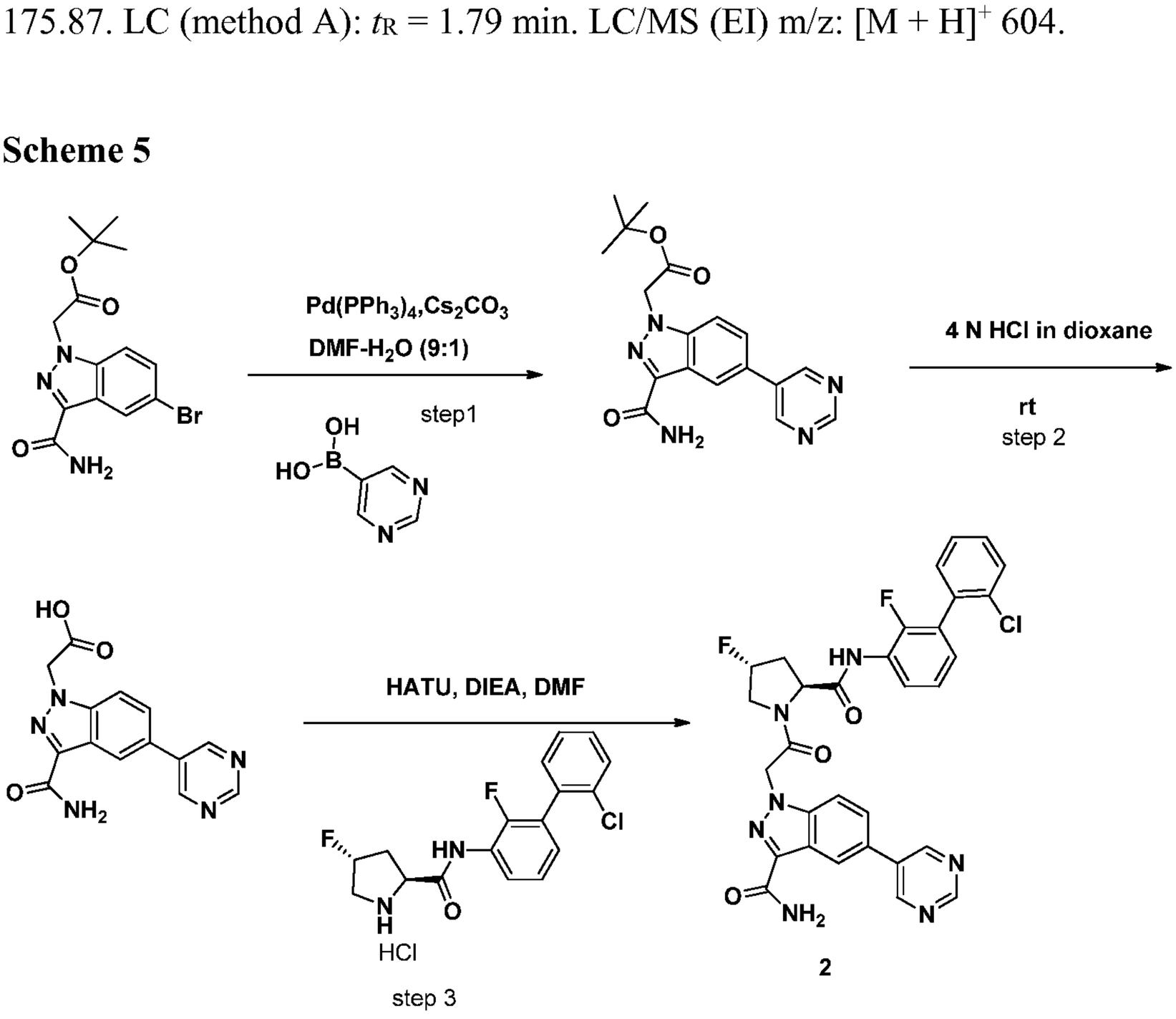
Step 2: 2-(3-Carbamoyl-5-(1*H*-pyrazol-4-yl)-1*H*-indazol-1-yl)acetic acid.

[0357] *tert*-Butyl 2-(3-carbamoyl-5-(1*H*-pyrazol-4-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((2*S*,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(1*H*-pyrazol-4-yl)-1*H*-indazole-3-carboxamide (1).

[0358] 2-(3-Carbamoyl-5-(1*H*-pyrazol-4-yl)-1*H*-indazol-1-yl)acetic acid (100 mg, 1 equiv) was dissolved in DMF (10 mL) and DIEA (0.269 mL, 5 equiv) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (111 mg, 1 equiv) at 5 °C. HATU (263 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **1**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.01-2.21 (m, 1H), 2.49-2.55 (m, 1H), 3.80-3.92 (m, 1H), 4.08-4.21 (m, 1H), 4.61 (t, 1H), 5.47-5.62 (m, 3H), 7.05 (t, 1H), 7.15 (t, J = 8.0Hz, 1H), 7.31-7.40 (m, 4H), 7.49-7.62 (m, 5H), 7.77 (m, 1H), 8.21 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major rotamer) δ -126.75, -175.87. LC (method A): t_R = 1.79 min. LC/MS (EI) m/z: $[M + H]^+$ 604.

Scheme 5



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

[0359] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (211 mg), pyrimidin-5-ylboronic acid (82 mg), cesium carbonate (391 mg, 2 equiv), DMF (9 mL), and water (1.0 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (40 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

Step 2: 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid.

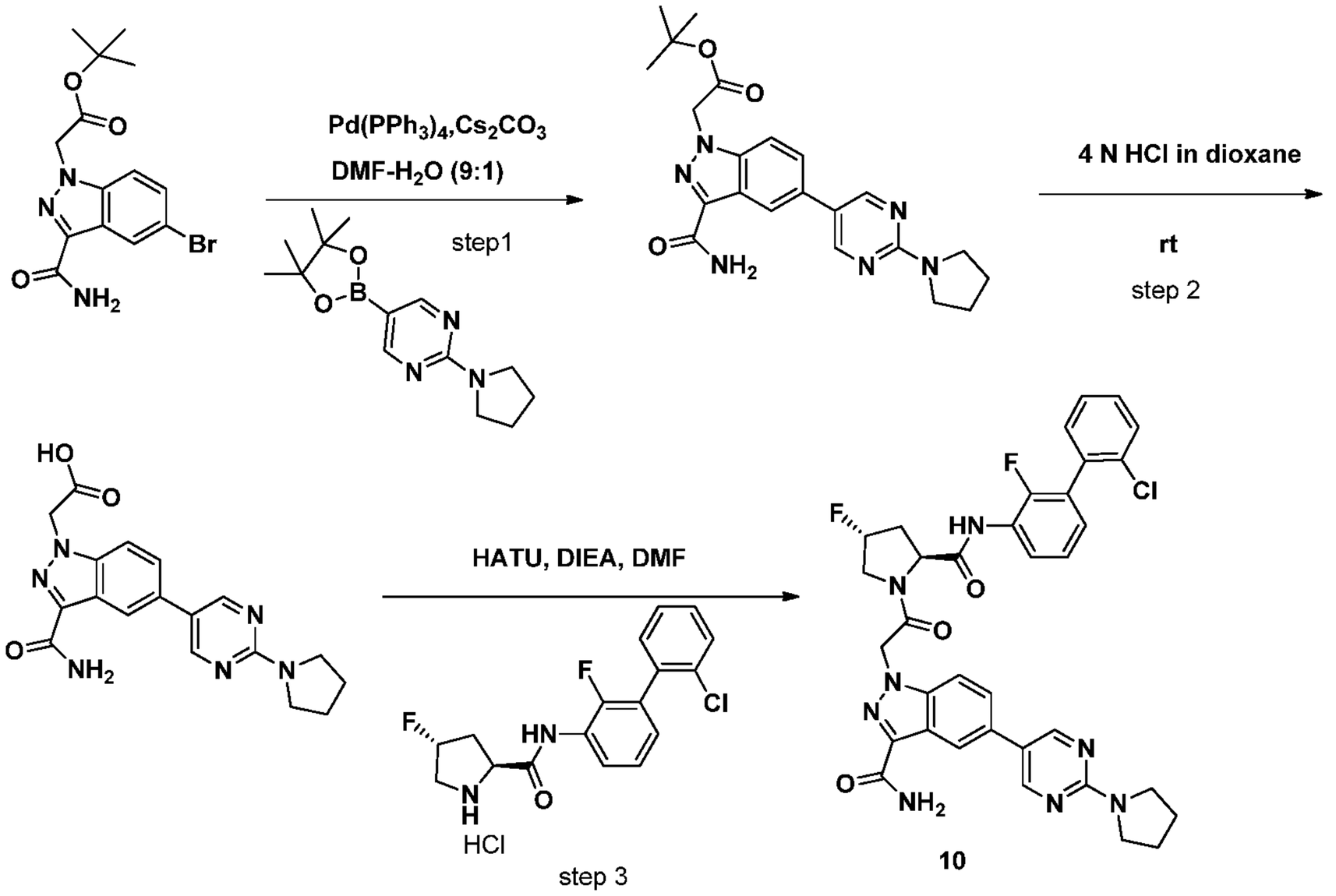
[0360] *tert*-butyl 2-(3-carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction), was taken in 4N HCl dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h .The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((2*S*,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1*H*-indazole-3-carboxamide (2).

[0361] 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid (45 mg, 1 equiv) from the previous step was dissolved in DMF (10 mL) and DIEA (0.12 mL, 5 equiv) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (50 mg, 1 equiv) at 5 °C. HATU (118 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (25 mL + 5 g solid NaCl) and extracted with DCM (2 × 15 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **2**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.11-2.29 (m, 1H), 2.51-2.62 (m, 1H), 3.89-4.08 (m, 1H), 4.18-4.30 (m, 1H), 4.76 (t, 1H), 5.48-5.76 (m, 3H), 7.06 (t, 1H), 7.23 (t, J = 8.0Hz, 1H), 7.37-7.48 (m, 4H), 7.57 (m, 1H), 7.72-7.88 (m, 2H), 7.86 (t, 1H), 8.47 (s, br,1H), 9.15 (s, 2H), 9.21 (s, 1H), 9.99 (s, 1H); ^{19}F NMR (376

MHz, DMSO-d_6, 300K): (major) δ -126.69, -175.86. LC (method A): t_R = 1.82 min. LC/MS (EI) m/z: [M + H]+ 616.

Scheme 6



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate.

[0362] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (316 mg), 2-(pyrrolidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin (271 mg), cesium carbonate (350 mg, 2 equiv), DMF (10 mL), and water (1.5 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (57 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

Step 2:. 2-(3-Carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid.

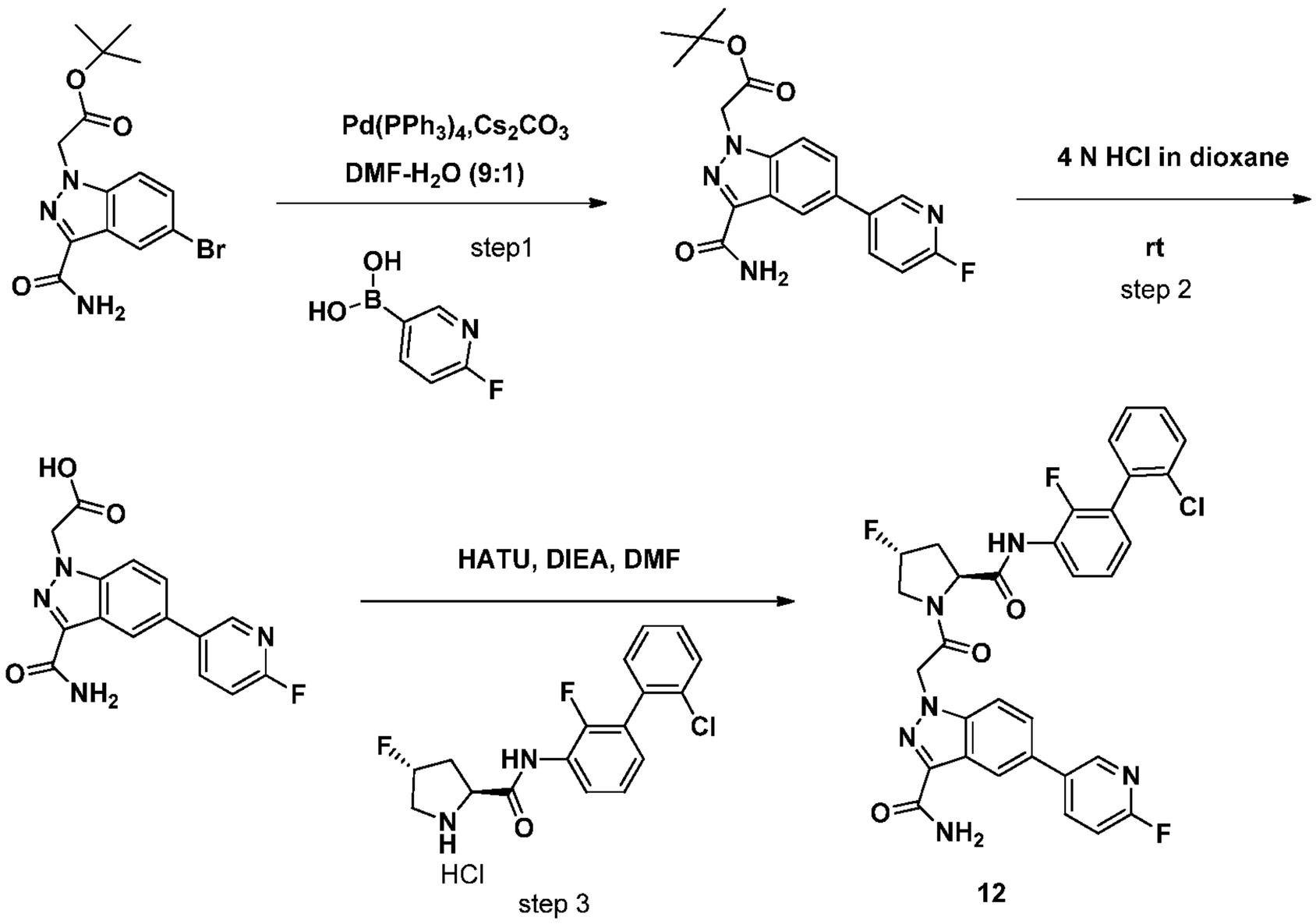
[0363] *tert*-Butyl 2-(3-carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction), was taken in 4 N HCl in dioxane (5 mL) and the resulting

reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((2*S*,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazole-3-carboxamide (10).

[0364] 2-(3-Carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid (110 mg, 1 equiv) was dissolved in DMF (10 mL) and DIEA (0.3 mL) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (110 mg, 1 equiv) at 5 °C. HATU (118 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 20 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **10**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 1.96 (m, 4H), 2.07-2.25 (m, 1H), 2.49-2.62 (m, 1H), 3.53 (m, 4H), 3.78 -3.92 (m, 1H), 4.18-4.27 (m, 1H), 4.66 (t, 1H), 5.45-5.51 (m, 1H), 5.58-5.69 (m, 2H), 7.04 (t, 1H), 7.21 (t, J = 8.0Hz, 1H), 7.32-7.48 (m, 4H), 7.53-7.69 (m, 4H), 7.95 (m, 1H), 8.24 (s, 1H), 9.97 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major rotamer) δ -126.70, -175.88. LC (method A): t_R = 2.33 min. LC/MS (EI) m/z: $[M + H]^+$ 685.

Scheme 7



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(6-fluoropyridin-3-yl)-1*H*-indazol-1-yl)acetate.

[0365] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (211 mg), 6-fluoropyridin-3-ylboronic acid (135 mg), cesium carbonate (350 mg, 2 equiv), DMF (9 mL), and water (1.0 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (50 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

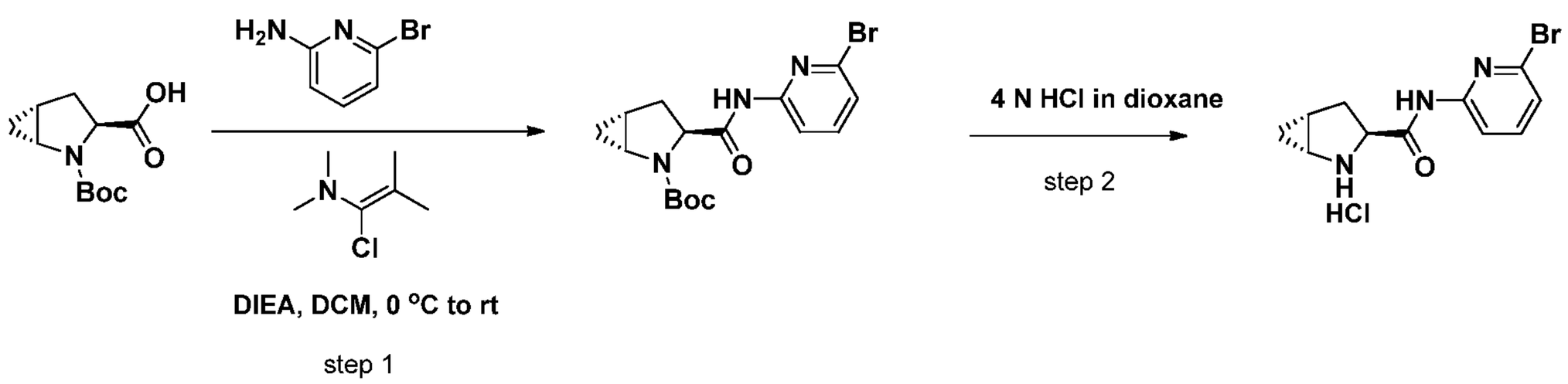
Step 2: 2-(3-Carbamoyl-5-(6-fluoropyridin-3-yl)-1*H*-indazol-1-yl)acetic acid.

[0366] *tert*-Butyl 2-(3-carbamoyl-5-(6-fluoropyridin-3-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction), was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((2*S*,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(6-fluoropyridin-3-yl)-1*H*-indazole-3-carboxamide (12).

[0367] 2-(3-Carbamoyl-5-(6-fluoropyridin-3-yl)-1*H*-indazol-1-yl)acetic acid (110 mg, 1 equiv) was dissolved in DMF (10 mL) and DIEA (0.3 mL) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (110 mg, 1 equiv) at 5 °C. HATU (118 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 20 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give 12. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.10-2.32 (m, 1H), 2.49-2.65 (m, 1H), 3.88-4.06(m, 1H), 4.18-4.29 (m, 1H), 4.73 (t, 1H), 5.95-5.74 (m, 3H), 7.05 (t, 1H), 7.21 (t, J = 8.0Hz, 1H), 7.31-7.48 (m, 5H), 7.46 (m, 1H), 8.27 (m, 1H), 8.39 (s, 1H), 8.55 (s, 1H), 9.98 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major rotamer) δ -125.25, -175.87. LC (method A): t_R = 2.43 min. LC/MS (EI) m/z: $[M + H]^+$ 633.

Scheme 8



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

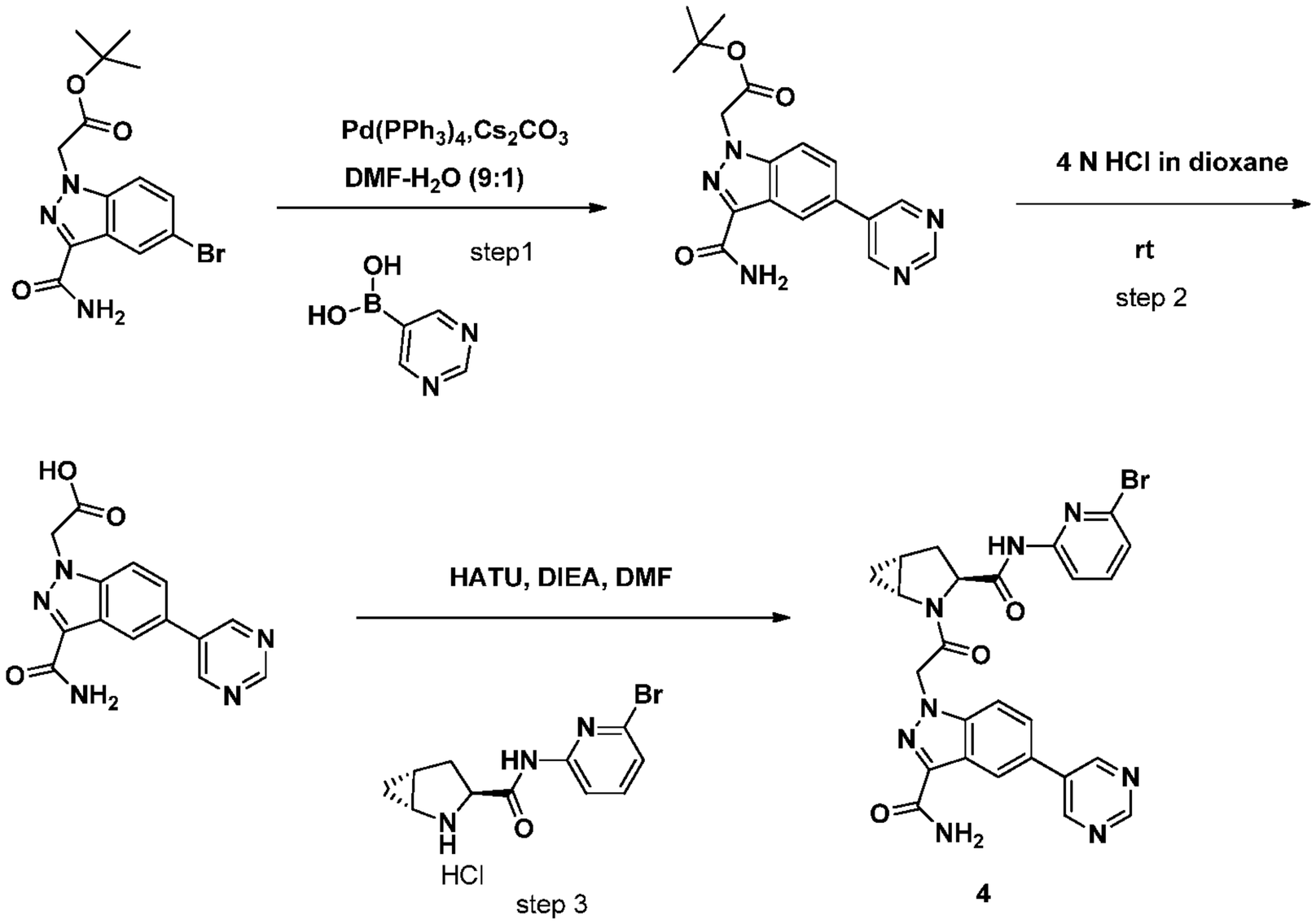
[0368] To an ice-cold solution of (*1R,3S,5R*)-*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic acid (1.5 g) in DCM (20 mL) was added 1-chloro-N,N,2-trimethyl-1-propenylamine (998 mg, 1.1 equiv) dropwise with stirring. The stirring was

continued for 3 h at this temperature, and then solid 6-bromopyridin-2-amine (1.3g, 1.1 equiv) was added, followed by DIEA (3.34 mL, 3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water (20 mL) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with hexanes/EtOAc) to give (*1R,3S,5R*)-*tert*-butyl 3-((6-bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexane-2-carboxylate.

Step 2: (*1R,3S,5R*)-*N*-(6-Bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide Hydrochloride.

[0369] (*1R,3S,5R*)-*tert*-Butyl 3-((6-bromopyridin-2-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. The solvent was removed under reduced pressure and the remaining residue was used directly in the next synthetic step.

Scheme 9



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

[0370] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (211 mg), pyrimidin-5-yl boronic acid (135 mg), cesium carbonate (350 mg, 2 equiv), DMF (9 mL), and water (1.0 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (50 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

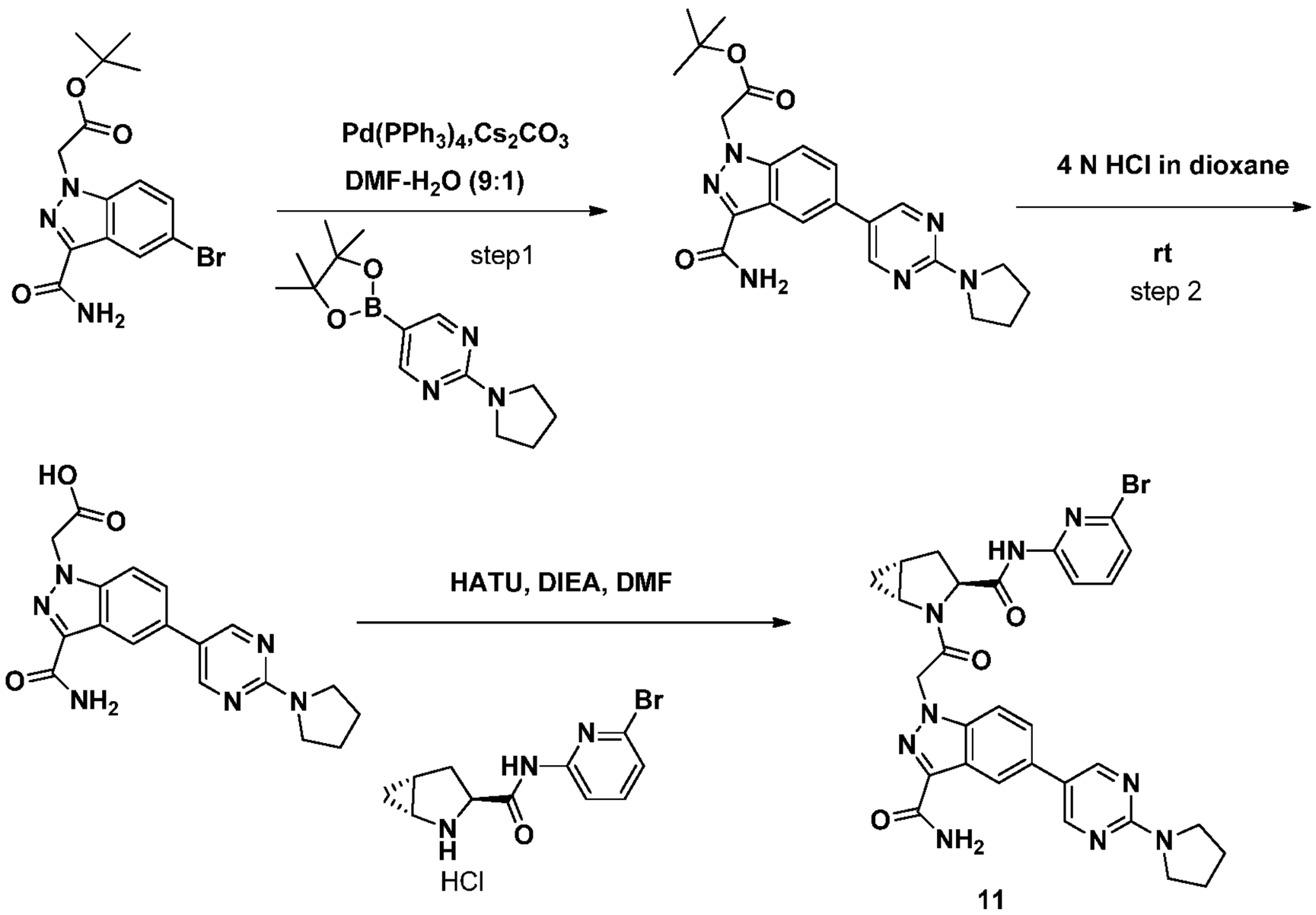
Step 2: 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid.

[0371] *tert*-Butyl 2-(3-carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((*1R,3S,5R*)-3-((6-Bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl-2-oxoethyl)5-(pyrimidin-5-yl)-1*H*-indazole-3-carboxamide (4).

[0372] 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid (110 mg) from the previous step was dissolved in DMF (20 mL) and DIEA (0.3 mL) was added, which was followed by the addition of (*1R,3S,5R*)-*N*-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (126 mg) at 5 °C. HATU (350 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 20 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **4**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 0.75 (m, 1H), 1.02 (m, 1H), 1.85 (m, 1H), 2.16-2.35 (m, 2H), 3.80 (m, 1H), 4.42 (m, 1H), 5.54 (d, 1H), 5.86 (d, 1H), 7.32 (t, 1H), 7.48 (br s, 1H), 7.68-7.88 (m, 4H), 8.03 (d, 1H), 8.46 (s, 1H), 9.23 (s, 2H), 10.76 (s, 1H); LC (method A): t_R = 1.42 min. LC/MS (EI) m/z: $[M + H]^+$ 561.

Scheme 10



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate.

[0373] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (316 mg), 2-(pyrrolidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (271 mg), cesium carbonate (350 mg), DMF (10 mL), and water (1.5 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (57 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

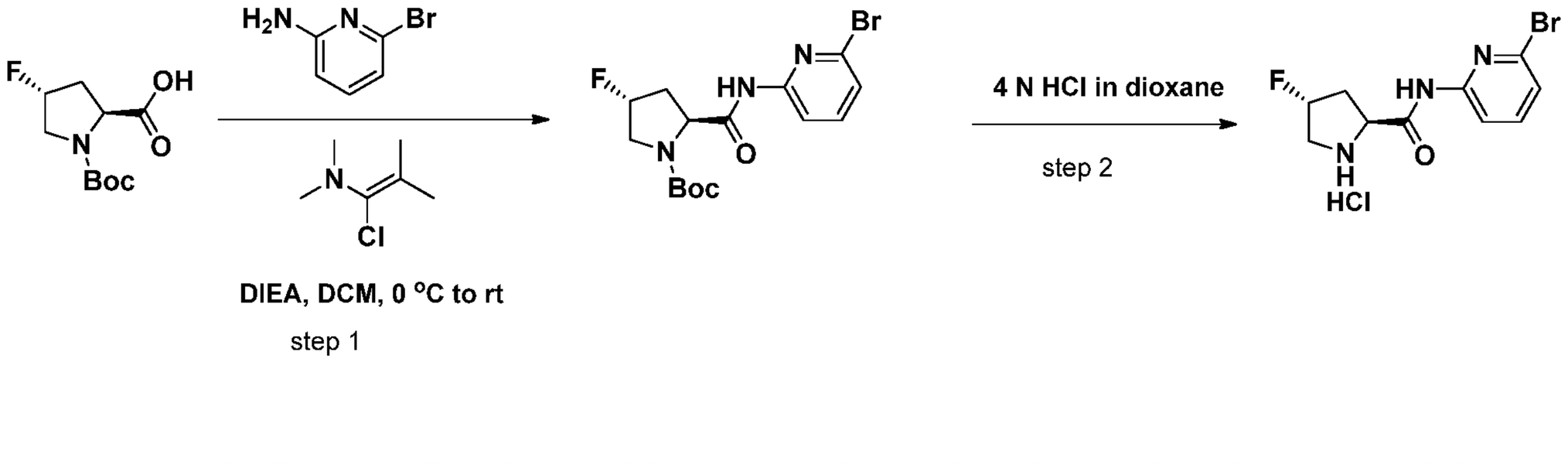
Step 2: 2-(3-Carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid

[0374] *tert*-Butyl 2-(3-carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((*1R,3S,5R*)-3-((6-Bromopyridin-2-yl)carbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl-2-oxoethyl)5-((2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazole-3-carboxamide (11).

[0375] 2-(3-Carbamoyl-5-(2-pyrrolidin-1-yl)pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid (131 mg) from the previous step was dissolved in DMF (20 mL) and DIEA (0.25 mL) was added, which was followed by the addition of (*1R,3S,5R*)-*N*-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide hydrochloride (110 mg) at 5 °C. HATU (240 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 20 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **11**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 0.74 (m, 1H), 1.01 (m, 1H), 1.25 (m, 1H), 1.86-1.98 (m, 5H), 2.13-2.38 (m, 2H), 3.56 (m, 4H), 3.80 (m, 1H), 4.42 (m, 1H), 5.51 (d, 1H), 5.82 (d, 1H), 7.19 (d, J = 6.8 Hz, 1H), 7.40 (br s, 1H), 7.64-7.72 (m, 4H), 8.01 (d, 1H), 8.27 (s, 1H), 8.66 (s, 2H), 10.75 (s, 1H); LC (method A): t_R = 1.82 min. LC/MS (EI) m/z: $[M + H]^+$ 630.

Scheme 11



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

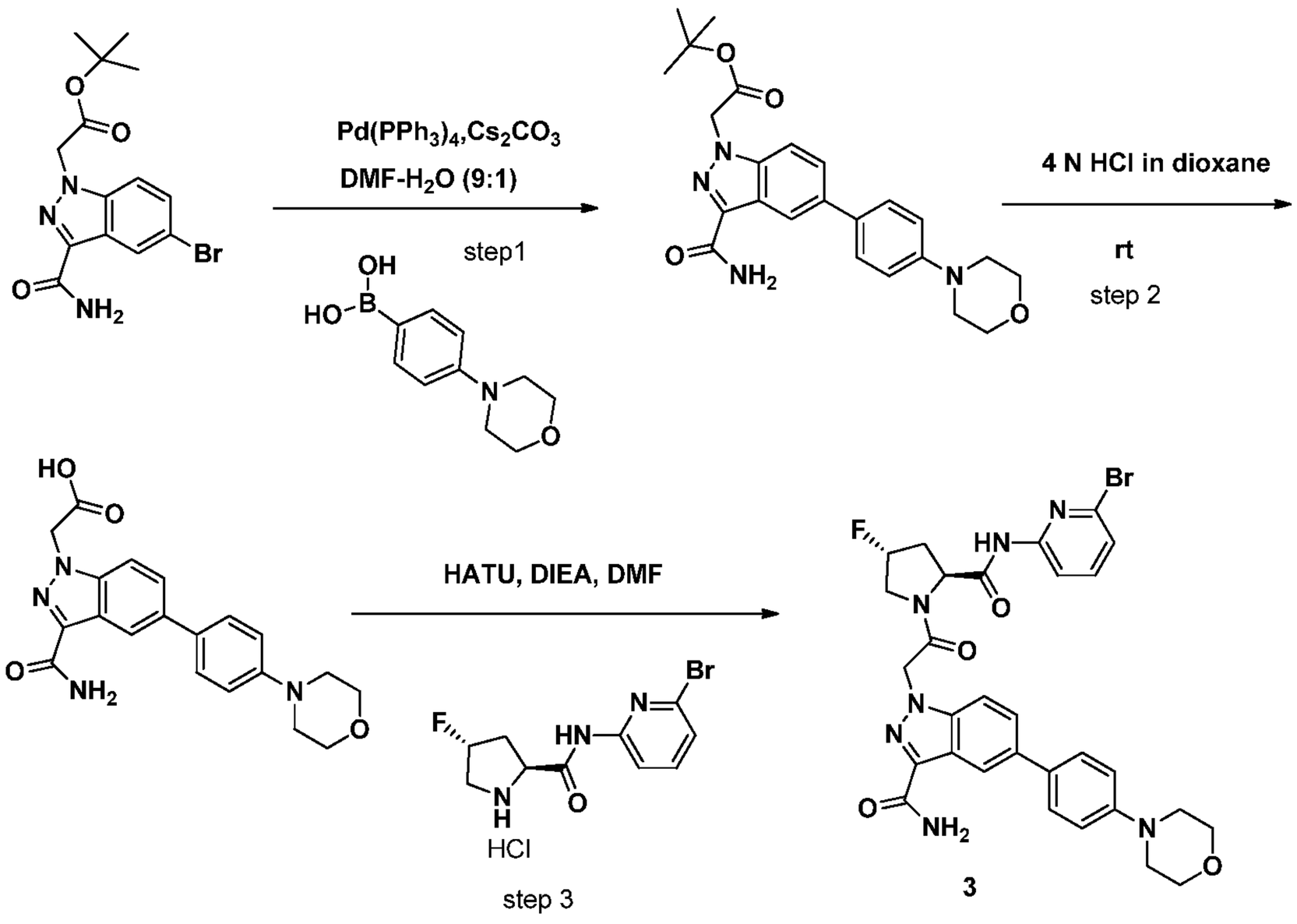
[0376] To an ice-cold solution of (*2S,4R*)-1-*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.59 g) in DCM (20 mL), was added 1-chloro-N,N,2-trimethyl-1-propenylamine (998 mg, 1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this

temperature, and then solid 6-bromopyridin-2-amine (1.3 g, 1.1 equiv) was added, followed by DIEA (3.34 mL, 3 equiv). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water (20 mL) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with hexanes/EtOAc) to give (*2S,4R*)-1-*tert*-Butyl 2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate.

Step 2: (*2S,4R*)-*N*-(6-Bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide Hydrochloride.

[0377] (*2S,4R*)-1-*tert*-Butyl 2-((6-bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (1.5 g) was taken in 4 N HCl in dioxane (25 mL) 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.

Scheme 12



Step 1: *tert*-Butyl 2-(3-carbamoyl-5-(4-morpholinophenyl)-1*H*-indazol-1-yl)acetate.

[0378] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (316 mg), (4-morpholinophenyl)boronic acid (224 mg), cesium carbonate (585 mg, 2 equiv), DMF (20mL), and water (2 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (45 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

Step 2: 2-(3-Carbamoyl-5-(4-morpholinophenyl)-1*H*-indazol-1-yl)acetic acid.

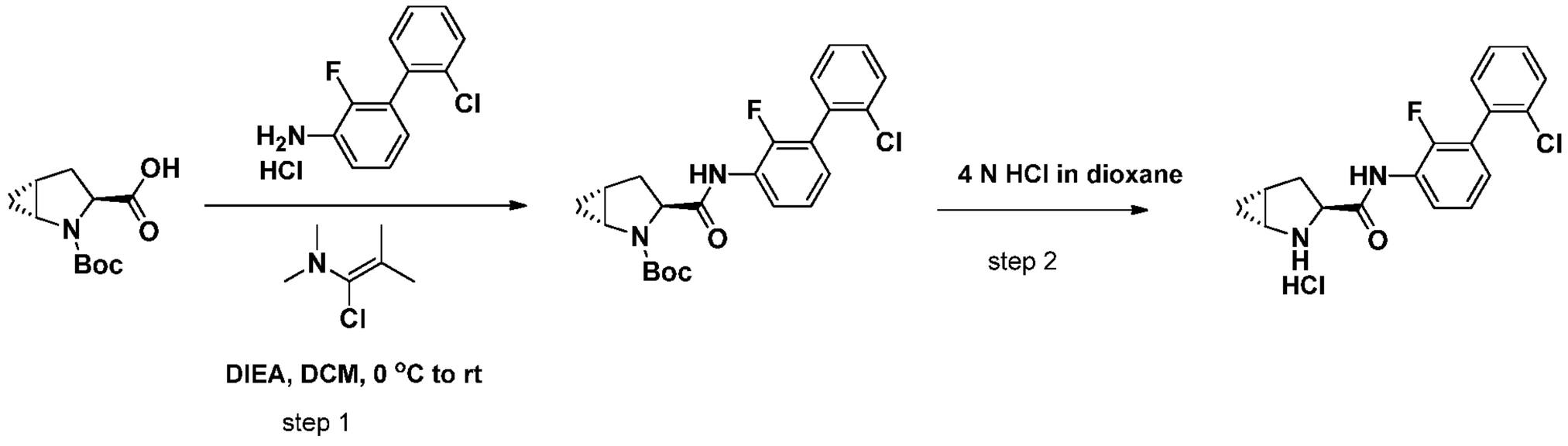
[0379] *tert*-Butyl 2-(3-carbamoyl-5-(4-morpholinophenyl)-1*H*-indazol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((2*S*,4R)-2-((6-Bromopyridin-2-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(4-morphlinophenyl)-1*H*-indazole-3-carboxamide (3).

[0380] 2-(3-Carbamoyl-5-(4-morpholinophenyl)-1*H*-indazol-1-yl)acetic acid (177 mg, 1 equiv) from the previous step was dissolved in DMF (10 mL) and DIEA (0.25 mL) was added, which was followed by the addition of (*2S,4R*)-*N*-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (118 mg, 1 equiv) at 5 °C. HATU (248 mg) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g solid NaCl) and extracted with DCM (2 × 20 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **3**. 1H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.07-2.22 (m, 1H), 2.49-2.61 (m, 1H), 3.12-3.18 (m, 4H), 3.73-3.78 (m, 4H), 3.86-4.09 (m, 1H), 4.13-4.25 (m, 1H), 4.66 (t, J = 8.4Hz, 1H), 5.42-5.48 (m, 1H), 5.58-5.70 (m, 2H), 7.04 (t, J = 6.4 Hz, 1H), 7.31 (t, J = 8.0Hz, 1H), 7.35-7.52 (m, 1H), 7.50-7.58 (d, J = 8.4 Hz, 2H), 7.63-7.75 (m, 4H), 8.02 (d, J = 8 Hz, 1H),

8.32 (s, 1H), 10.99 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major) δ -175.70. LC (method A): t_R = 1.82 min. LC/MS (EI) m/z: $[M + H]^+$ 650.

Scheme 13



Step 1: (*1R,3S,5R)-tert*-Butyl 3-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)2-azabicyclo[3.1.0]hexan-2-carboxylate.

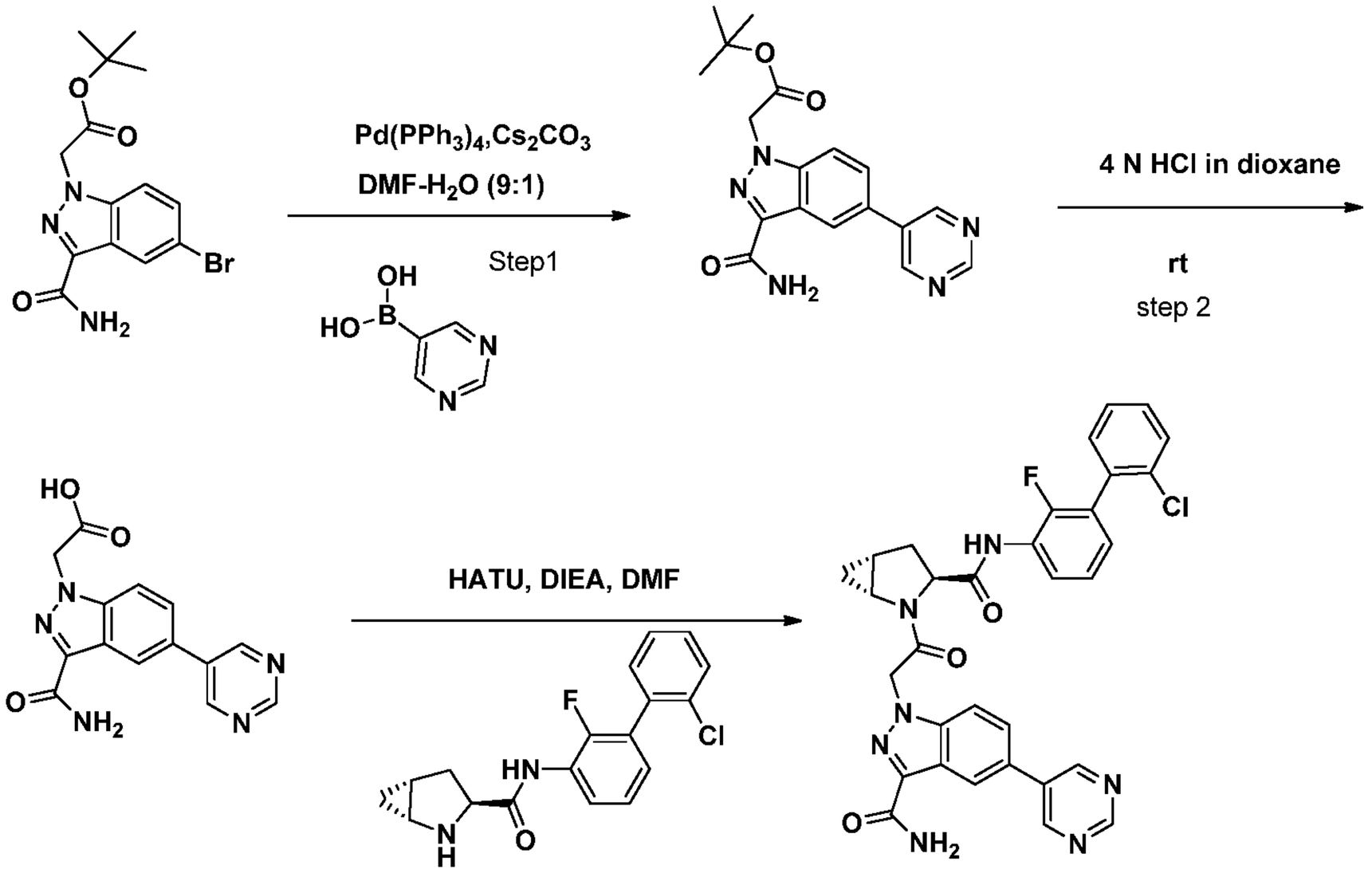
[0381] To an ice-cold solution of (*1R,3S,5R*)-*tert*-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-2-carboxylic acid (1.13 g) in DCM (20 mL) was added 1-chloro-N,N,2-trimethyl-1-propenylamine (731 mg, 1.1 equiv) dropwise with stirring. The stirring was continued for 3 h at this temperature, and then solid of 2'-chloro-2-fluoro-[1,1'-biphenyl]-3-amine hydrochloride (1.3 g, 1 equiv) was added, followed by DIEA (2.45 mL). The cooling bath was removed and the reaction mixture was stirred overnight at rt. The reaction mixture was then added to water (20 mL) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with hexanes/EtOAc) to give (*1R,3S,5R)-tert*-Butyl 3-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)2-azabicyclo[3.1.0]hexan-2-carboxylate.

Step 2: (*1R,3S,5R)-N*-(2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)2-azabicyclo[3.1.0]hexane-3-carboxamide Hydrochloride.

[0382] (*1R,3S,5R)-tert*-Butyl 3-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)2-azabicyclo[3.1.0]hexan-2-carboxylate (700 mg) was taken in 4 N HCl in dioxane (25 mL) 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.

Scheme 14



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

[0383] A mixture of *tert*-butyl-2-(5-bromo-3-carbamoyl-1*H*-indazol-1-yl)acetate (211 mg), pyrimidin-5-ylboronic acid (82 mg), cesium carbonate (391 mg, 2 equiv), DMF (9 mL), and water (1.0 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (40 mg) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

Step 2: 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid.

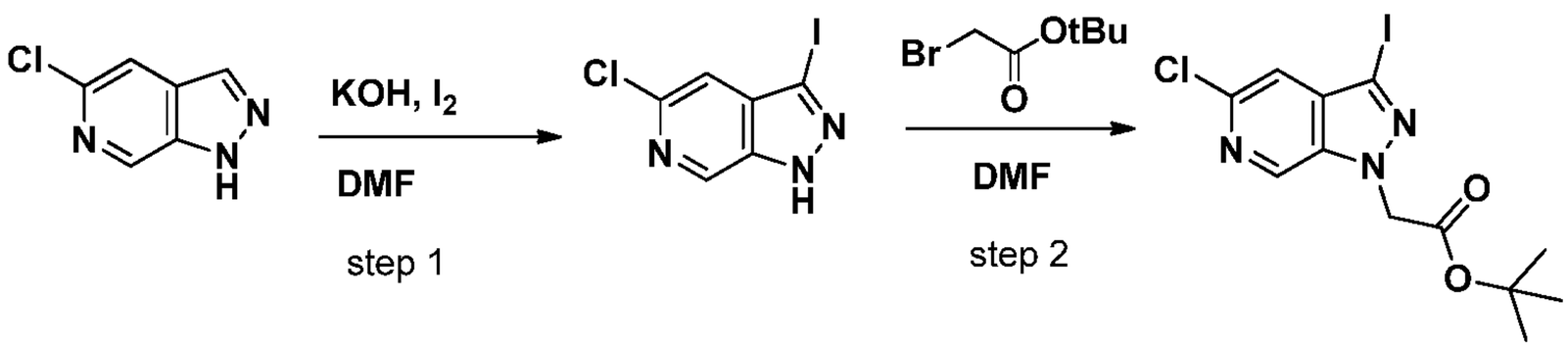
[0384] *tert*-Butyl 2-(3-carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetate (crude from above reaction) was taken in 4 N HCl in dioxane (5 mL) and the resulting reaction mixture

was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: 1-(2-((*1R,3S,5R*)-3-((2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1*H*-indazole-3-carboxamide (6).

[0385] 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1*H*-indazol-1-yl)acetic acid (131 mg, 1 equiv) from the previous step was dissolved in DMF (10 mL) and DIEA (0.33 mL, 5 equiv) was added, which was followed by the addition of (*1R,3S,5R)-N*-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)2-azabicyclo[3.1.0]hexane-3-carboxamide Hydrochloride (131 mg, 1 equiv) at 5 °C. HATU (350 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (25 mL + 5 g solid NaCl) and extracted with DCM (2 × 15 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **6**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 0.73 (m, 1H), 1.07 (m, 1H), 1.26 (m, 1H), 1.90 (m, 1H), 2.28-2.35 (m, 2H), 3.78-3.83 (m, 1H), 4.54 (m, 1H), 5.52 (d, 1H), 5.84 (d, 1H), 7.07 (t, J = 6.4 Hz, 1H), 7.27 (t, J = 8.0Hz, 1H), 7.35-7.58 (m, 4H), 7.55 (d, 1H), 7.72-7.84 (m, 4H), 8.47(s, 1H), 9.72 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major) δ -126.54. LC (method A): t_R = 1.96 min. LC/MS (EI) m/z: [M + H]+ 610.

Scheme 15



Step-1: 5-Chloro-3-iodo-1H-pyrazolo[3,4]pyridine.

[0386] To a solution of 5-chloro-1H-pyrazolo[3,4-c]pyridine (15 g, 1 equiv) in DMF (150 mL) was added iodine (37.2 g, 1.5 equiv) and potassium hydroxide (13.7 g, 2.5 equiv) at 0 °C. The reaction mixture was stirred at rt for 12 h and then diluted with 10% aqueous sodium thiosulfate (250 mL) and extracted with EtOAc. The combined organic extracts were washed with brine and then dried. The obtained solid (15 g) was slurried with MTBE, filtered and dried.

Step-2: *tert*-Butyl 2-(5-chloro-3-iodo-1H-pyrazolo[3,4]pyridine-1-yl)acetate.

[0387] To a mixture of 5-chloro-3-iodo-1H-pyrazolo[3,4]pyridine (14 g, 1 equiv) and potassium carbonate (8.3 g, 1.2 equiv) in DMF (140 mL) was added tert-butyl bromoacetate (8.9 mL, 1.2 equiv) dropwise at rt and the resulting mixture was stirred at 50 °C for 3 h. The reaction mixture was then poured into water and extracted with EtOAc; the combined organic extracts were concentrated under reduced pressure. The material obtained was taken to next step without further purification.

Step-3: *tert*-Butyl 2-(5-chloro-3-cyano-1H-pyrazolo[3,4-c]pyridine-1-yl)acetate.

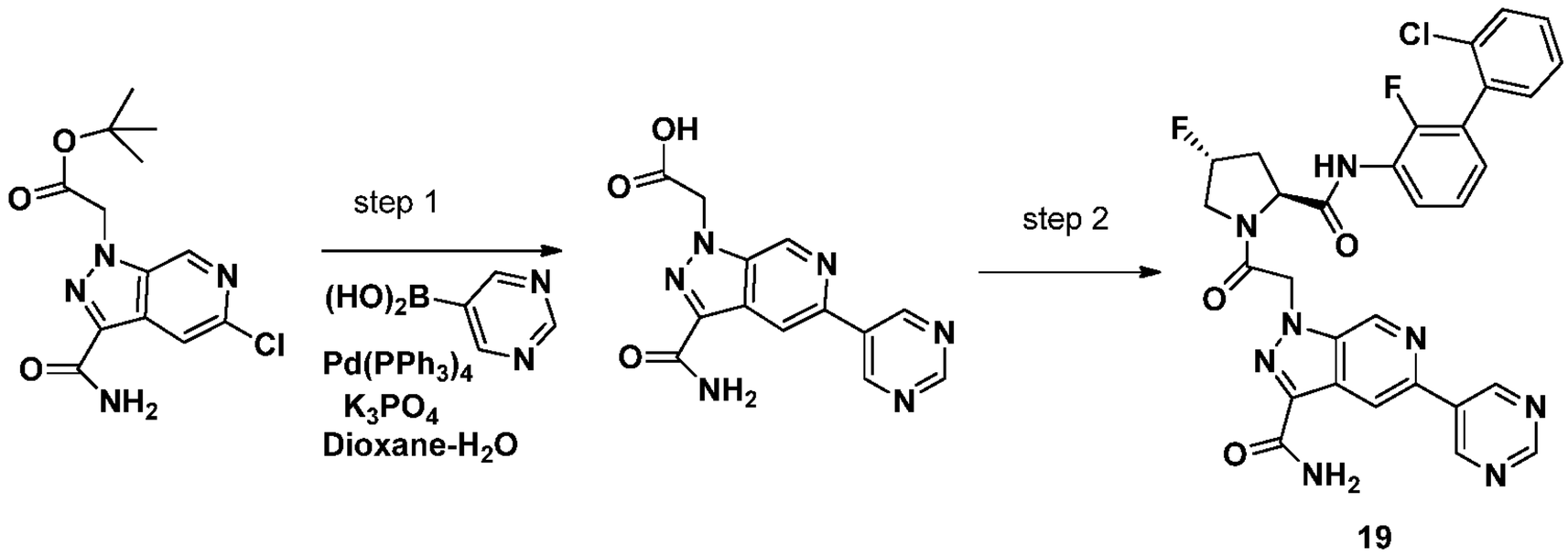
[0388] A mixture of *tert*-butyl 2-(5-chloro-3-iodo-1H-pyrazolo[3,4]pyridine-1-yl)acetate (12.5 g, 1 equiv), Zn(CN) 2 (4.5 g, 1.2 equiv), Pd (dppf)Cl_2 (2.6 g, 0.1 equiv), $Pd_2(dba)_3$ (2.9 g, 0.1 equiv), water (25 mL), and DMF (125 mL) was stirred at 100 °C for 5 h under an atmosphere

of nitrogen. The reaction mixture was diluted with EtOAc and then washed successively with water, saturated aqueous $NaHCO_3$, and brine. The combined organic layer was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc) to give the title compound.

Step-4: tert-Butyl 2-(3-carbamoyl-5-chloro-1H-pyrazolo[3,4-c]pyridine-1-yl)acetate.

[0389] A mixture of *tert*-butyl 2-(5-chloro-3-cyano-1H-pyrazolo[3,4-c]pyridine-1-yl)acetate (5.7 g, 1 equiv), acetaldoxime (2.3 g, 2 equiv), $Pd(OAc)_2$ (0.22 g, 0.05 equiv), and PPh_3 (0.54 g, 0.1 equiv) in aqueous ethanol (143 mL, H_2O/EtOH (29 mL/114 mL) was heated to 90 °C for 3 h under an atmosphere of nitrogen. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc) to give the title compound (3.5 g).

Scheme 16



Step 1: 2-(3-Carbamoyl-5-(pyrimidin-5-yl)-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid.

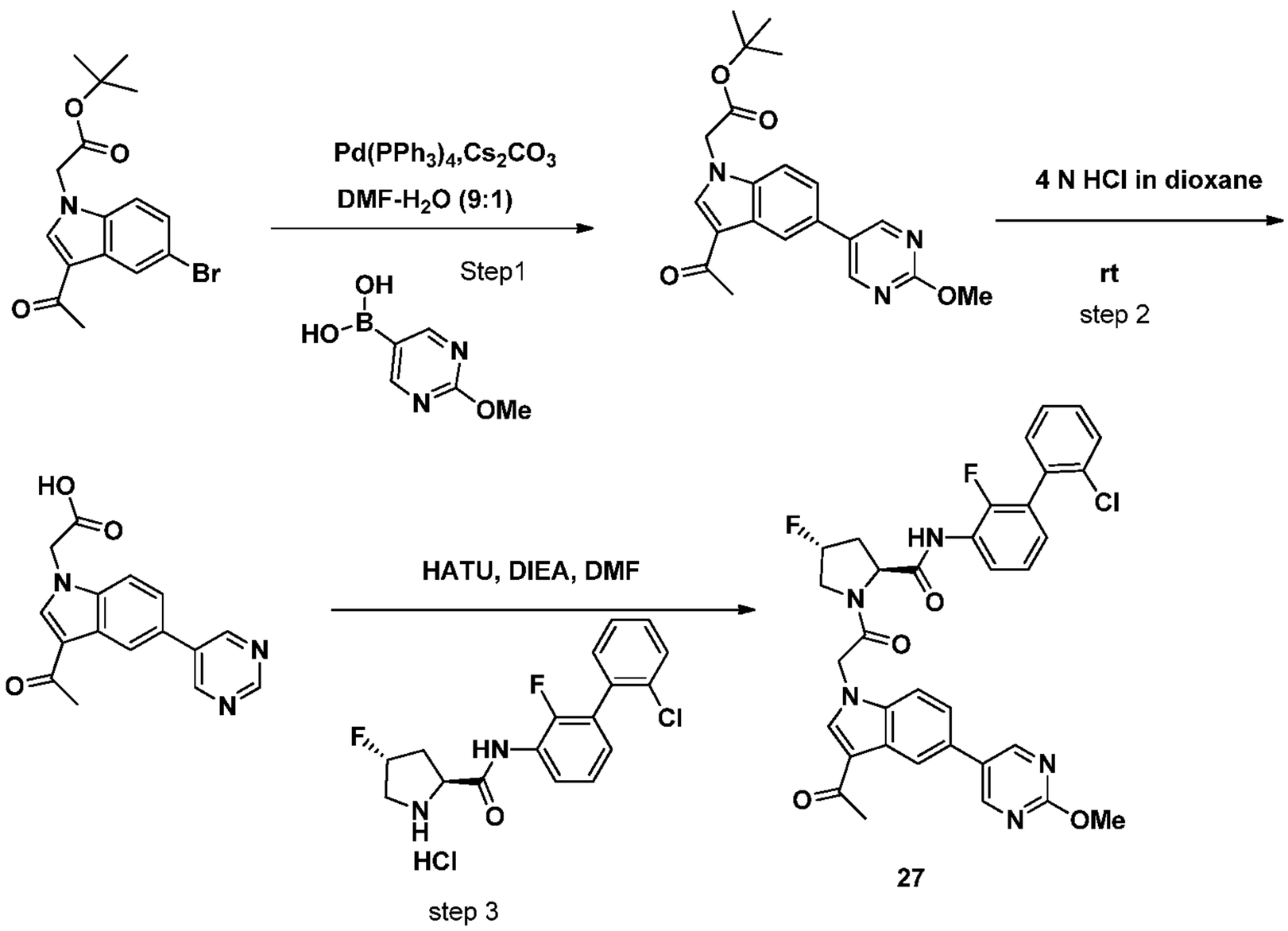
[0390] A mixture of tert-butyl 2-(3-carbamoyl-5-chloro-1H-pyrazolo[3,4-c]pyridin-1-yl)acetate (311 mg, 1 mmol), pyrimidin-5-ylboronic acid (248 mg, 2mmol), K_3PO_4 (634 mg, 3 mmol), dioxane (9 mL), and water (1 mL) was degassed and refilled with argon three times. To this mixture was added $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) under an atmosphere of argon, and the reaction mixture was heated in a 85 °C oil bath overnight. Additional $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) was added to the solution and the reaction was kept at 85°C for an additional 24 h. The reaction was cooled to rt and the volatiles were removed under reduced pressure. The remaining residue was acidified with 10% aqueous citric acid (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was discarded and the aqueous phase was evaporated to dryness. The

remaining solid was loaded on a pad of silica gel and flushed with methanol. The methanol solution was concentrated and co-evaporated with toluene. The obtained solid was dried under high vacuum and used in the next step without further purification.

Step 2: 1-(2-((2S,4R)-2-((2'-Chloro-2-fluoro-[1,1'-biphenyl]-3-yl)carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (19)

[0391] To a mixture of 2-(3-carbamoyl-5-(pyrimidin-5-yl)-1H-pyrazolo[3,4-c]pyridin-1-yl)acetic acid (77 mg, 0.26mmol), HATU (120 mg, 0.32 mmol, 1.2 equiv), (2S,4R)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (96mg, 0.26mmol), and DMF (2.5 mL) was added DIEA (0.15 mL, 0.86 mmol) at rt. The reaction mixture was stirred for 30 min at rt and then the volatiles were removed under reduced pressure. The remaining residue was subjected to preparative HPLC to afford 40.9 mg of title product. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.17-2.25 (m, 1H), 2.49-2.57 (m, 1H), 3.86-3.99 (m, 1H), 4.13-4.22 (m, 1H), 4.73 (t, J = 8.4 Hz, 1H), 5.57-5.61 (m, 1H), 5.65-5.84 (m, 2H), 6.99 (t, J = 6.4 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.28-7.42 (m, 4H), 7.50-7.58 (m, 1H), 7.83-7.92 (m, 2H), 8.58 (s, 1H), 9.15 (s, 1H), 9.23 (s, 1H), 9.38 (s, 2H), 9.95 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300K): (major rotamer) δ -126.77, -175.85. LC (method A): t_R = 2.47 min. LC/MS (EI) m/z: $[M + H]^+$ 617.

Scheme 17



Step 1: tert-Butyl 2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetate.

[0392] A mixture of of *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate (351 mg, 1 equiv), (2-methoxypyrimidin-5-yl)boronic acid (230 mg. 1.5 equiv), cesium carbonate (650 mg, 2 equiv), DMF (15 mL), and water (1.5 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (57 mg, 0.05 equiv) was then added under argon and the pressure vessel was sealed and heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was used directly in the next synthetic step.

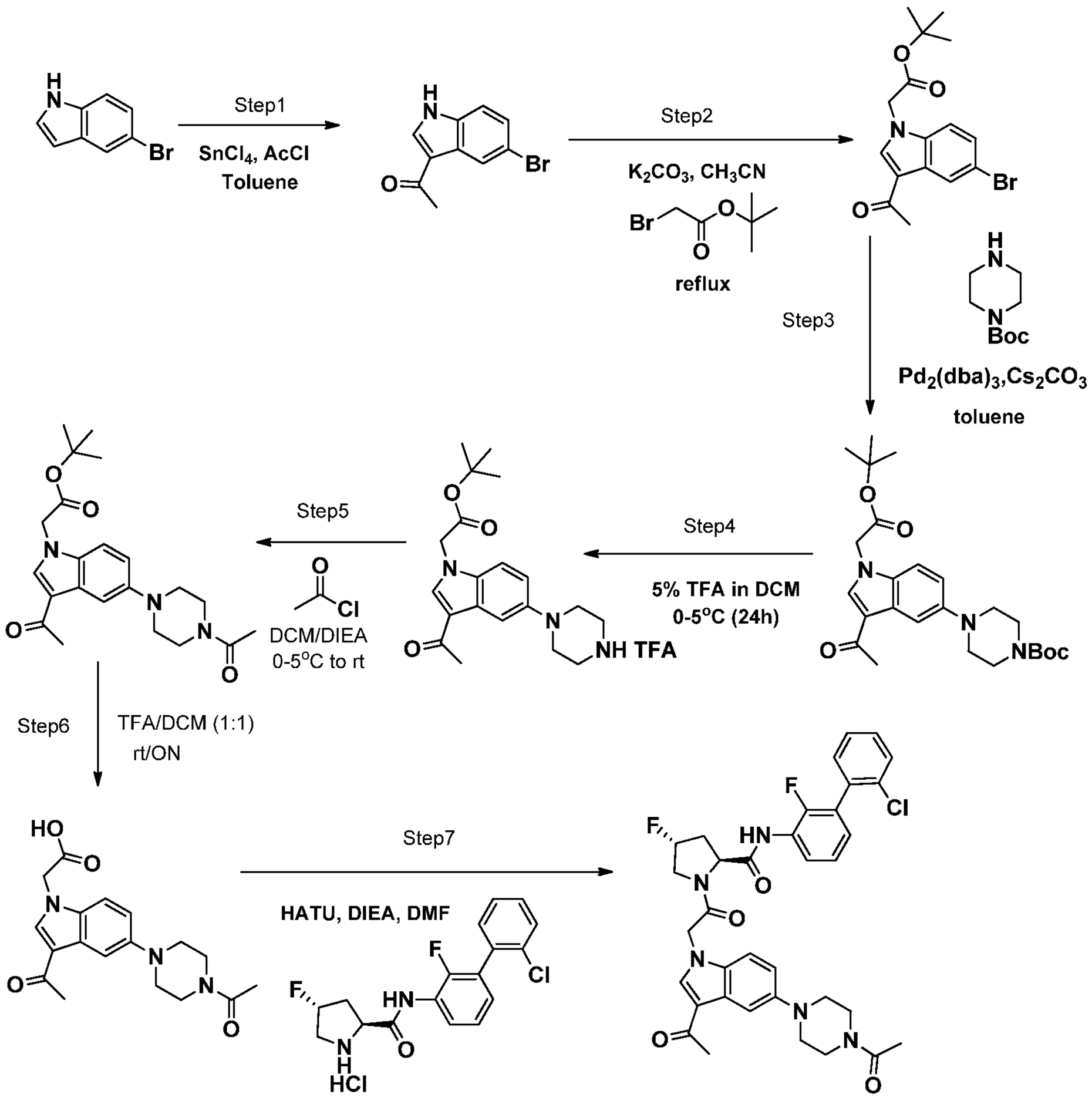
Step 2: 2-(3-Acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetic acid.

[0393] Crude tert-butyl 2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetate (from above) was taken in 4 N HCl in dioxane (20 mL) and the resulting reaction mixture was stirred at rt for 4 h. The solvent was removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (27).

[0394] 2-(3-Acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetic acid (100 mg, 1 equiv) from the previous step was dissolved in DMF (10 mL) and DIEA (0.269 mL, 5 equiv) was added, which was followed by the addition of (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (111 mg, 1 equiv) at 5 °C. HATU (263 mg, 2.1 equiv) was then added slowly at this same temperature and the reaction mixture was stirred for 3 h at rt. The reaction mixture was then added to water (50 mL + 10 g NaCl) and extracted with DCM (2 × 25 mL). The organic layer was washed successively with an aqueous solution of $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (eluted with DCM/MeOH) to give **27**. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.13-2.3 (m, 1H), 2.45 (s, 3H), 2.68-2.70 (m, 1H), 3.95-4.05 (m, 4H), 4.16-4.24 (m, 1 H), 4.78 (t, J = 8 Hz, 1H), 5.28 (d, J = 20 Hz, 1H), 5.45 (d, J = 20 Hz, 1H), 5.50-5.63 (m, 1H), 7.04-7.08 (m, 1H), 7.20-7.24 (m, 1H), 7.37-7.61 (m, 7H), 7.75-7.78 (m, 1H), 7.94-7.98 (m, 1H), 8.31 (s, 1H), 8.88 (s 1H), 8.97 (s 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -126.64, -175.79. LC (method A): t_R = 2.16 min. LC/MS (EI) m/z: $[M + H]^+$ 644.

Scheme 18: Synthesis of (2S,4R)-1-(2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (16)



Step 1: 1-(5-Bromo-1H-indol-3-yl)ethanone

[0395] 1-(5-Bromo-1*H*-indol-3-yl)ethanone was prepared from 5-bromoindole according to the procedure of MacKay *et al.* (MacKay, J. A.; Bishop, R.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421-3424.)

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

[0396] A mixture of 1-(5-bromo-1H-indol-3-yl)ethanone (3.9 g, 16.4 mmol), *tert*-butyl bromoacetate (2.63 mL (18.02 mmol), and potassium carbonate (2.50 g, 18.02 mmol) in anhydrous acetonitrile (80 mL) was refluxed for 5 h. The reaction mixture was then cooled to rt and the solvent was removed under reduced pressure. The residue was taken in a 1:1 mixture of DCM and water (100 mL:100 mL). The two layers were separated and the organic layer was washed with water (2 × 100 mL). Finally, the organic layer was dried (Na_2SO_4) and concentrated. The resulting residue was stirred with 50 mL of heptane for 30 min, cooled in an ice bath and the solid was filtered, washed with cold heptane (10 mL). The solid was dried under high vacuum to give *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate (5.6 g).

Step 3: tert-Butyl 4-(3-acetyl-1-(2-(tert-butoxy)-2-oxoethyl)-1H-indol-5-yl)piperazine-1-carboxylate

[0397] A mixture of *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate (379 mg), *tert*-butyl piperazine-1-carboxylate (223 mg, 1.2 equiv), cesium carbonate (489 mg, 1.4 equiv), (S)-(-)-2,2-bis(diphenylphosphino)-1,1-binaphthyl (40 mg), and toluene (8 mL) was purged with argon for 5 min. Tris(dibenzylideneacetone)dipalladium (0) (40 mg) was then added under argon and the reaction mixture was heated at 100 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (EtOAc in hexanes gradient) to give tert-butyl 4-(3-acetyl-1-(2-(tert-butoxy)-2-oxoethyl)-1H-indol-5-yl)piperazine-1-carboxylate (89 mg).

Step 4: tert-Butyl 2-(3-acetyl-5-(piperazin-1-yl)-1H-indol-1-yl)acetate TFA salt

[0398] *tert*-Butyl 4-(3-acetyl-1-(2-(*tert*-butoxy)-oxoethyl-1*H*-indole-5-yl)piperazine-1-carboxylate (65 mg) was taken in 5% TFA (0.5 mL) in DCM (10 mL) at 0–5 °C and the resulting reaction mixture was stirred at 0–5 °C for 24 h. The solvent was then removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 5: tert-Butyl 2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetate

[0399] The TFA salt of tert-butyl 2-(3-acetyl-5-(piperazin-1-yl)-1H-indol-1-yl)acetate from step 4 was dissolved in DCM (4 mL) and DIEA (0.14 mL, excess) was added, then

followed by the addition of AcCl (0.02 mL, 1 equiv) at 0–5 °C. After stirring for 10 min, the reaction mixture was diluted with EtOAc (10 mL) and water (4 mL). The EtOAc layer was separated, washed with brine (15 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The remaining material was used directly in the next step.

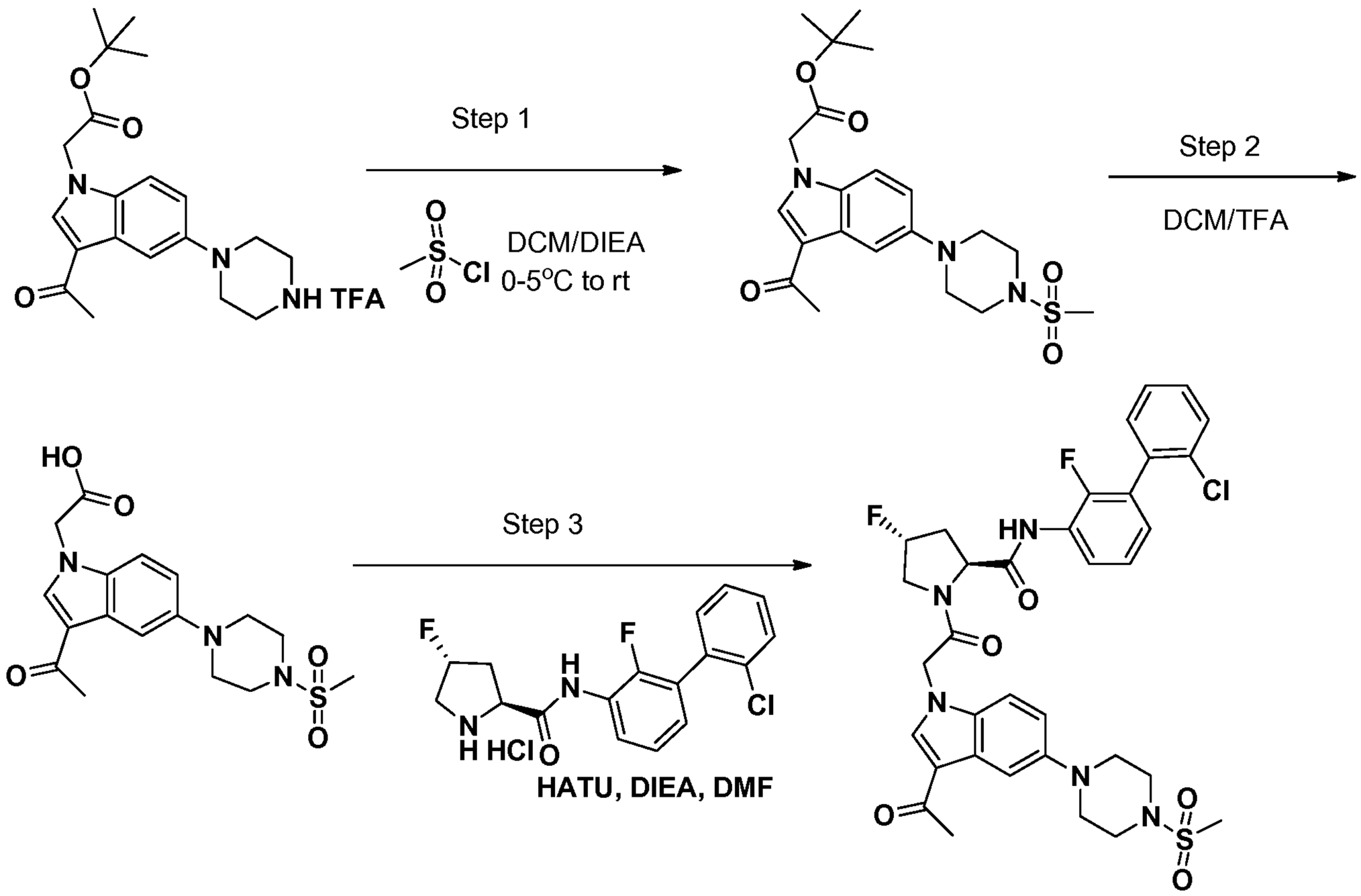
Step 6: 2-(3-Acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetic acid

[0400] *tert*-Butyl 2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetate from the previous step was dissolved in DCM (5 mL) and TFA (1 mL) was added. The reaction mixture was stirred overnight at rt. The solvent was then removed under reduced pressure and the remaining material was used directly in the next synthetic step.

Step 7: (2S,4R)-1-(2-(3-Acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide

[0401] To a solution of 2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetic acid from step 6 in DMF (5 mL) was added DIEA (0.13 mL, 3 equiv) followed by (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (108 mg, 1.1 equiv). HATU (120 mg, 1.2 equiv) was then added slowly and the reaction mixture was stirred for 18 h at rt. The reaction mixture was then added to water (10 mL) and extracted with EtOAc (2 × 15 mL). The separated organic layer was washed successively with an aqueous solution of $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography (eluted with DCM/CH_3OH) to give the title compound. ^1H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.18 (s, 3H), 2.24-2.41 (m, 1H), 2.50 (s, 3H), 2.64-2.78 (m, 1H), 3.08-3.19 (m, 4H), 3.69-3.80 (m, 4H), 3.91-4.09 (m, 1H), 4.16-4.27 (m, 1 H), 4.78 (t, J = 8 Hz, 1H), 5.16 (d, J = 17 Hz, 1H), 5.26 (d, J = 17 Hz, 1H), 5.45-5.61 (m, 1H), 7.04-7.08 (m, 1H), 7.18-7.25 (m, 1H), 7.38-7.47 (m, 4H), 7.51-7.56 (m, 1H), 7.86-7.90 (s, 1H), 7.93-7.98 (m, 1H), 8.12 (s, 1H),; ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -128.56, -178.51. LC (method A): t_R = 2.30 min. LC/MS (EI) m/z: $[M + H]^+$ 664.

Scheme 19: Synthesis of (2S,4R)-1-(2-(3-acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (33)



Step 1: tert-Butyl 2-(3-acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetate

[0402] The TFA salt of tert-butyl 2-(3-acetyl-5-(piperazin-1-yl)-1H-indol-1-yl)acetate (90 mg) was dissolved in DCM (4 mL). To this solution was added DIEA (0.14 mL) followed by methylsulfonyl chloride (0.06 mL) at 0–5 °C. After stirring 10 min, the reaction mixture was diluted with EtOAc (10 mL) and water (4 mL). The separated organic layer was washed with brine (15 mL), dried (Na_2SO_4), and evarporated to dryness under reduced pressure. The remaining material was used directly in the next step.

Step 2: 2-(3-Acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetic acid

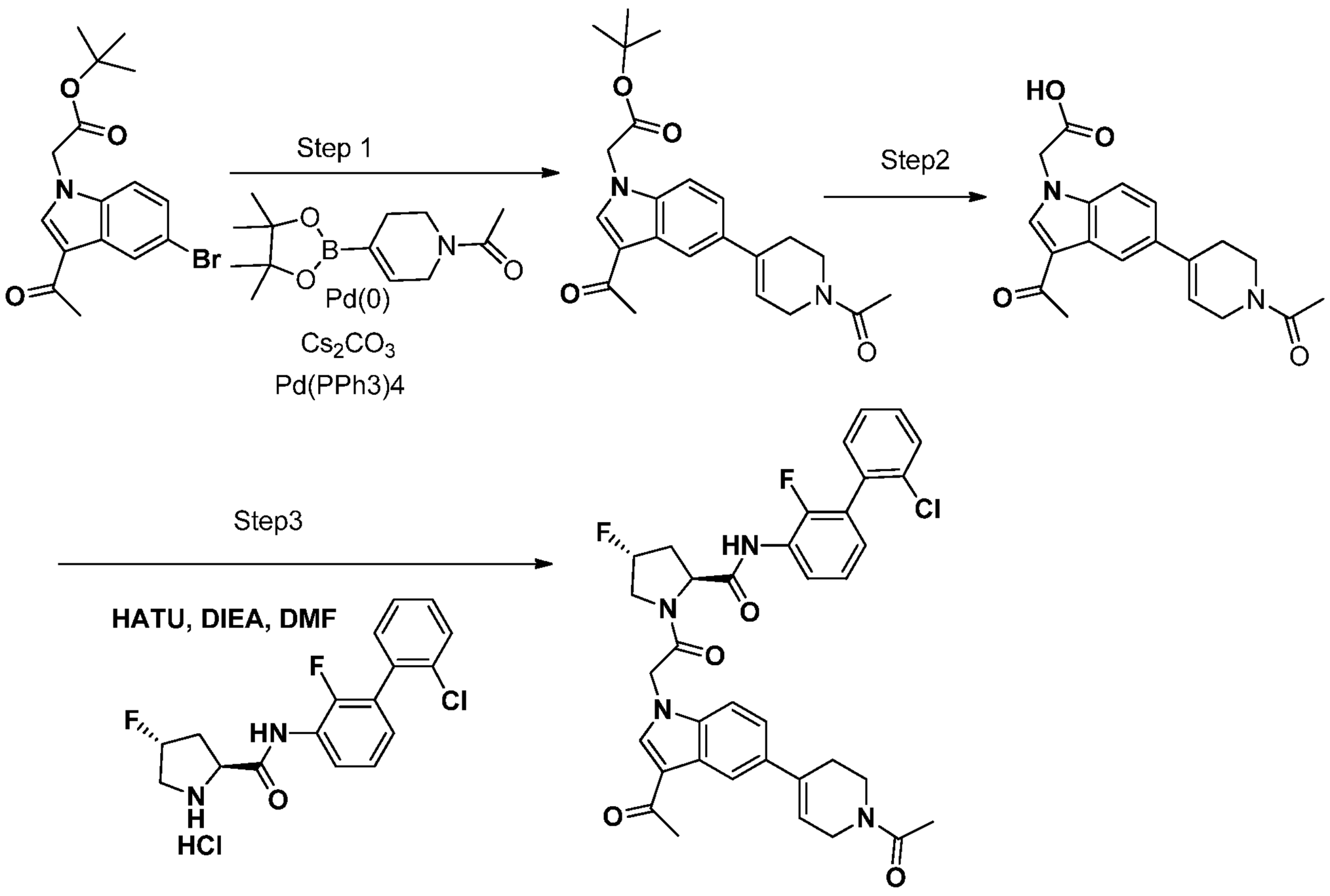
[0403] *tert*-Butyl 2-(3-acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetate was dissolved in DCM (5 mL) and TFA (1 mL) was added. The reaction mixture was stirred

overnight at rt and then the solvent was removed under reduced pressure. The remaining material was used directly in the next step.

Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide

[0404] To a solution of 2-(3-acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetic acid DMF (5 mL) was added DIEA (0.17 mL, 4 equiv) followed by (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (102 mg, 1.1 equiv). HATU (120 mg, 1.2 equiv) was then added slowly and the reaction mixture was stirred for 18 h at rt. The reaction mixture was then added to water (10 mL) and extracted with EtOAc (2 × 15 mL). The organic layer was washed successively with an aq solution of $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by HPLC to give the title compound. ^1H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.18 (s, 3H), 2.27-2.42 (m, 1H), 2.50 (s, 3H), 2.67-2.80 (m, 1H), 2.98 (s, 3H), 3.52 (m, 8H), 3.95-4.29 (m, 2H), 4.78 (t, J = 8 Hz, 1H), 5.21 (d, J = 18 Hz, 1H), 5.35 (d, J = 18 Hz, 1H), 5.42-5.63 (m, 1H), 7.04-7.08 (m, 1H), 7.14-7.20 (m, 1H), 7.22-7.29 (m, 1H), 7.30-7.42 (m, 3H), 7.43-7.51 (m, 3H), 7.93-7.96 (m, 1H), 8.15 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -128.49, -178.41. LC (method A): t_R = 2.09 min. LC/MS (EI) m/z: $[M + H]^+$ 698.

Scheme 20: Synthesis of (2S,4R)-1-(2-(3-acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide (28)



Step 1: tert-Butyl 2-(3-acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetate

[0405] A mixture of *tert*-butyl 2-(3-acetyl-5-bromo-1*H*-indol-1-yl)acetate (113 mg, 0.32 mmol), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridin-1(2H)-yl)ethanone (80 mg. 0.32 mmol), cesium carbonate (209 mg, 0.64 mmol), and DMF (10 mL) was purged with argon in a pressure vessel for 5 min. Tetrakis(triphenylphosphine)palladium (0) (18 mg, 0.016 mmol) was then added under argon and the pressure vessel was sealed and heated at 90 °C overnight. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The remaining crude product was used directly in the next synthetic step.

Step 2: 2-(3-Acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetic acid

[0406] tert-Butyl 2-(3-acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetate was taken in 4 N HCl in dioxane (10 mL) and the resulting reaction mixture was stirred at rt for 4 h The solvent was then removed under reduced pressure and the remaining material was used directly in the next synthetic step.

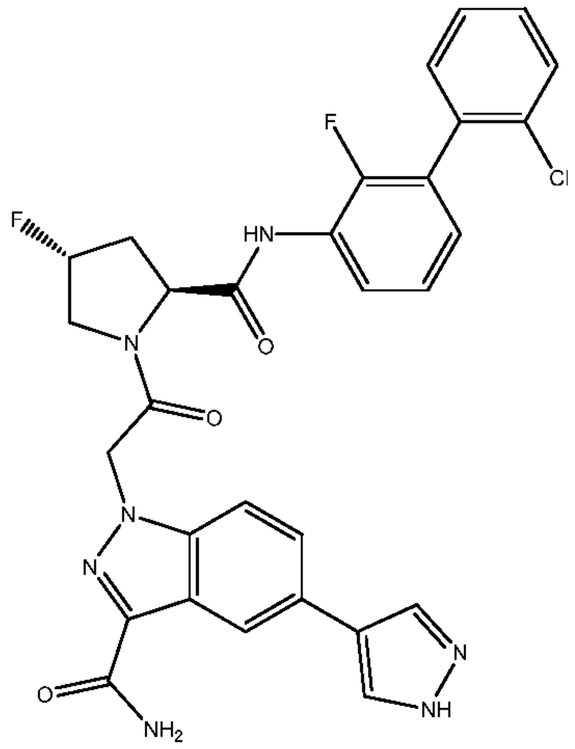
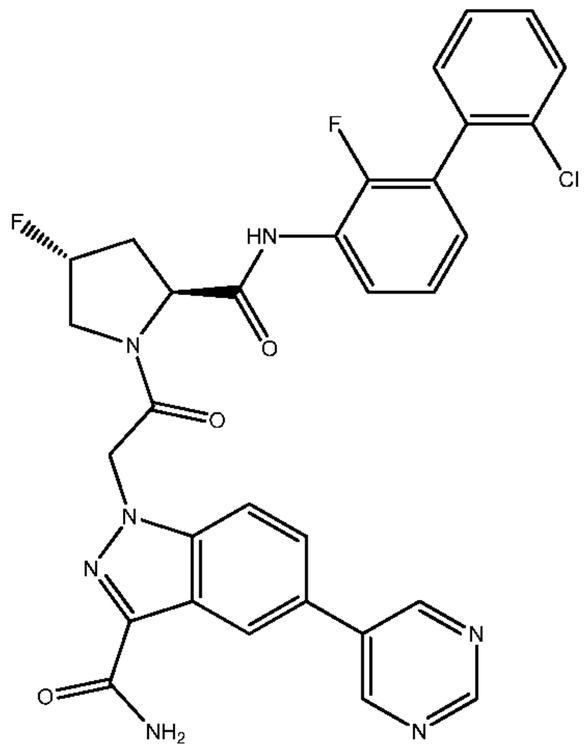
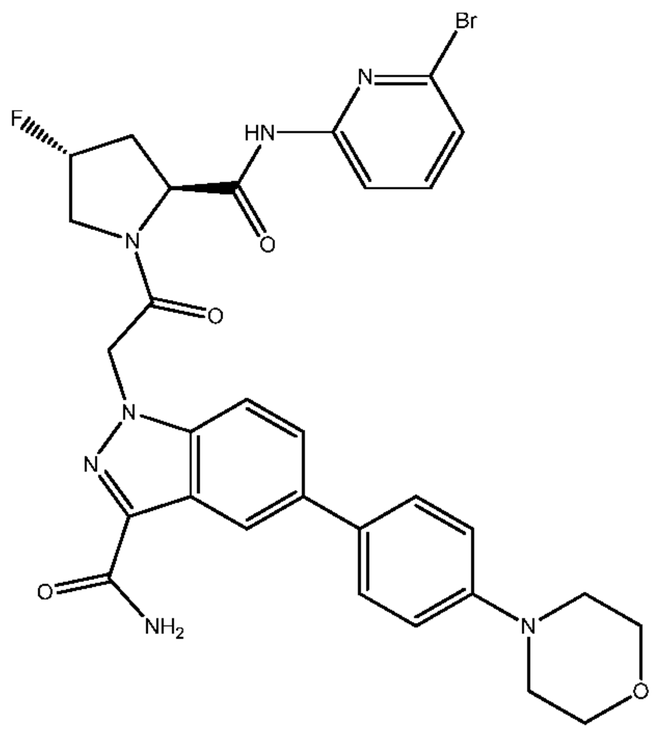
Step 3: (2S,4R)-1-(2-(3-Acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide

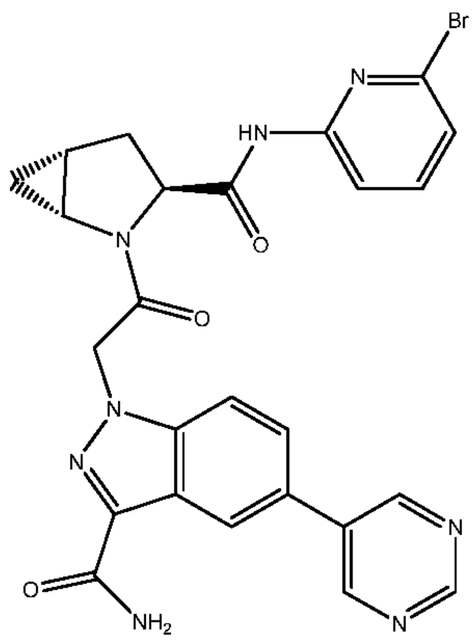
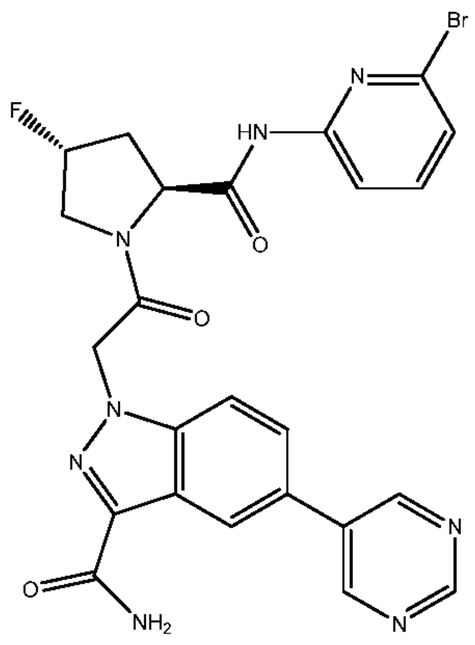
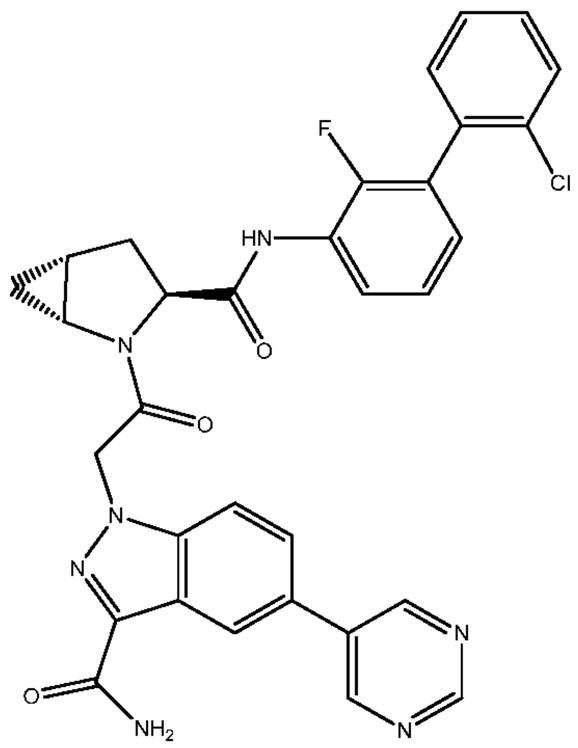
[0407] The title compound was prepared from 2-(3-acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetic acid (100 mg, 0.29 mmol) and (2S,4R)-N-(3-chloro-(2S,4R)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (110 mg, 0.29 mmol) in a manner similar to that described above for (2S,4R)-1-(2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): (major rotamer) δ 2.05-2.07 (s, 3H), δ 2.31-2.38 (m, 1H), 2.50 (s, 3H), 2.50-2.70 (m, 3H), 3.73-3.79 (m, 2H), 4.01-4.31 (m, 4H), 4.85 (t, J = 8.4 Hz, 1H), 5.28-5.50 (m, 2H), 5.64 (d, J = 52.8 Hz, 1H), 6.18 (s, 1H), 7.16 (t, J = 6.8 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H),7.41-7.68 (m, 6H), 8.04 (t, J = 7.6 Hz, 1H), 8.30 (d, J = 8 Hz, 1H), 8.35 (s, 1H), 10.05 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6, 300 K): (major rotamer) δ -126.64, -175.81. LC (method A): t_R = 2.07 min. LC/MS (EI) m/z: $[M + H]^+$ 659.

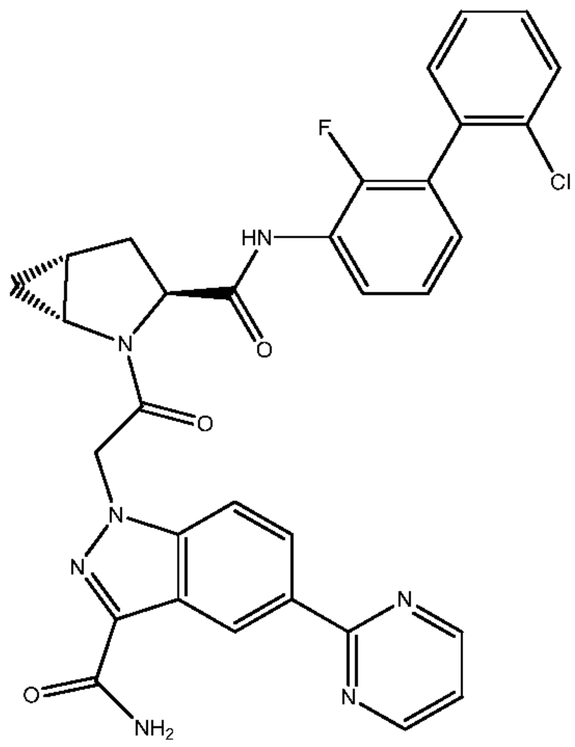
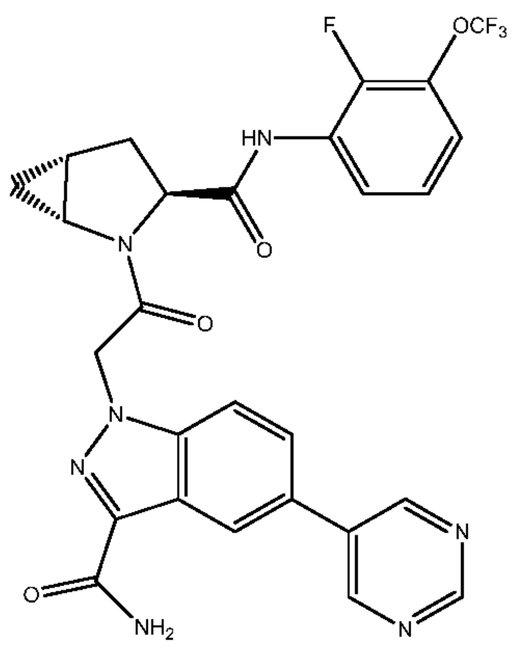
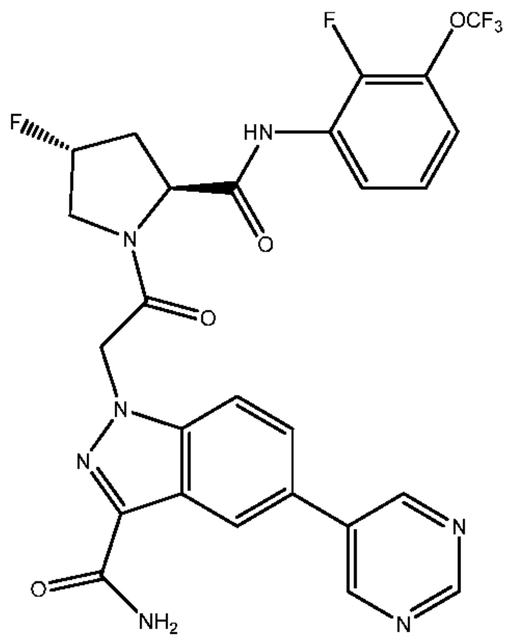
EXAMPLE 6. NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I

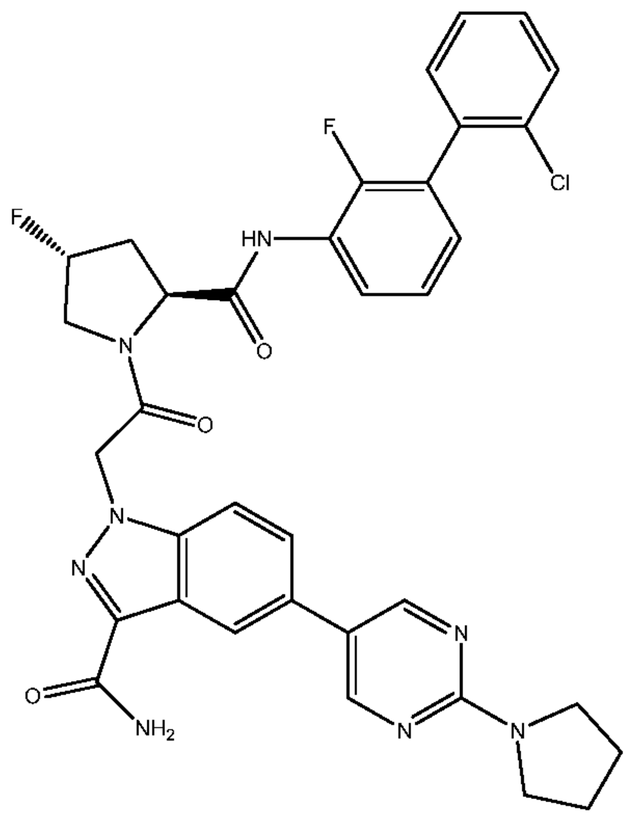
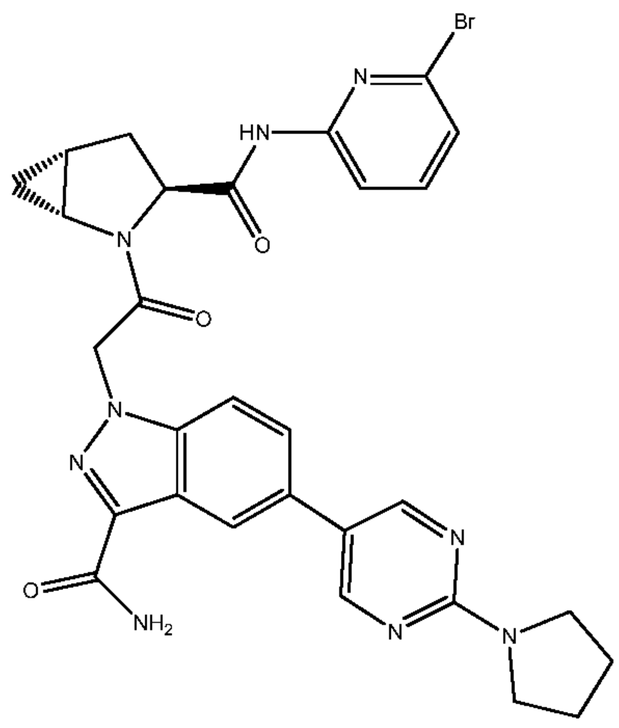
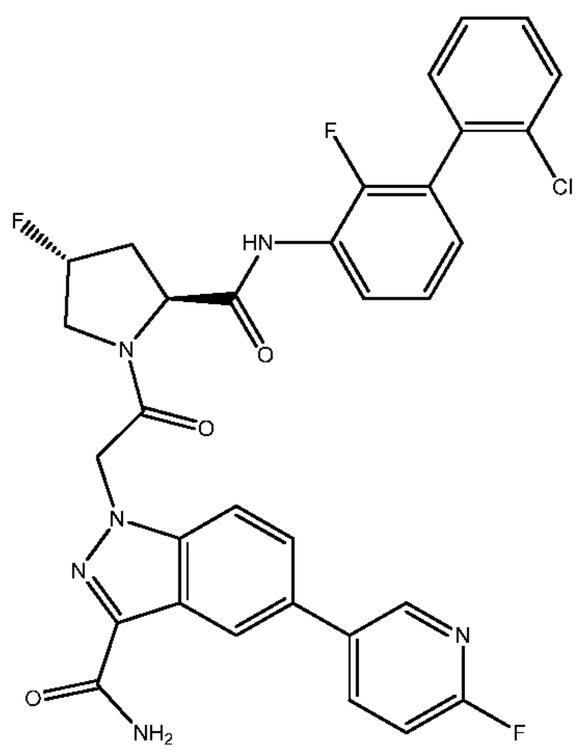
[0408] Table 1 shows illustrative compounds of Formula I with characaterizing data. The assay of Example 7 was used to determine the IC_{50}'s of the compounds. Other standard factor D inhibition assays are also available. Three ***s are used to denote compounds with an IC_{50} less than 1 micromolar; two **s indicate compound with an IC_{50} between 1 micromolar and 10 micromolar, and one * denotes compounds with an IC_{50} greater than 10 micromolar.

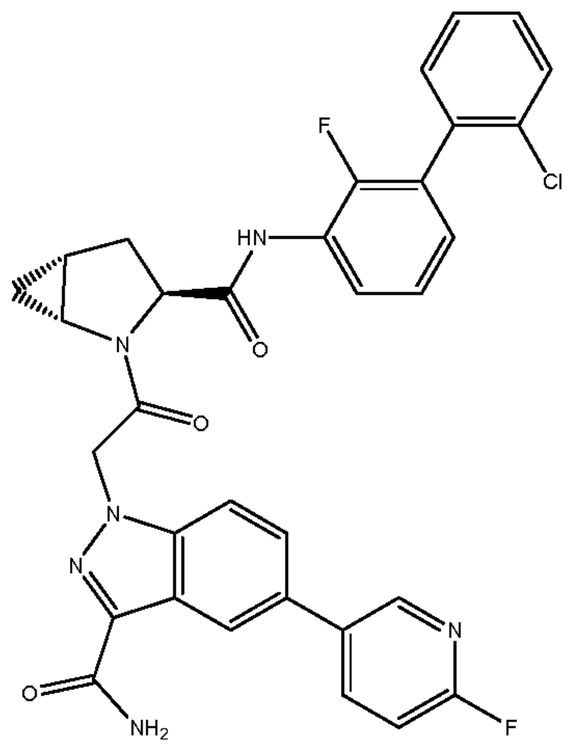
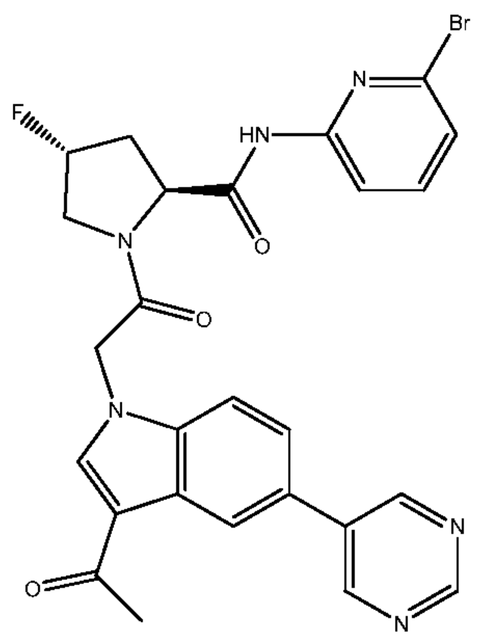
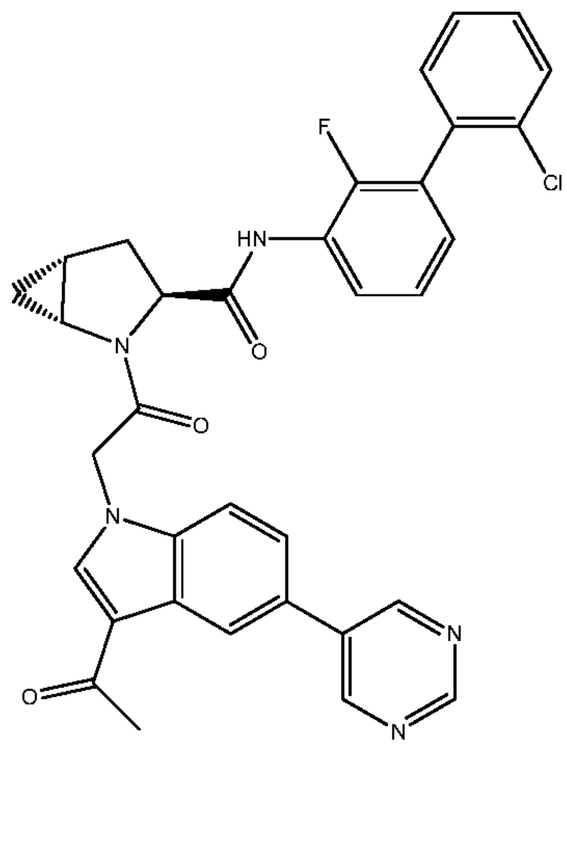
TABLE 1

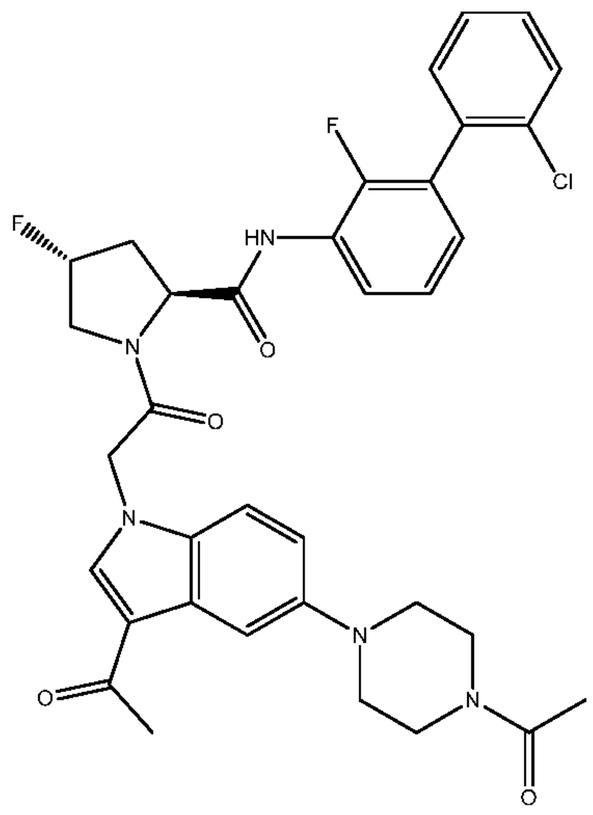
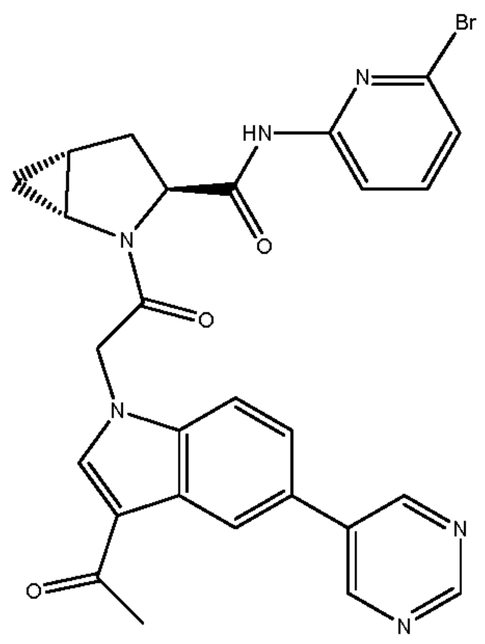
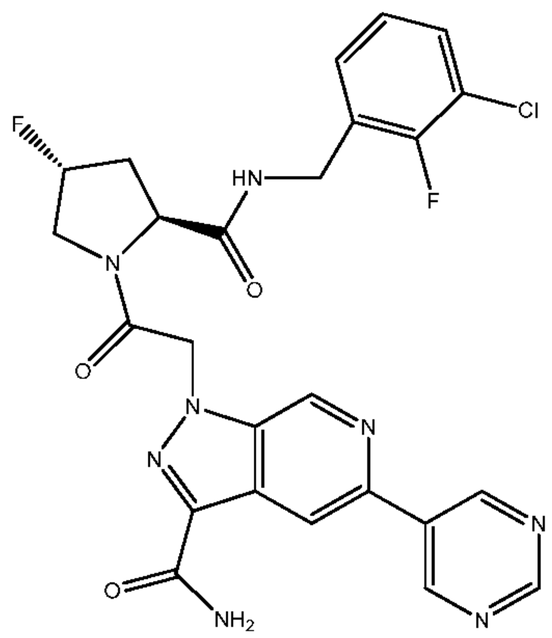
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
1		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(1H-pyrazol-4-yl)-1H-indazole-3-carboxamide	***	1.79 (A)	604
2		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.82 (A)	616
3		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(4-morpholinophenyl)-1H-indazole-3-carboxamide	***	1.82 (A)	650

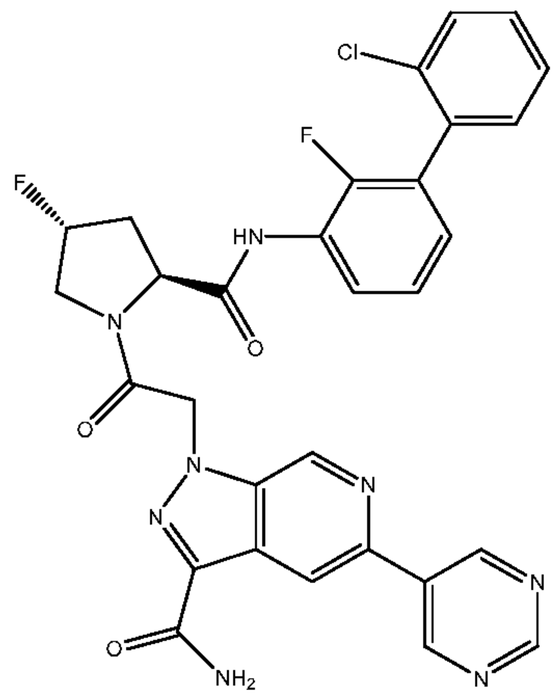
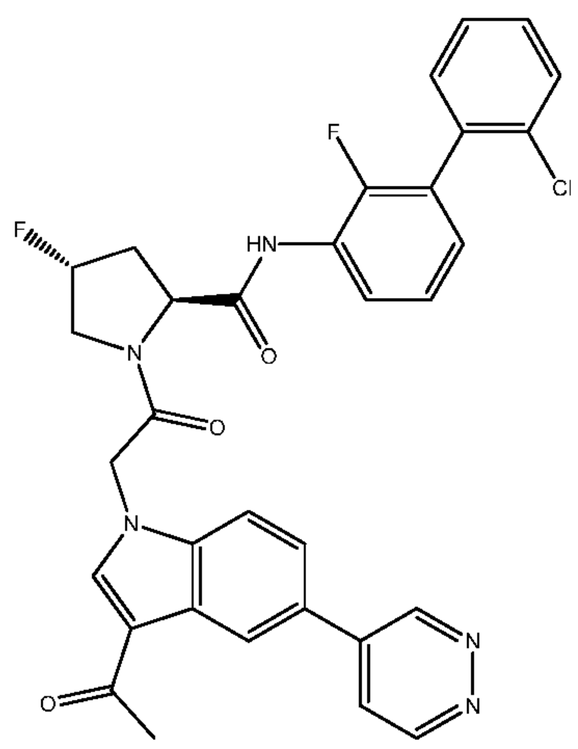
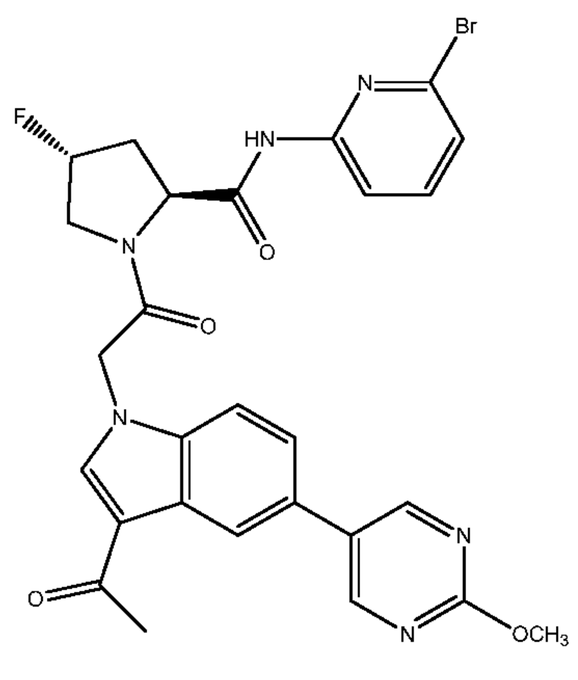
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
4		1-(2-((1R,3S,5R)-3-(6-bromopyridin-2-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.42 (A)	561
5		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.30 (A)	567
6		1-(2-((1R,3S,5R)-3-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.96 (A)	610

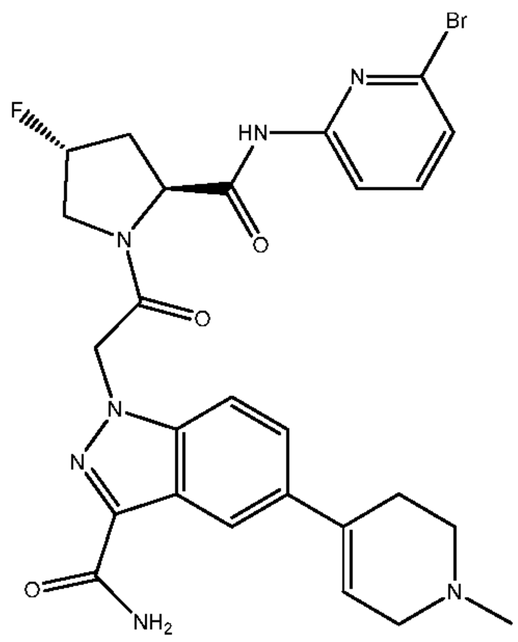
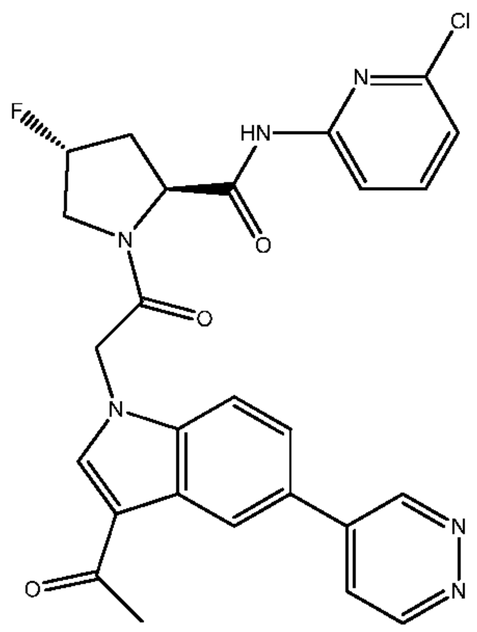
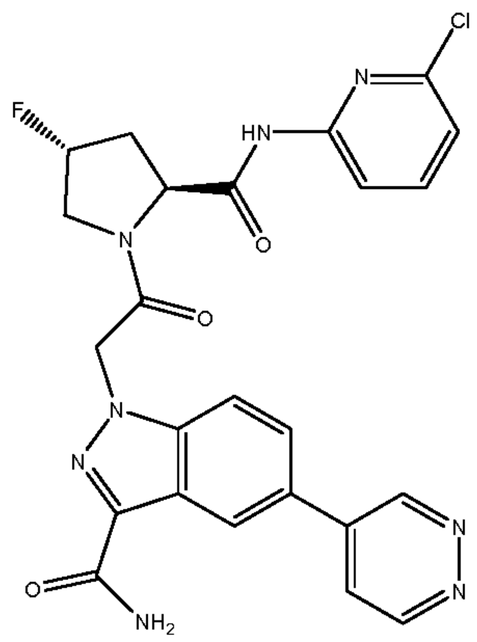
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
7		1-(2-((1R,3S,5R)-3-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(pyrimidin-2-yl)-1H-indazole-3-carboxamide	***	2.15 (A)	610
8		1-(2-((1R,3S,5R)-3-(2-fluoro-3-(trifluoromethoxy)phenylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.74 (A)	584
9		1-(2-((2S,4R)-4-fluoro-2-(2-fluoro-3-(trifluoromethoxy)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.64 (A)	590

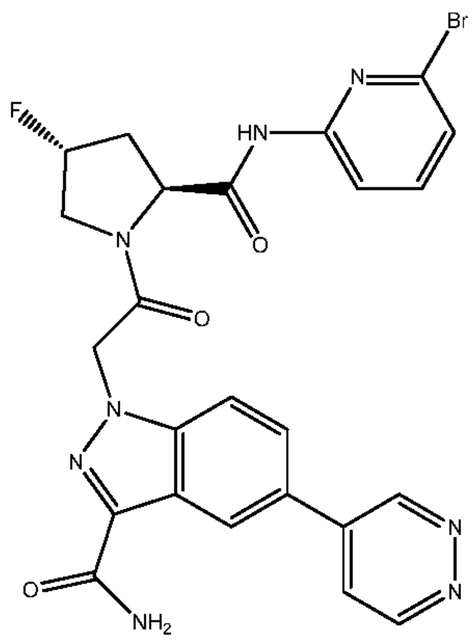
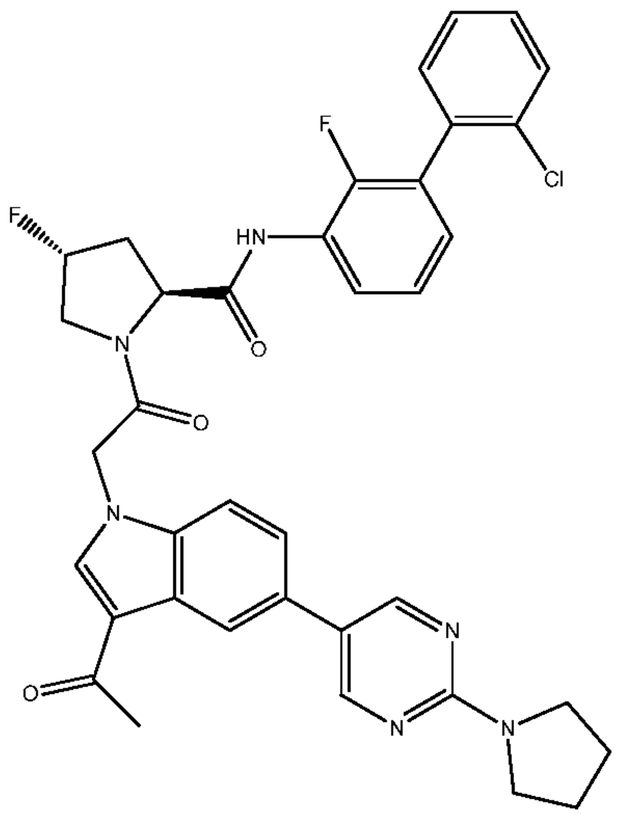
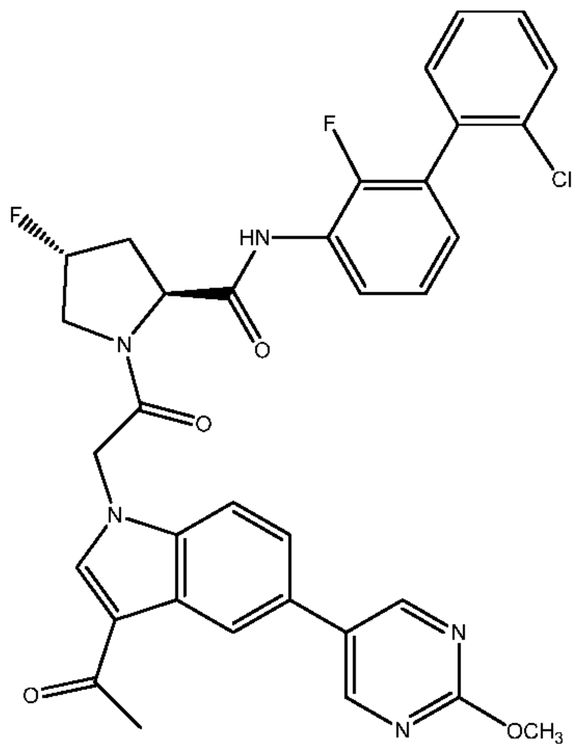
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
10		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	2.33 (A)	685
11		1-(2-((1R,3S,5R)-3-(6-bromopyridin-2-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.82 (A)	630
12		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(6-fluoropyridin-3-yl)-1H-indazole-3-carboxamide	***	2.43 (A)	633

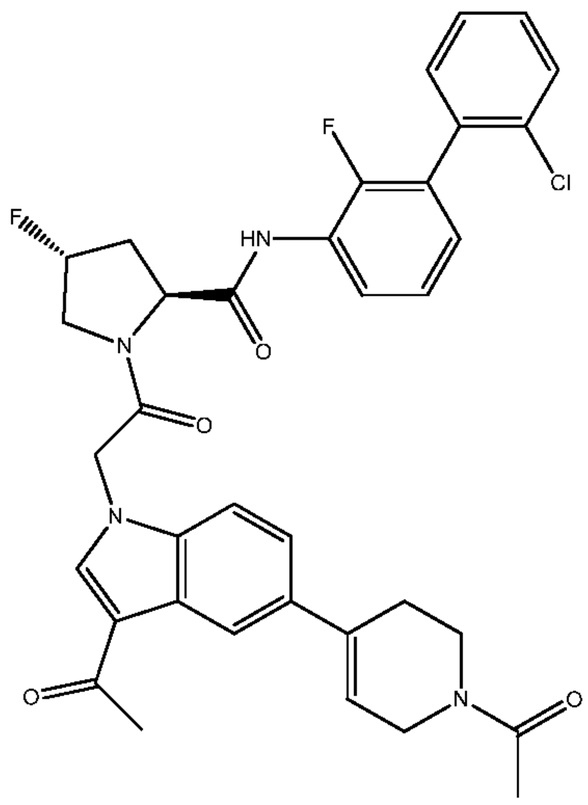
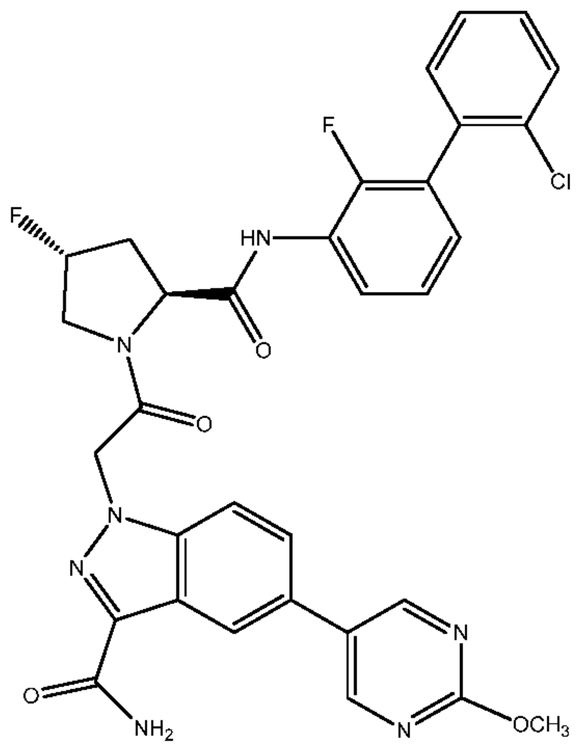
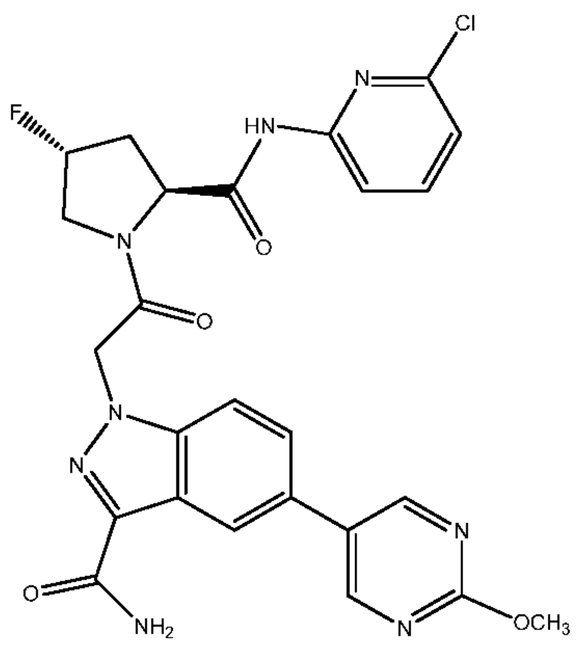
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
13		1-(2-((1R,3S,5R)-3-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-2-azabicyclo[3.1.0]hexan-2-yl)-2-oxoethyl)-5-(6-fluoropyridin-3-yl)-1H-indazole-3-carboxamide	***	2.53 (A)	627
14		(2S,4R)-1-(2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.04 (A)	565
15		(1R,3S,5R)-2-(2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	2.63 (A)	608

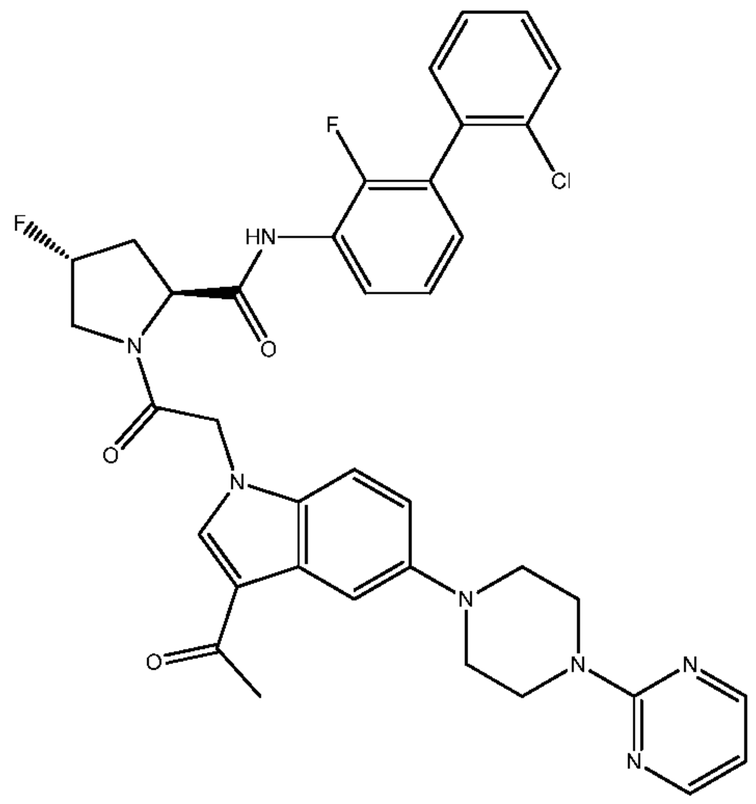
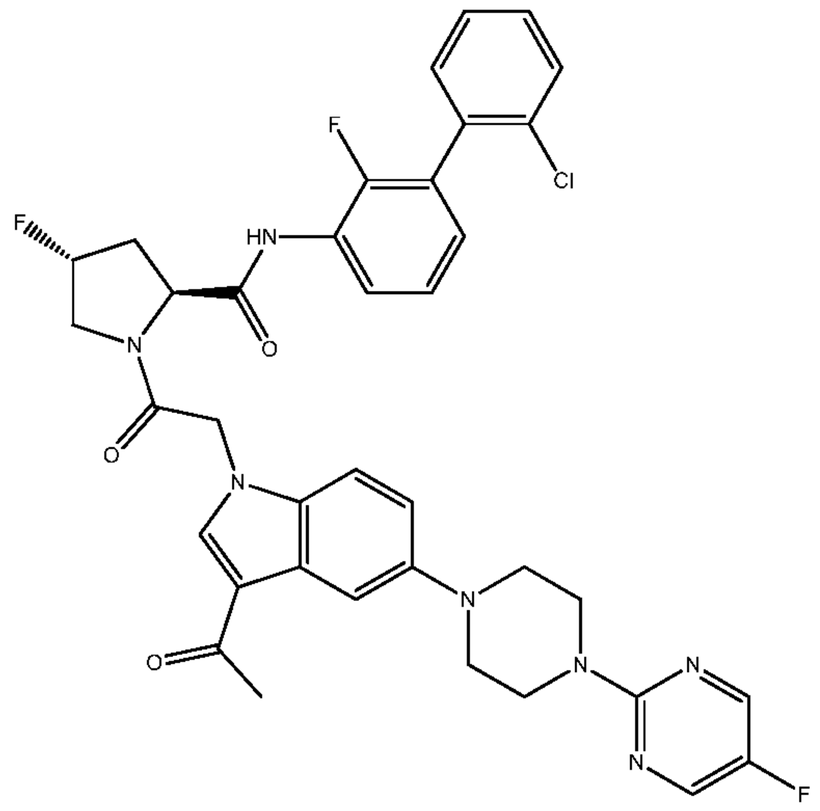
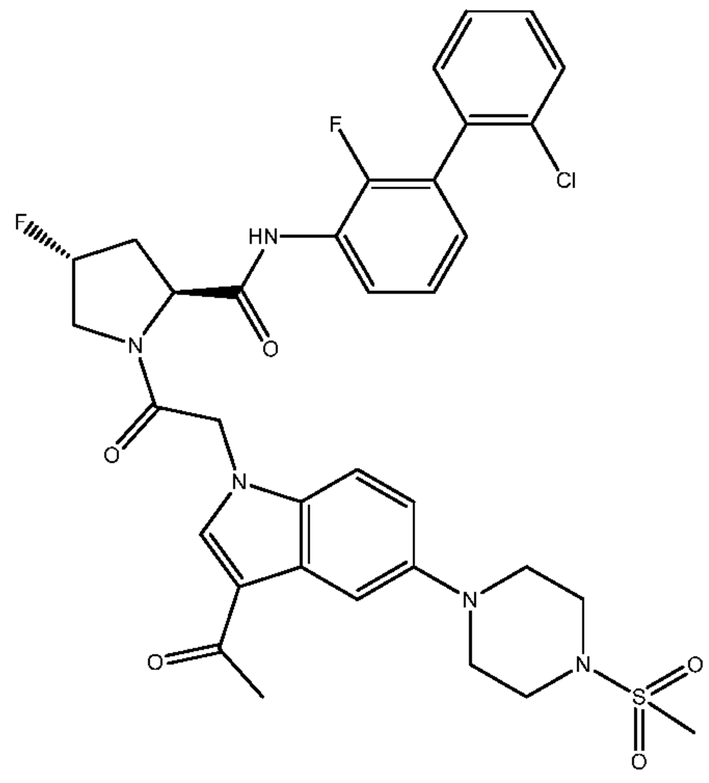
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
16		(2S,4R)-1-(2-(3-acetyl-5-(4-acetylpiperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.30 (A)	664
17		(1R,3S,5R)-2-(2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	2.44 (A)	559
18		1-(2-((2S,4R)-2-(3-chloro-2-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	***	1.75 (A)	555

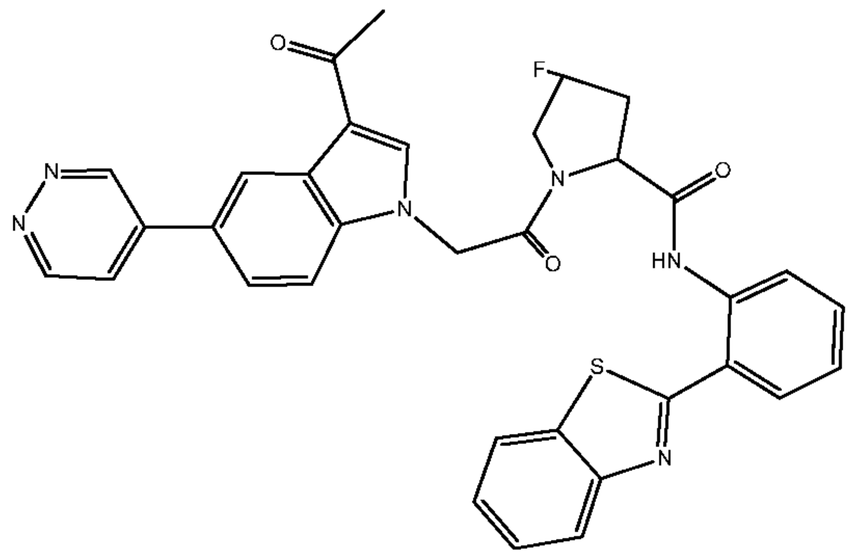
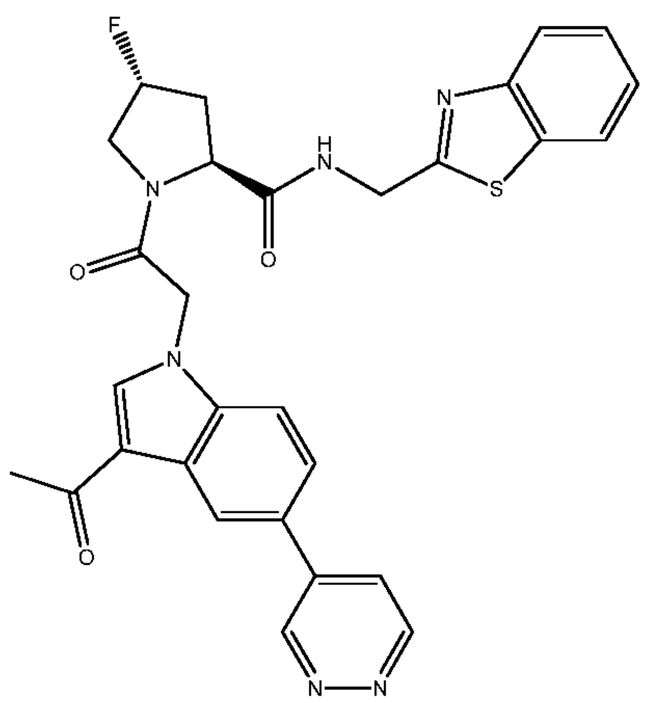
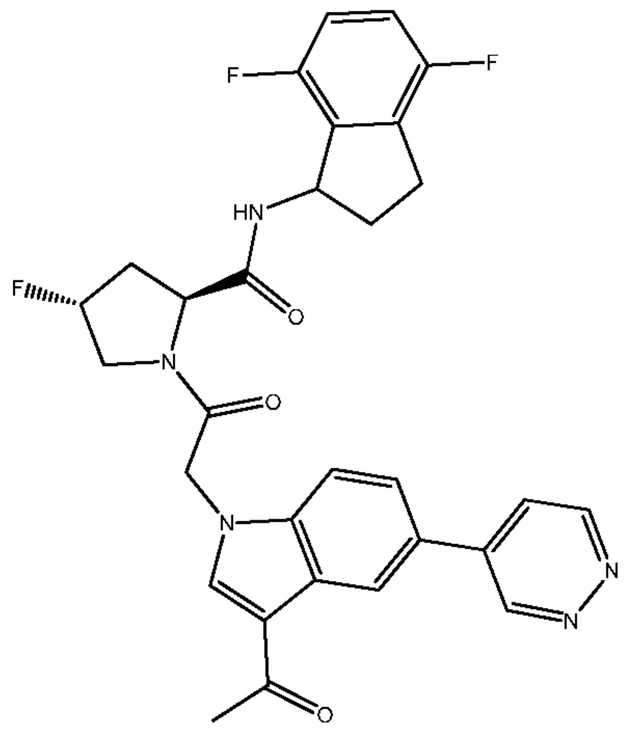
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
19		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-pyrazolo[3,4-c]pyridine-3-carboxamide	***	2.47 (A)	617
20		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.58 (A)	614
21		(2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.05 (A)	595

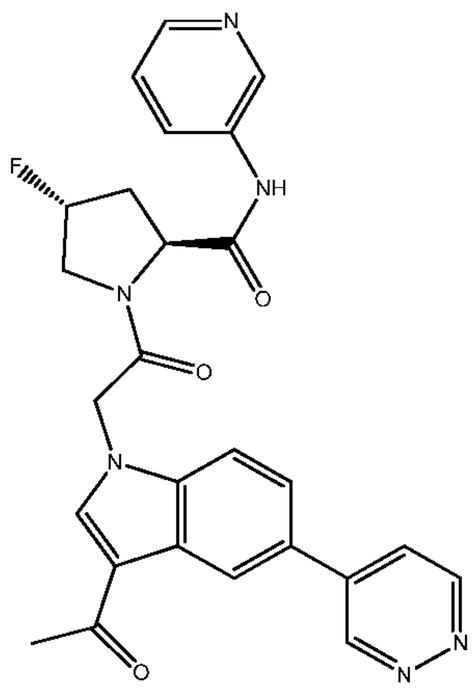
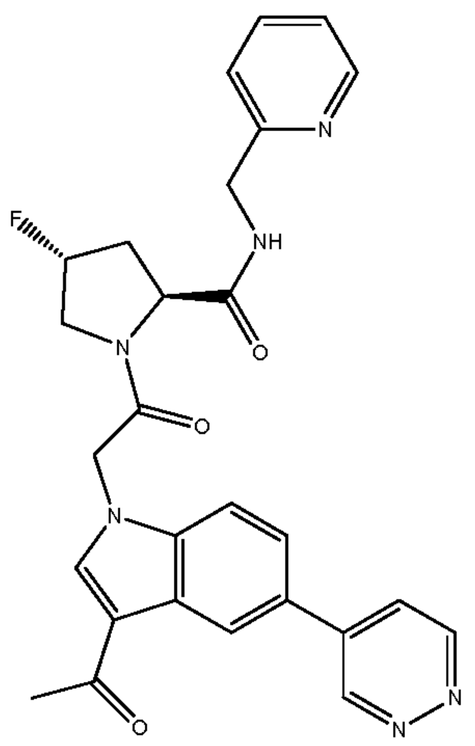
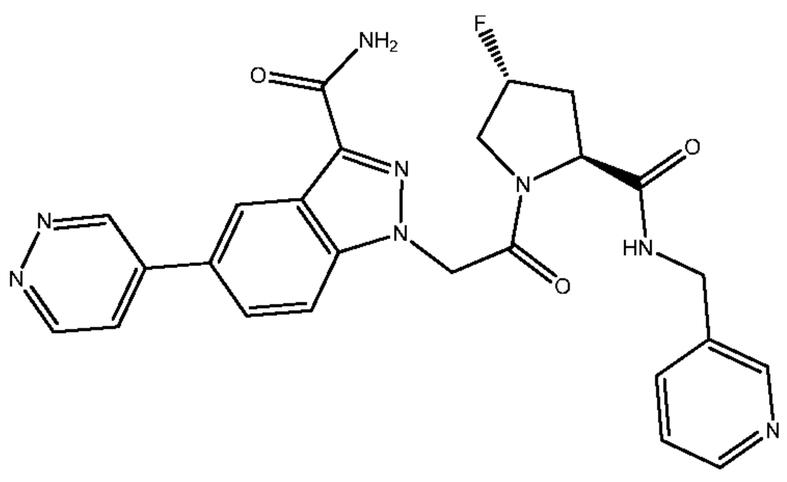
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
22		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indazole-3-carboxamide	***	1.19 (A)	586
23		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.24 (A)	520
24		1-(2-((2S,4R)-2-(6-chloropyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.23 (A)	522

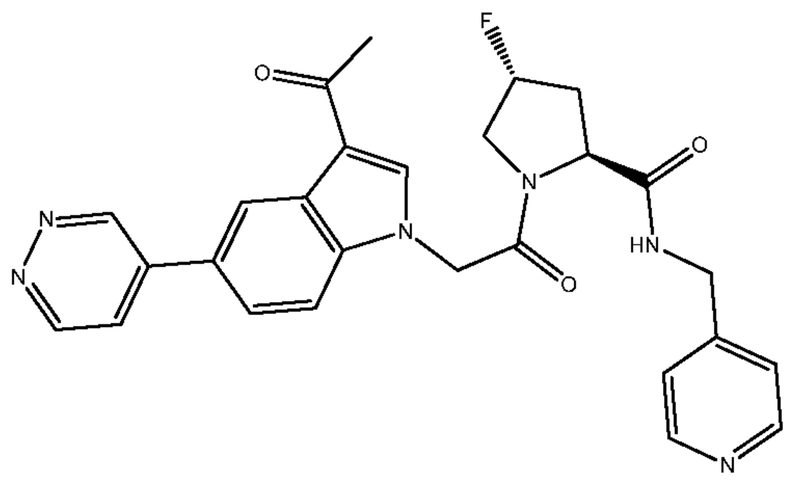
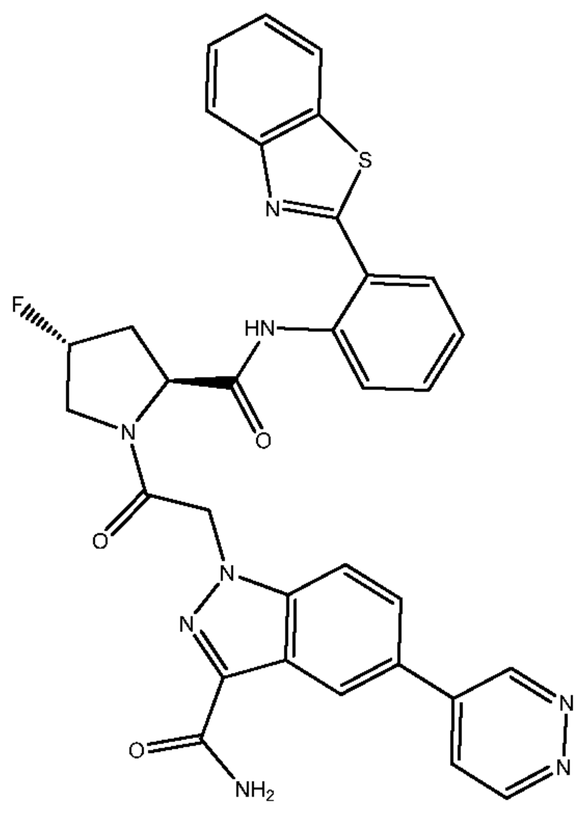
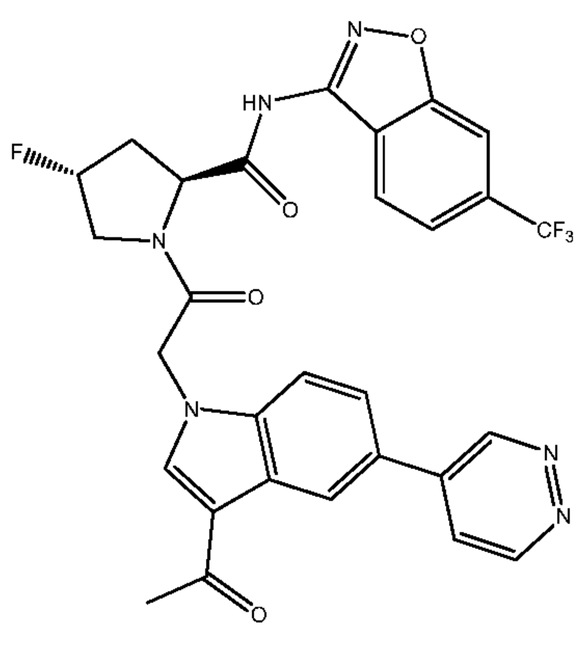
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
25		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	1.60 (A)	567
26		(2S,4R)-1-(2-(3-acetyl-5-(2-(pyrrolidin-1-yl)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.42 (A)	683
27		(2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.16 (A)	644

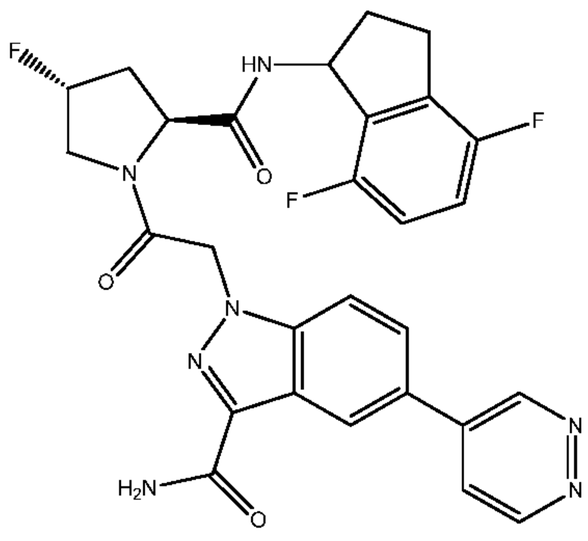
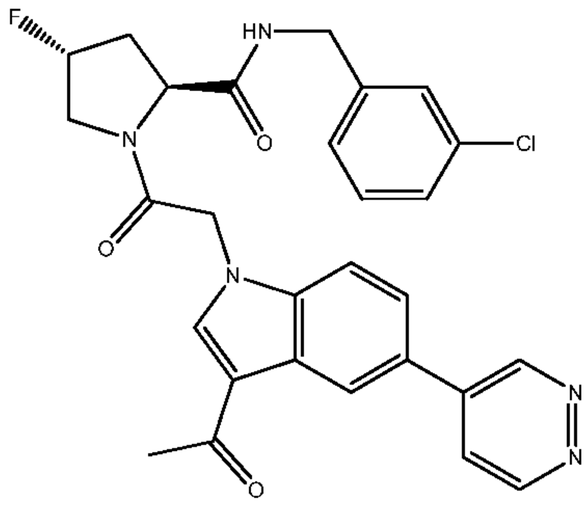
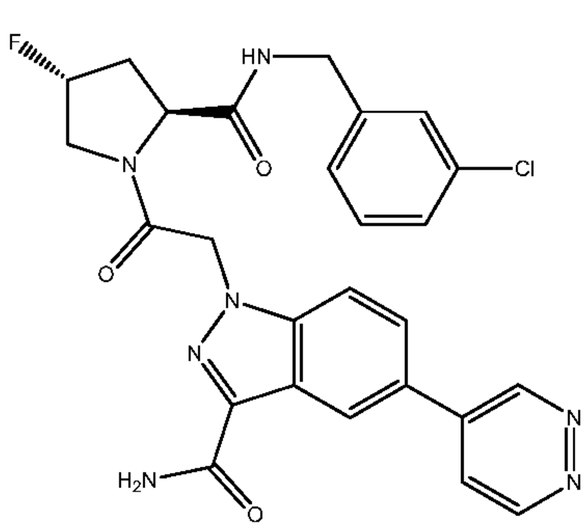
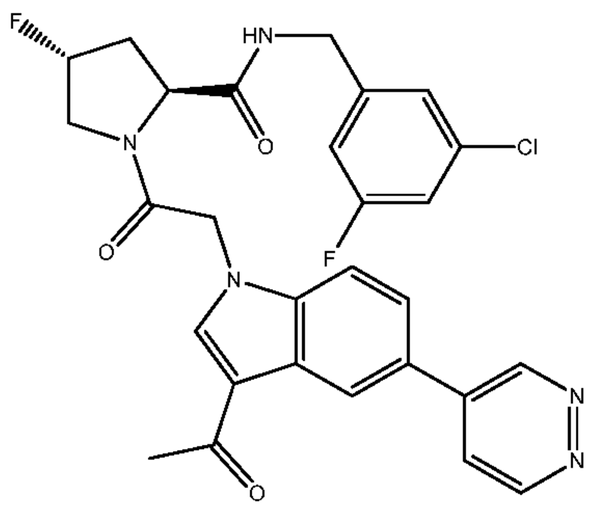
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
28		(2S,4R)-1-(2-(3-acetyl-5-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.07 (A)	659
29		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methoxypyrimidin-5-yl)-1H-indazole-3-carboxamide	***	2.01 (A)	646
30		1-(2-((2S,4R)-2-(6-chloropyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methoxypyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.43 (A)	553

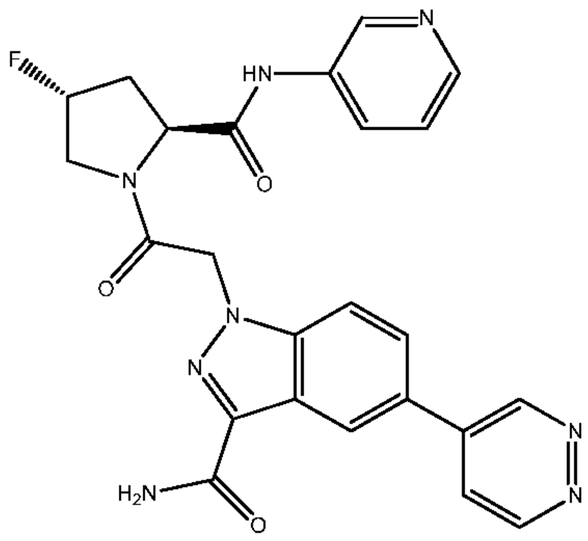
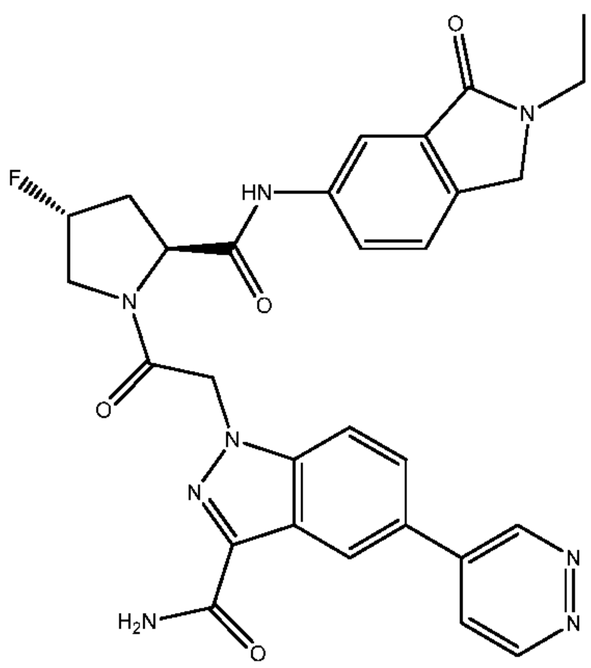
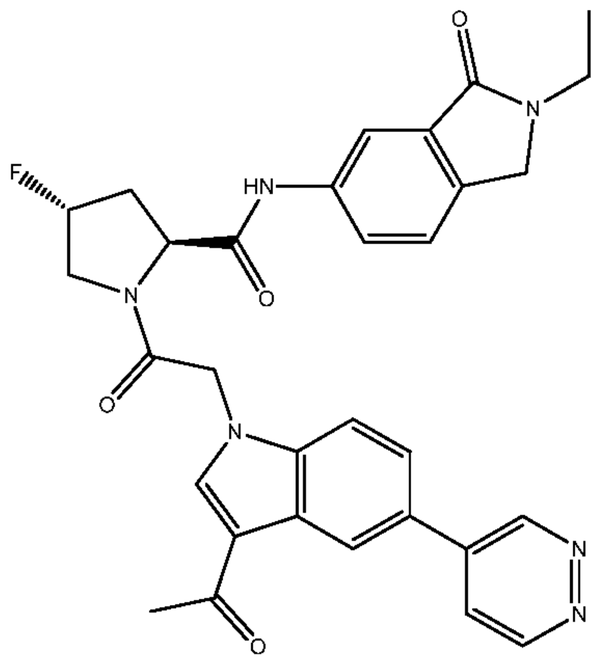
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
31		(2S,4R)-1-(2-(3-acetyl-5-(4-(pyrimidin-2-yl)piperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.21 (A)	698
32		(2S,4R)-1-(2-(3-acetyl-5-(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.43 (A)	716
33		(2S,4R)-1-(2-(3-acetyl-5-(4-(methylsulfonyl)piperazin-1-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.09 (A)	698

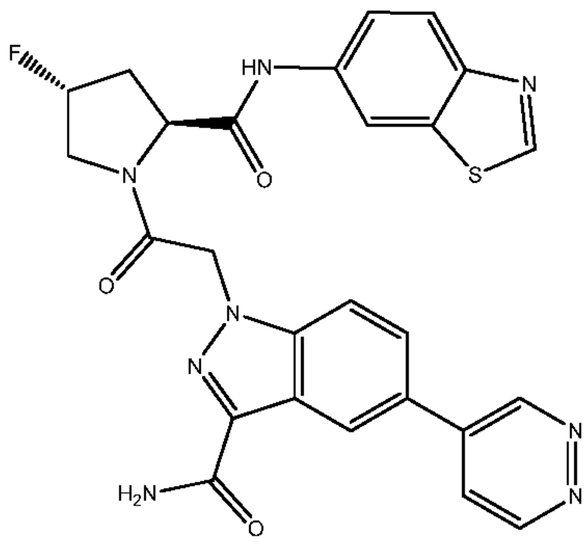
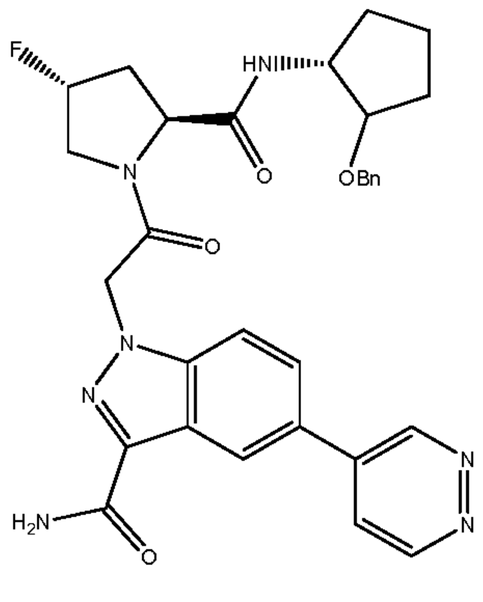
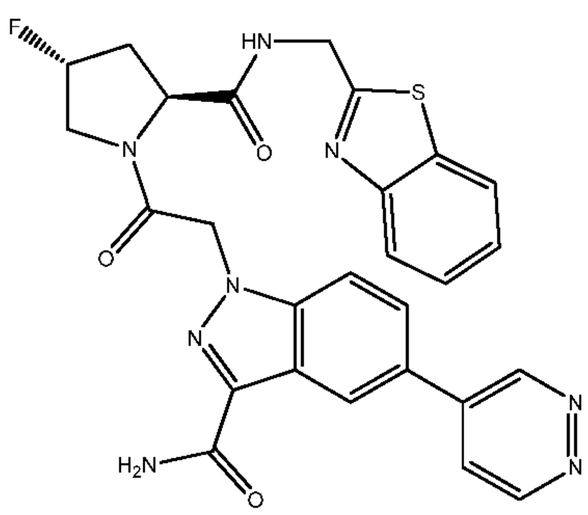
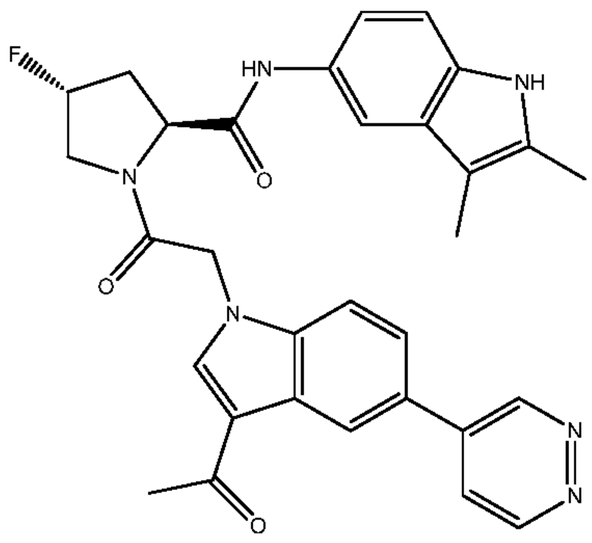
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
34		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2-(benzo[d]thiazol-2-yl)phenyl)-4-fluoropyrrolidine-2-carboxamide	*	3.91 (B)	619
35		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(benzo[d]thiazol-2-ylmethyl)-4-fluoropyrrolidine-2-carboxamide	**	2.33 (B)	557
36		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(4,7-difluoro-2,3-dihydro-1H-inden-1-yl)-4-fluoropyrrolidine-2-carboxamide	**	2.89 (B)	562

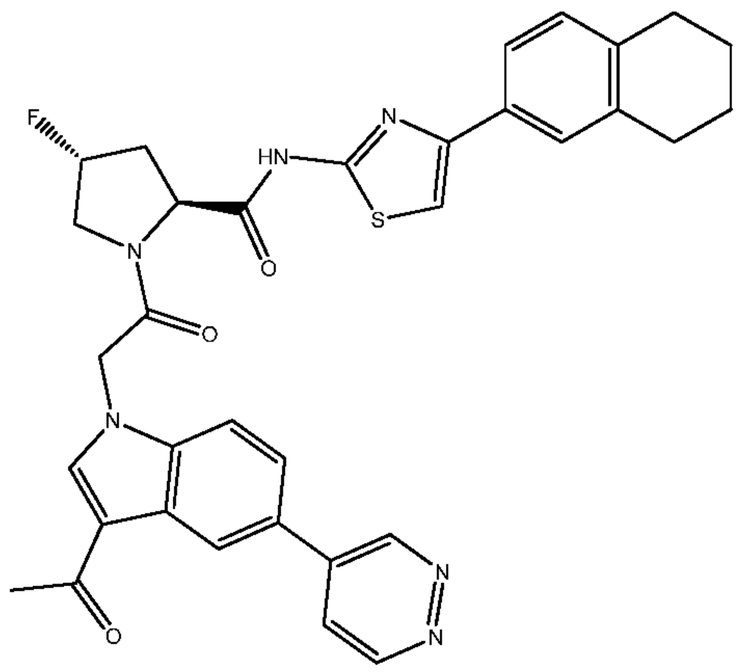
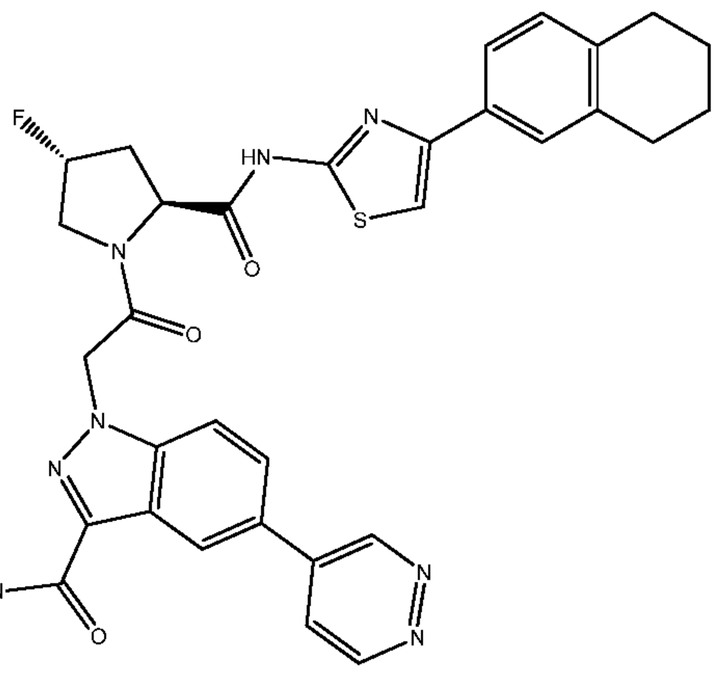
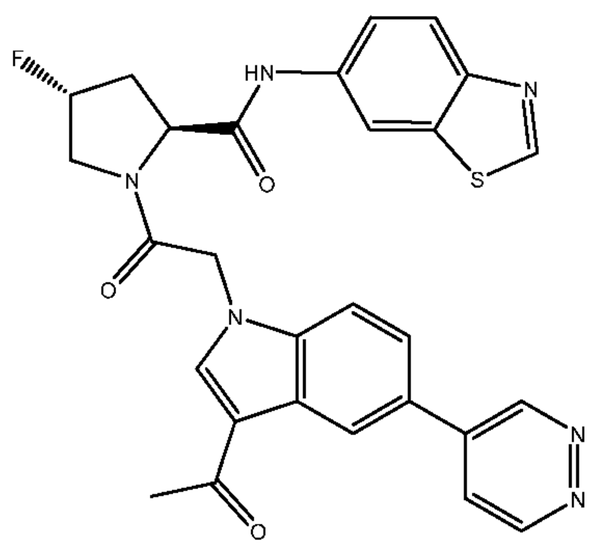
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
37		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(pyridin-3-yl)pyrrolidine-2-carboxamide	**	2.08 (B)	487
38		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(pyridin-2-ylmethyl)pyrrolidine-2-carboxamide	***	2.03 (B)	501
39		1-(2-((2S,4R)-4-fluoro-2-(pyridin-3-ylmethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.77 (B)	503

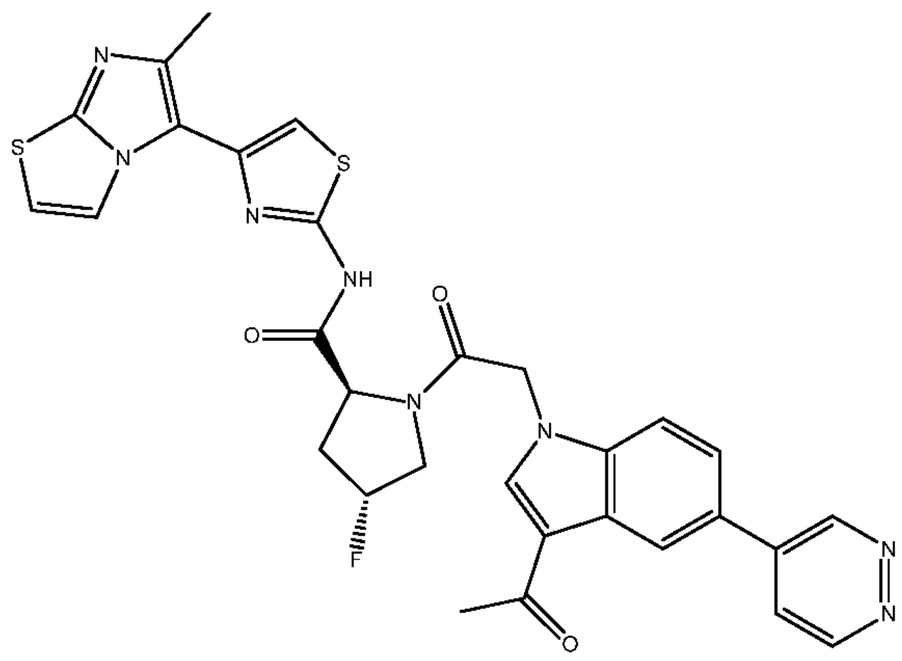
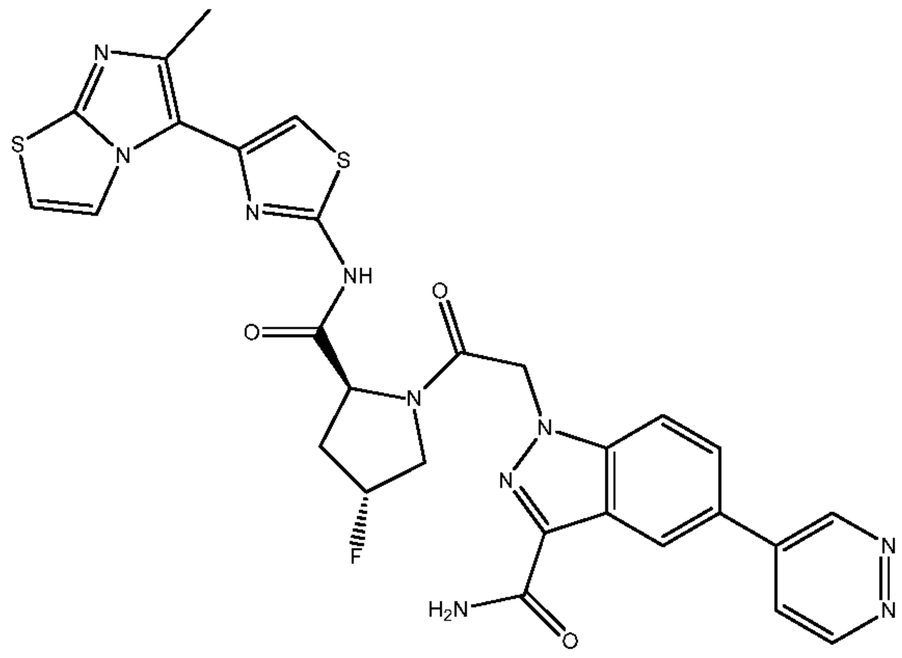
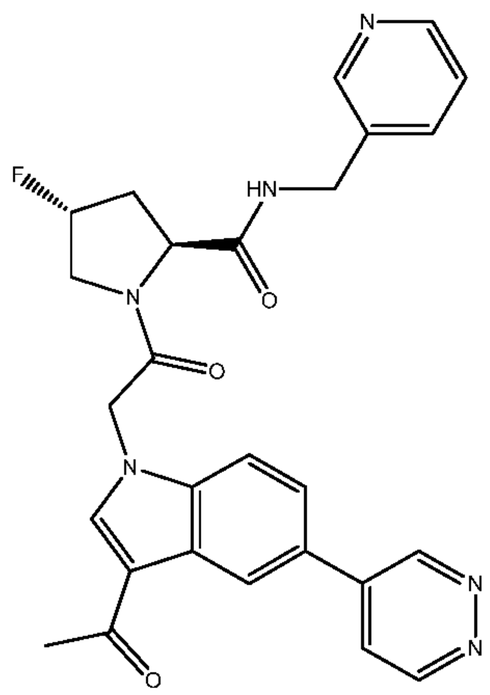
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
40		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(pyridin-4-ylmethyl)pyrrolidine-2-carboxamide	**	0.58 (B)	501
41		1-(2-((2S,4R)-2-(2-(benzo[d]thiazol-2-yl)phenylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.49 (B)	621
42		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(6-(trifluoromethyl)benzo[d]isoxazol-3-yl)pyrrolidine-2-carboxamide	*	3.24 (B)	595

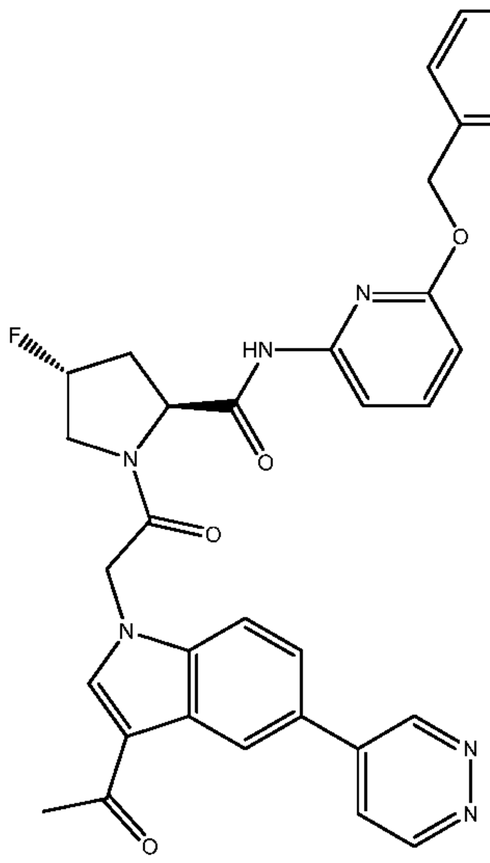
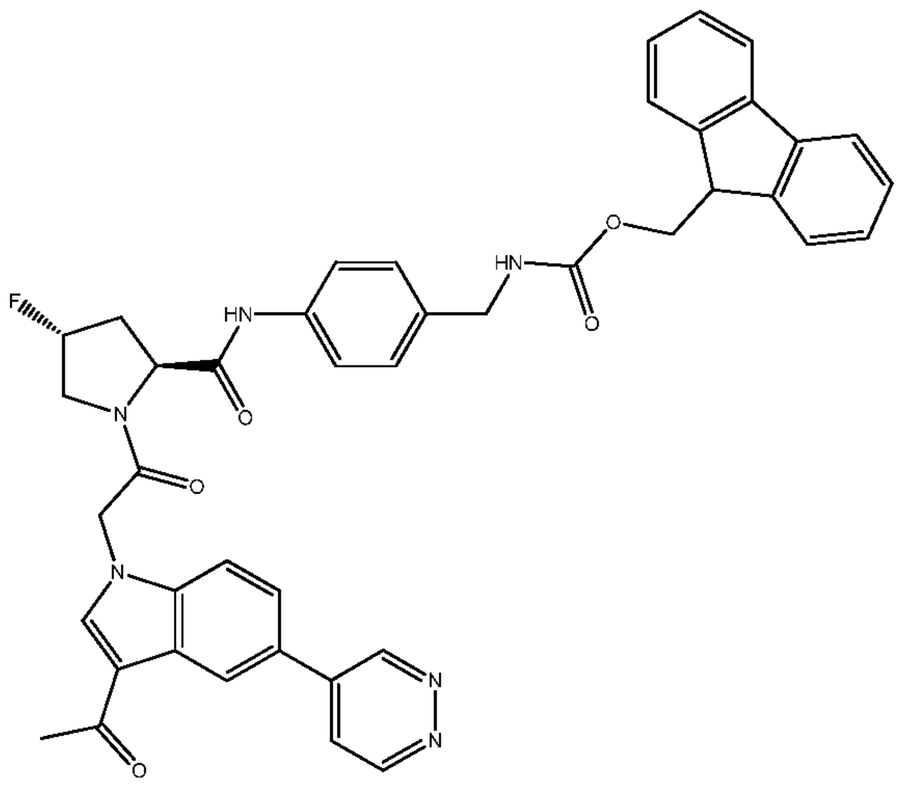
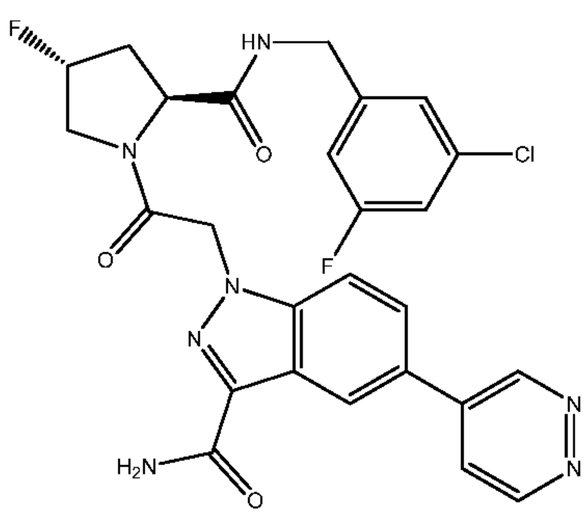
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
43		1-(2-((2S,4R)-2-(4,7-difluoro-2,3-dihydro-1H-inden-1-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.69 (B)	564
44		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-chlorobenzyl)-4-fluoropyrrolidine-2-carboxamide	***	2.78 (B)	534
45		1-(2-((2S,4R)-2-(3-chlorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.48 (B)	536
46		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-5-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide	***	2.98 (B)	552

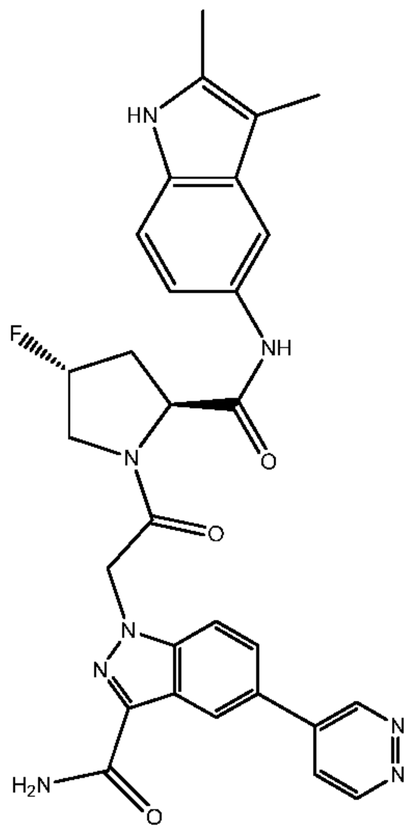
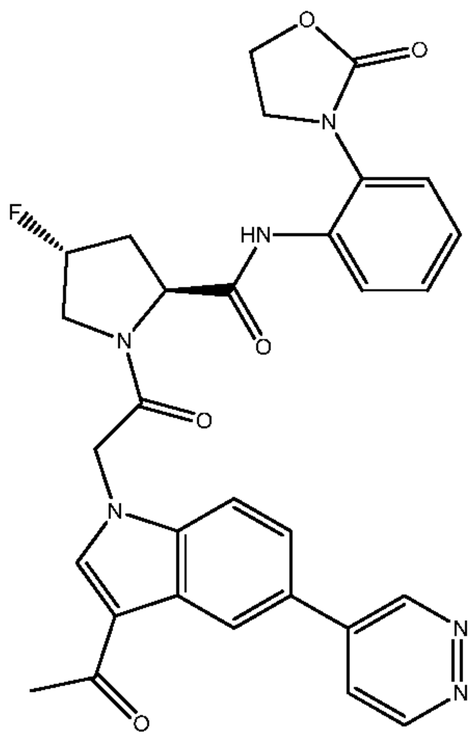
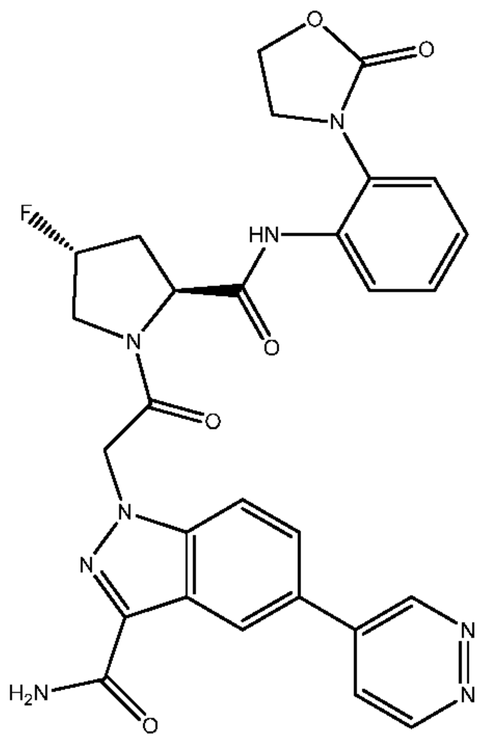
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
47		1-(2-((2S,4R)-4-fluoro-2-(pyridin-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.34 (B)	489
48		1-(2-((2S,4R)-2-(2-ethyl-3-oxoisoindolin-5-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.97 (B)	571
49		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2-ethyl-3-oxoisoindolin-5-yl)-4-fluoropyrrolidine-2-carboxamide	**	2.49 (B)	569

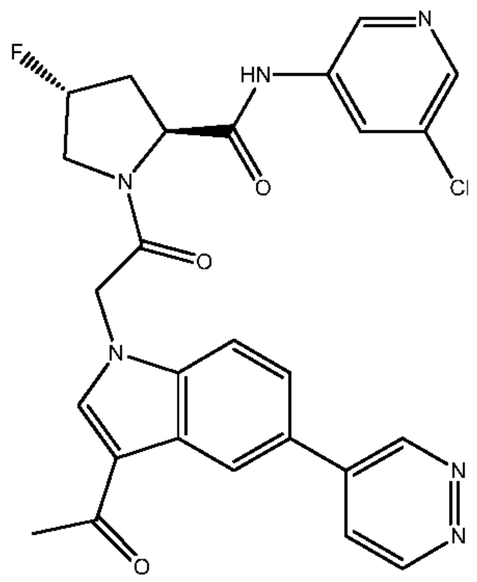
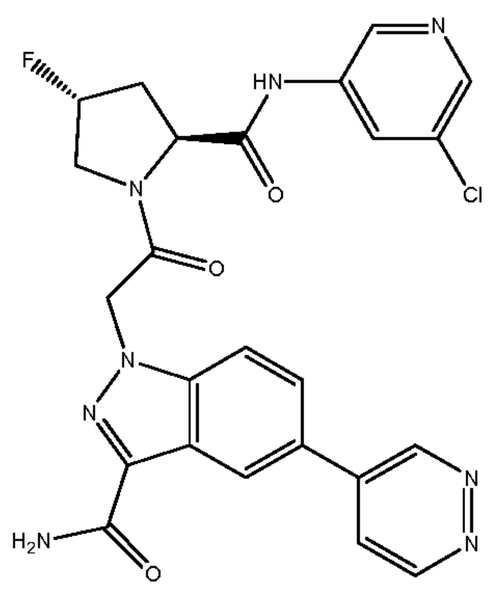
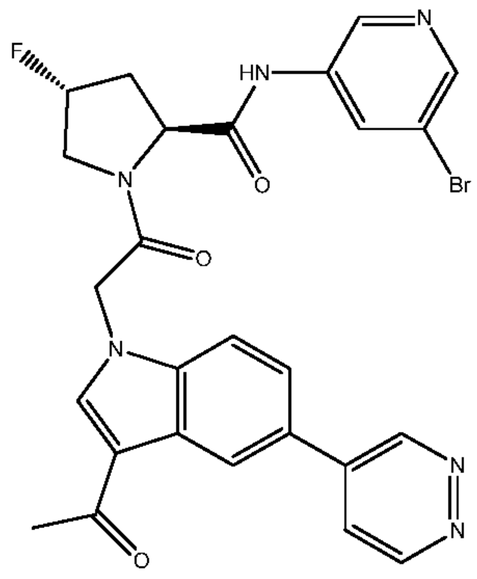
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
50		1-(2-((2S,4R)-2-(benzo[d]thiazol-6-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.03 (B)	545
51		1-(2-((2S,4R)-2-((1R,2S)-2-(benzyloxy)cyclopentyl carbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.81 (B)	586
52		1-(2-((2S,4R)-2-(benzo[d]thiazol-2-ylmethylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.15 (B)	559
53		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2,3-dimethyl-1H-indol-5-yl)-4-fluoropyrrolidine-2-carboxamide	**	2.91 (B)	553

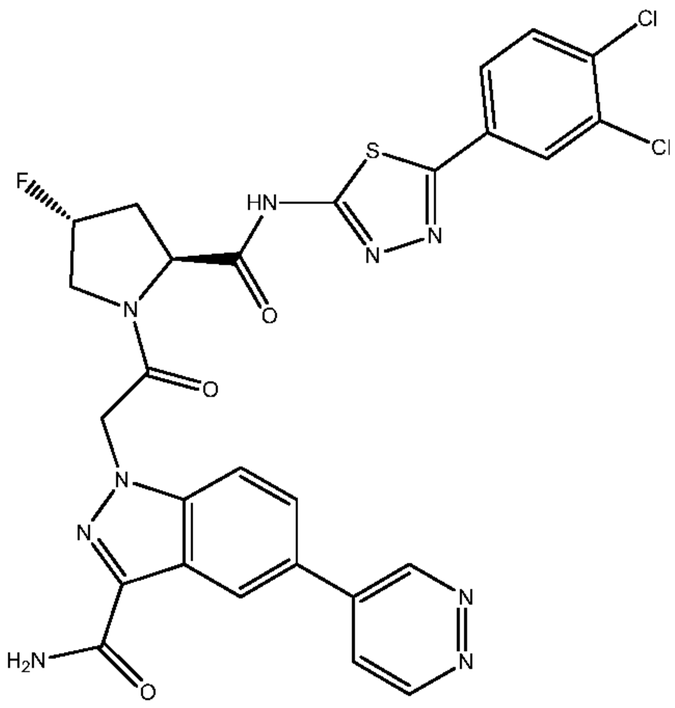
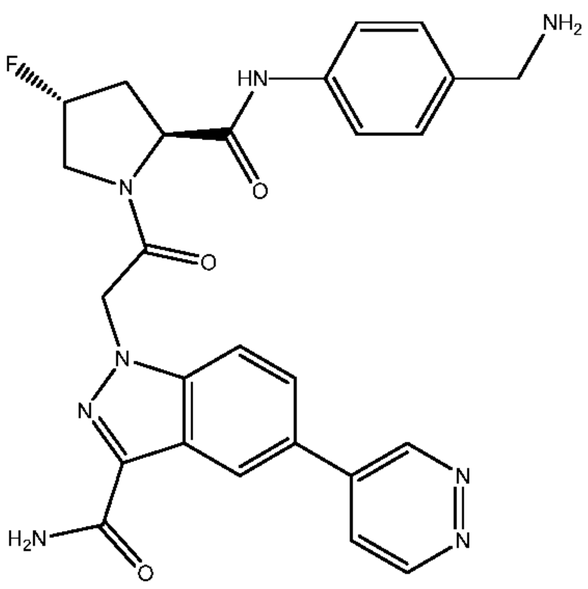
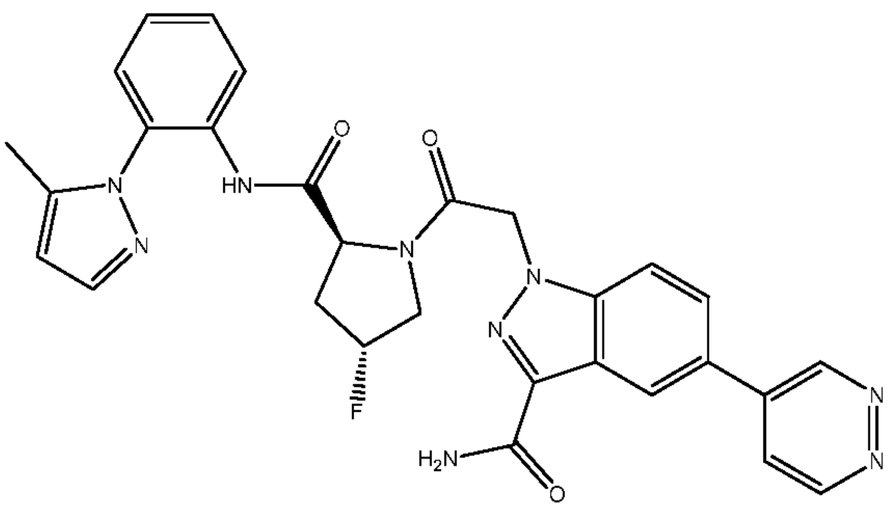
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
54		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)pyrrolidine-2-carboxamide	*	4.15 (B)	623
55		1-(2-((2S,4R)-4-fluoro-2-(4-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.88 (B)	625
56		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(benzo[d]thiazol-6-yl)-4-fluoropyrrolidine-2-carboxamide	**	2.41 (B)	543

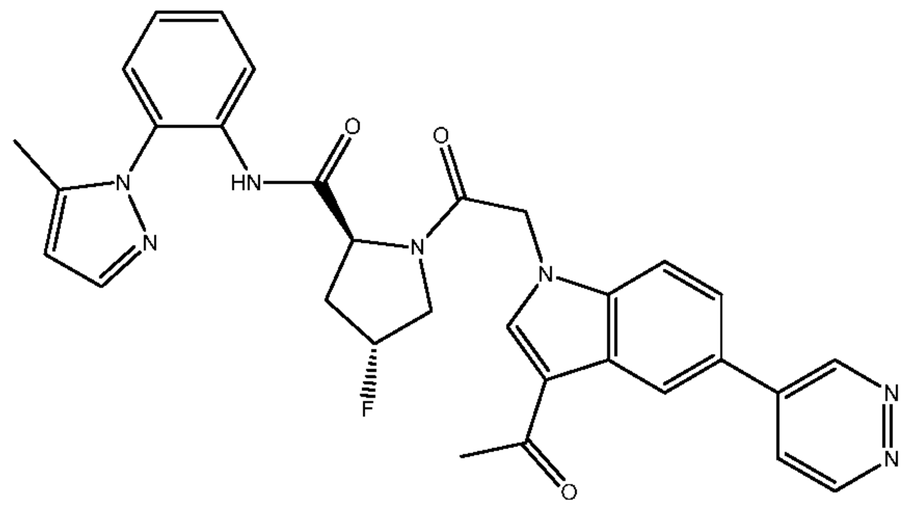
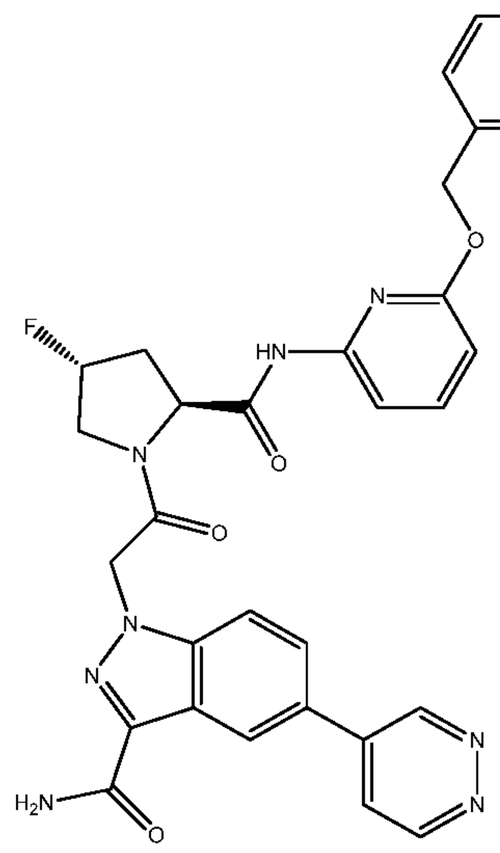
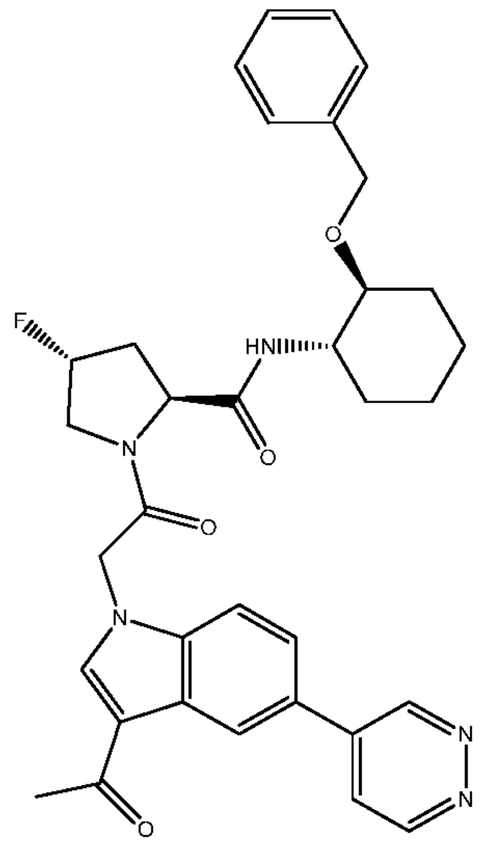
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
57		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-(6-methylimidazo[2,1-b]thiazol-5-yl)thiazol-2-yl)pyrrolidine-2-carboxamide	*	2.25 (B)	629
58		1-(2-((2S,4R)-4-fluoro-2-(4-(6-methylimidazo[2,1-b]thiazol-5-yl)thiazol-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.83 (B)	631
59		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(pyridin-3-ylmethyl)pyrrolidine-2-carboxamide	**	0.62 (B)	501

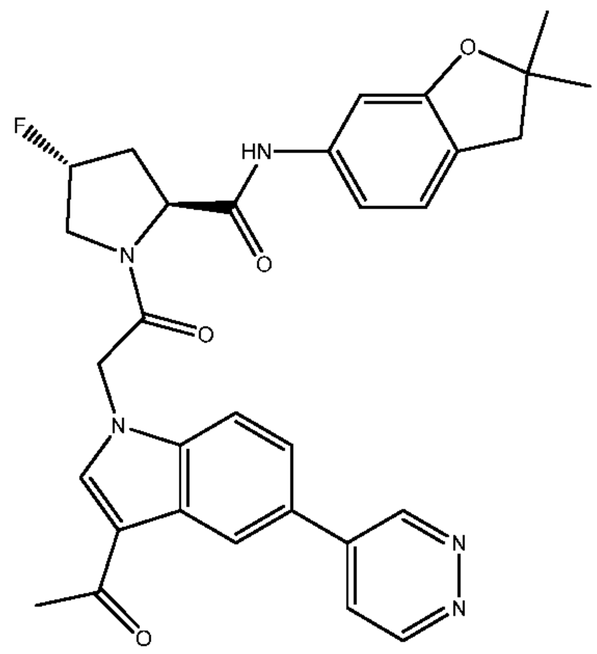
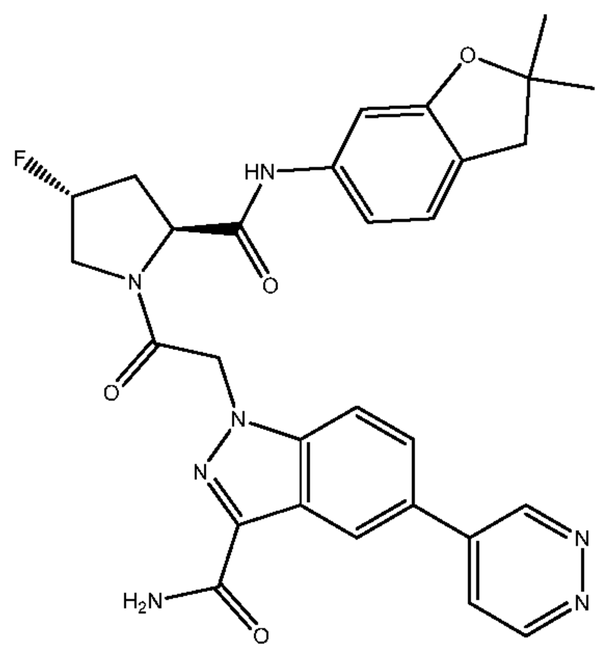
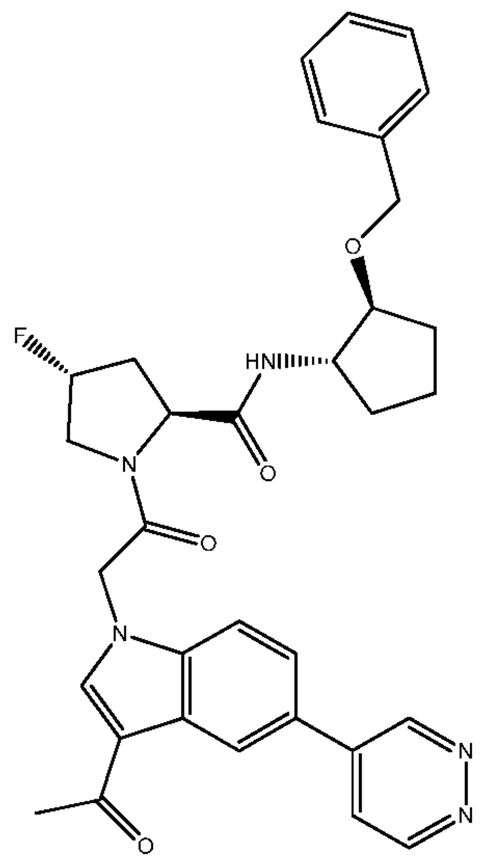
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
60		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(6-(benzyloxy)pyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	**	3.63 (B)	593
61		(9H-fluoren-9-yl)methyl acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)benzylcarbamate	*	3.81 (B)	737
62		1-(2-((2S,4R)-2-(3-chloro-5-fluorobenzylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.61 (B)	554

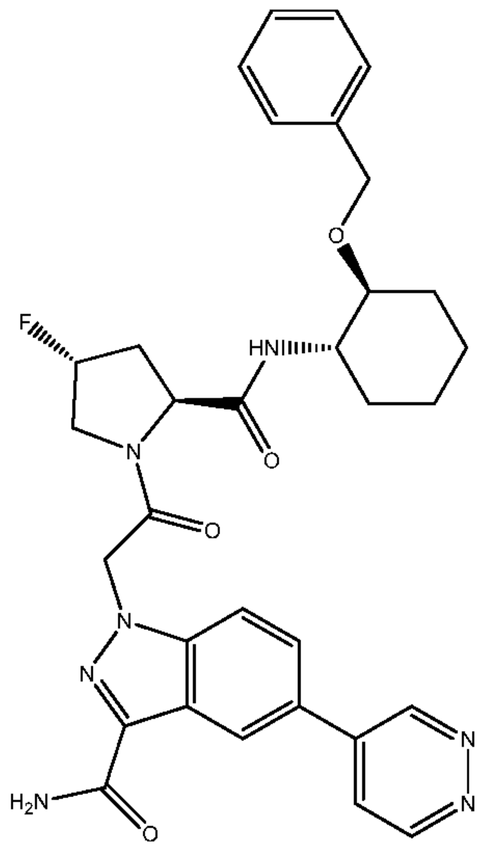
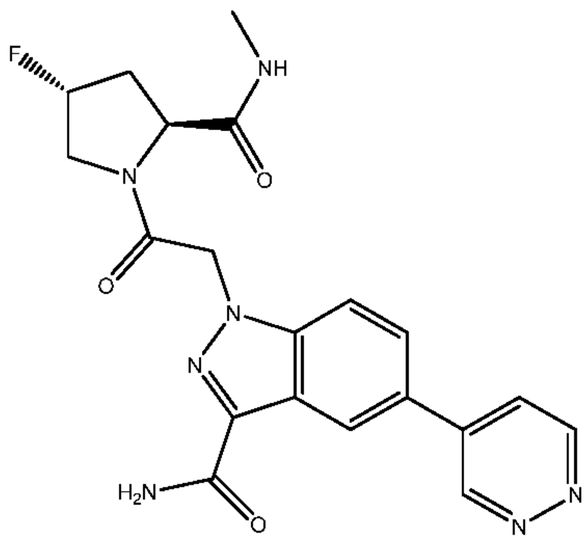
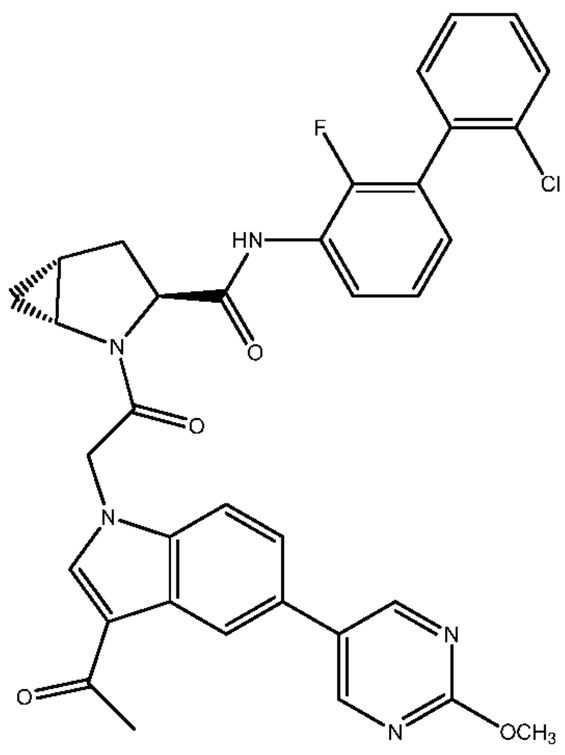
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
63		1-(2-((2S,4R)-2-(2,3-dimethyl-1H-indol-5-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.55 (B)	555
64		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-(2-oxooxazolidin-3-yl)phenyl)pyrrolidine-2-carboxamide	*	2.29 (B)	571
65		1-(2-((2S,4R)-4-fluoro-2-(2-(2-oxooxazolidin-3-yl)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.63 (B)	573

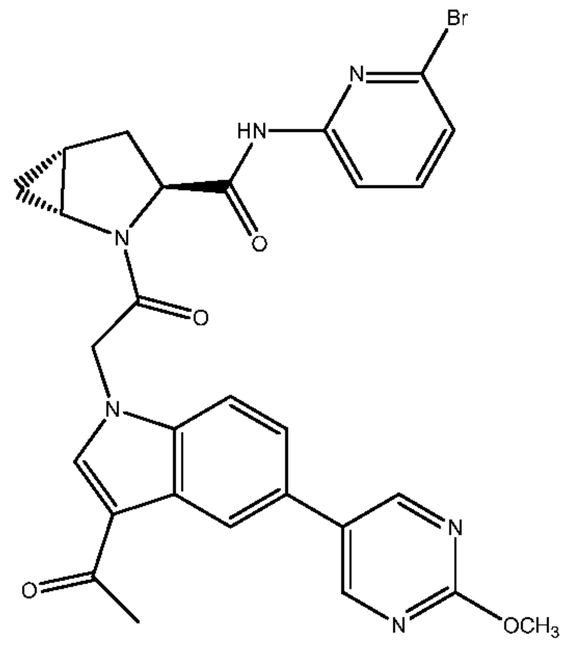
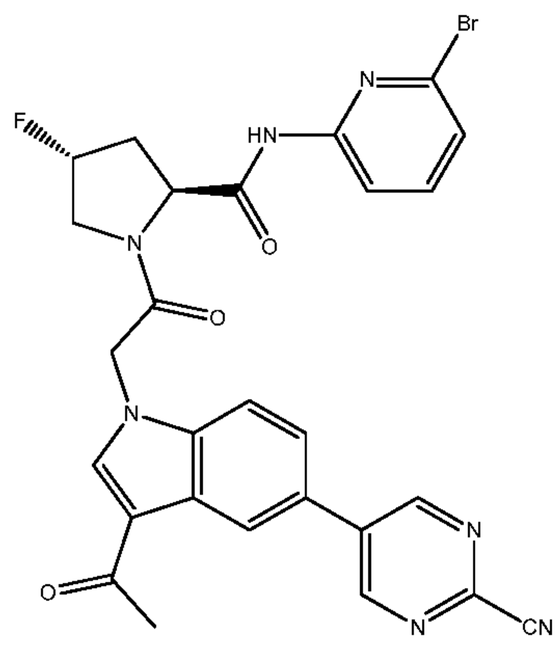
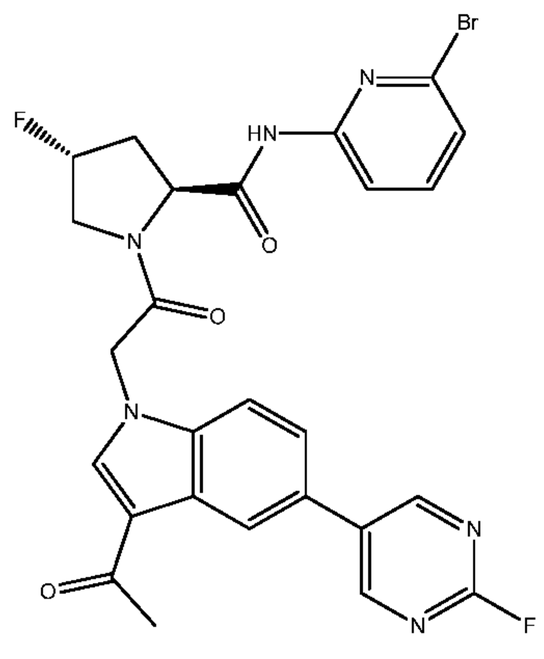
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
66		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-chloropyridin-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.63 (B)	521
67		1-(2-((2S,4R)-2-(5-chloropyridin-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.34 (B)	523
68		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-bromopyridin-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.79 (B)	565

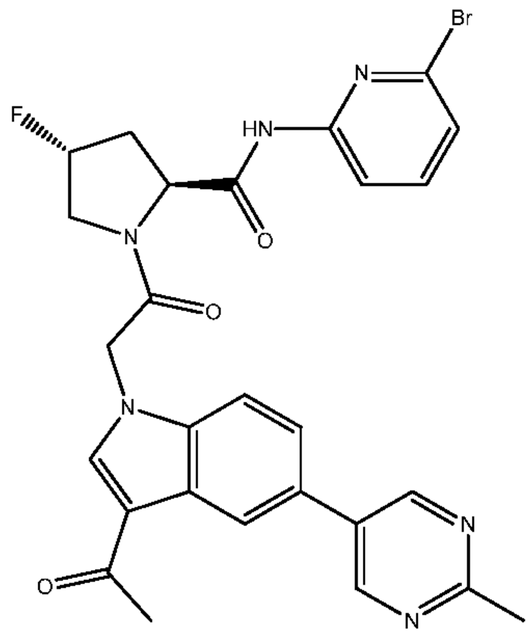
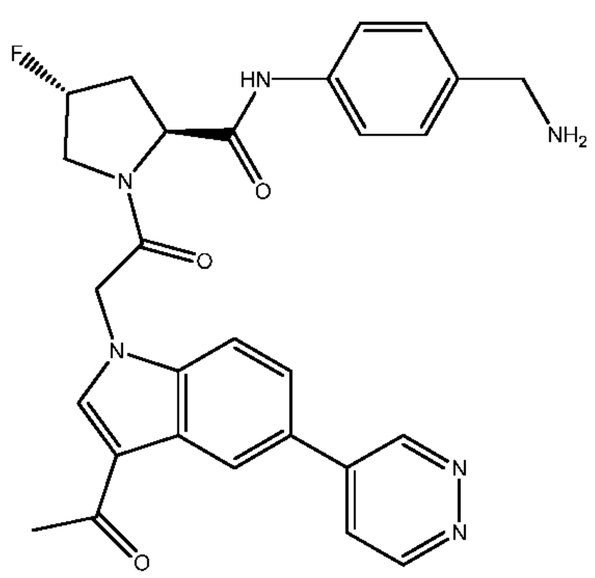
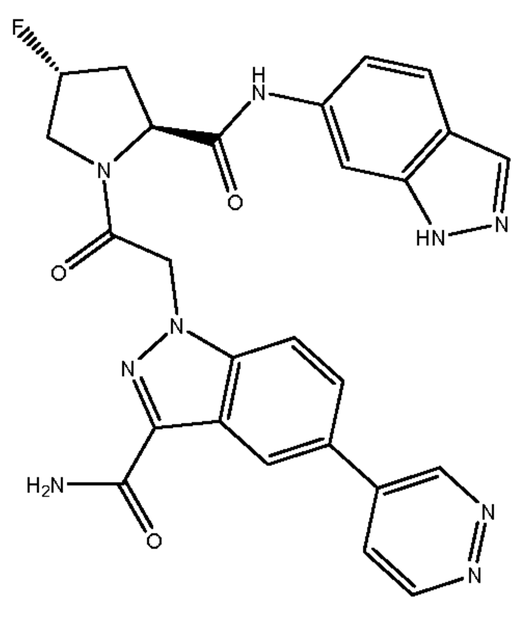
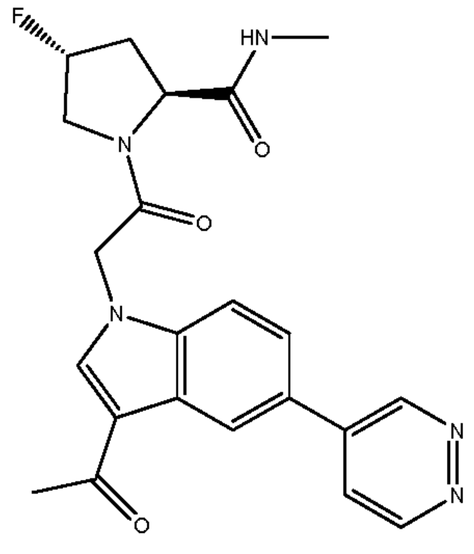
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
69		1-(2-((2S,4R)-2-(5-(3,4-dichlorophenyl)-1,3,4-thiadiazol-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.61 (B)	640
70		1-(2-((2S,4R)-2-(4-(aminomethyl)phenylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	0.42 (B)	517
71		1-(2-((2S,4R)-4-fluoro-2-(2-(5-methyl-1H-pyrazol-1-yl)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.54 (B)	568

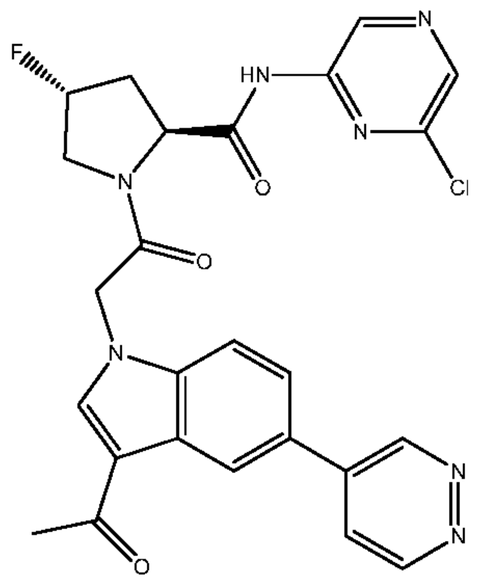
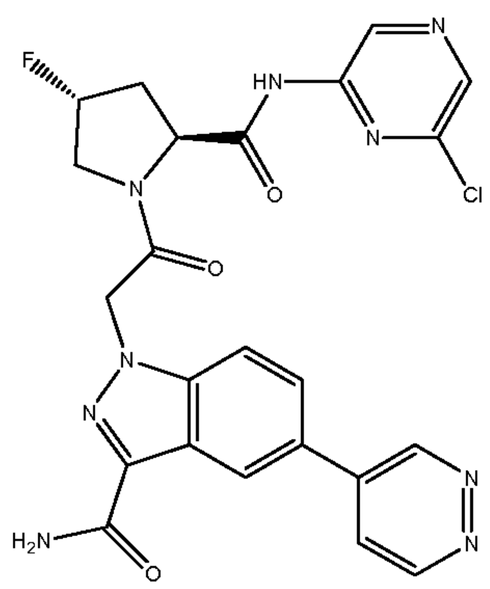
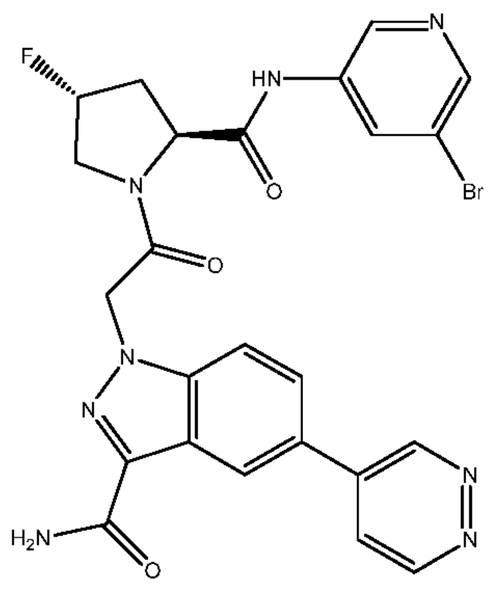
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
72		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-(5-methyl-1H-pyrazol-1-yl)phenyl)pyrrolidine-2-carboxamide	*	2.84 (B)	566
73		1-(2-((2S,4R)-2-(6-(benzyloxy)pyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.43 (B)	595
74		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-((1S,2S)-2-(benzyloxy)cyclohexyl)-4-fluoropyrrolidine-2-carboxamide	*	3.53 (B)	598

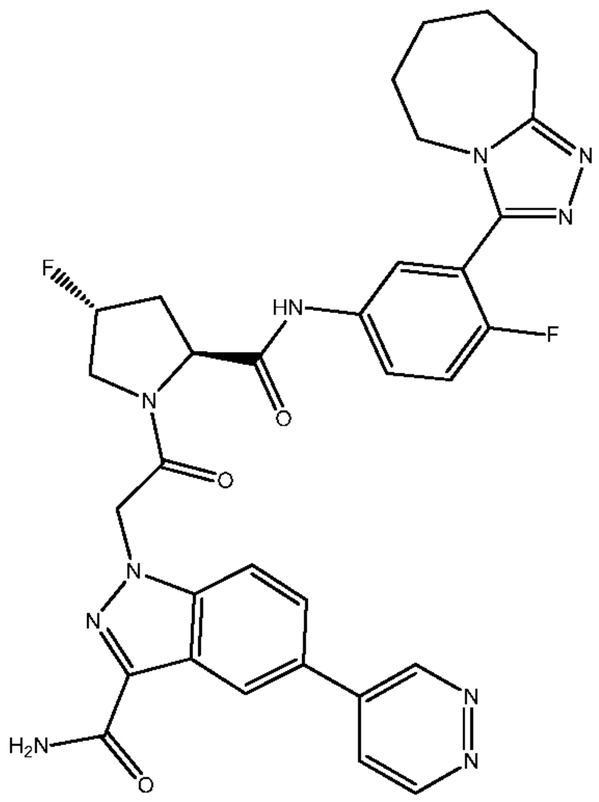
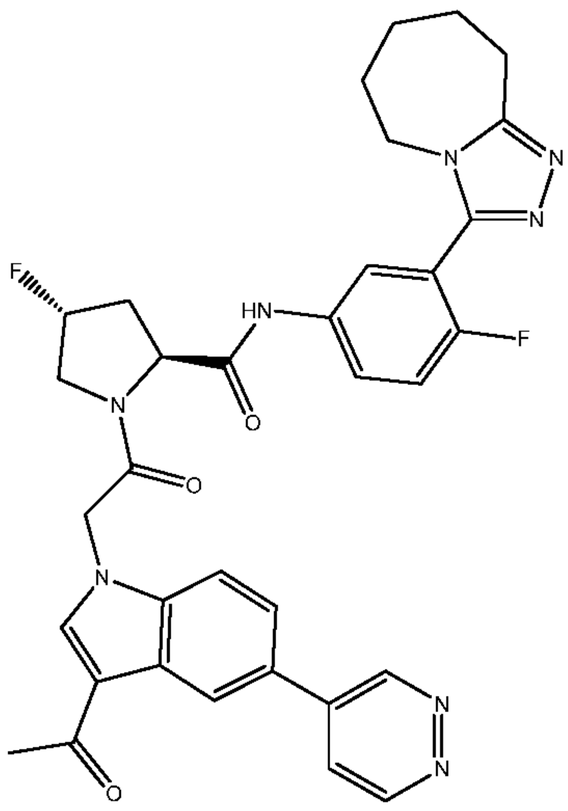
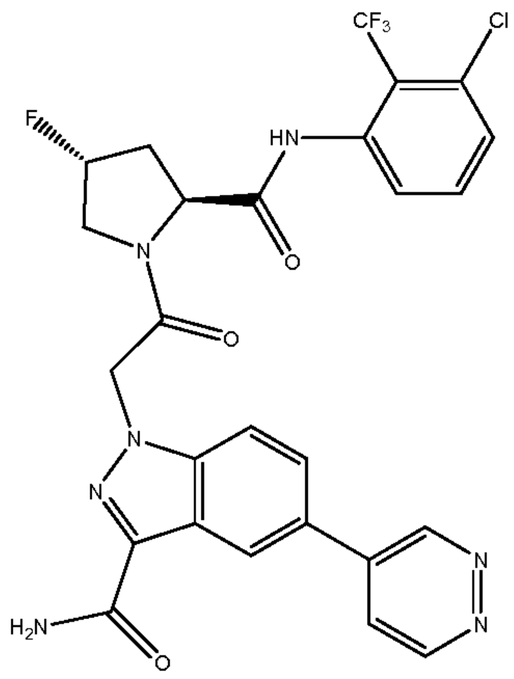
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
75		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2,2-dimethyl-2,3-dihydrobenzofuran-6-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.14 (B)	556
76		1-(2-((2S,4R)-2-(2,2-dimethyl-2,3-dihydrobenzofuran-6-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.92 (B)	558
77		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-((1S,2S)-2-(benzyloxy)cyclopentyl)-4-fluoropyrrolidine-2-carboxamide	*	3.33 (B)	584

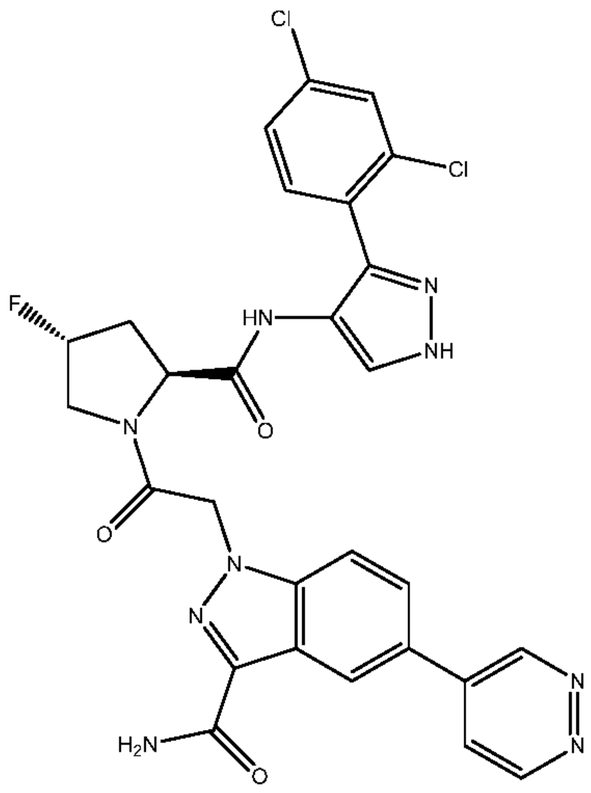
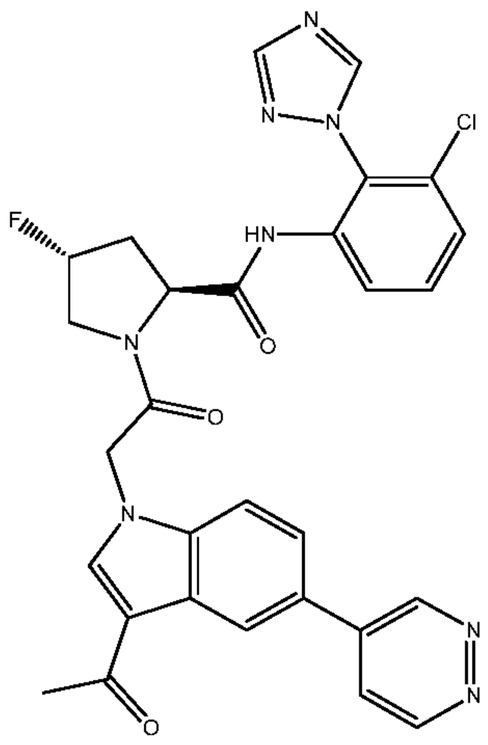
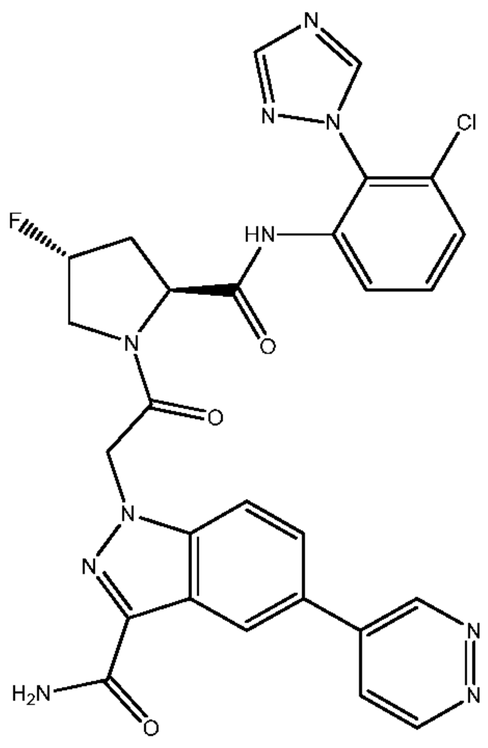
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
78		1-(2-((2S,4R)-2-((1S,2S)-2-(benzyloxy)cyclohexylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.38 (B)	600
79		1-(2-((2S,4R)-4-fluoro-2-(methylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.10 (B)	426
80		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	2.36 (A)	638

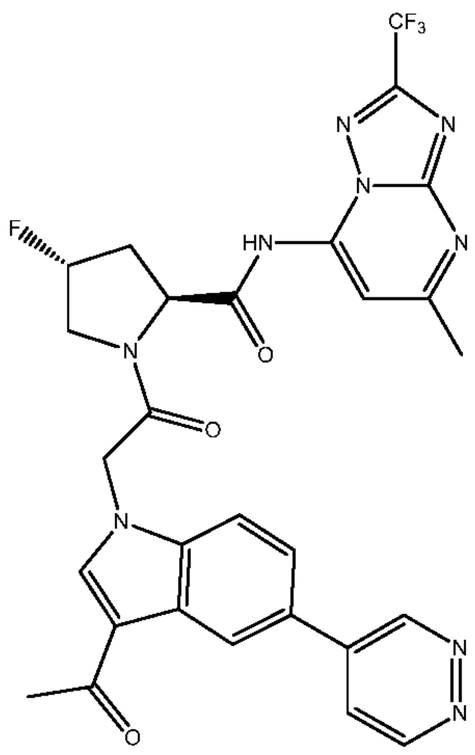
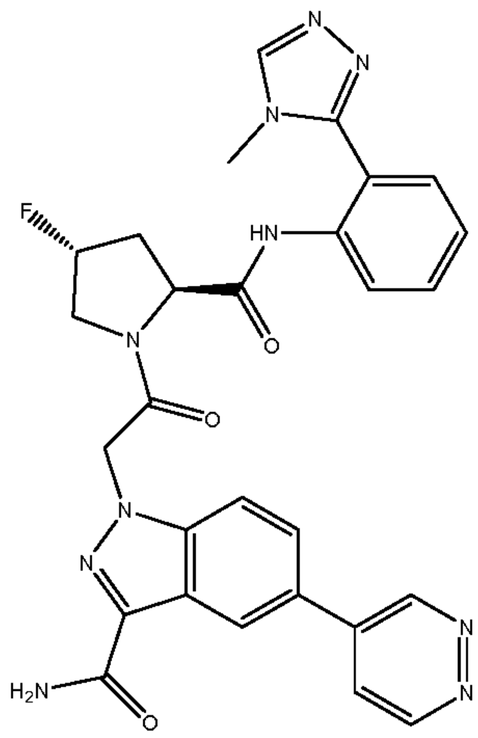
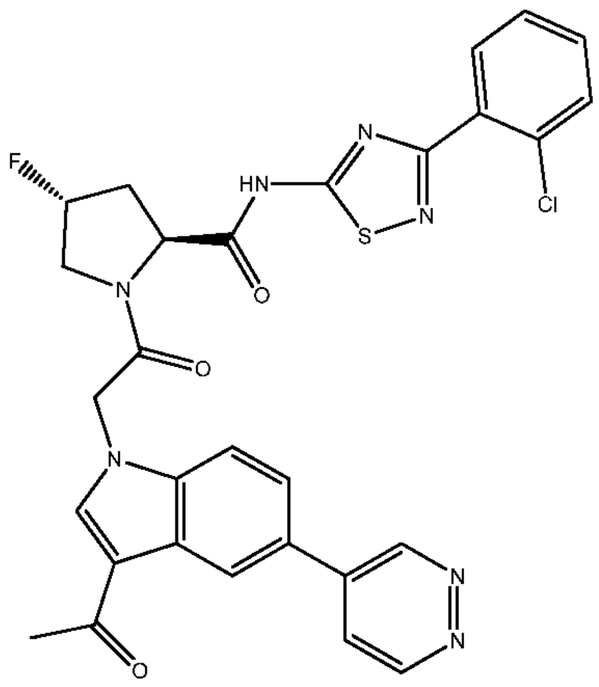
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
81		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	1.91 (A)	591
82		(2S,4R)-1-(2-(3-acetyl-5-(2-cyanopyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.97 (A)	592
83		(2S,4R)-1-(2-(3-acetyl-5-(2-fluoropyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.86 (A)	585

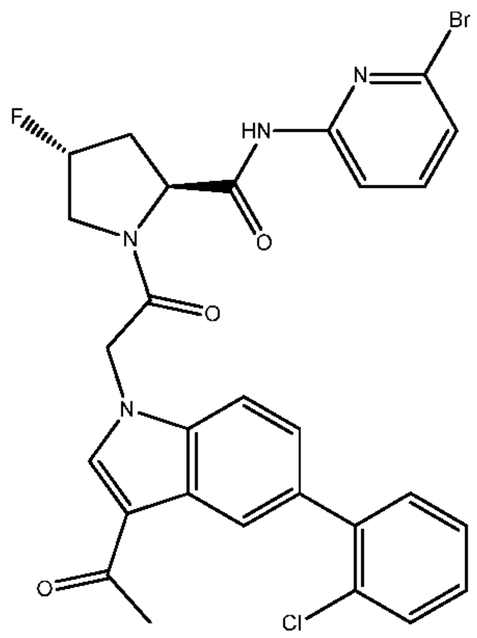
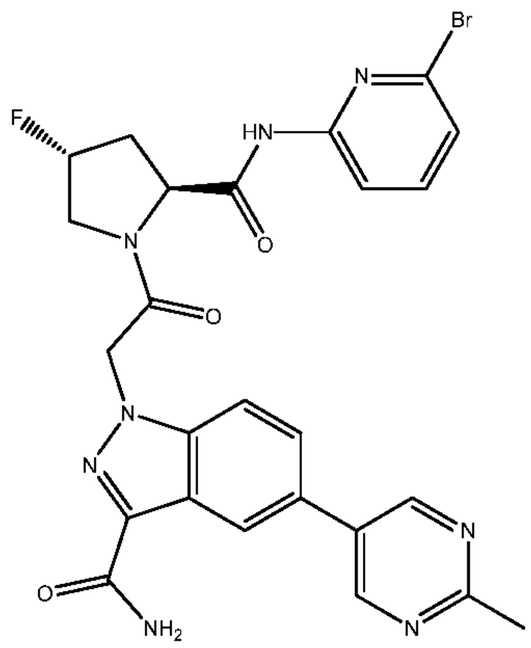
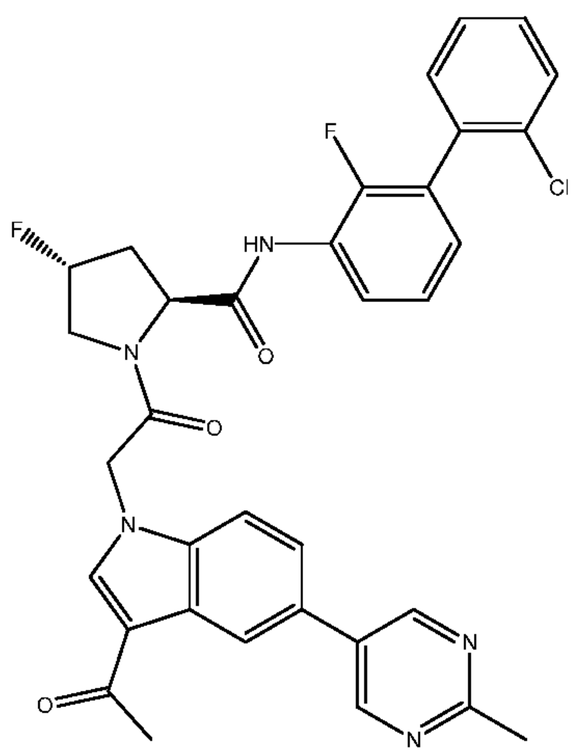
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
84		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.58 (A)	581
85		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(4-(aminomethyl)phenyl)-4-fluoropyrrolidine-2-carboxamide	*	0.69 (B)	515
86		1-(2-((2S,4R)-2-(1H-indazol-6-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.04 (B)	528
87		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-methylpyrrolidine-2-carboxamide	**	1.83 (B)	424

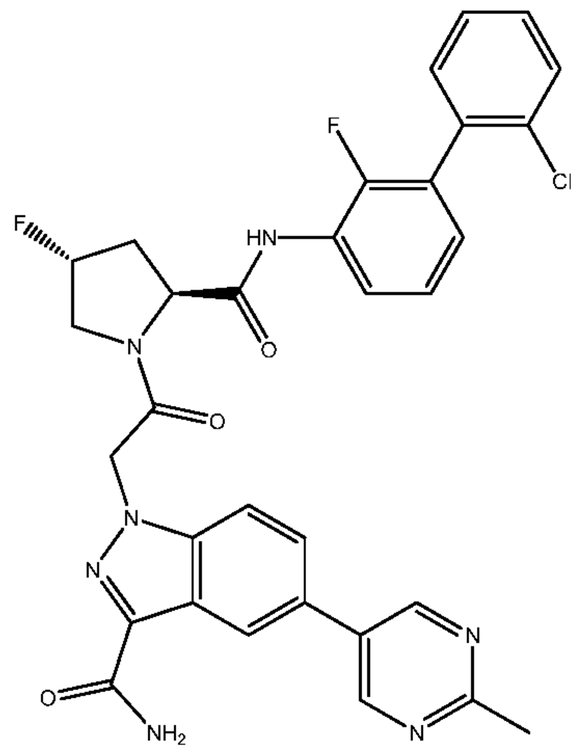
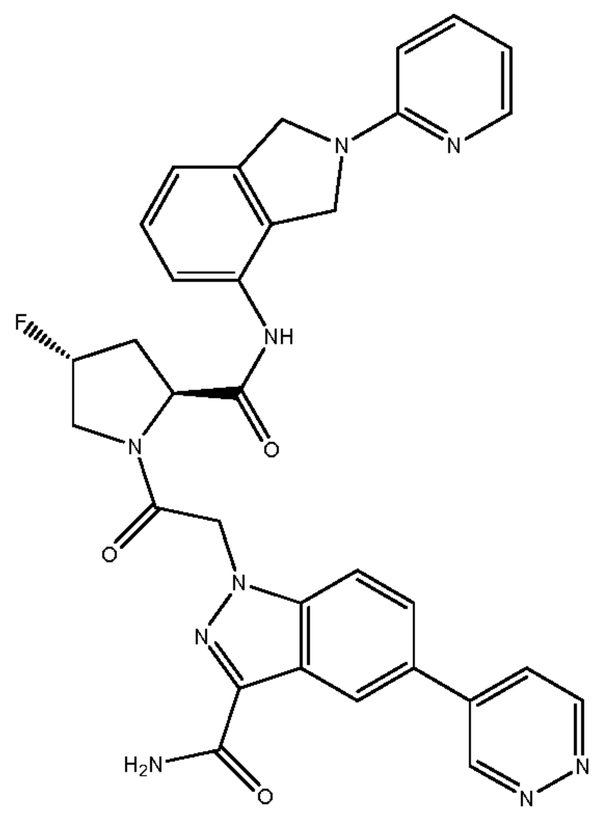
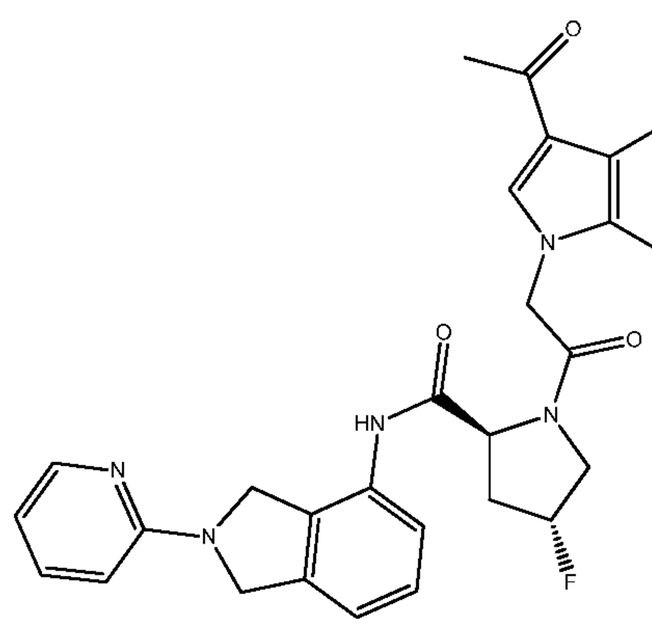
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
88		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(6-chloropyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.56 (B)	522
89		1-(2-((2S,4R)-2-(6-chloropyrazin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.43 (B)	524
90		1-(2-((2S,4R)-2-(5-bromopyridin-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.40 (B)	567

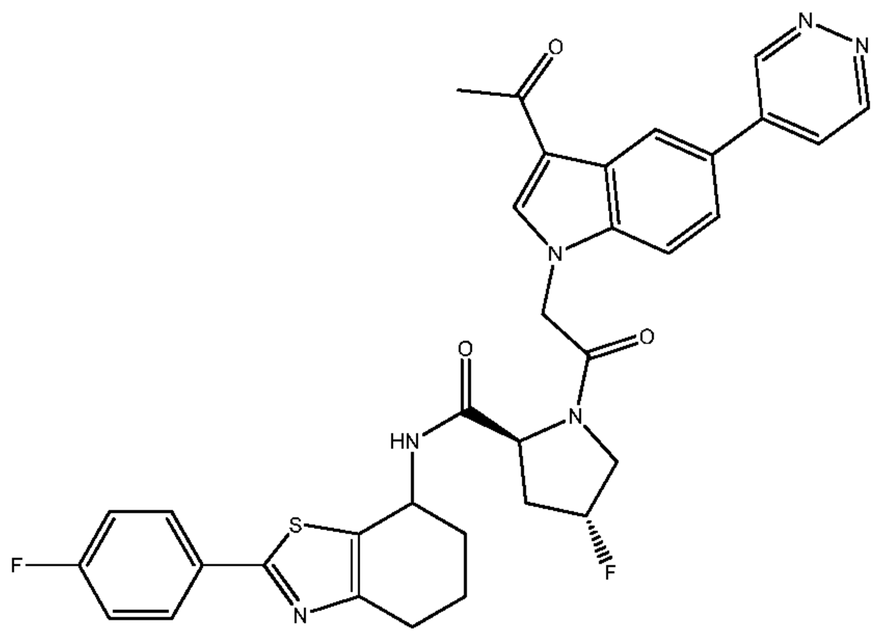
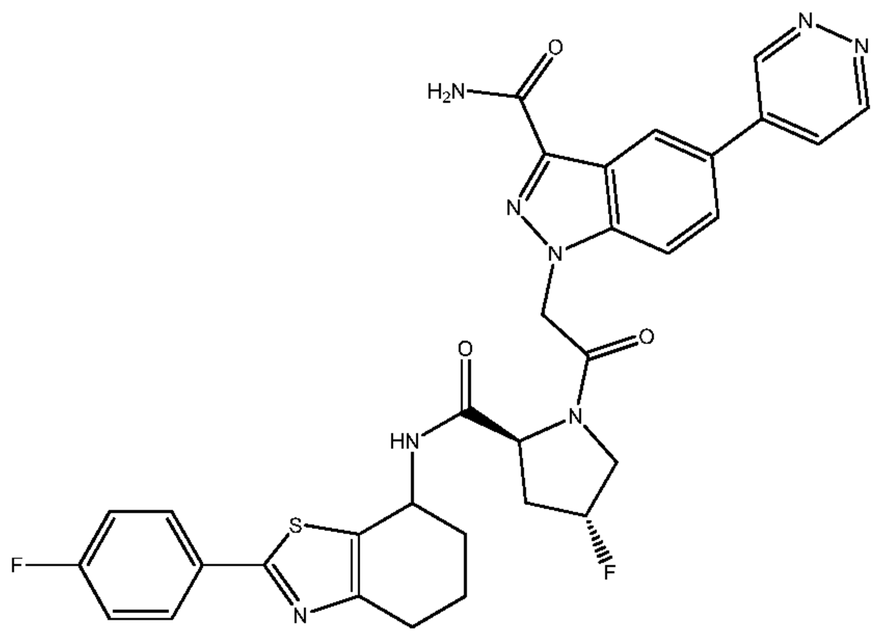
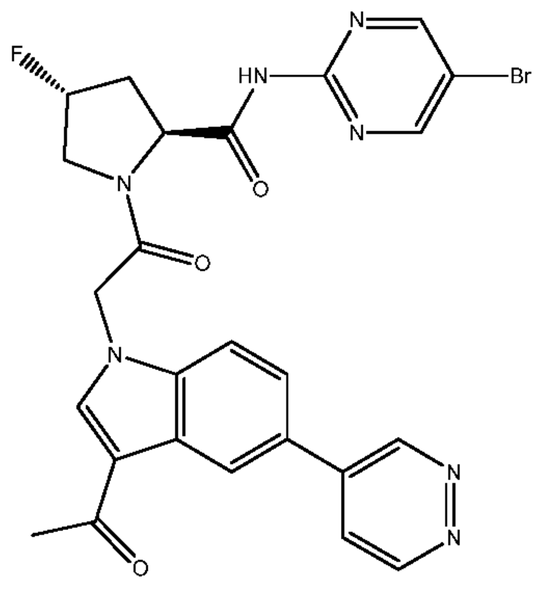
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
91		1-(2-((2S,4R)-4-fluoro-2-(4-fluoro-3-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.59 (B)	641
92		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-fluoro-3-(6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepin-3-yl)phenyl)pyrrolidine-2-carboxamide		2.78 (B)	639
93		1-(2-((2S,4R)-2-(3-chloro-2-(trifluoromethyl)phenylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.24 (B)	590

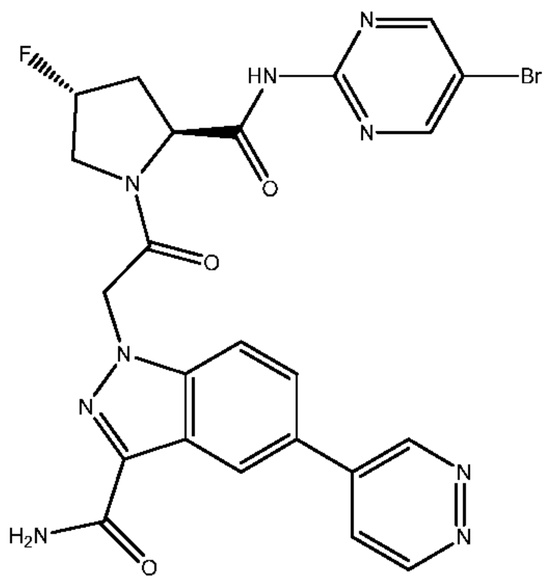
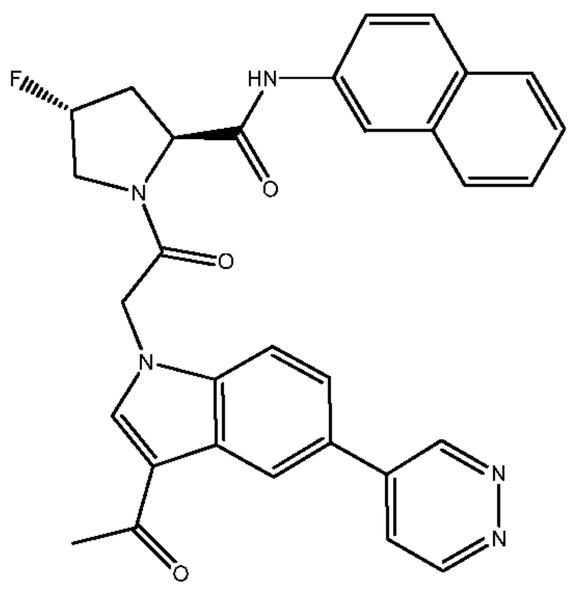
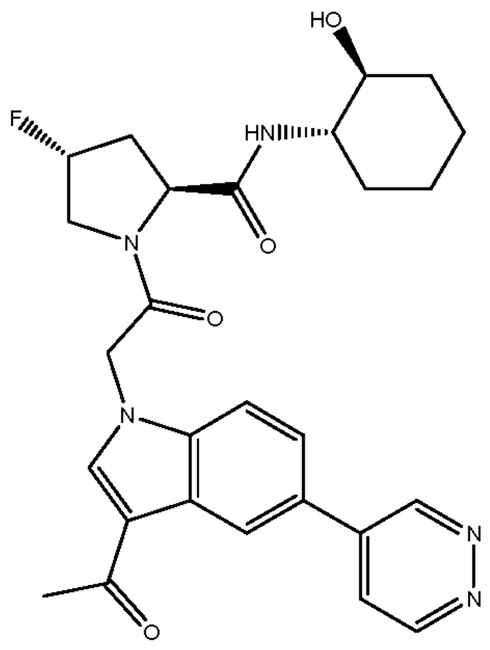
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
94		1-(2-((2S,4R)-2-(3-(2,4-dichlorophenyl)-1H-pyrazol-4-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.62 (B)	622
95		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-(1H-1,2,4-triazol-1-yl)phenyl)-4-fluoropyrrolidine-2-carboxamide	*	2.31 (B)	587
96		1-(2-((2S,4R)-2-(3-chloro-2-(1H-1,2,4-triazol-1-yl)phenylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.94 (B)	589

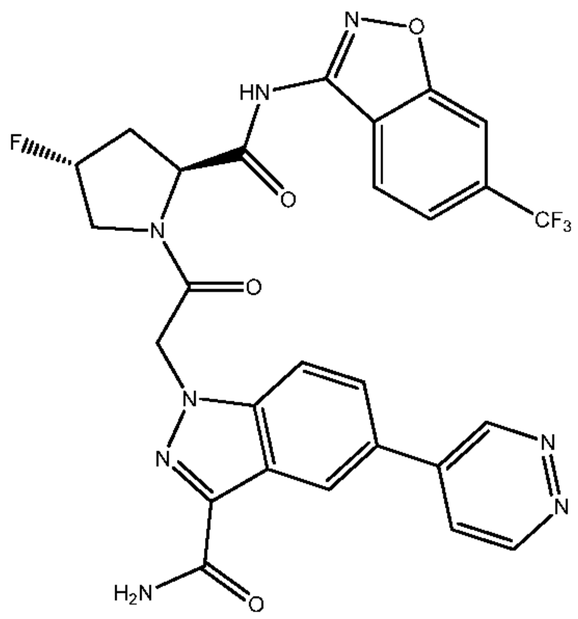
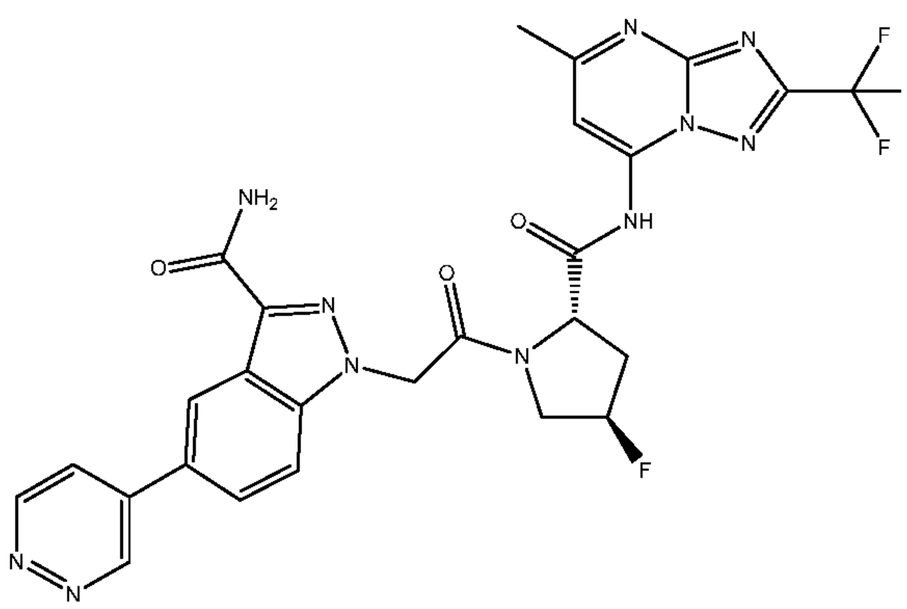
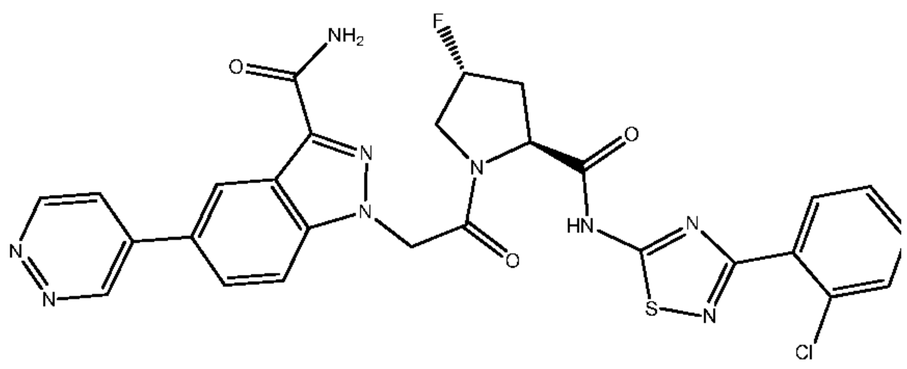
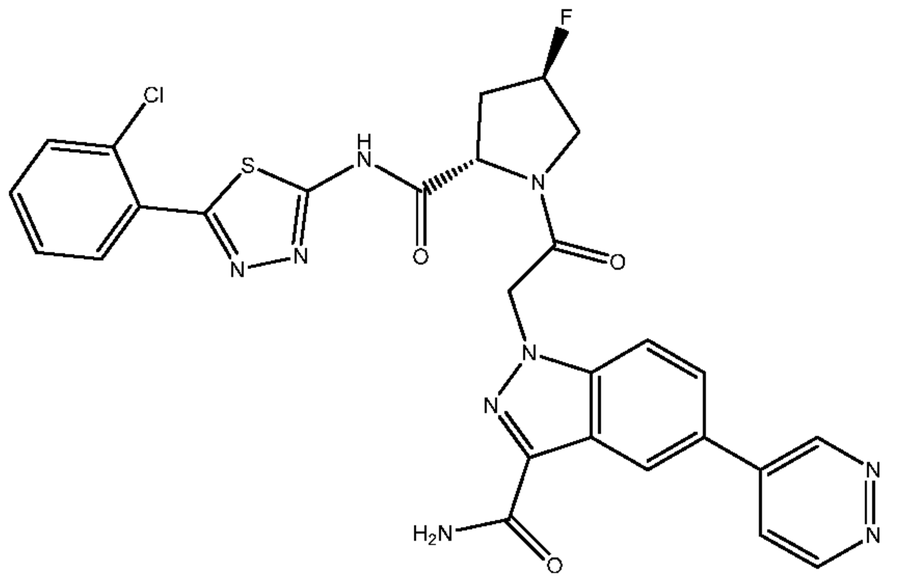
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
97		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(5-methyl-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)pyrrolidine-2-carboxamide	*	2.46 (B)	610
98		1-(2-((2S,4R)-4-fluoro-2-(2-(4-methyl-4H-1,2,4-triazol-3-yl)phenylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.42 (B)	569
99		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-(2-chlorophenyl)-1,2,4-thiadiazol-5-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.29 (B)	604

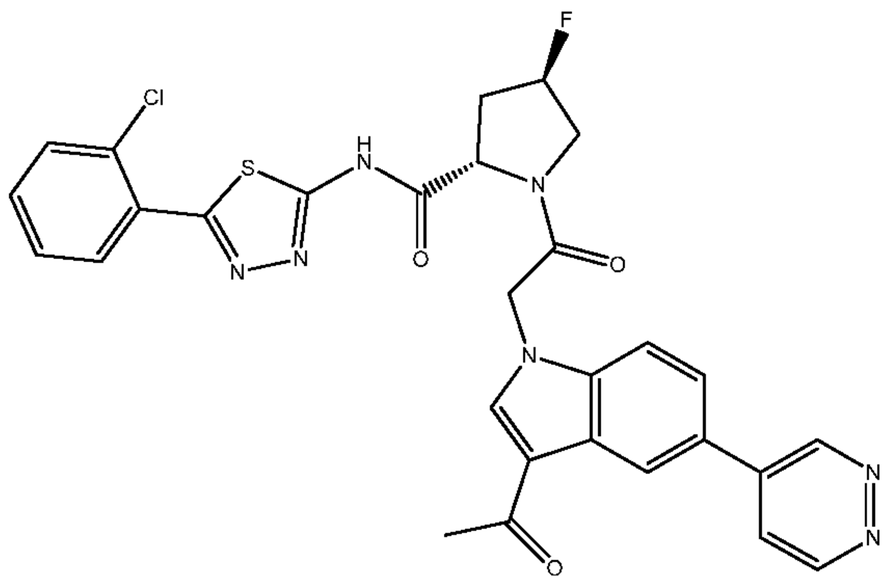
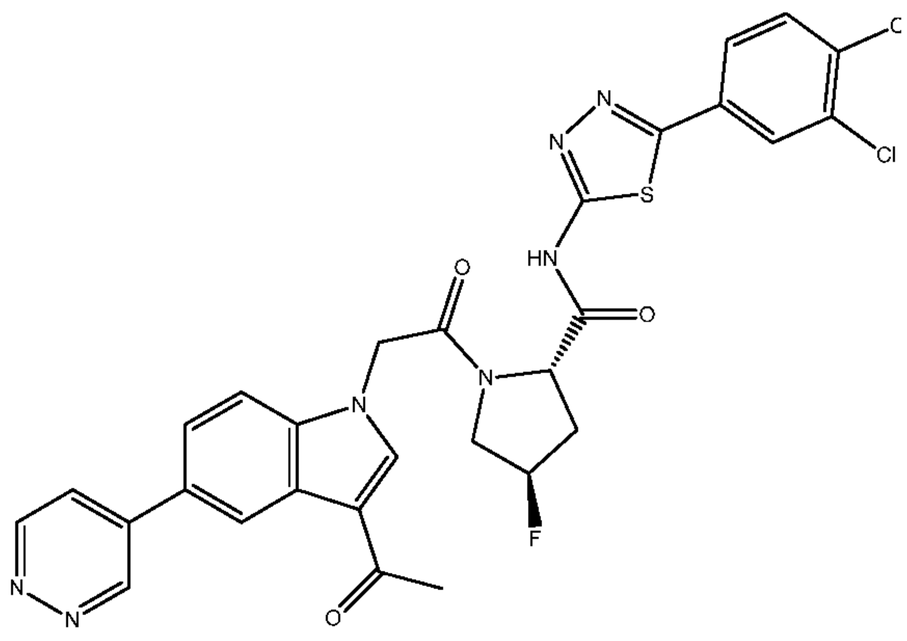
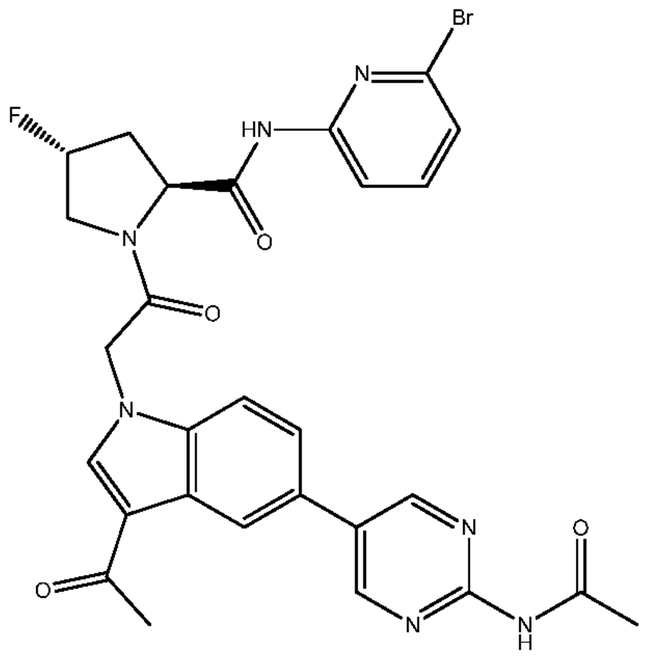
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
100		(2S,4R)-1-(2-(3-acetyl-5-(2-chlorophenyl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.45 (A)	599
101		1-(2-((2S,4R)-2-(6-bromopyridin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.40 (A)	583
102		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.10 (A)	628

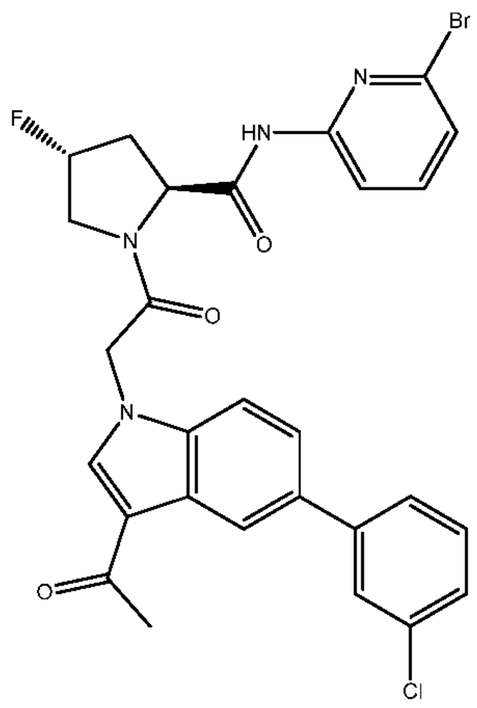
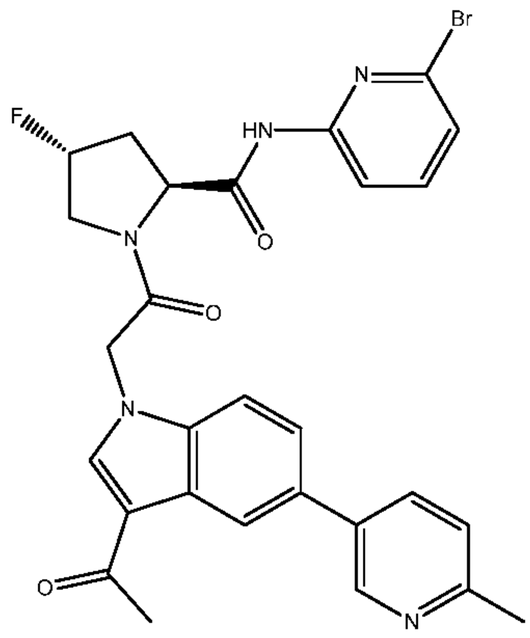
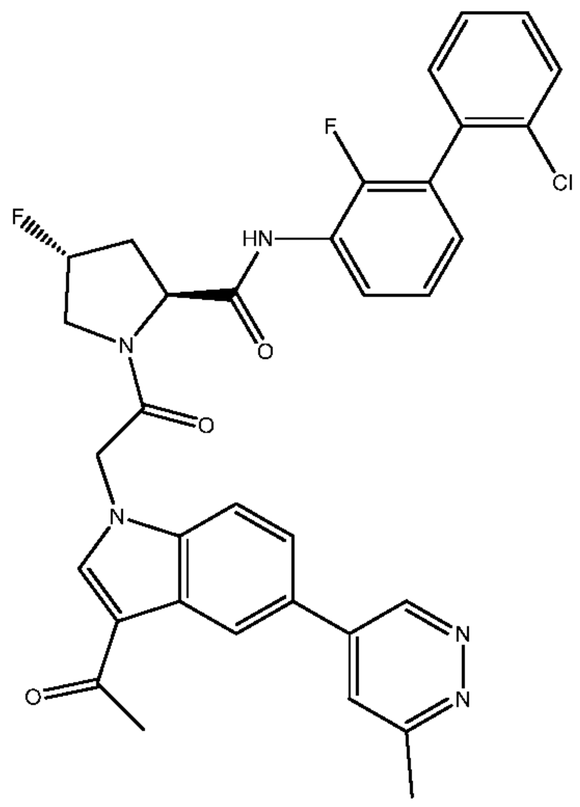
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
103		1-(2-((2S,4R)-2-(2'-chloro-2-fluorobiphenyl-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(2-methylpyrimidin-5-yl)-1H-indazole-3-carboxamide	***	1.91 (A)	630
104		1-(2-((2S,4R)-4-fluoro-2-(2-(pyridin-2-yl)isoindolin-4-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.91 (B)	606
105		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-(pyridin-2-yl)isoindolin-4-yl)pyrrolidine-2-carboxamide	*	1.97 (B)	604

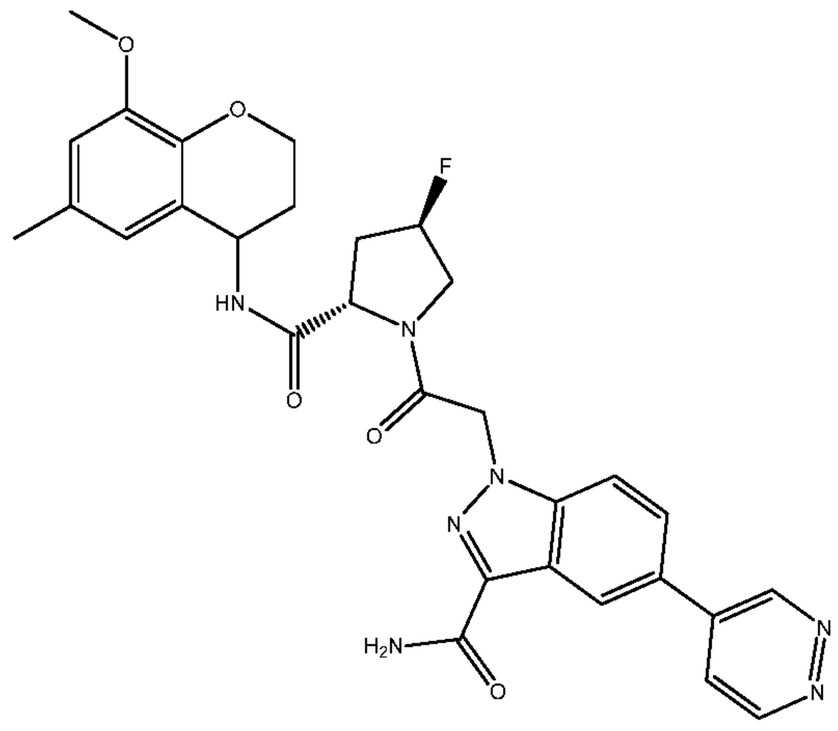
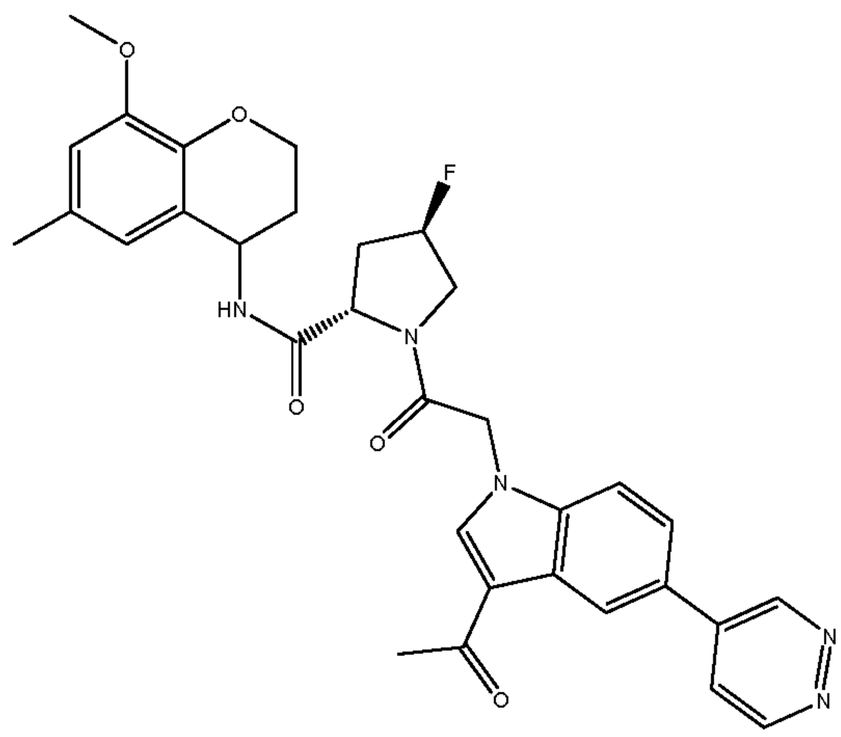
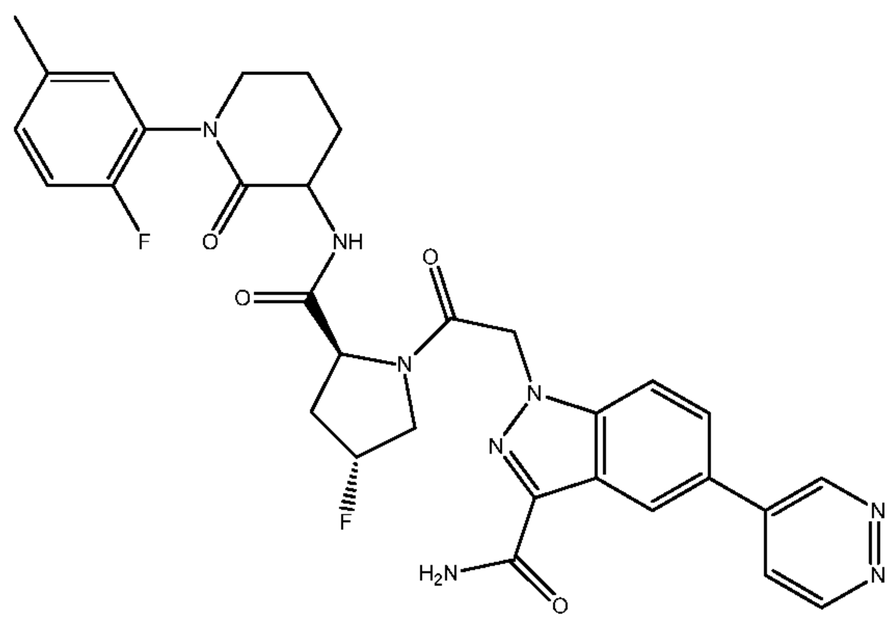
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
106		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-(4-fluorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-7-yl)pyrrolidine-2-carboxamide	*	2.94 (B)	641
107		1-(2-((2S,4R)-4-fluoro-2-(2-(4-fluorophenyl)-4,5,6,7-tetrahydrobenzo[d]thiazol-7-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.97 (B)	643
108		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-bromopyrimidin-2-yl)-4-fluoropyrrolidine-2-carboxamide	**	1.85 (B)	566

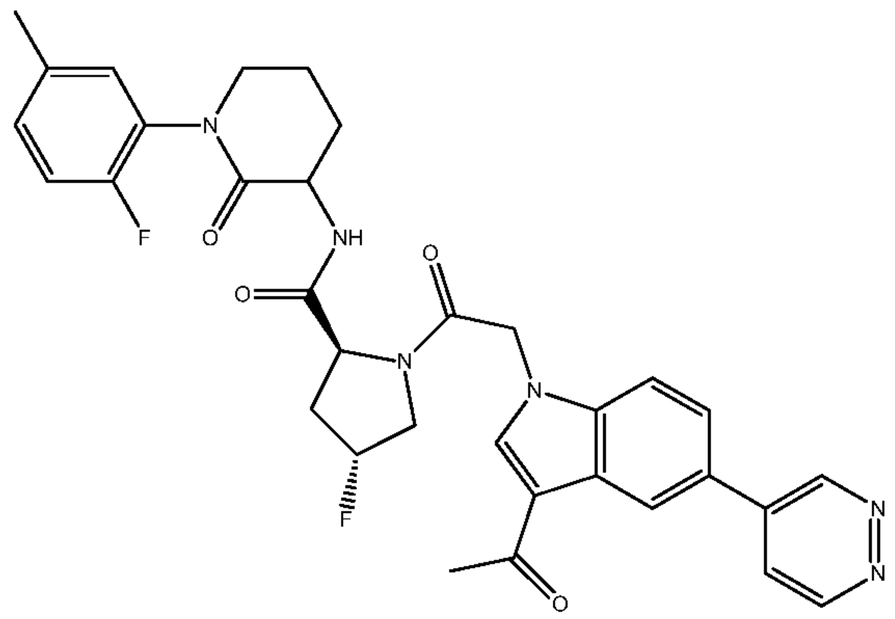
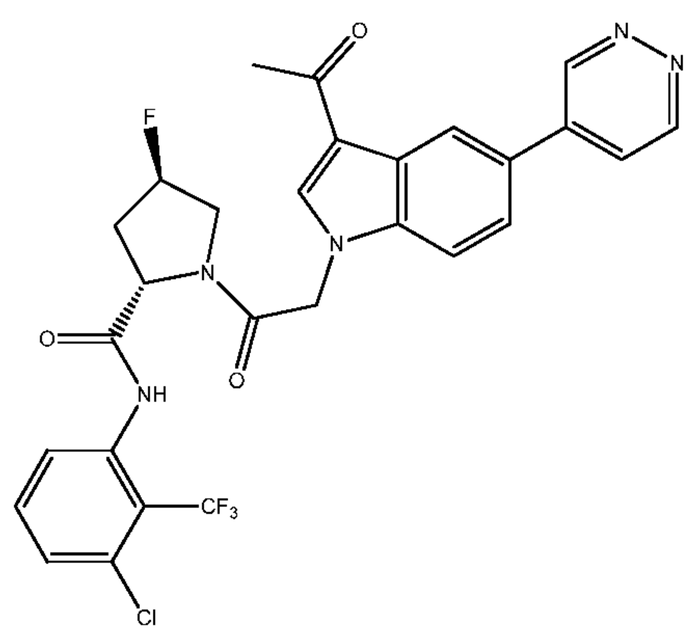
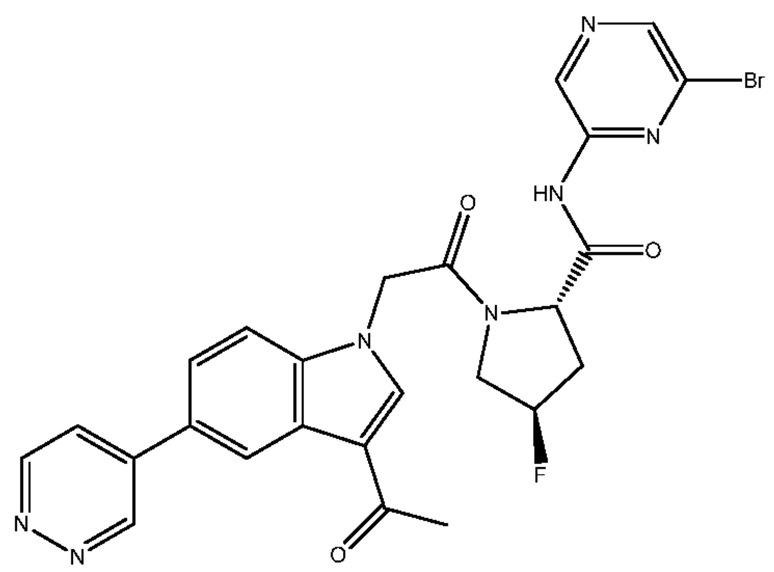
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
109		1-(2-((2S,4R)-2-(5-bromopyrimidin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	1.86 (B)	568
110		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(naphthalen-2-yl)pyrrolidine-2-carboxamide	*	3.14 (B)	536
111		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)pyrrolidine-2-carboxamide	**	1.75 (B)	508

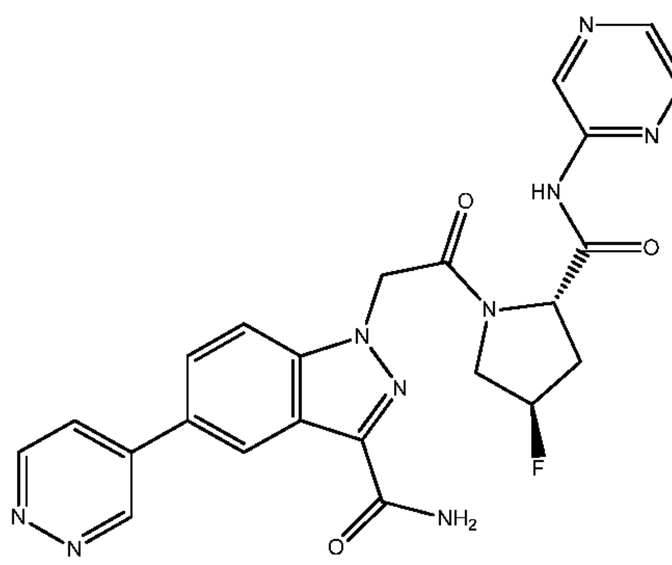
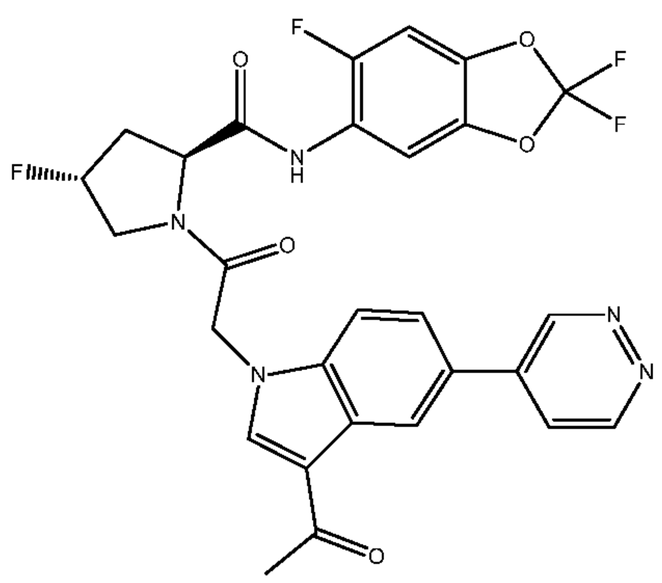
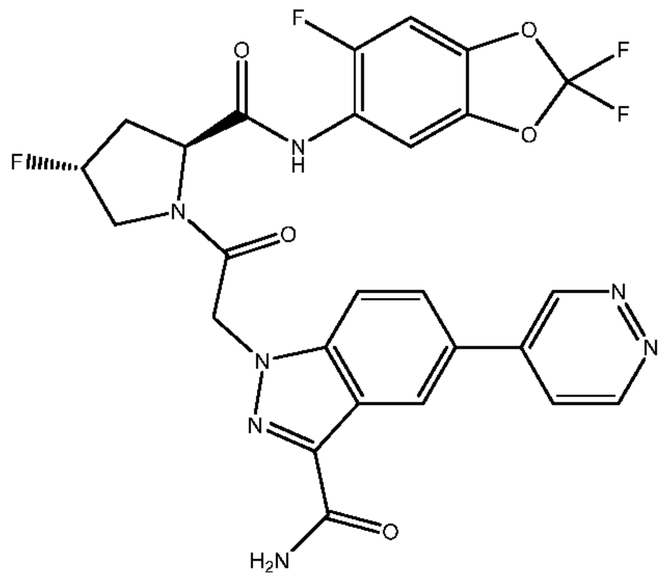
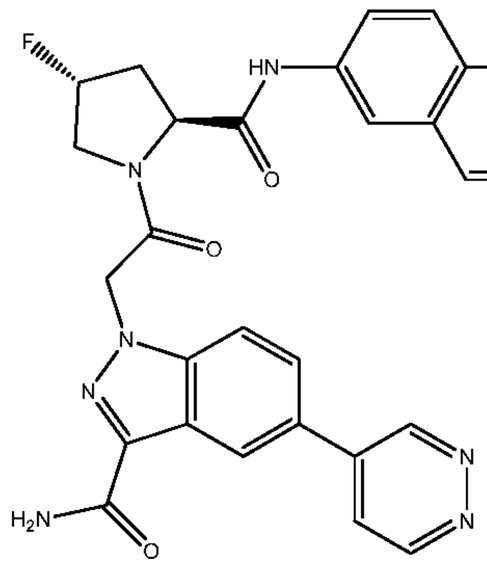
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
112		1-(2-((2S,4R)-4-fluoro-2-(6-(trifluoromethyl)benzo[d]isoxazol-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.95 (B)	597
113		1-(2-((2S,4R)-4-fluoro-2-(5-methyl-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.07 (B)	612
114		1-(2-((2S,4R)-2-(3-(2-chlorophenyl)-1,2,4-thiadiazol-5-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.89 (B)	606
115		1-(2-((2S,4R)-2-(5-(2-chlorophenyl)-1,3,4-thiadiazol-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.67 (B)	606

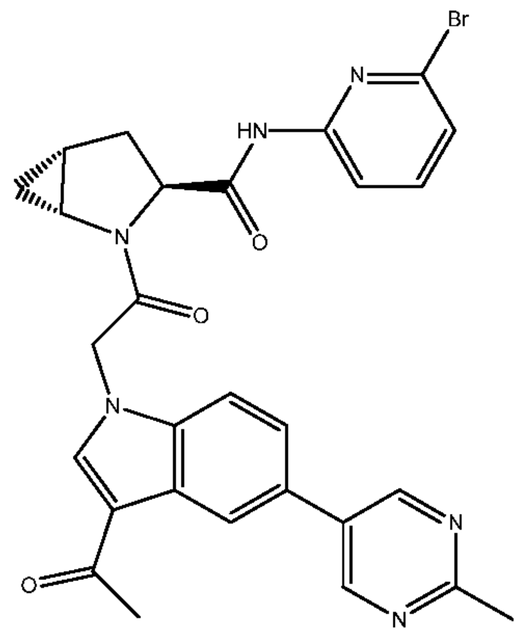
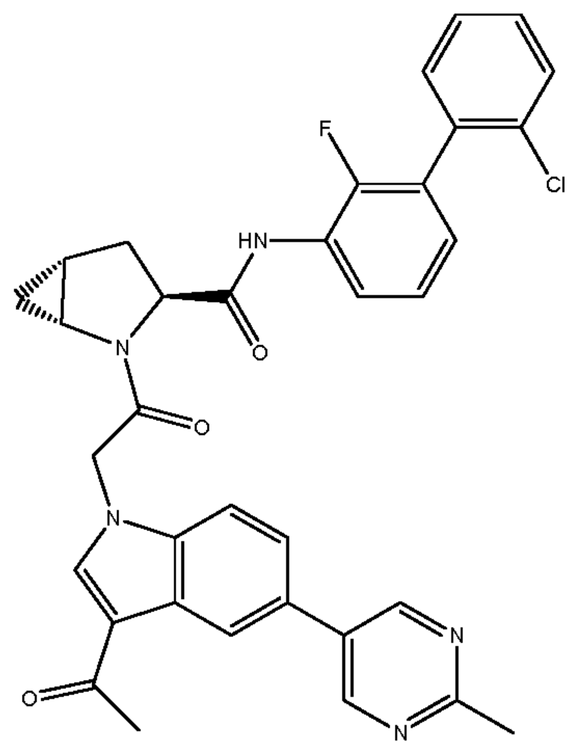
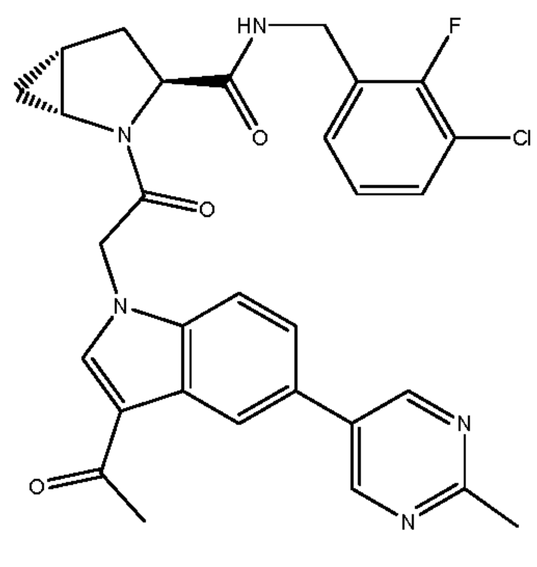
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
116		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-(2-chlorophenyl)-1,3,4-thiadiazol-2-yl)-4-fluoropyrrolidine-2-carboxamide	**	3.30 (B)	604
117		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-(3,4-dichlorophenyl)-1,3,4-thiadiazol-2-yl)-4-fluoropyrrolidine-2-carboxamide	*	3.73 (B)	638
118		(2S,4R)-1-(2-(5-(2-acetamidopyrimidin-5-yl)-3-acetyl-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.44 (A)	622

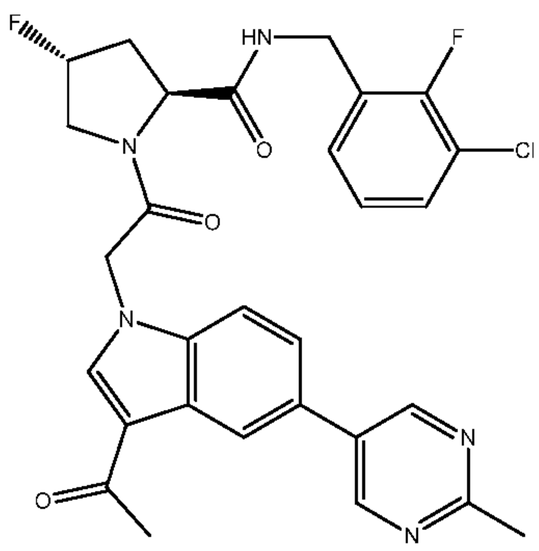
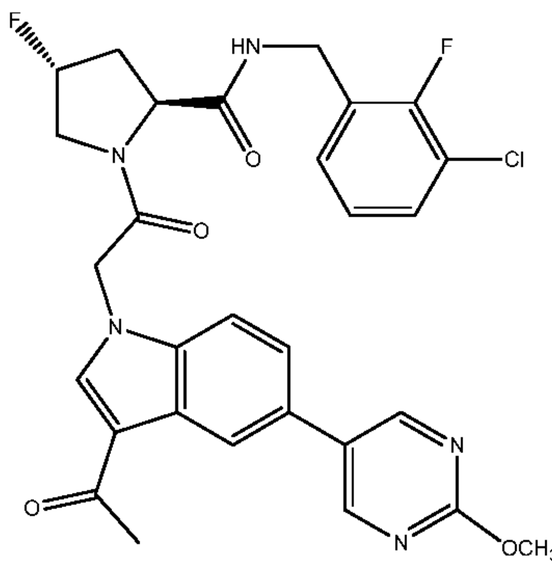
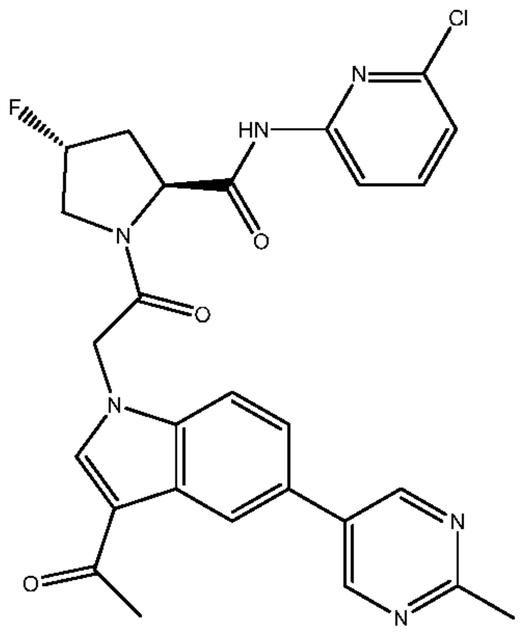
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
119		(2S,4R)-1-(2-(3-acetyl-5-(3-chlorophenyl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.54 (A)	599
120		(2S,4R)-1-(2-(3-acetyl-5-(6-methylpyridin-3-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.34 (A)	578
121		(2S,4R)-1-(2-(3-acetyl-5-(6-methylpyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.96 (A)	628

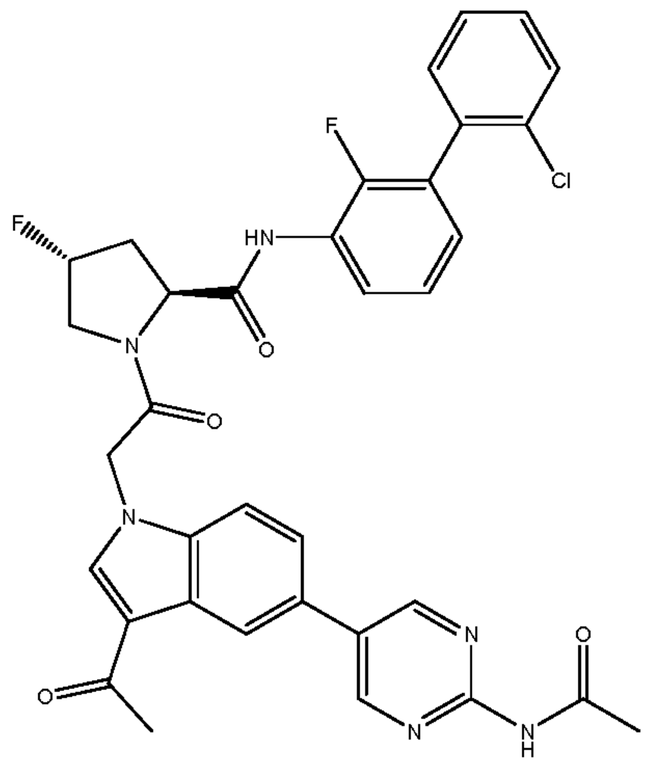
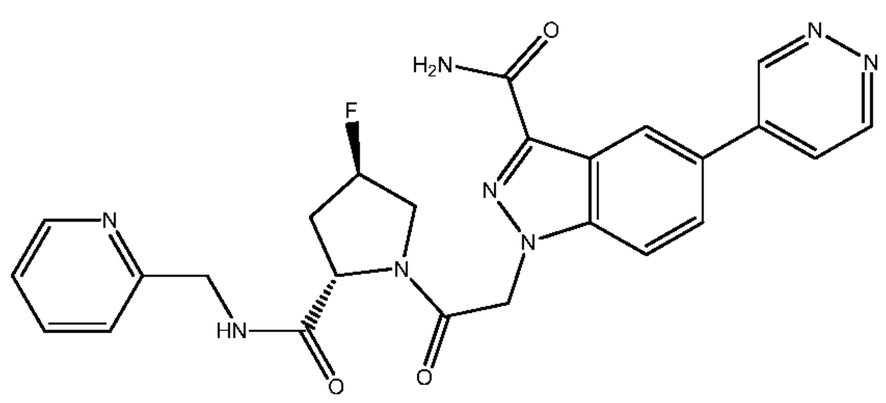
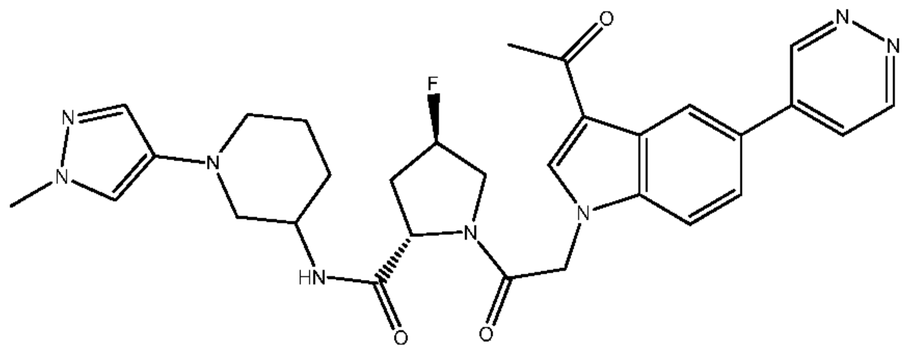
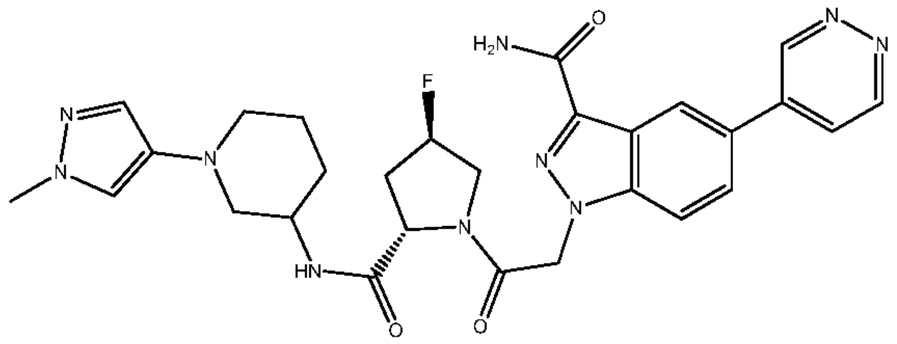
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
122		1-(2-((2S,4R)-4-fluoro-2-(8-methoxy-6-methylchroman-4-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.38 (B)	588
123		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(8-methoxy-6-methylchroman-4-yl)pyrrolidine-2-carboxamide	*	2.58/2.73 (B)	586
124		1-(2-((2S,4R)-4-fluoro-2-(1-(2-fluoro-5-methylphenyl)-2-oxopiperidin-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.61 (B)	617

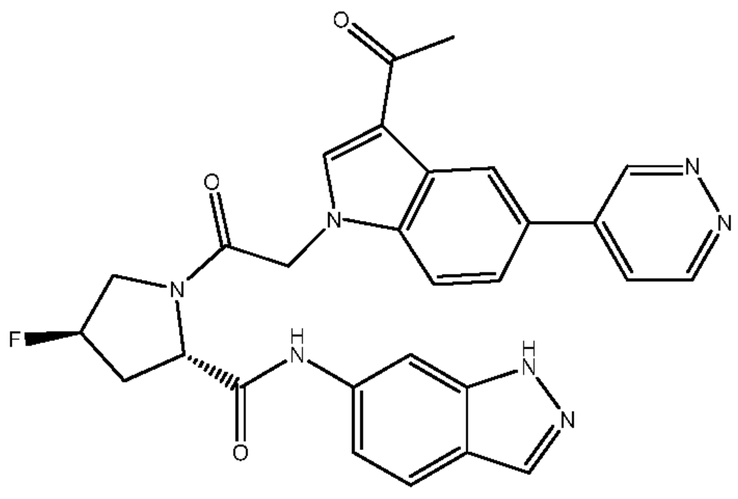
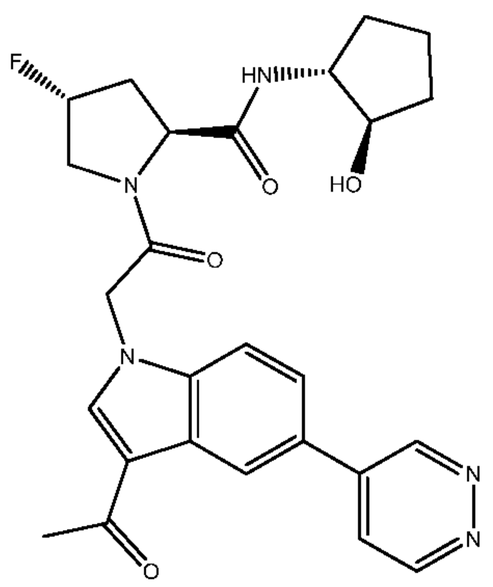
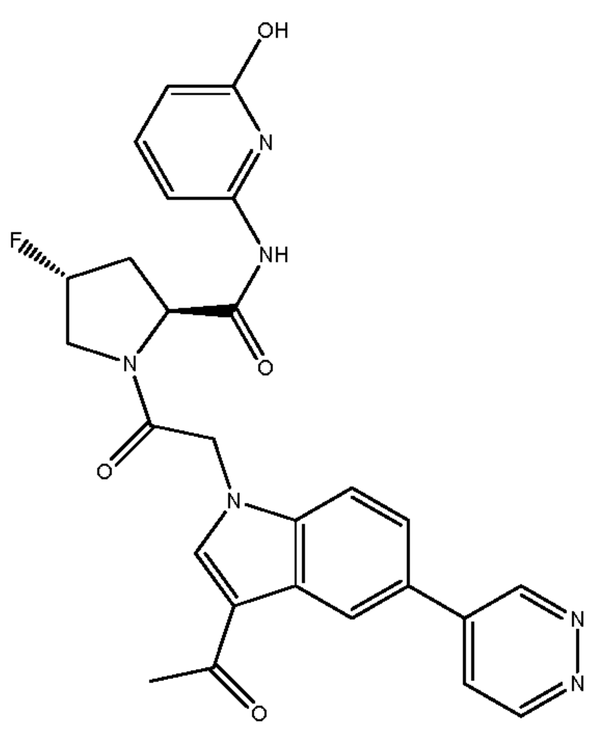
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
125		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1-(2-fluoro-5-methylphenyl)-2-oxopiperidin-3-yl)pyrrolidine-2-carboxamide	**	2.92 (B)	615
126		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-(trifluoromethyl)phenyl)-4-fluoropyrrolidine-2-carboxamide	*	3.09 (B)	588
127		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyrazin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.47 (B)	566

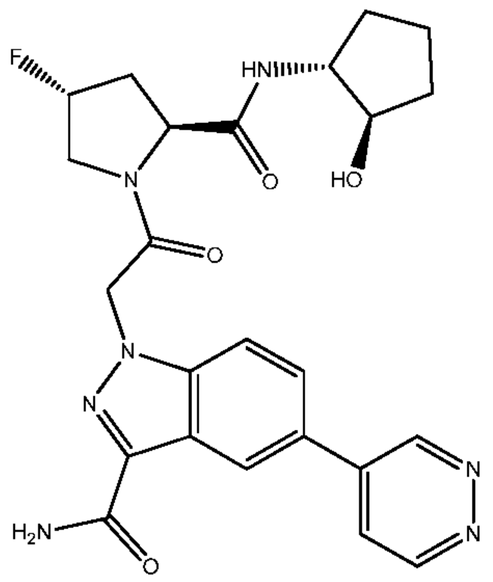
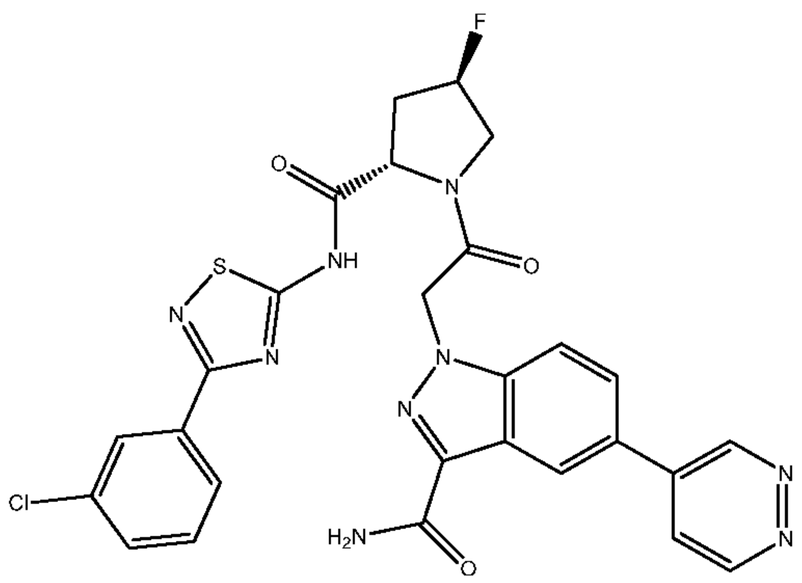
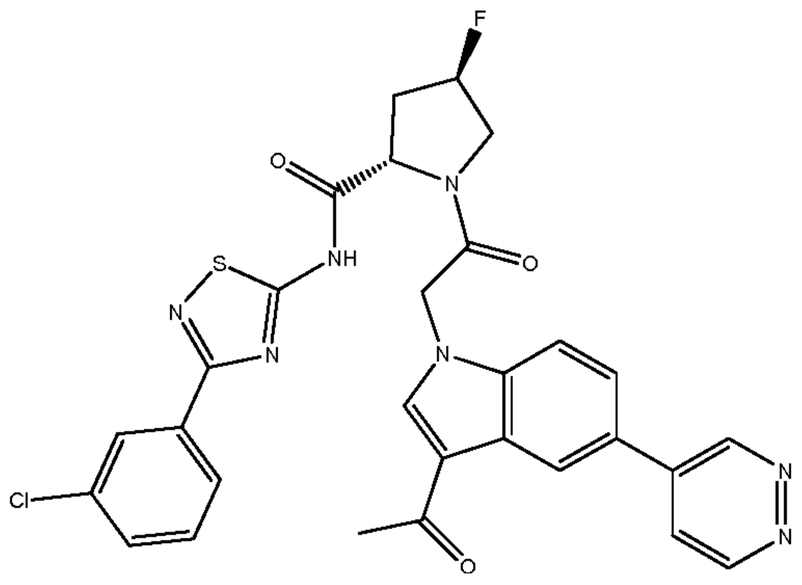
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
128		1-(2-((2S,4R)-2-(6-bromopyrazin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	***	2.22 (B)	568
129		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2,2,6-trifluorobenzo[d][1,3]dioxol-5-yl)pyrrolidine-2-carboxamide	**	3.19 (B)	584
130		1-(2-((2S,4R)-4-fluoro-2-(2,2,6-trifluorobenzo[d][1,3]dioxol-5-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.86 (B)	586
131		1-(2-((2S,4R)-4-fluoro-2-(naphthalen-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.77 (B)	538

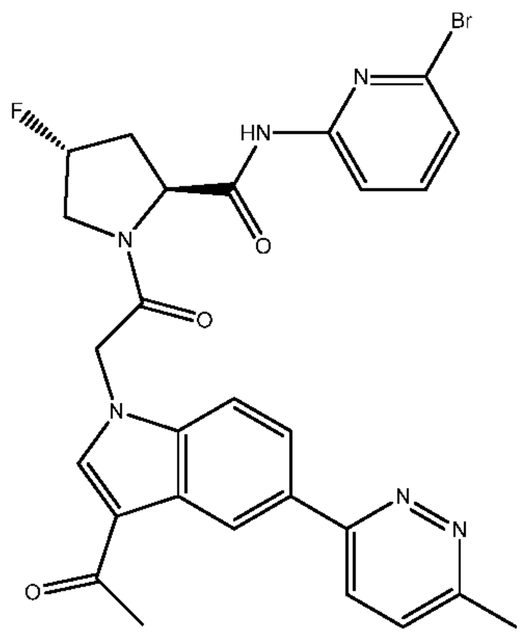
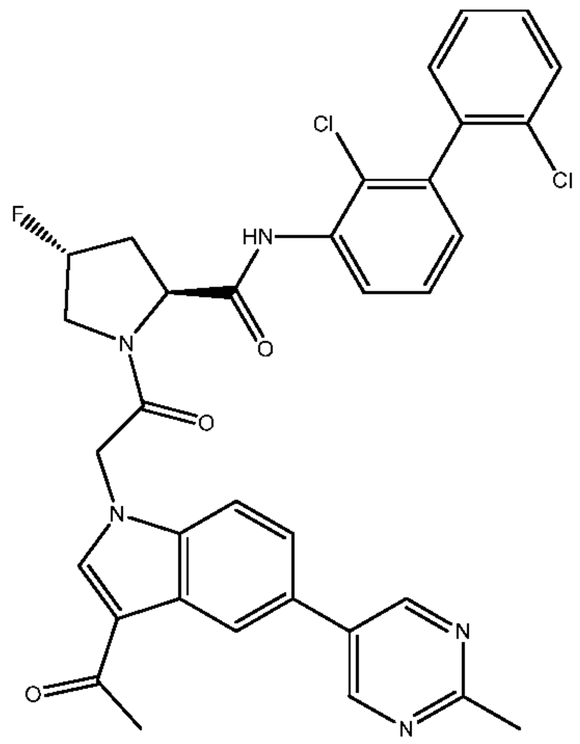
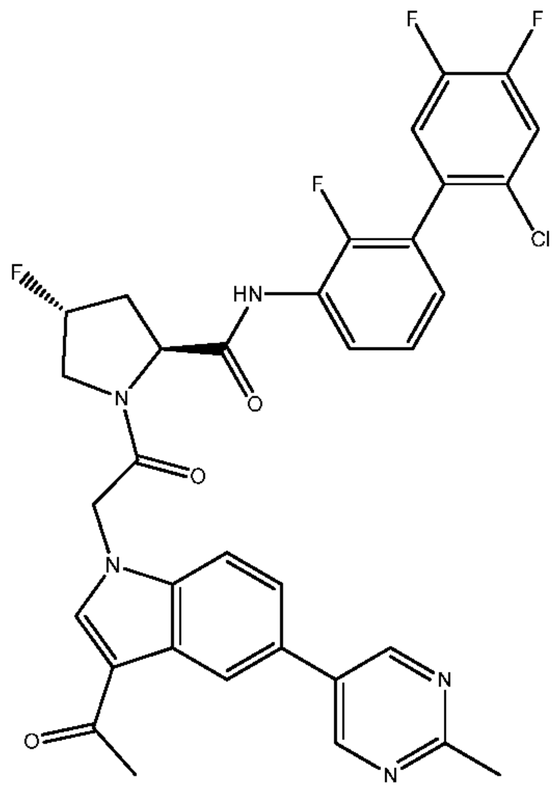
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
132		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	1.74 (A)	573
133		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	2.21 (A)	622
134		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	***	1.71 (A)	560

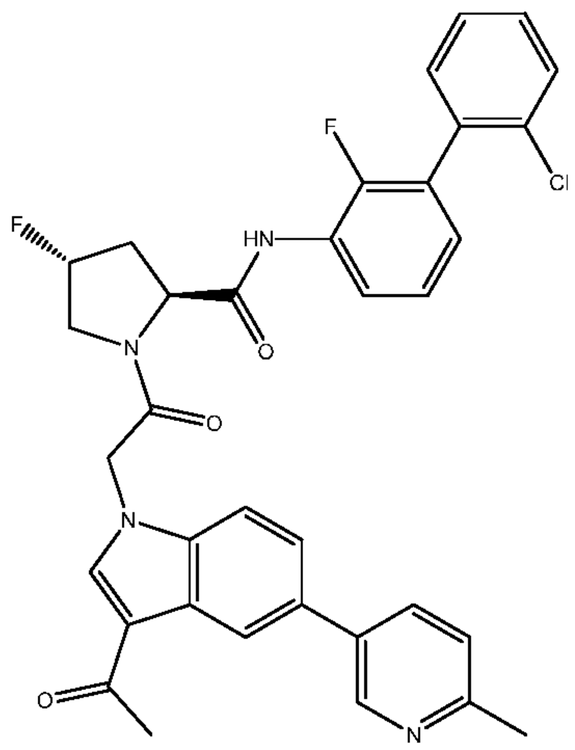
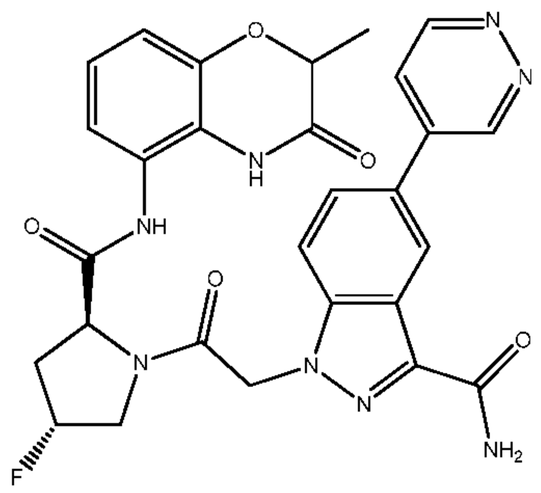
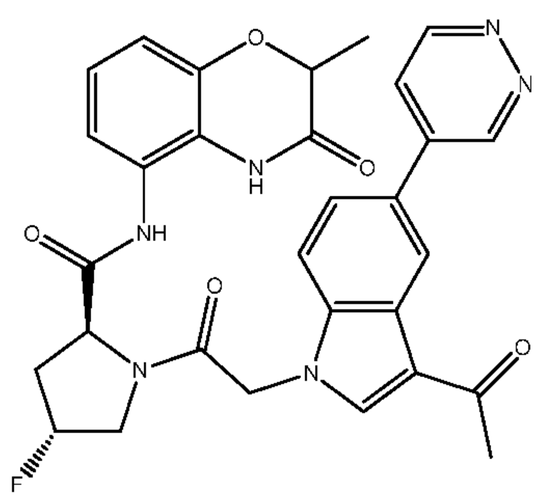
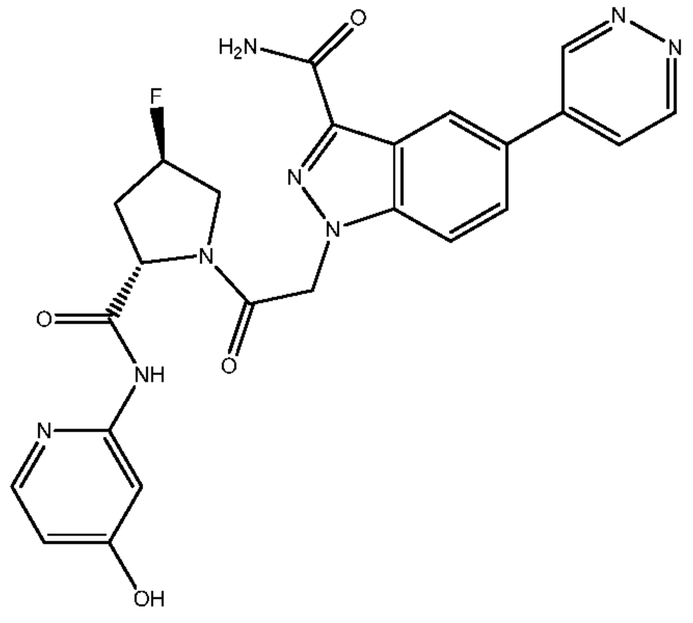
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
135		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide	***	1.64 (A)	566
136		(2S,4R)-1-(2-(3-acetyl-5-(2-methoxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(3-chloro-2-fluorobenzyl)-4-fluoropyrrolidine-2-carboxamide	***	1.80 (A)	582
137		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(6-chloropyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.53 (A)	535

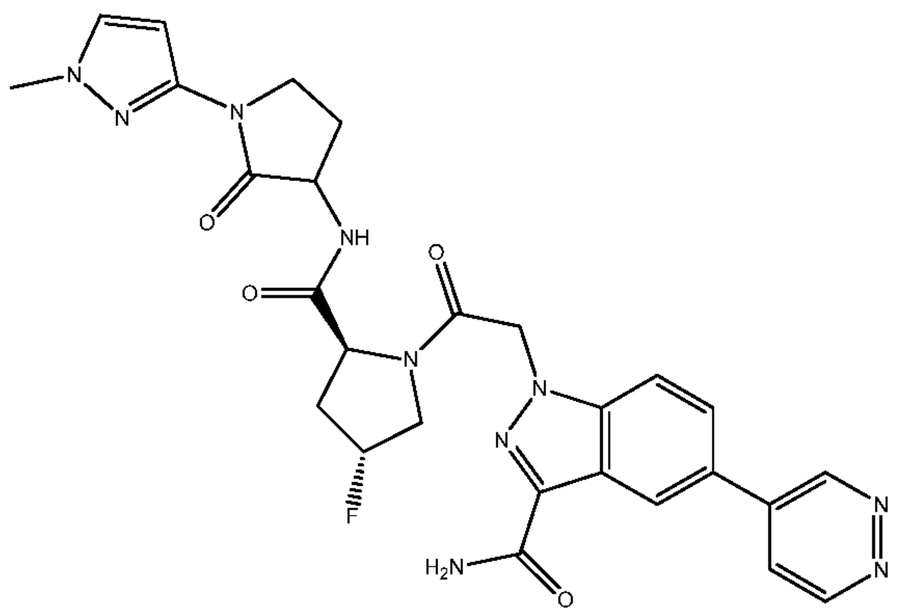
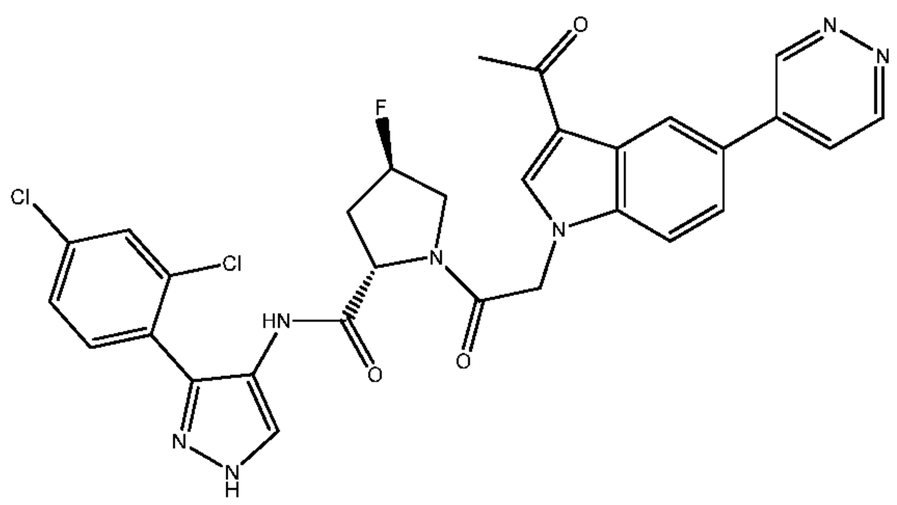
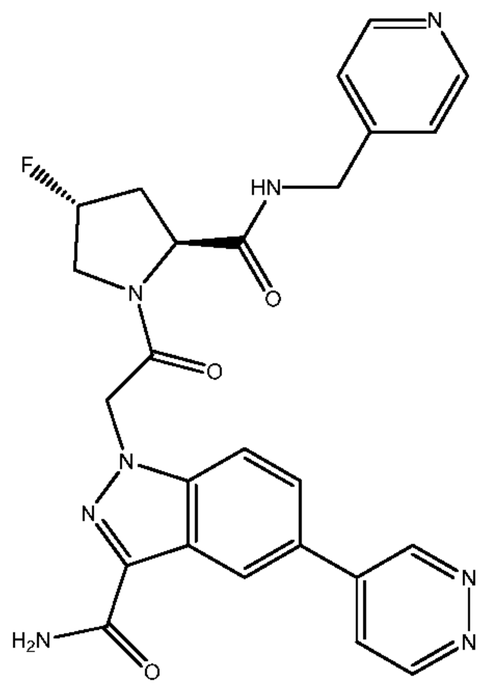
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
138		(2S,4R)-1-(2-(5-(2-acetamidopyrimidin-5-yl)-3-acetyl-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.95 (A)	671
139		1-(2-((2S,4R)-4-fluoro-2-(pyridin-2-ylmethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	3.38 (B)	503
140		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1-(1-methyl-1H-pyrazol-4-yl)piperidin-3-yl)pyrrolidine-2-carboxamide	**	1.51 (B)	573
141		1-(2-((2S,4R)-4-fluoro-2-(1-(1-methyl-1H-pyrazol-4-yl)piperidin-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.37 (B)	575

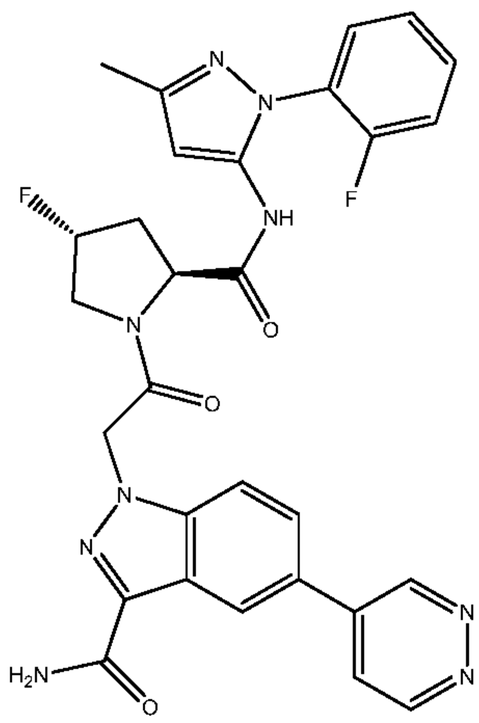
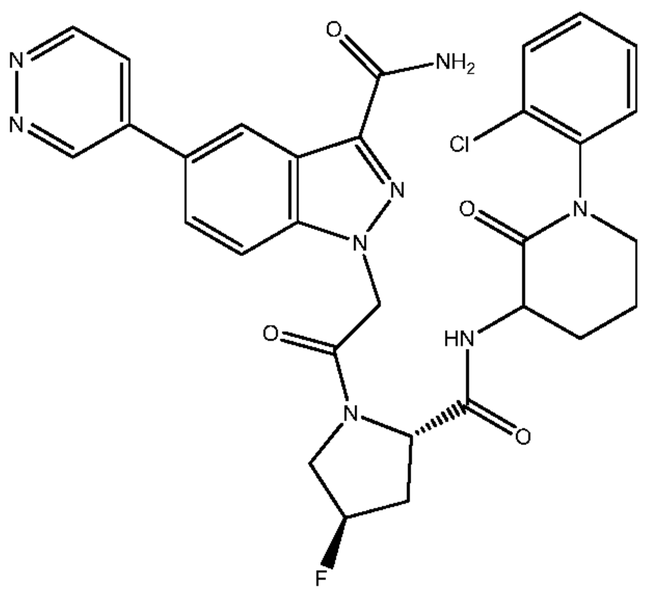
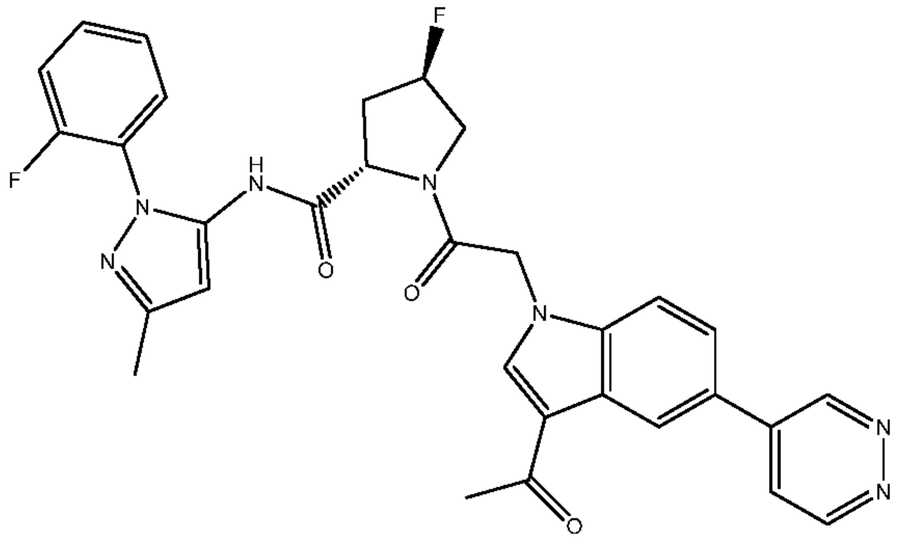
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
142		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1H-indazol-6-yl)pyrrolidine-2-carboxamide	**	2.10 (B)	526
143		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-((1R,2R)-2-hydroxycyclopentyl)pyrrolidine-2-carboxamide	*	1.59 (B)	494
144		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(6-hydroxypyridin-2-yl)pyrrolidine-2-carboxamide	*	1.43 (B)	503

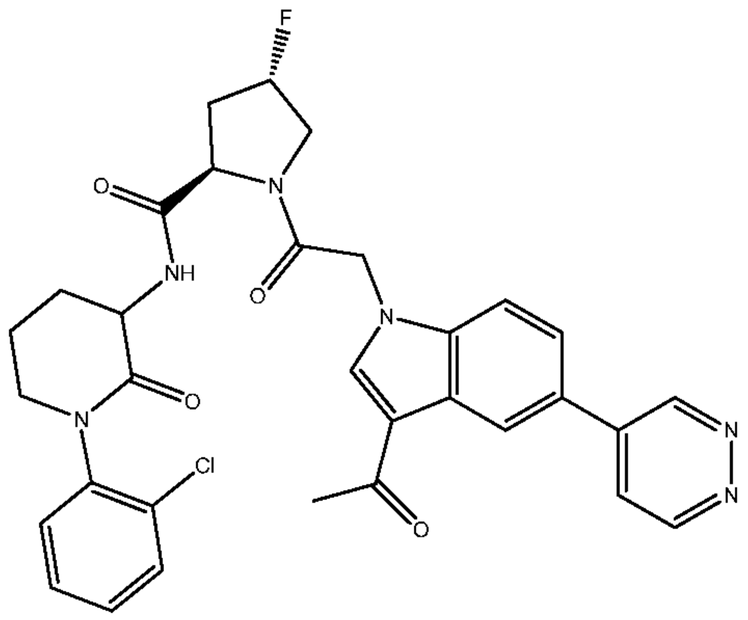
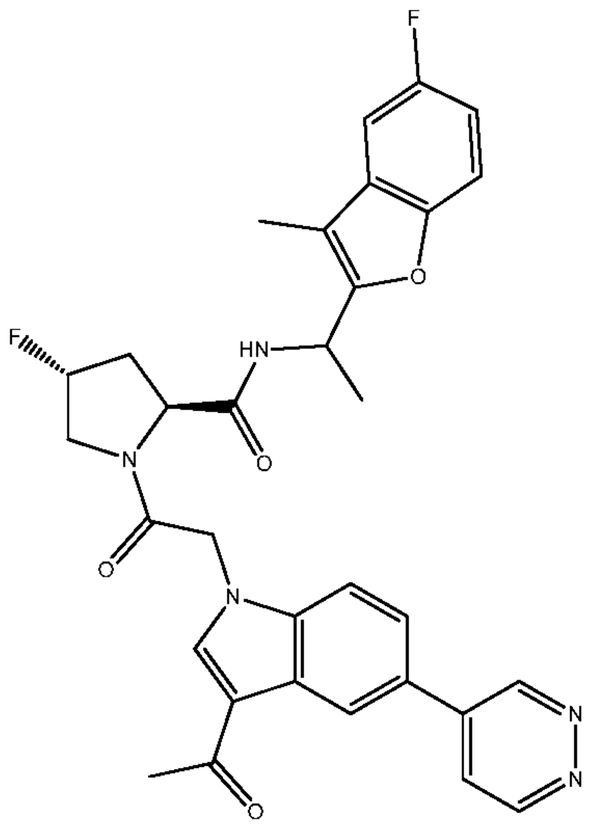
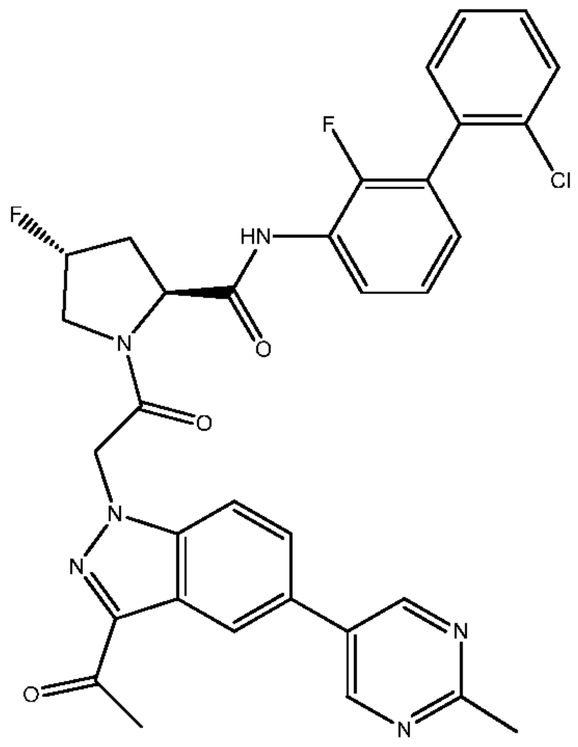
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
145		1-(2-((2S,4R)-4-fluoro-2-((1R,2R)-2-hydroxycyclopentylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.66 (B)	496
146		1-(2-((2S,4R)-2-(3-(3-chlorophenyl)-1,2,4-thiadiazol-5-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	3.47 (B)	606
147		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-(3-chlorophenyl)-1,2,4-thiadiazol-5-yl)-4-fluoropyrrolidine-2-carboxamide	*	3.67 (B)	604

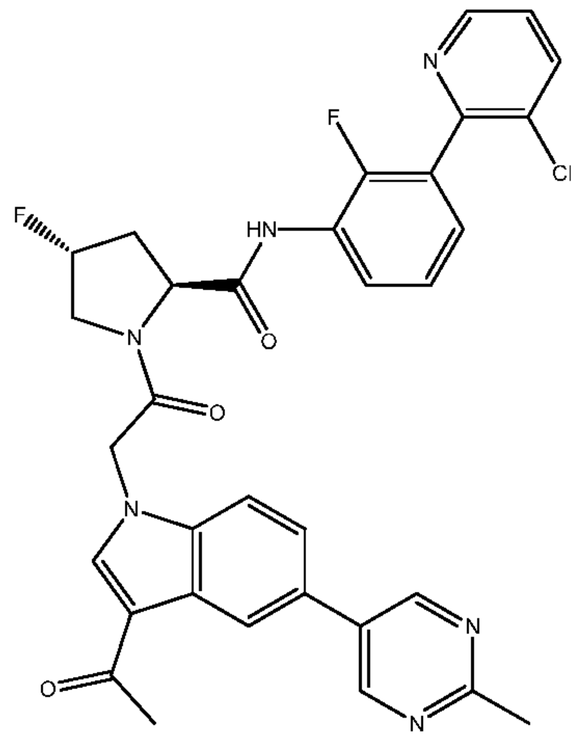
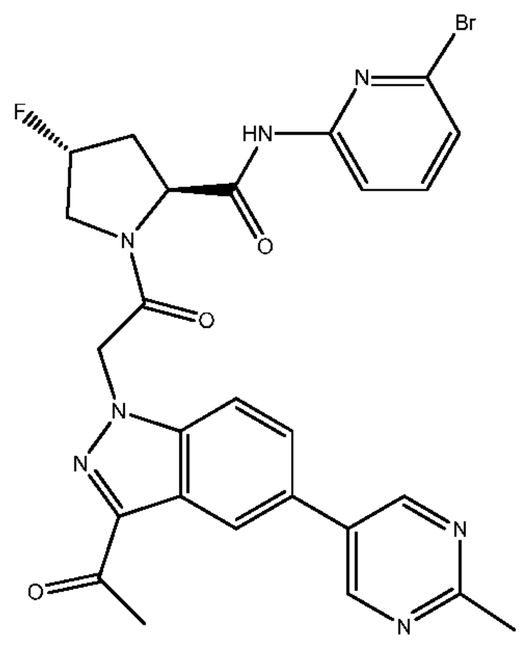
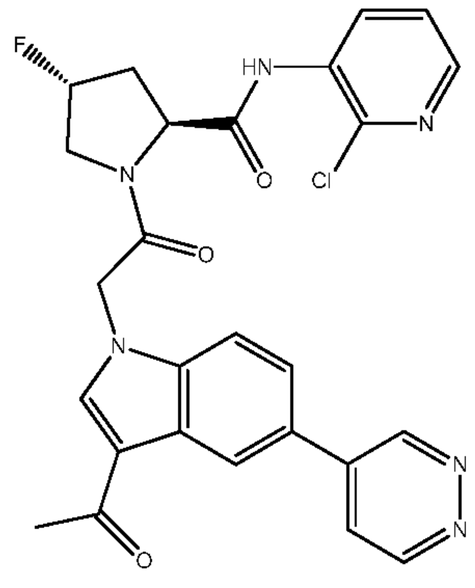
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
148		(2S,4R)-1-(2-(3-acetyl-5-(6-methylpyridazin-3-yl)-1H-indol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.49 (A)	580
149		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2,2'-dichlorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.17 (A)	644
150		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2,4',5'-trifluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.22 (A)	664

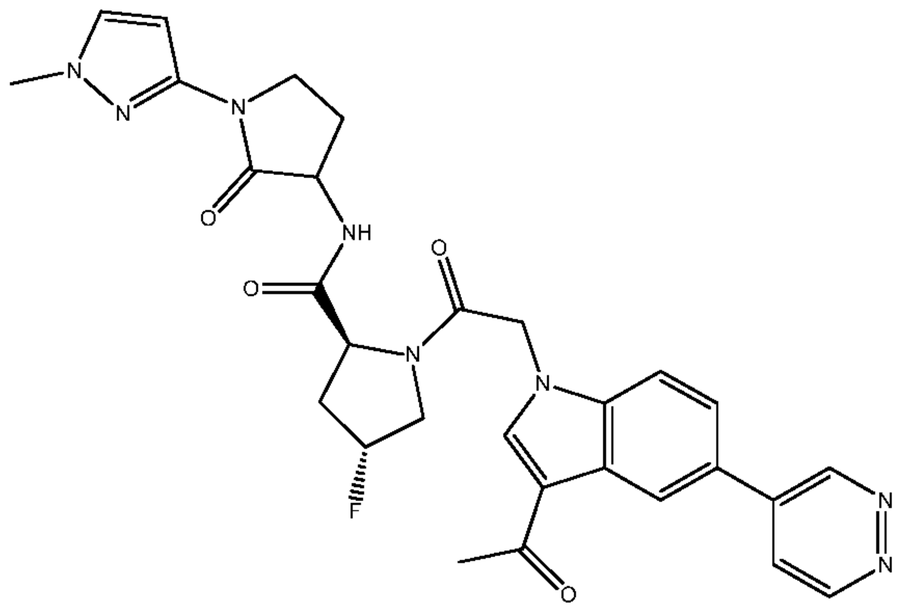
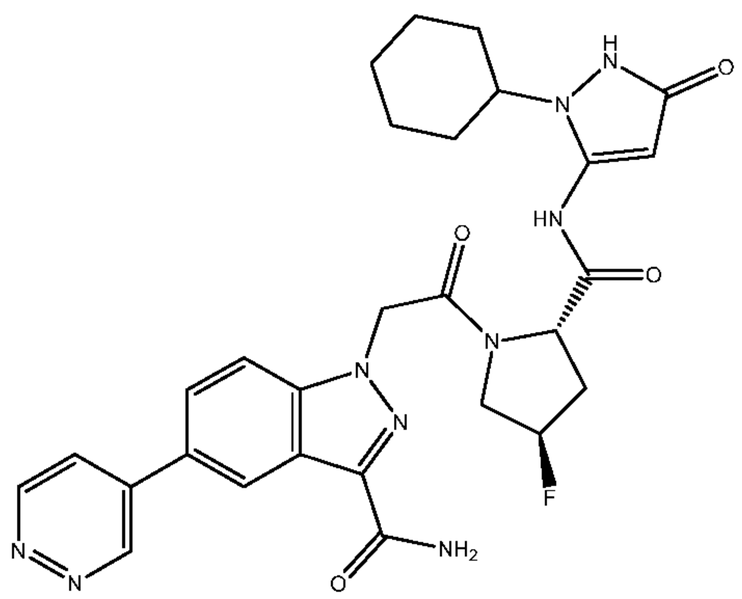
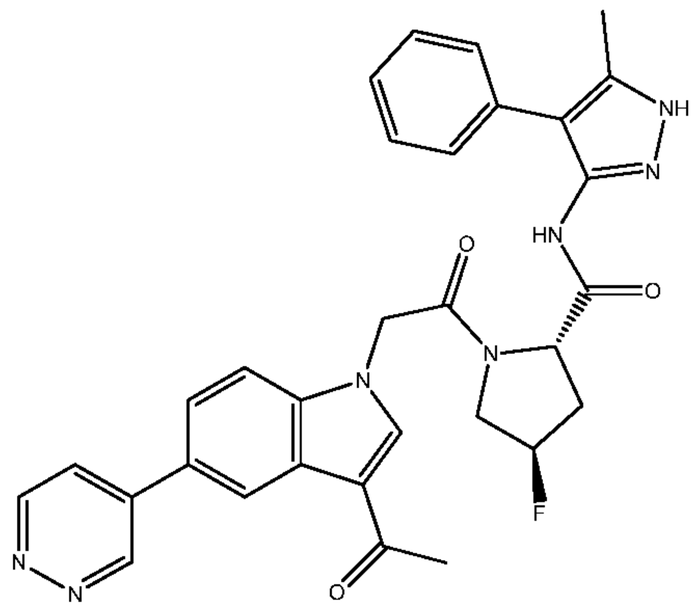
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
151		(2S,4R)-1-(2-(3-acetyl-5-(6-methylpyridin-3-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.91 (A)	627
152		1-(2-((2S,4R)-4-fluoro-2-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.97 (B)	573
153		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)pyrrolidine-2-carboxamide	*	2.31 (B)	571
154		1-(2-((2S,4R)-4-fluoro-2-(4-hydroxypyridin-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.17 (B)	505

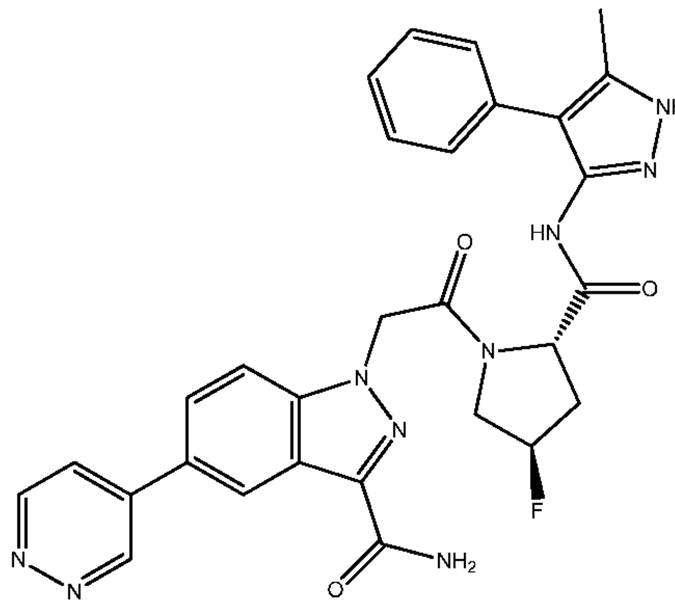
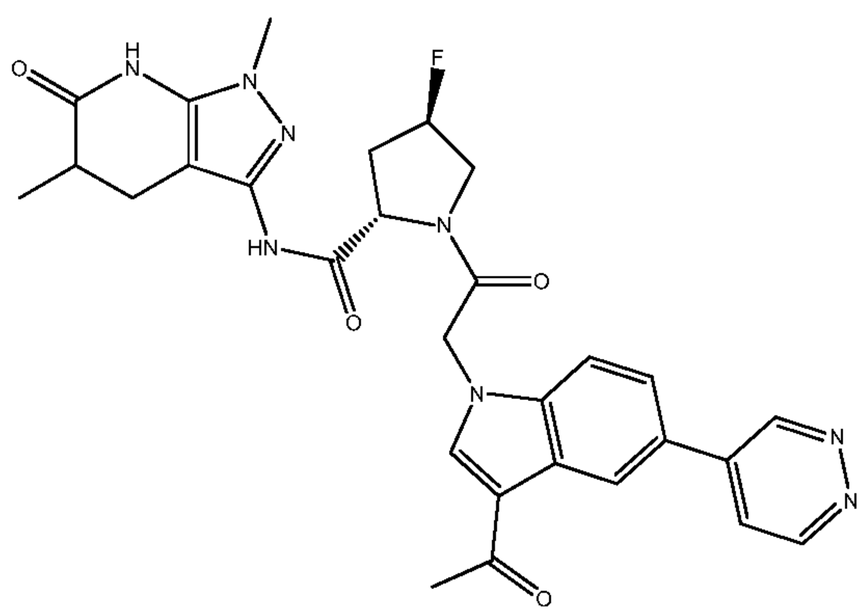
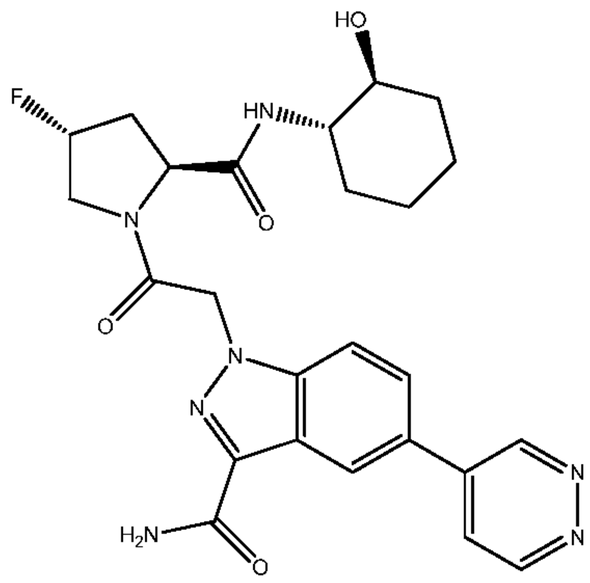
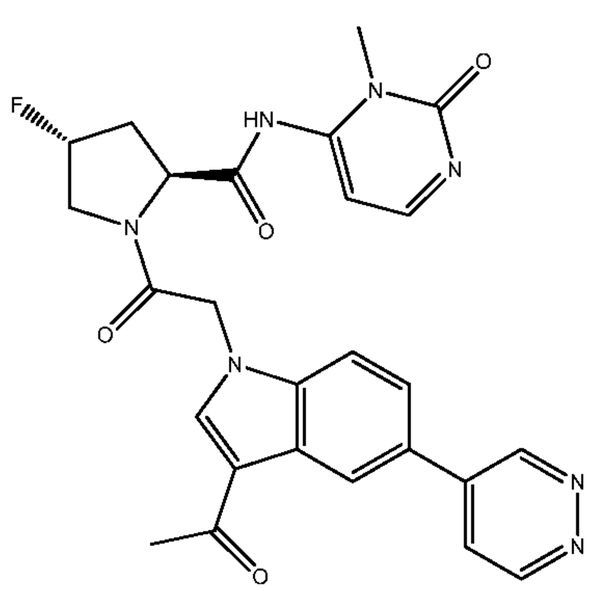
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
155		1-(2-((2S,4R)-4-fluoro-2-(1-(1-methyl-1H-pyrazol-3-yl)-2-oxopyrrolidin-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	1.19 (B)	575
156		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(3-(2,4-dichlorophenyl)-1H-pyrazol-4-yl)-4-fluoropyrrolidine-2-carboxamide	*	2.98 (B)	620
157		1-(2-((2S,4R)-4-fluoro-2-(pyridin-4-ylmethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	0.37 (B)	503

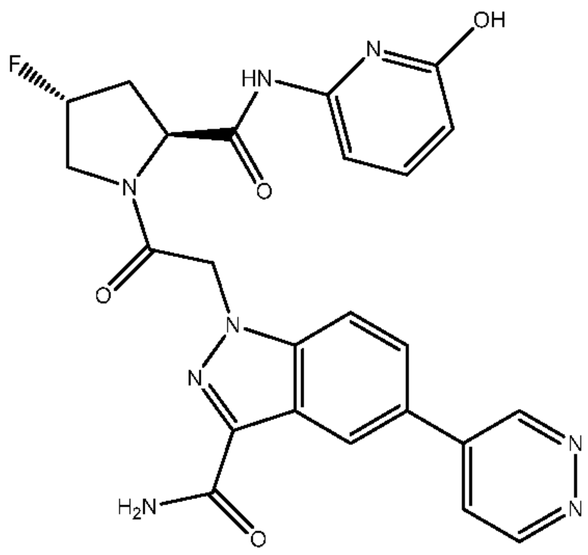
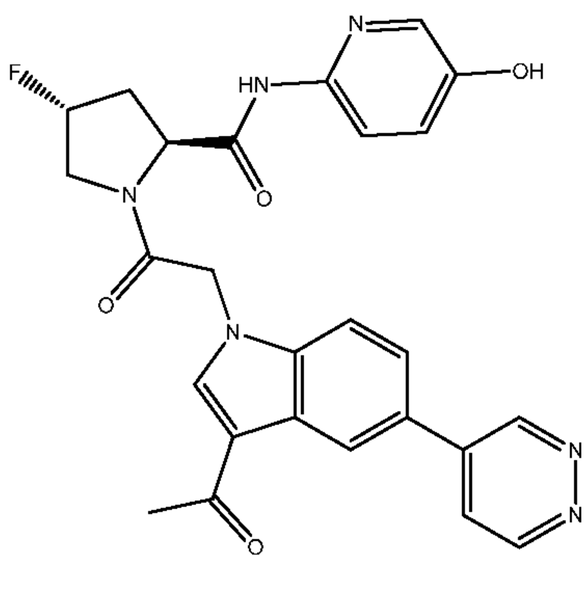
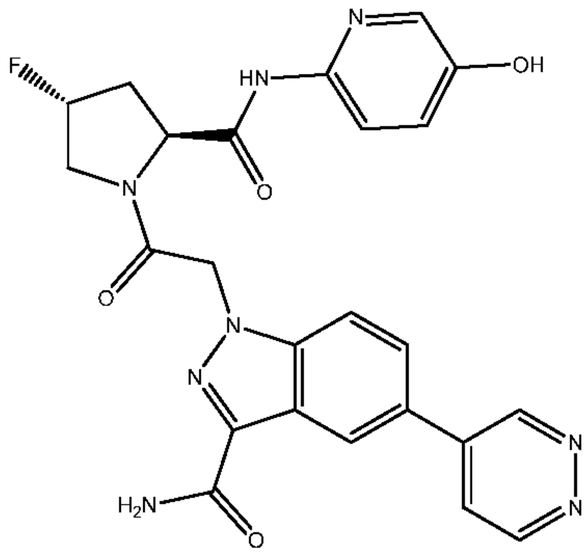
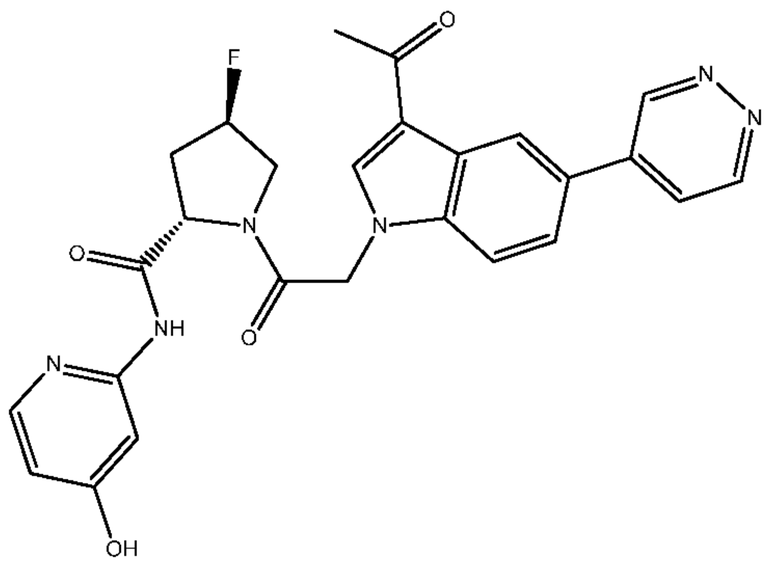
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
158		1-(2-((2S,4R)-4-fluoro-2-(1-(2-fluorophenyl)-3-methyl-1H-pyrazol-5-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	*	2.49 (B)	586
159		1-(2-((2S,4R)-2-(1-(2-chlorophenyl)-2-oxopiperidin-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	**	2.46 (B)	619
160		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1-(2-fluorophenyl)-3-methyl-1H-pyrazol-5-yl)pyrrolidine-2-carboxamide	**	2.36 (B)	584

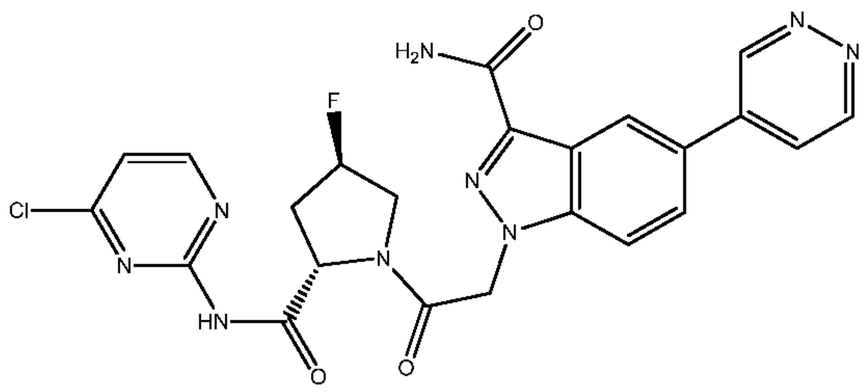
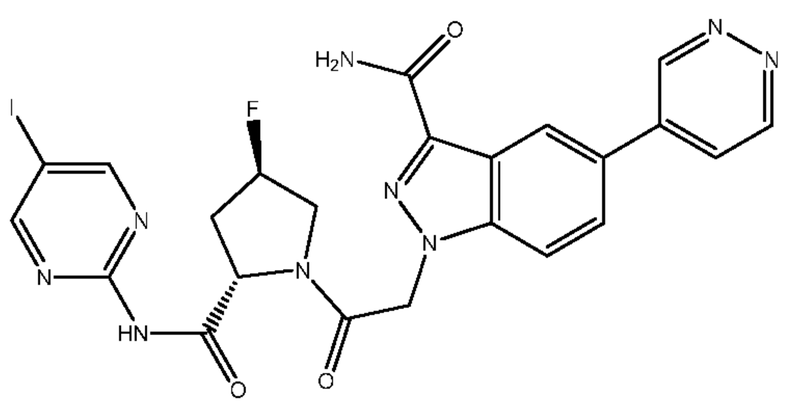
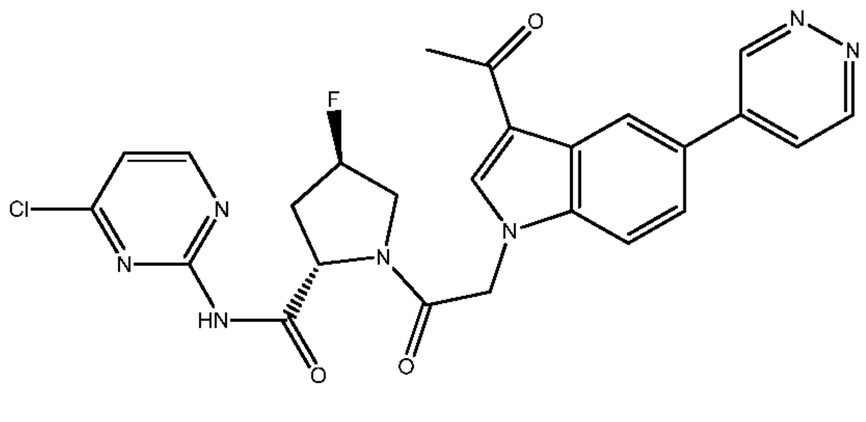
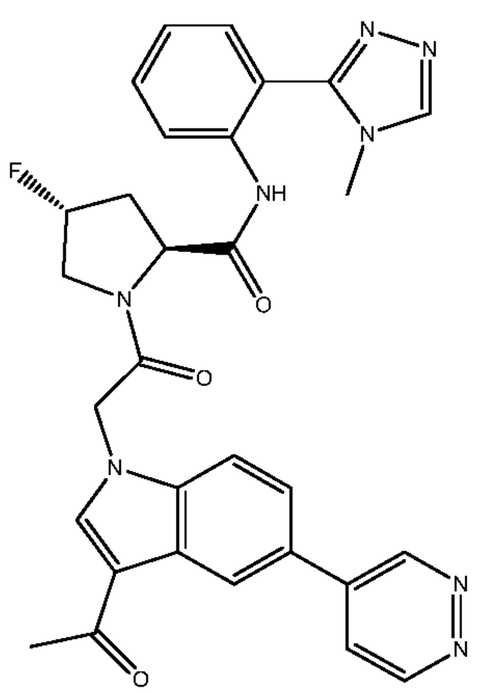
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
161		(2R,4S)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(1-(2-chlorophenyl)-2-oxopiperidin-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.85 (B)	617
162		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1-(5-fluoro-3-methylbenzofuran-2-yl)ethyl)pyrrolidine-2-carboxamide	**	3.52 (B)	586
163		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.23 (A)	629

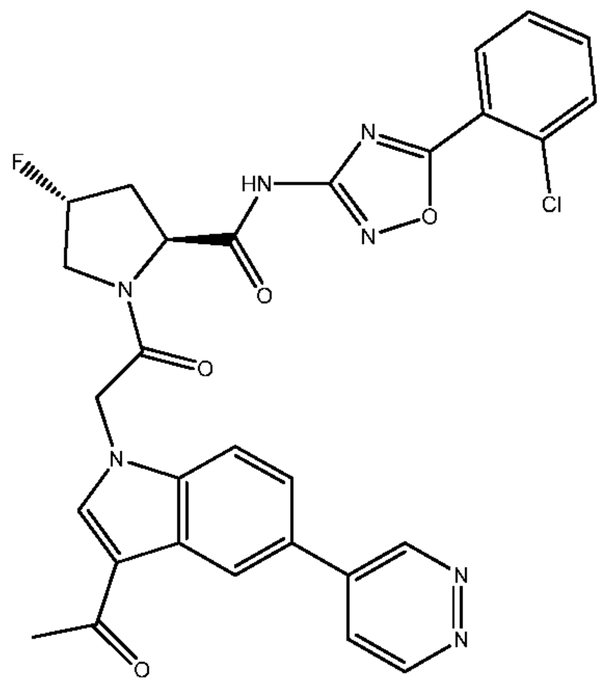
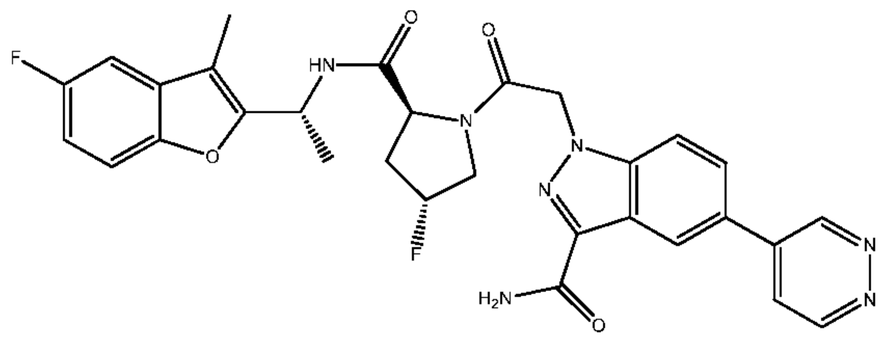
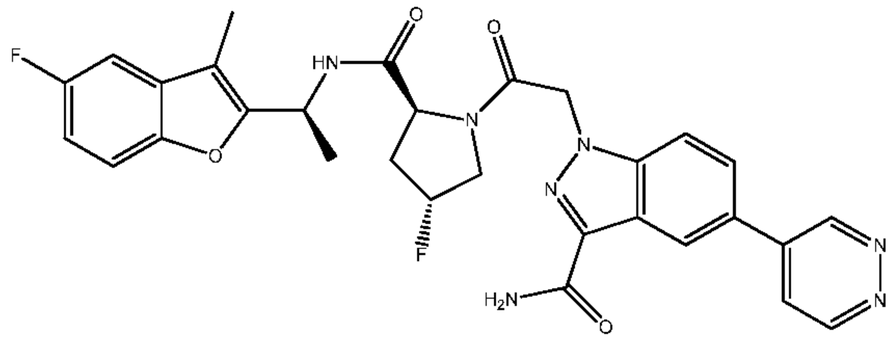
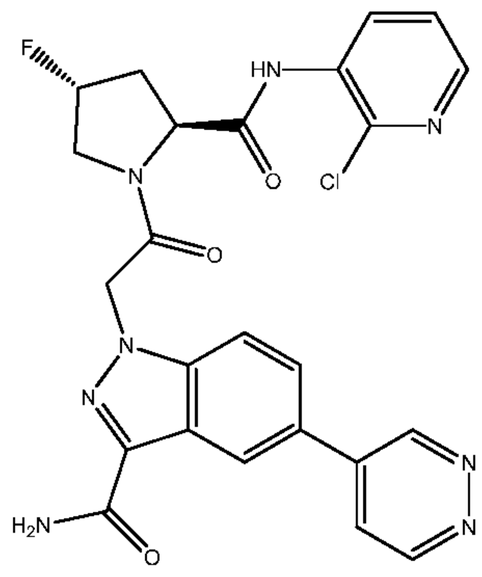
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
164		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(3-(3-chloropyridin-2-yl)-2-fluorophenyl)-4-fluoropyrrolidine-2-carboxamide	***	1.65 (A)	629
165		(2S,4R)-1-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.75 (A)	580
166		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(2-chloropyridin-3-yl)-4-fluoropyrrolidine-2-carboxamide		2.26 (B)	521

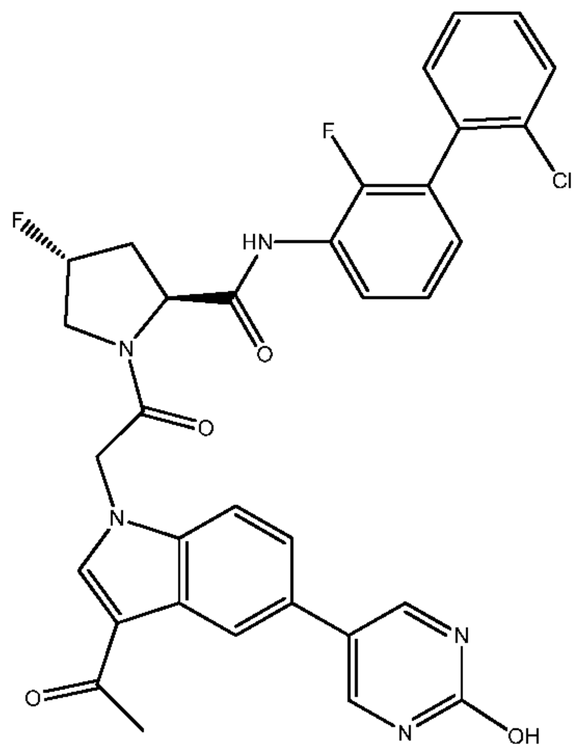
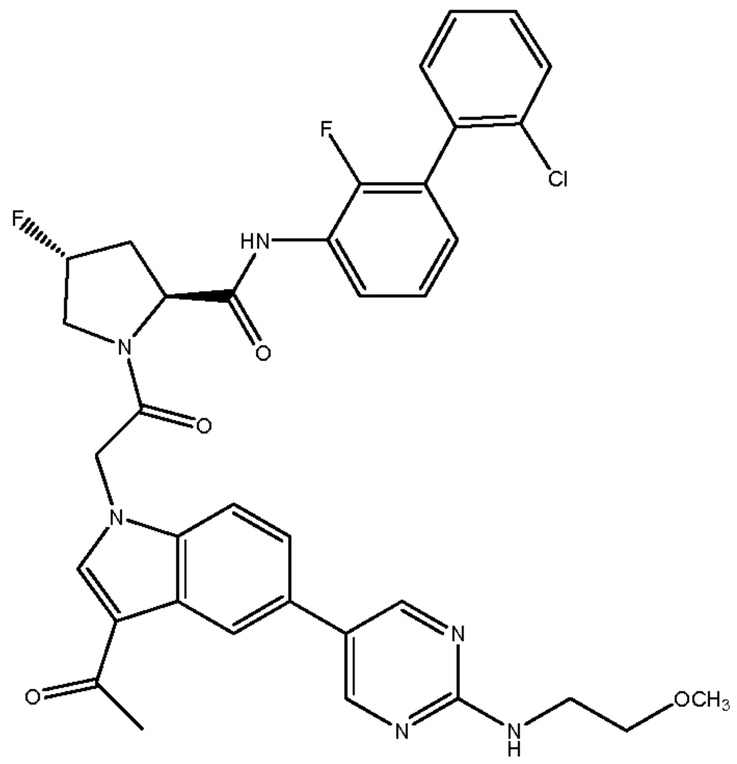
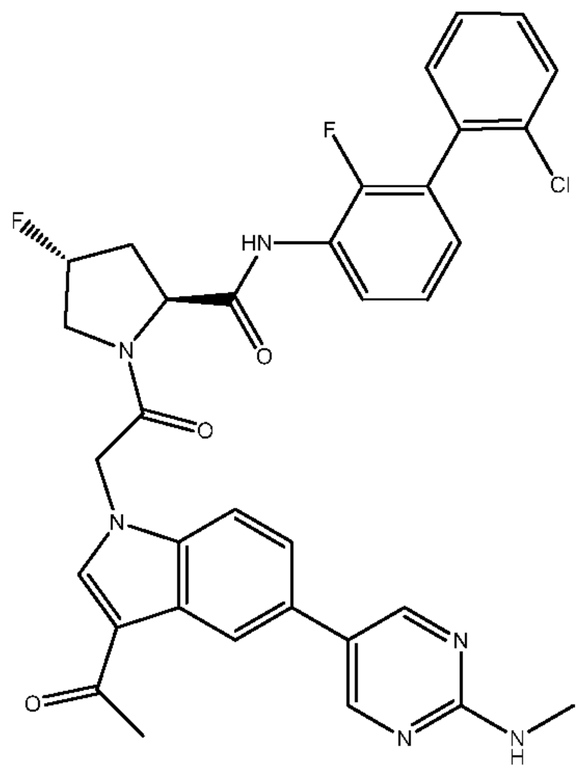
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
167		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(1-(1-methyl-1H-pyrazol-3-yl)-2-oxopyrrolidin-3-yl)pyrrolidine-2-carboxamide		2.15 (B)	573
168		1-(2-((2S,4R)-2-(2-cyclohexyl-5-oxo-2,5-dihydro-1H-pyrazol-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		2.20 (B)	576
169		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(5-methyl-4-phenyl-1H-pyrazol-3-yl)pyrrolidine-2-carboxamide		2.88 (B)	566

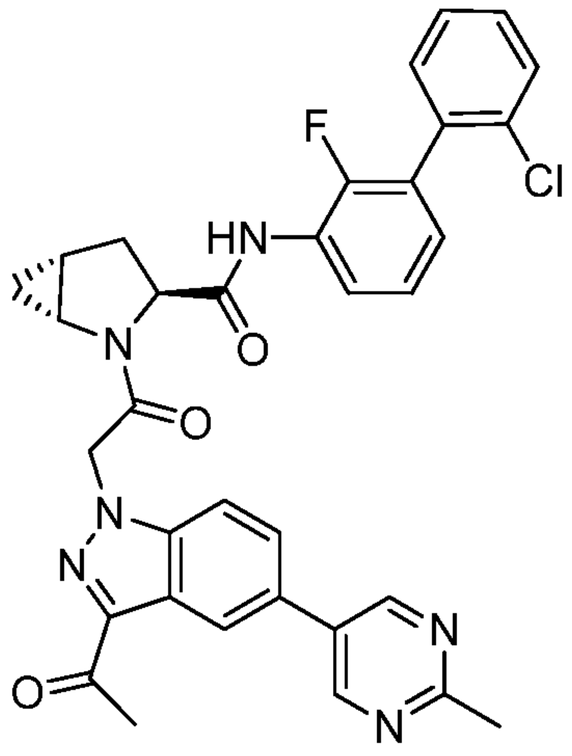
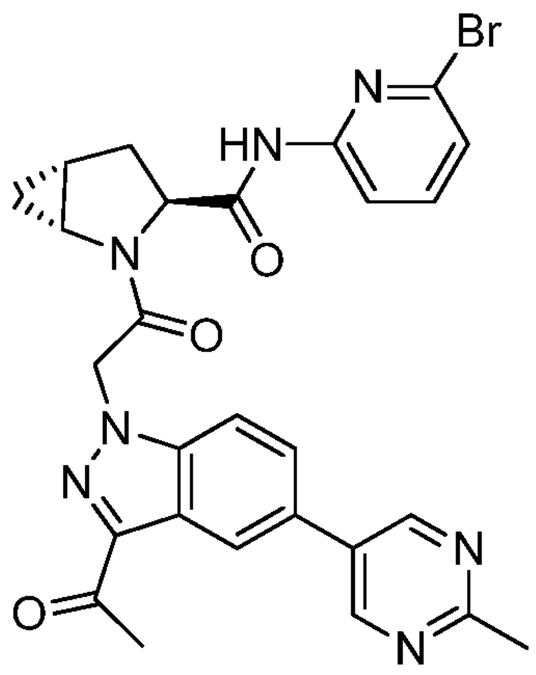
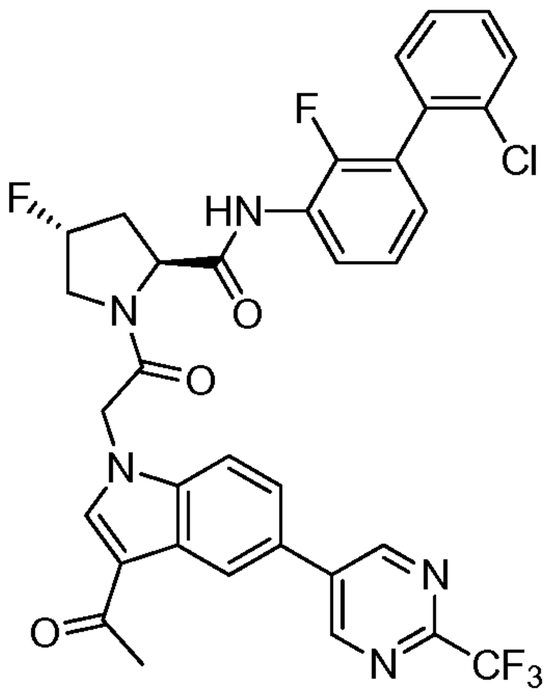
Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
170		1-(2-((2S,4R)-4-fluoro-2-(5-methyl-4-phenyl-1H-pyrazol-3-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		2.58 (B)	568
171		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(1,5-dimethyl-6-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-b]pyridin-3-yl)-4-fluoropyrrolidine-2-carboxamide		1.26 (B)	573
172		1-(2-((2S,4R)-4-fluoro-2-((1S,2S)-2-hydroxycyclohexylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		1.54 (B)	510
173		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(3-methyl-2-oxo-2,3-dihydropyrimidin-4-yl)pyrrolidine-2-carboxamide		2.17 (B)	518

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
174		1-(2-((2S,4R)-4-fluoro-2-(6-hydroxypyridin-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		1.71 (B)	505
175		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(5-hydroxypyridin-2-yl)pyrrolidine-2-carboxamide		2.25 (B)	503
176		1-(2-((2S,4R)-4-fluoro-2-(5-hydroxypyridin-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		1.06 (B)	505
177		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(4-hydroxypyridin-2-yl)pyrrolidine-2-carboxamide		2.08 (B)	503

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
178		1-(2-((2S,4R)-2-(4-chloropyrimidin-2-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		3.26 (B)	524
179		1-(2-((2S,4R)-4-fluoro-2-(5-iodopyrimidin-2-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide	2.78 (B)		616
180		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(4-chloropyrimidin-2-yl)-4-fluoropyrrolidine-2-carboxamide	3.57 (B)		522
181		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-4-fluoro-N-(2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)pyrrolidine-2-carboxamide	3.16 (B)		567

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
182		(2S,4R)-1-(2-(3-acetyl-5-(pyridazin-4-yl)-1H-indol-1-yl)acetyl)-N-(5-(2-chlorophenyl)-1,2,4-oxadiazol-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	3.45 (B)	588
183		1-(2-((2S,4R)-4-fluoro-2-((R)-1-(5-fluoro-3-methylbenzofuran-2-yl)ethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		3.02 (B)	588
184		1-(2-((2S,4R)-4-fluoro-2-((S)-1-(5-fluoro-3-methylbenzofuran-2-yl)ethylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		3.30 (B)	588
185		1-(2-((2S,4R)-2-(2-chloropyridin-3-ylcarbamoyl)-4-fluoropyrrolidin-1-yl)-2-oxoethyl)-5-(pyridazin-4-yl)-1H-indazole-3-carboxamide		1.70 (B)	523

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
186		(2S,4R)-1-(2-(3-acetyl-5-(2-hydroxypyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	1.79 (A)	630
187		(2S,4R)-1-(2-(3-acetyl-5-(2-(2-methoxyethylamino)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.16 (A)	687
188		(2S,4R)-1-(2-(3-acetyl-5-(2-(methylamino)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	***	2.08 (A)	643

Cmp No.	Structure	Name	IC_{50}	RT min (Method A or B)	MS (M+1)
189		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide		2.37 (A)	623
190		(1R,3S,5R)-2-(2-(3-acetyl-5-(2-methylpyrimidin-5-yl)-1H-indazol-1-yl)acetyl)-N-(6-bromopyridin-2-yl)-2-azabicyclo[3.1.0]hexane-3-carboxamide	1.90 (A)		574
191		(2S,4R)-1-(2-(3-acetyl-5-(2-(trifluoromethyl)pyrimidin-5-yl)-1H-indol-1-yl)acetyl)-N-(2'-chloro-2-fluorobiphenyl-3-yl)-4-fluoropyrrolidine-2-carboxamide	2.64 (A)		682

EXAMPLE 7. HUMAN FACTOR D ASSAY

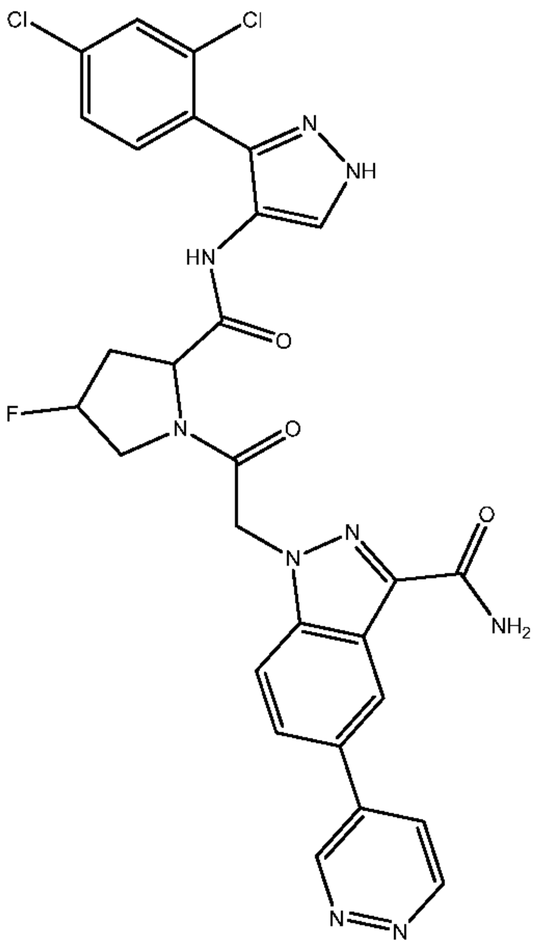
[0409] Human factor D (purified from human serum, Complement Technology, Inc.) at 80 nM final concentration is incubated with test compound at various concentrations for 5 minutes at room temperature in 50 mM Tris, 1M NaCl, pH 7.5. A synthetic substrate Z-L-Lys-SBzl and DTNB (Ellman's reagent) are added to final concentrations of 100 μM each. The increase in color is recorded at OD_{405} nm in a microplate in kinetic mode over 30 minutes with 30 second time points in a spectrofluorimeter. IC_{50} values are calculated by non-linear regression from the percentage of inhibition of complement factor D activity as a function of test compound concentration.

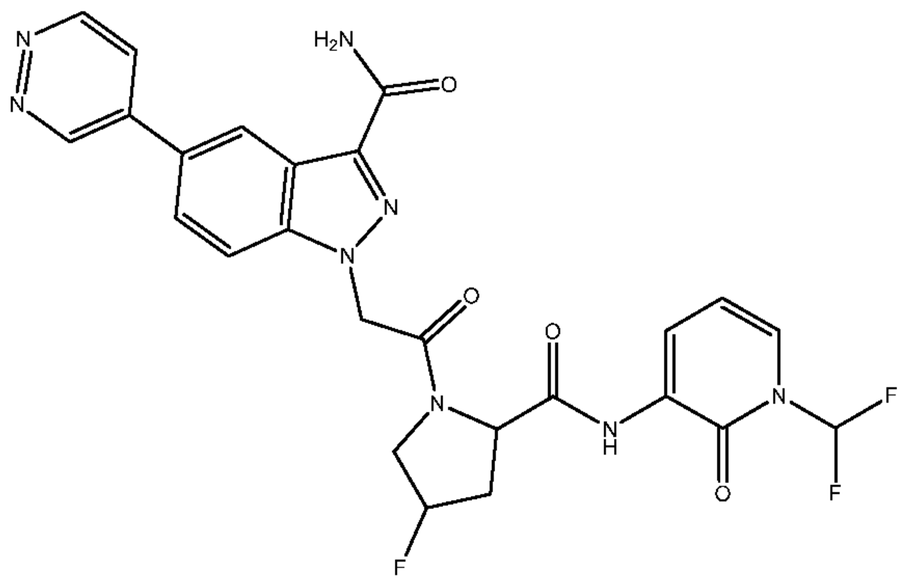
EXAMPLE 8. HEMOLYSIS ASSAY

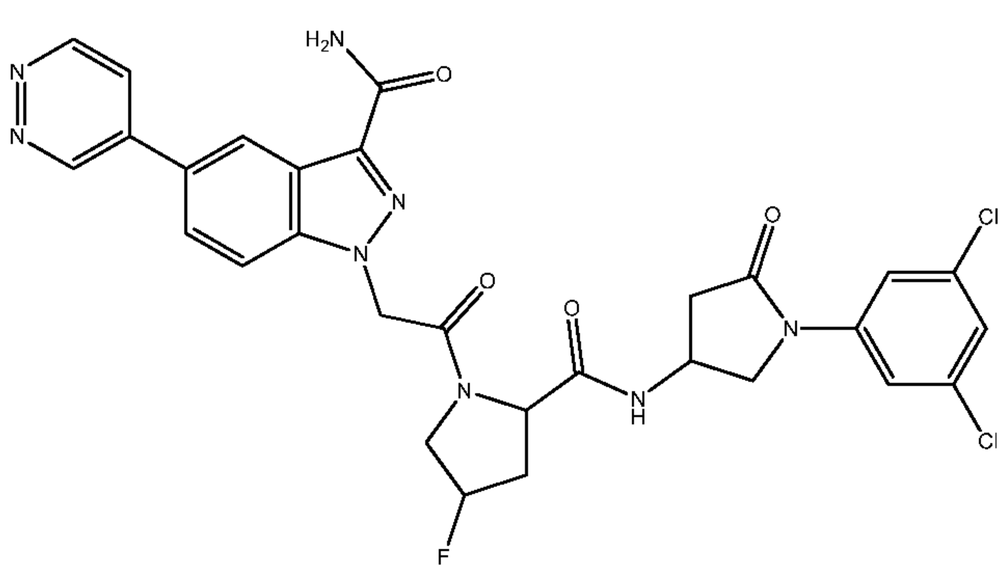
[0410] The hemolysis assay was previously described by G. Ruiz-Gomez, et al., J. Med. Chem. (2009) 52: 6042-6052. In the assay red blood cells (RBC), rabbit erythrocytes (purchased from Complement Technologies), are washed using GVB Buffer (0.1 % gelatin, 5 mM Veronal, 145 mM NaCl, 0.025 % NaN_3, pH 7.3) plus 10 mM final Mg-EGTA. Cells are used at a concentration of 1 x 10^8 cells/mL. Prior to the hemolysis assay, the optimum concentration of Normal Human Serum (NHS) needed to achieve 100% lysis of rabbit erythrocytes is determined by titration. NHS (Complement Technologies) is incubated with inhibitor for 15 min at 37 °C, rabbit erythrocytes in buffer were added and incubated for an additional 30 min at 37 °C. Positive control (100% lysis) consists of serum and RBC and negative control (0% lysis) of Mg-EGTA buffer and RBC only. Samples are centrifuged at 2000g for 5 min, and supernatants collected. Optical density of the supernatant is monitored at 405 nm using a UV/visible spectrophotometer. Percentage lysis in each sample is calculated relative to positive control (100% lysis).

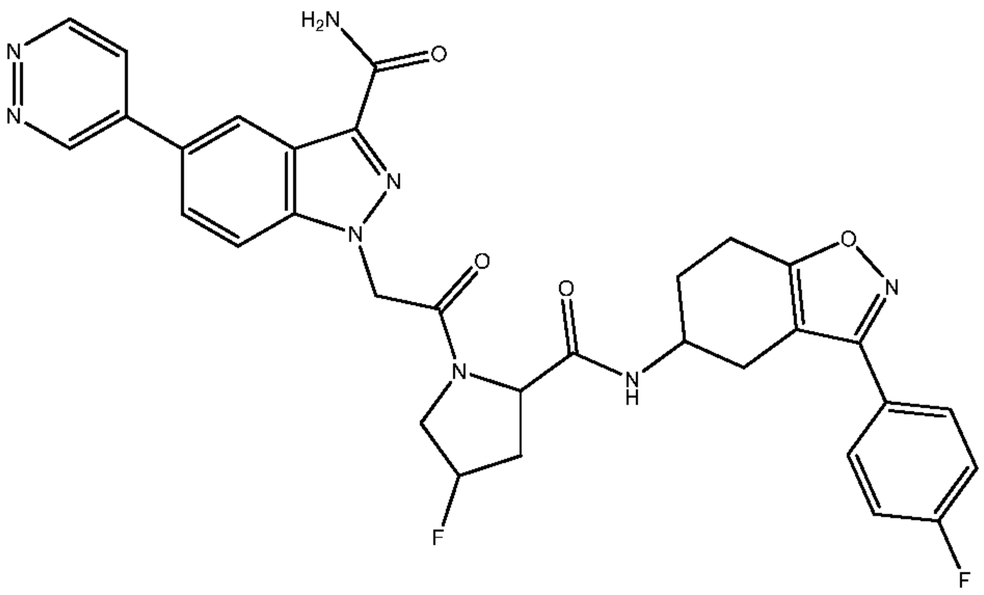
EXAMPLE 9. NON-LIMITING EXAMPLES OF COMPOUNDS OF FORMULA I

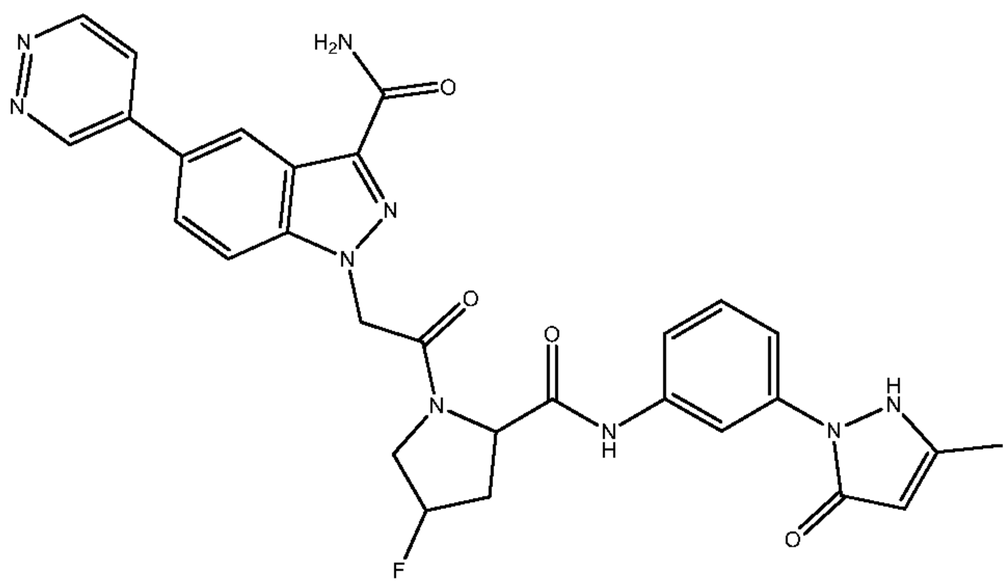
TABLE 2

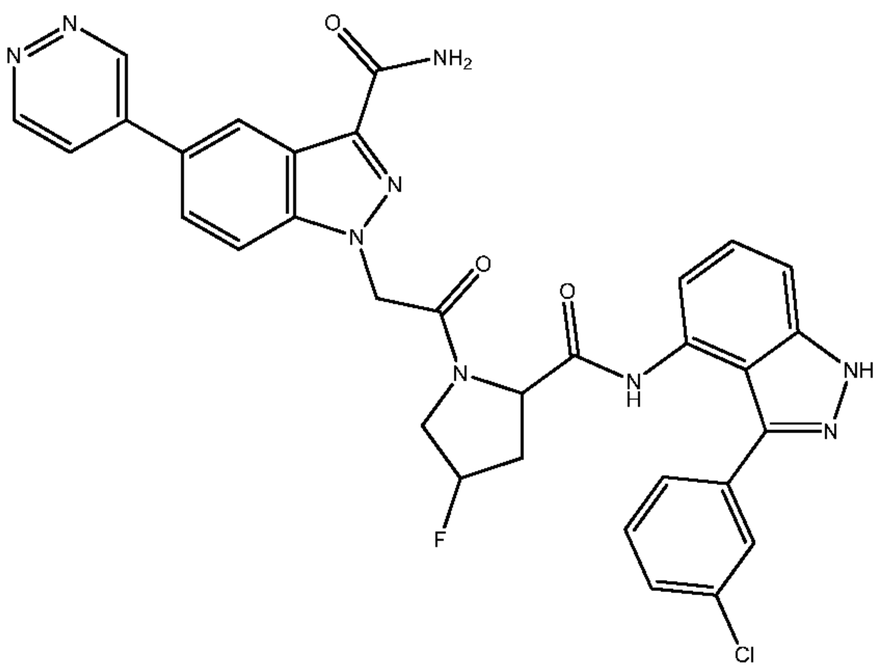


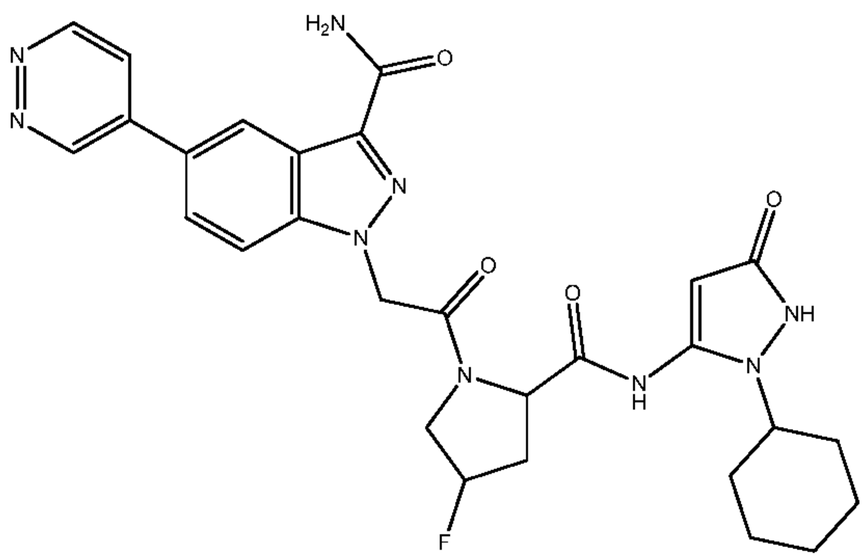


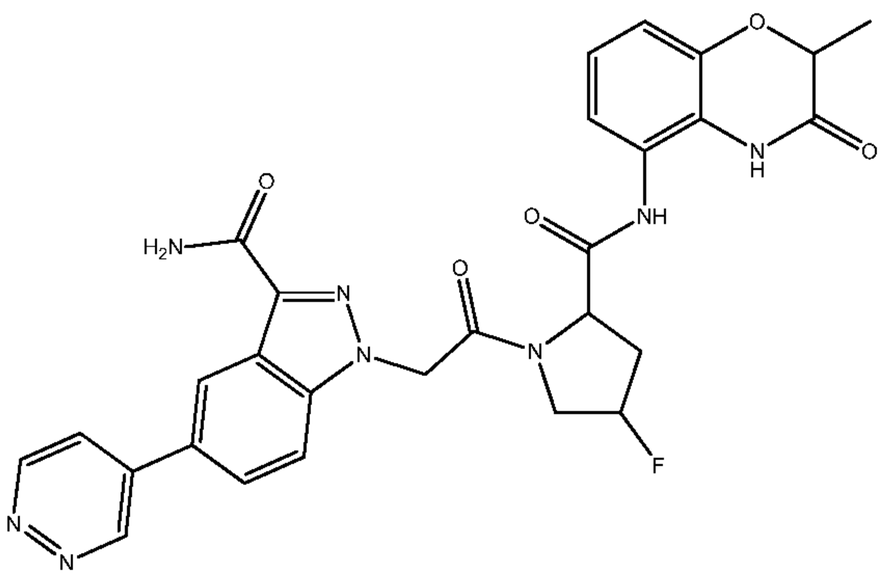


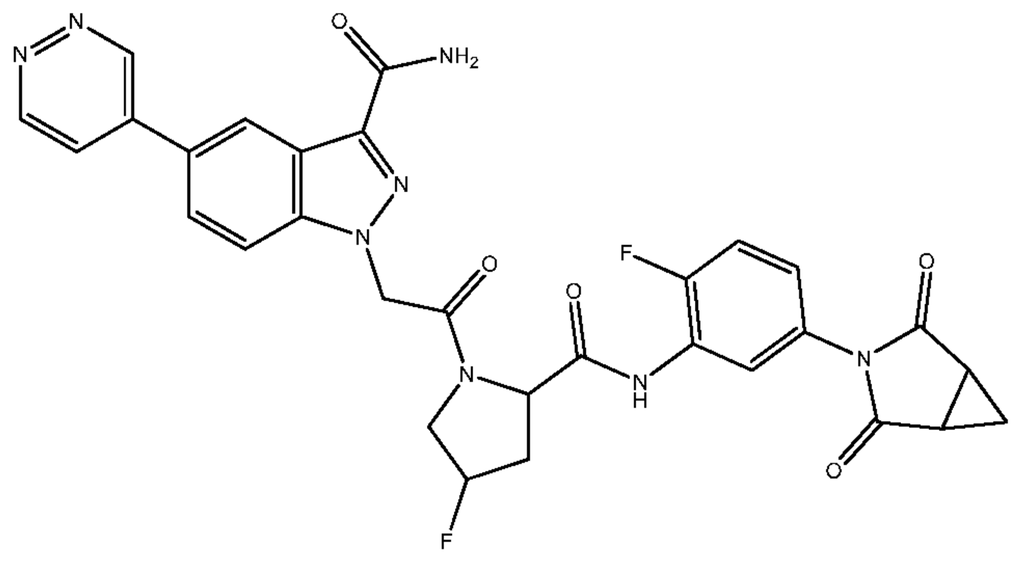


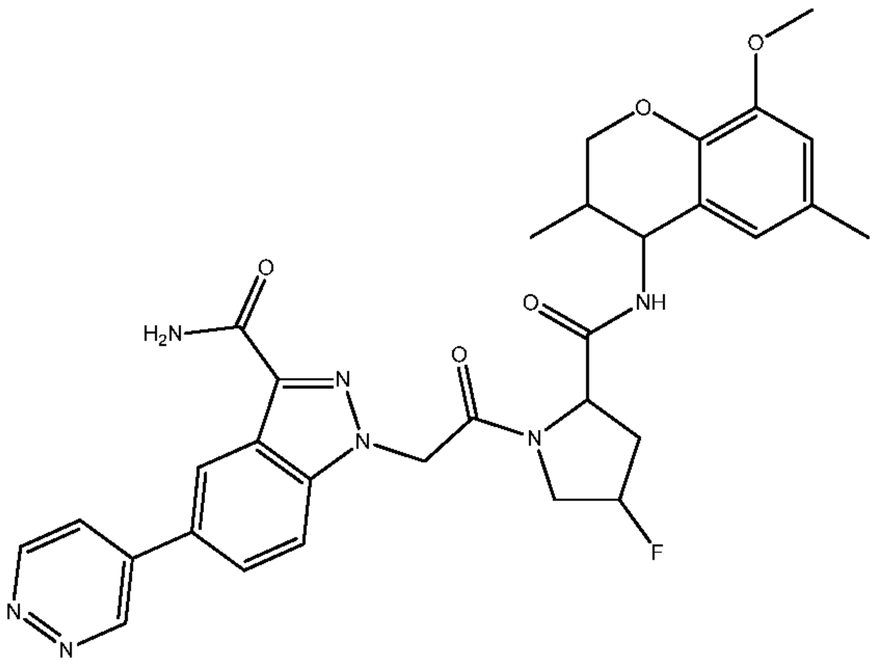


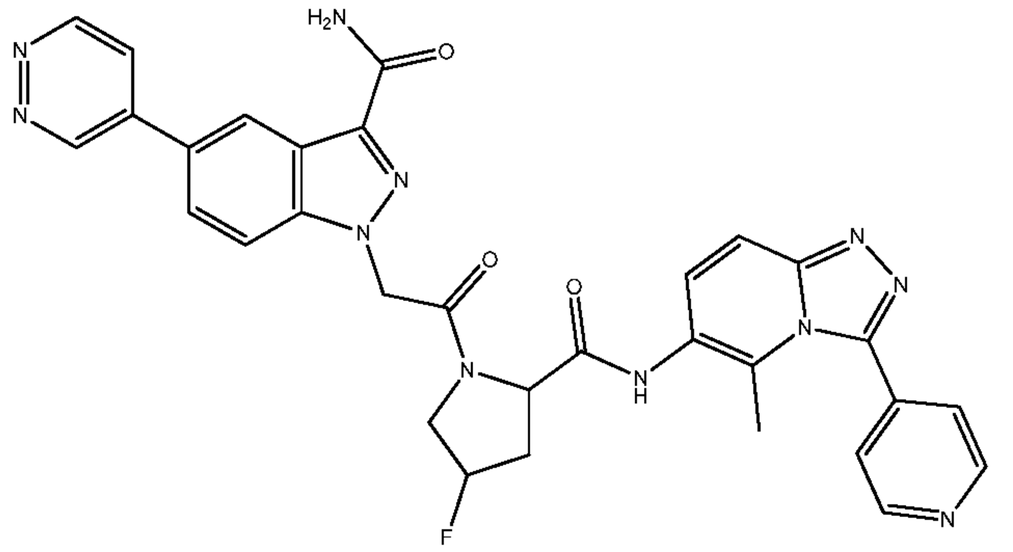


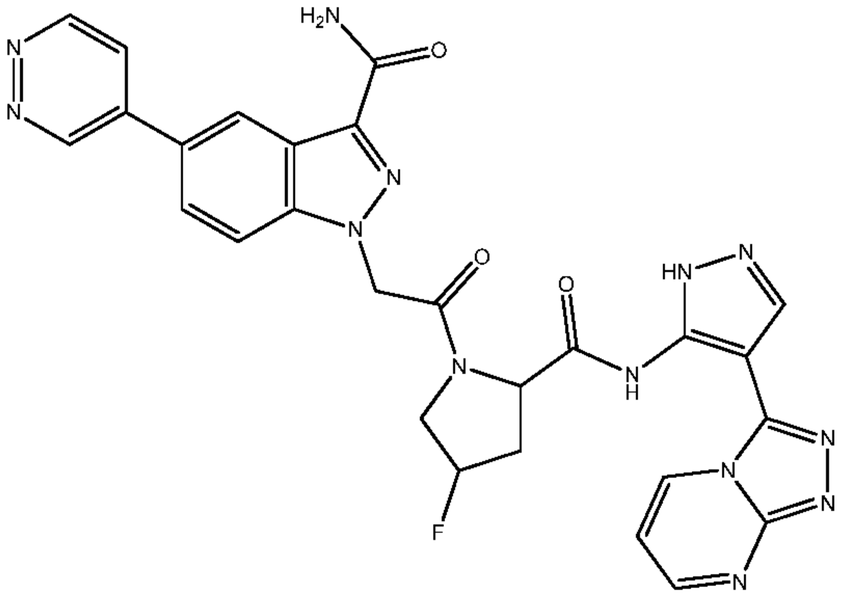


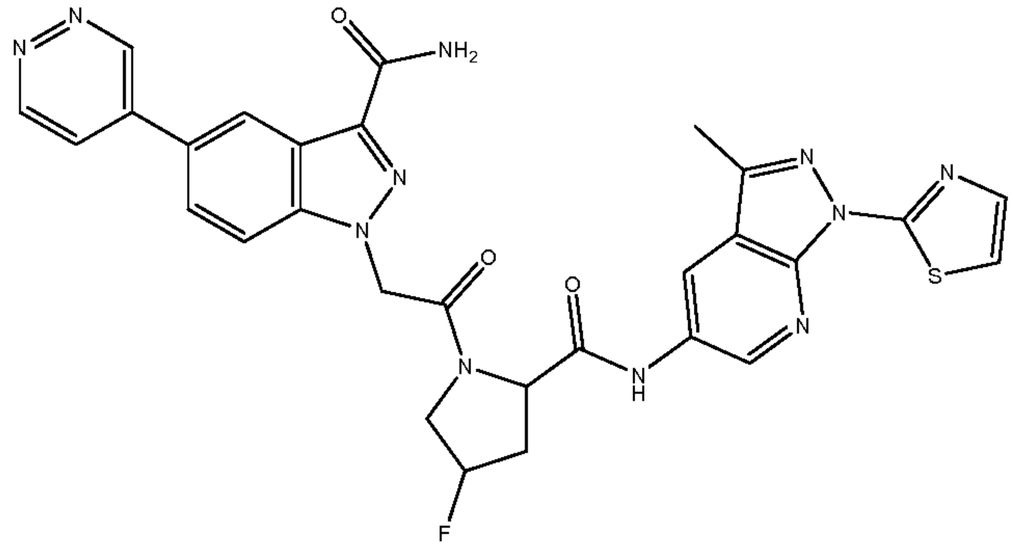


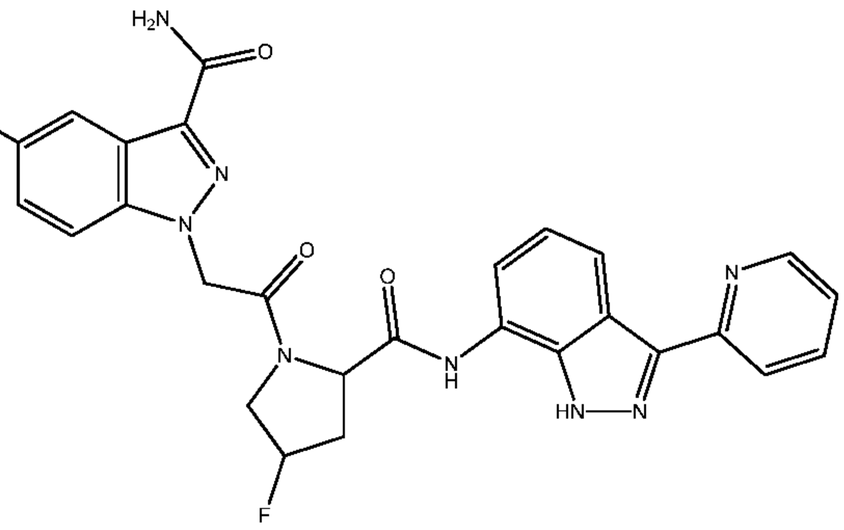


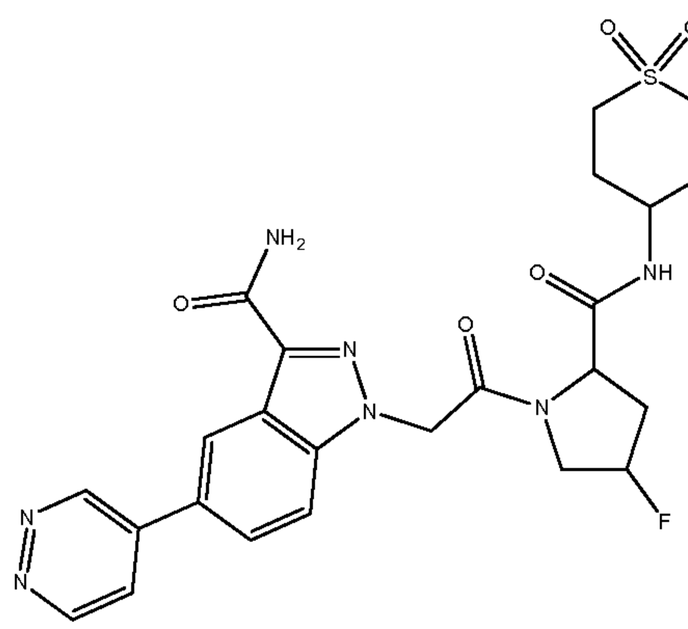


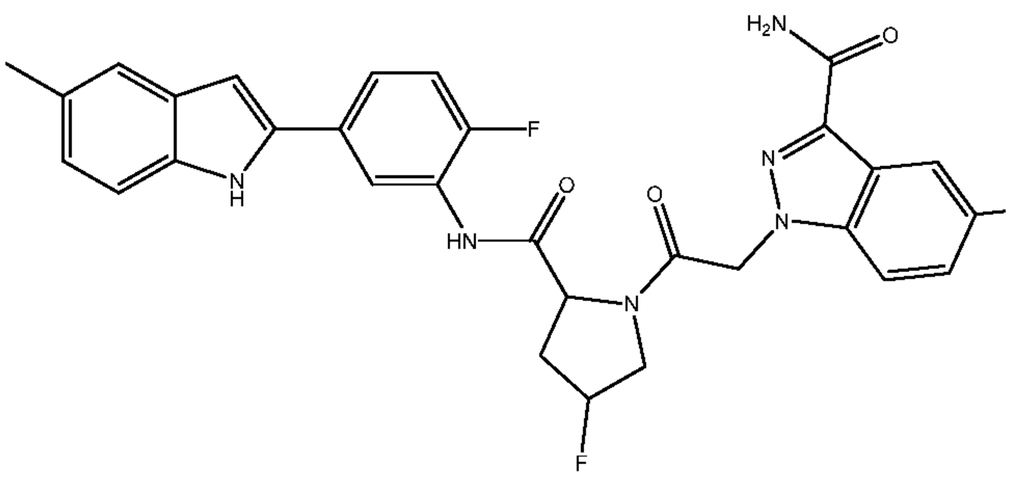


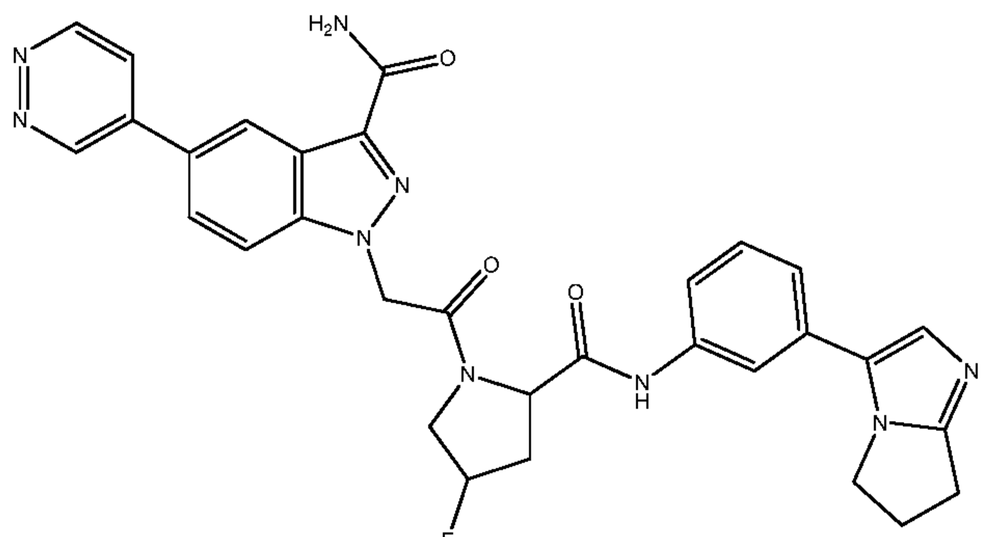


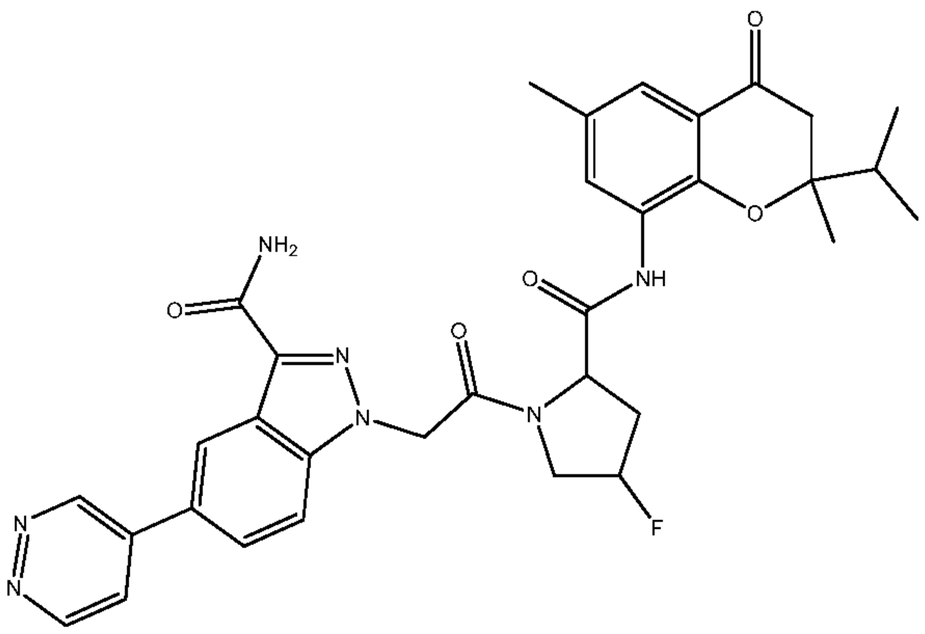


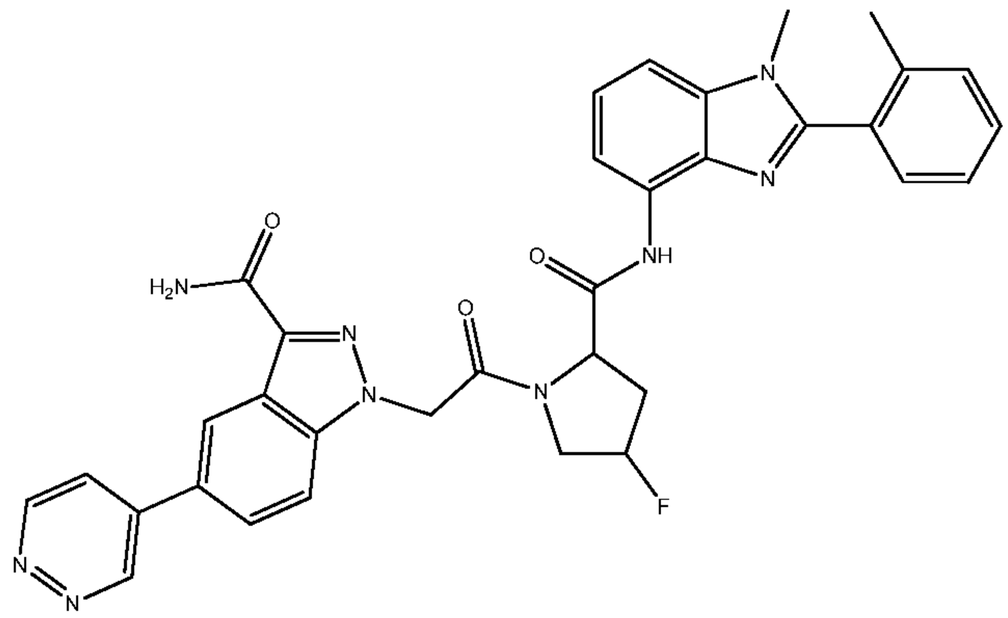


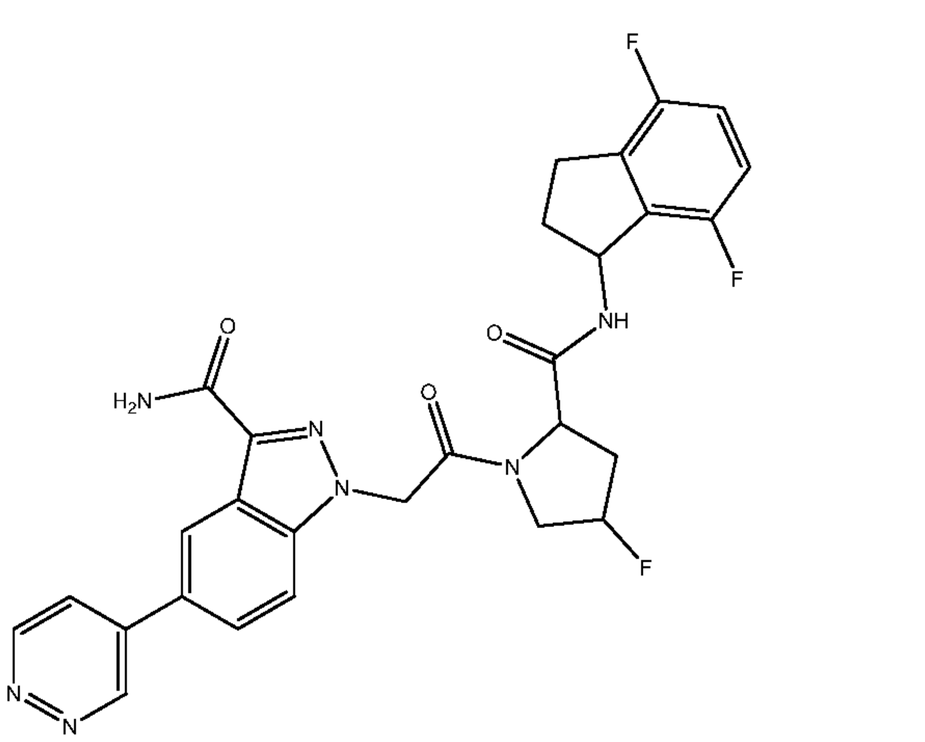


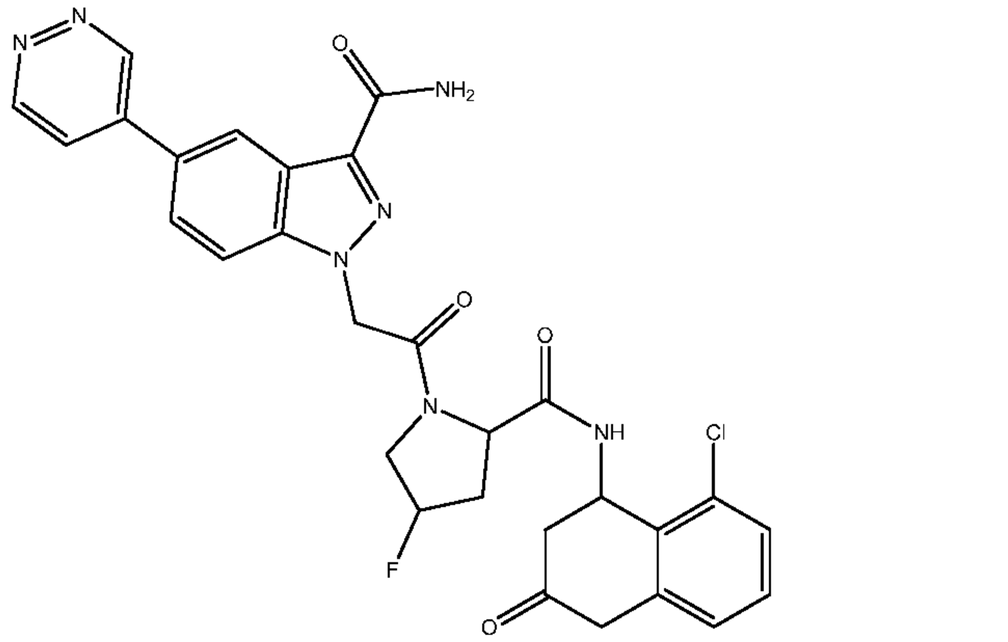


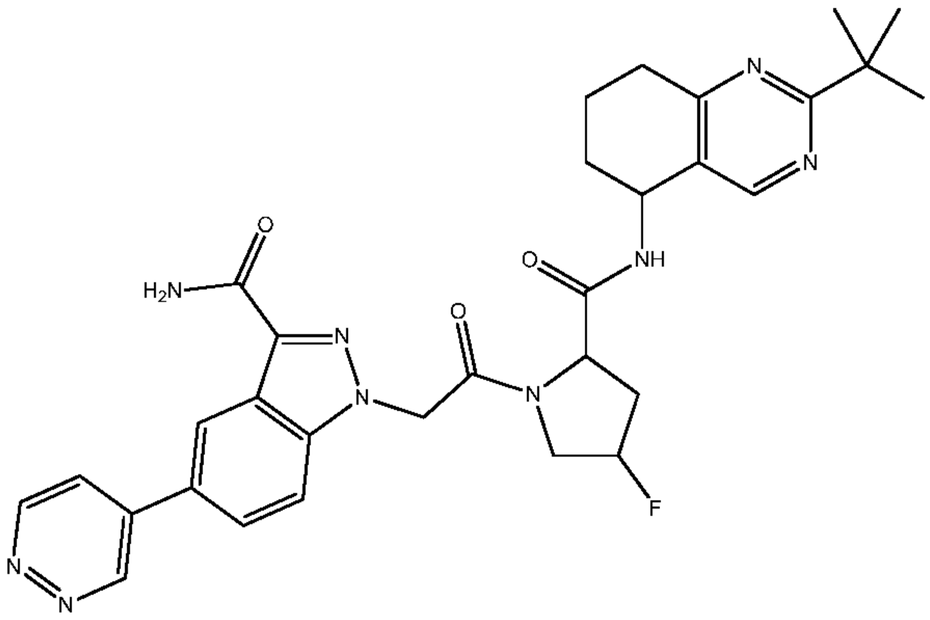


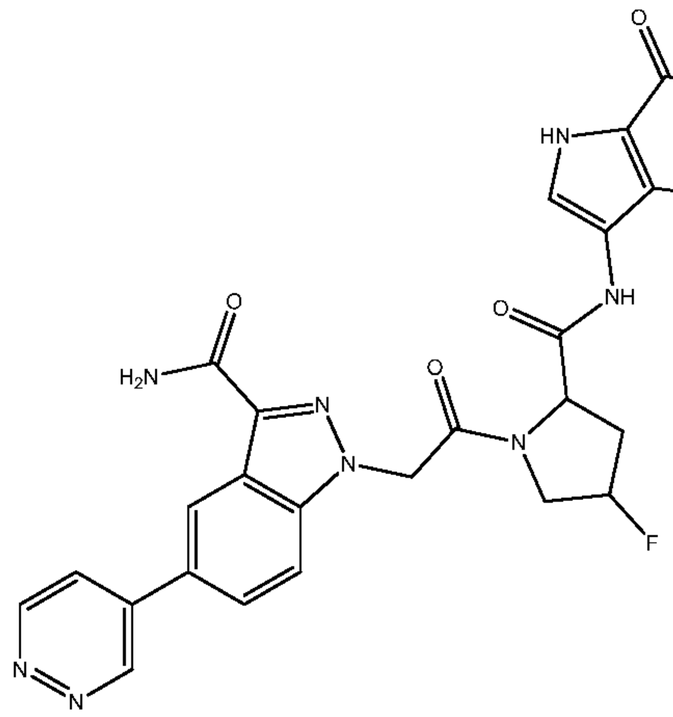


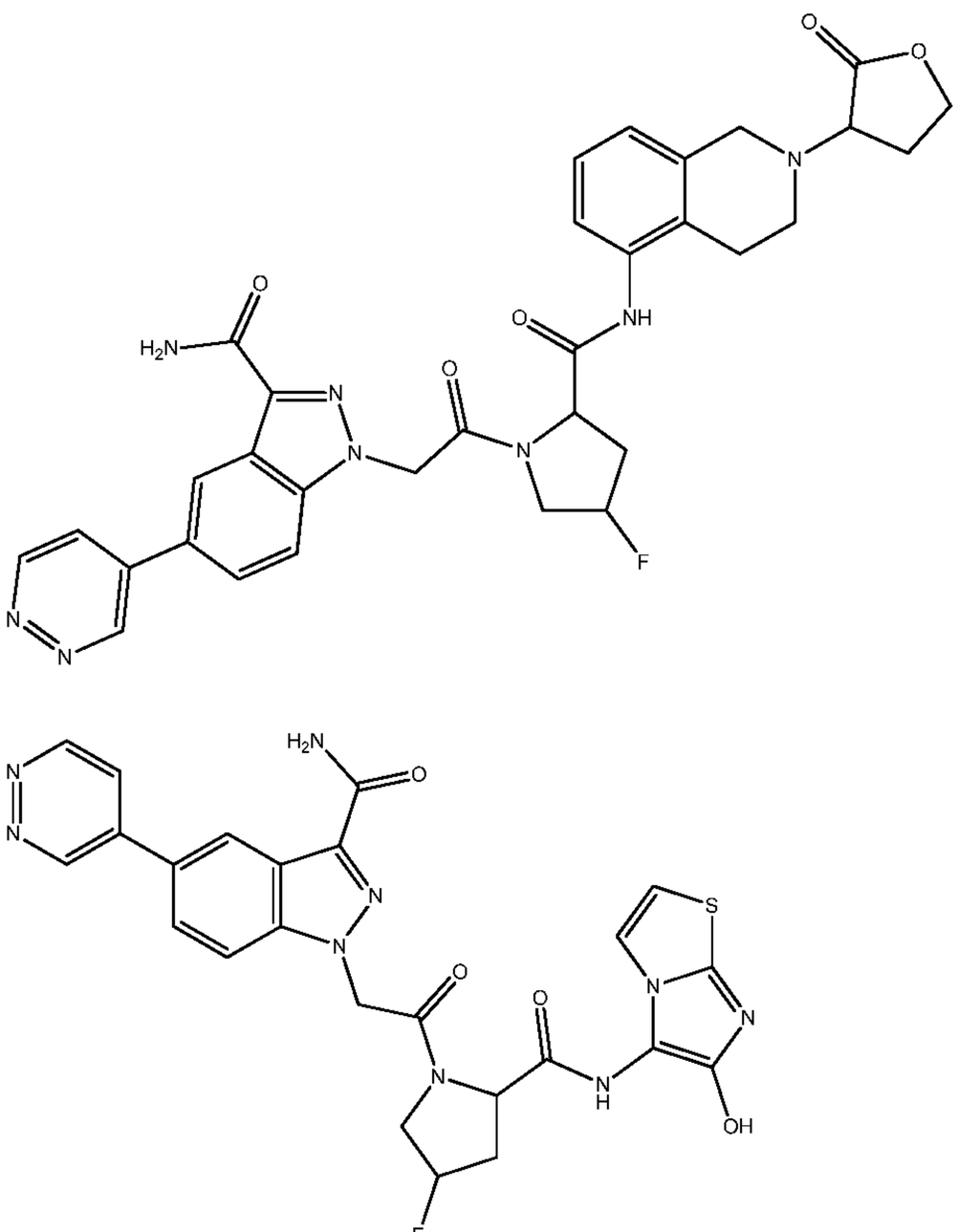


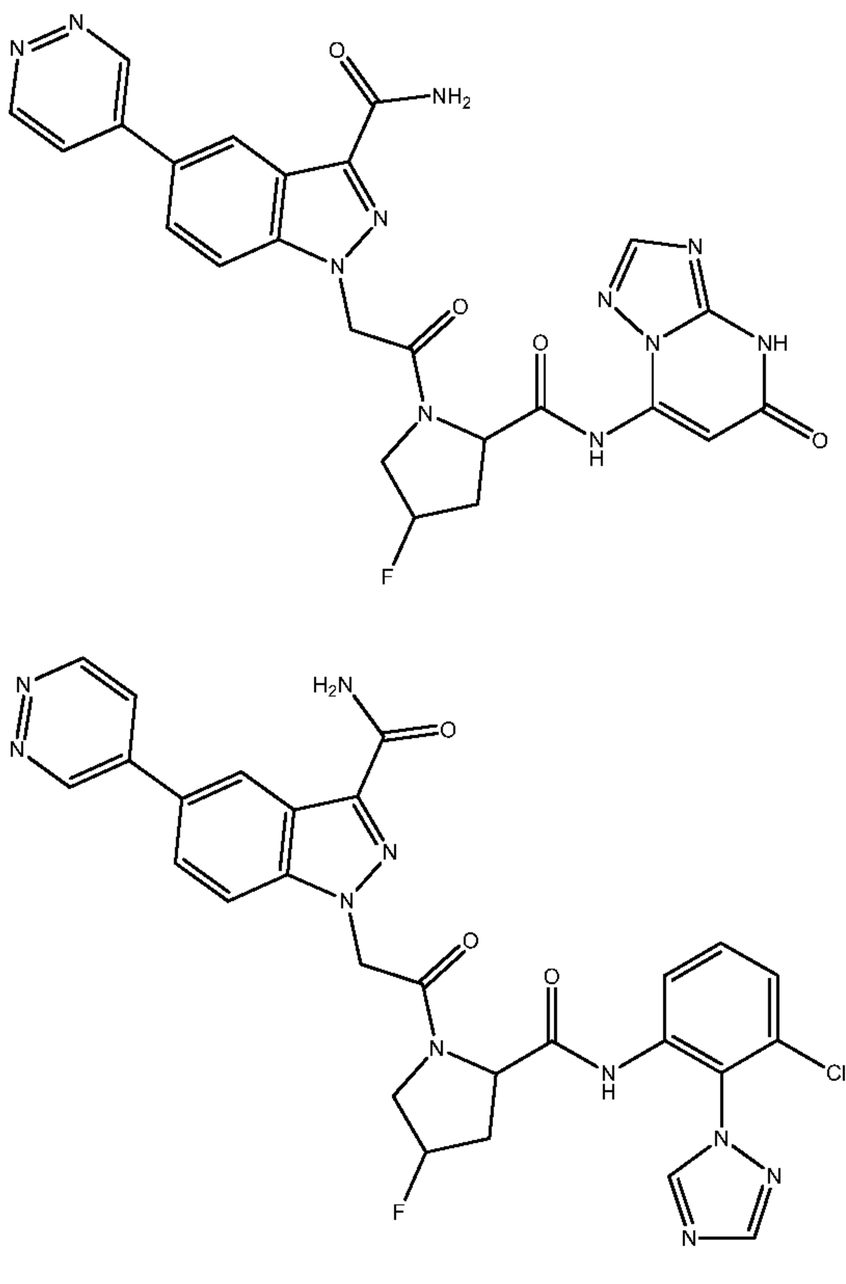


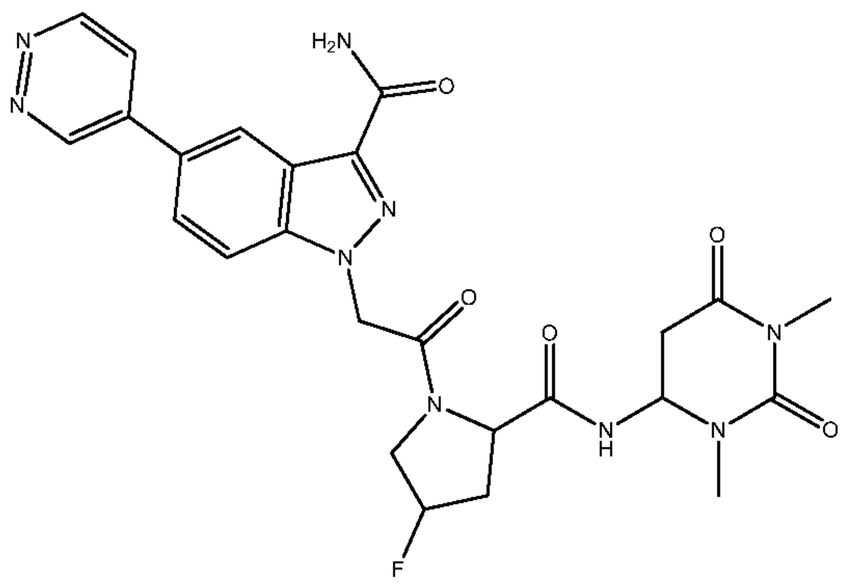


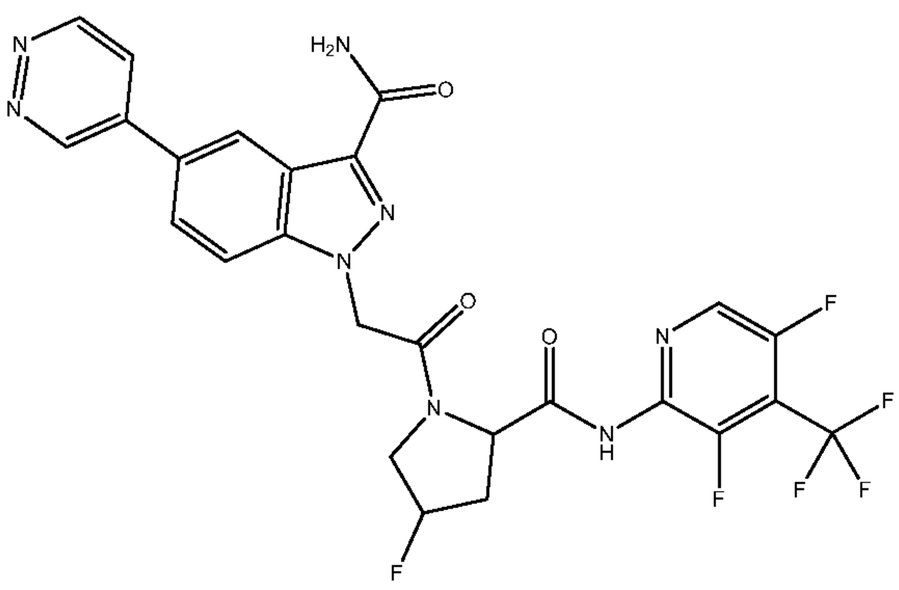


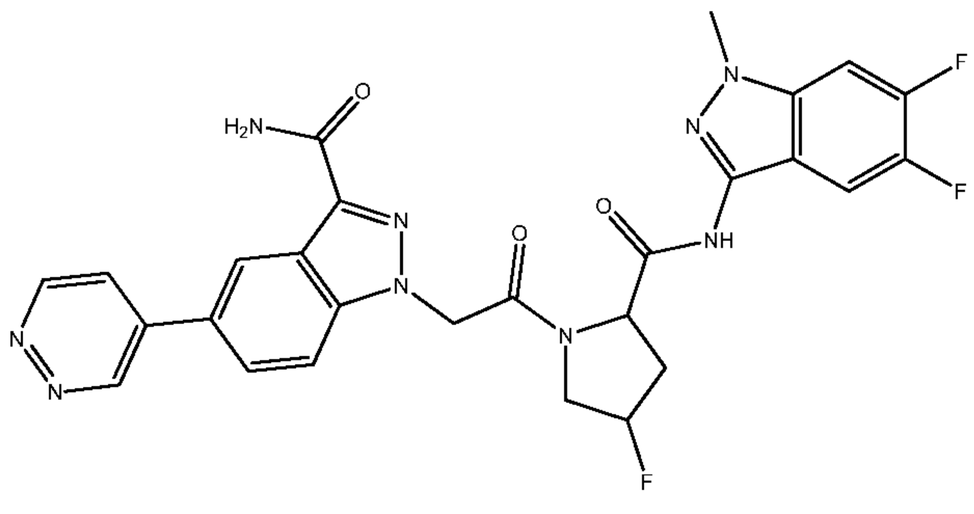


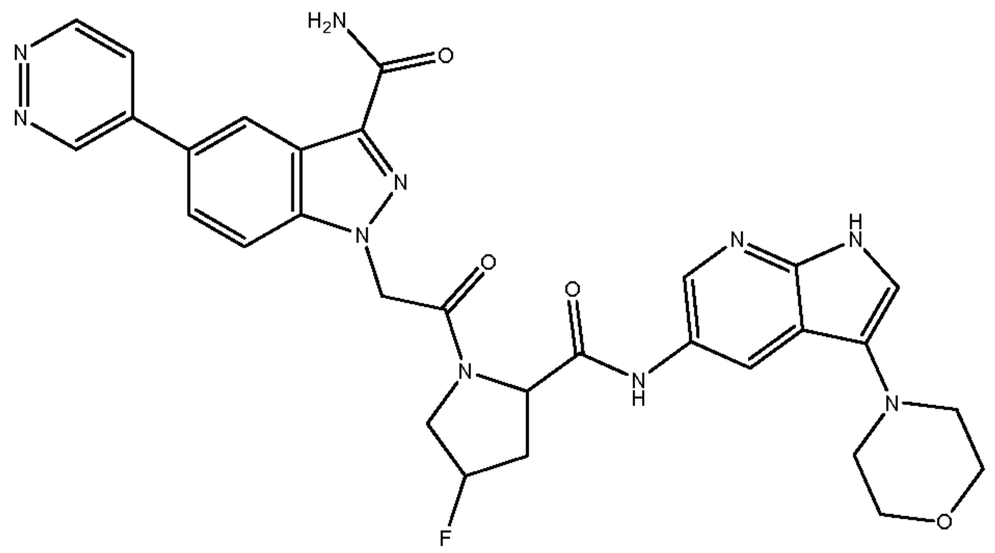


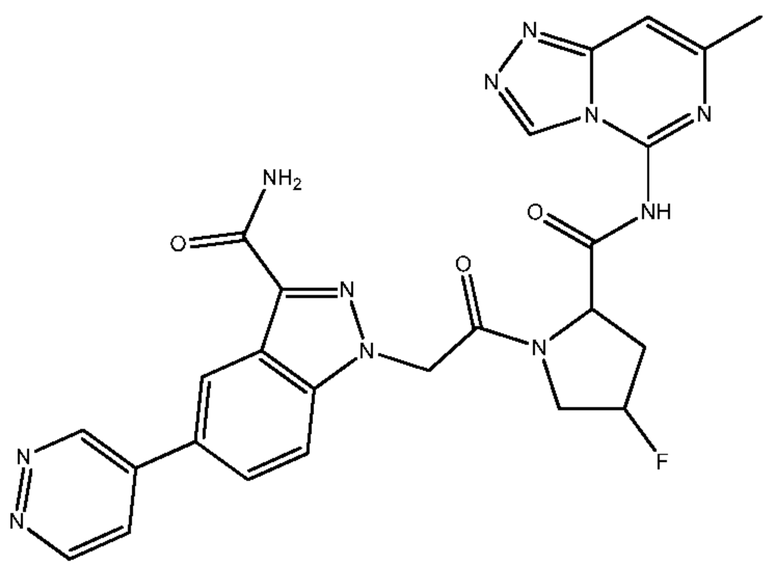


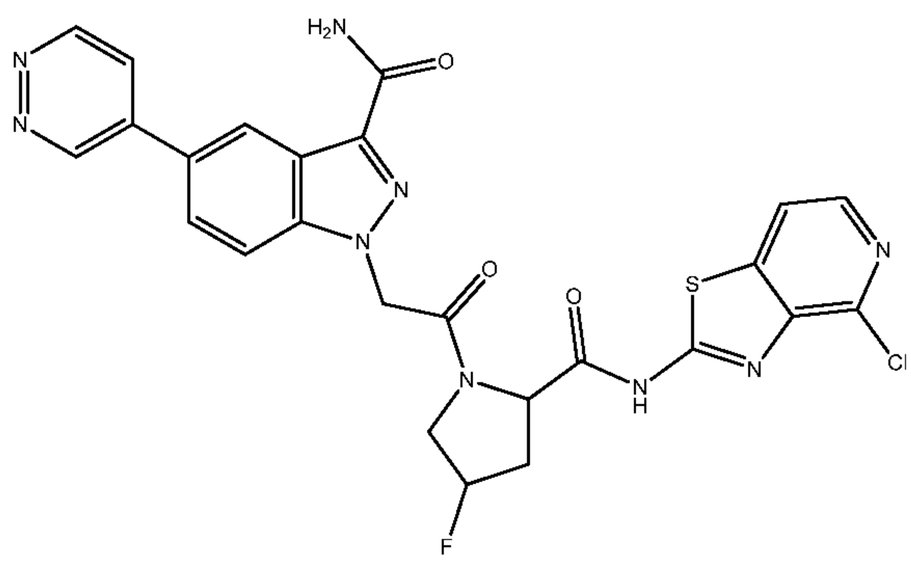


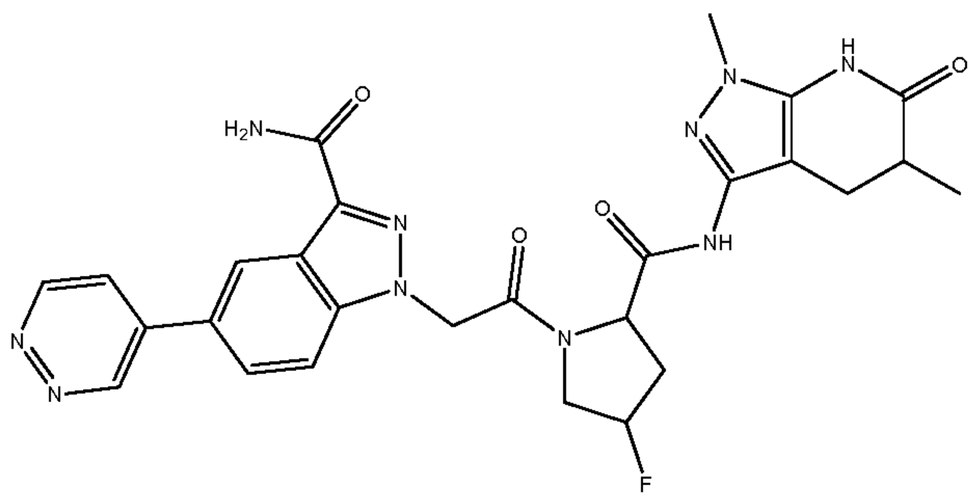


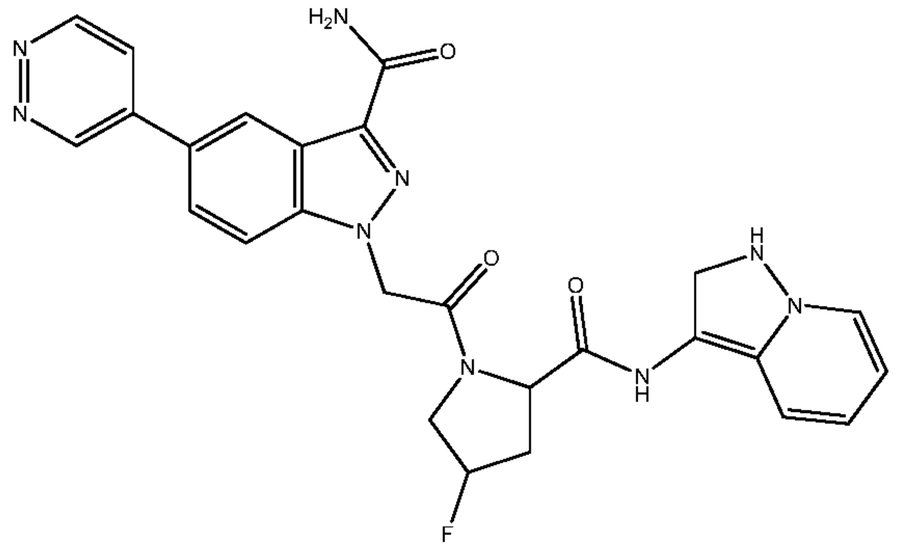


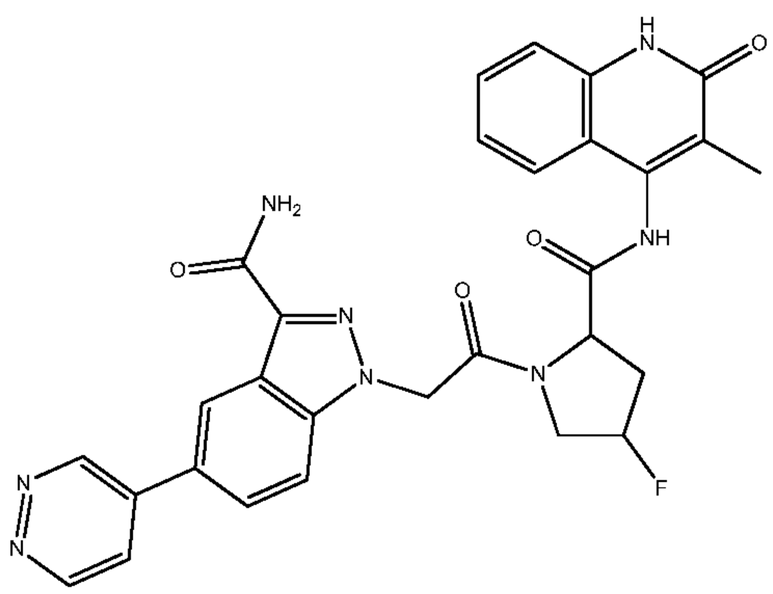


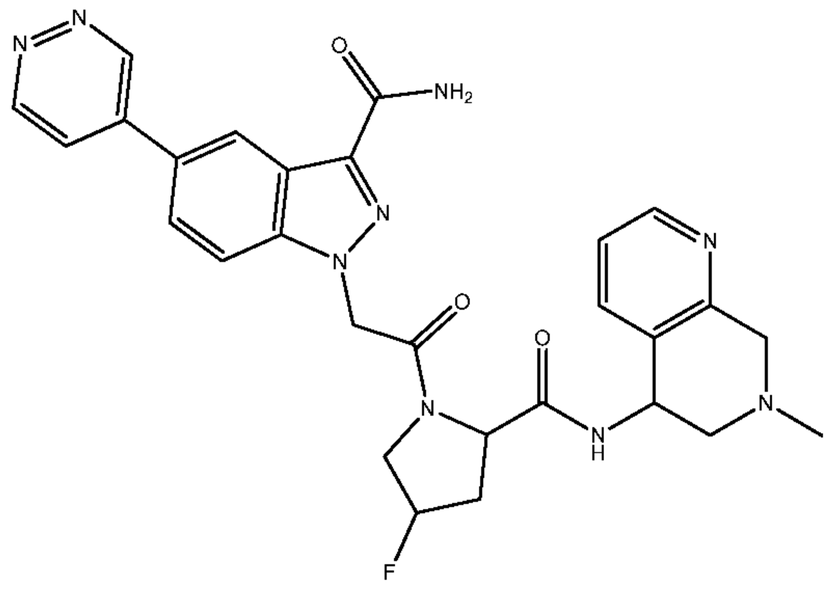


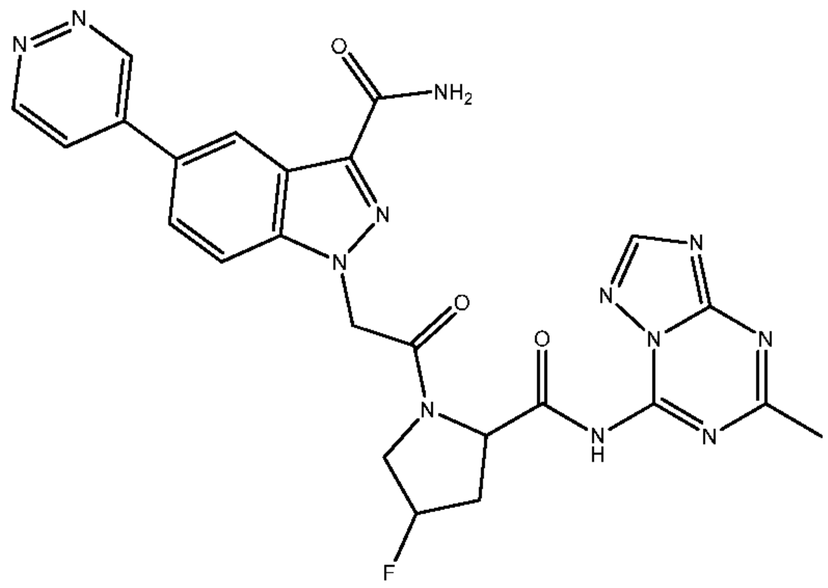


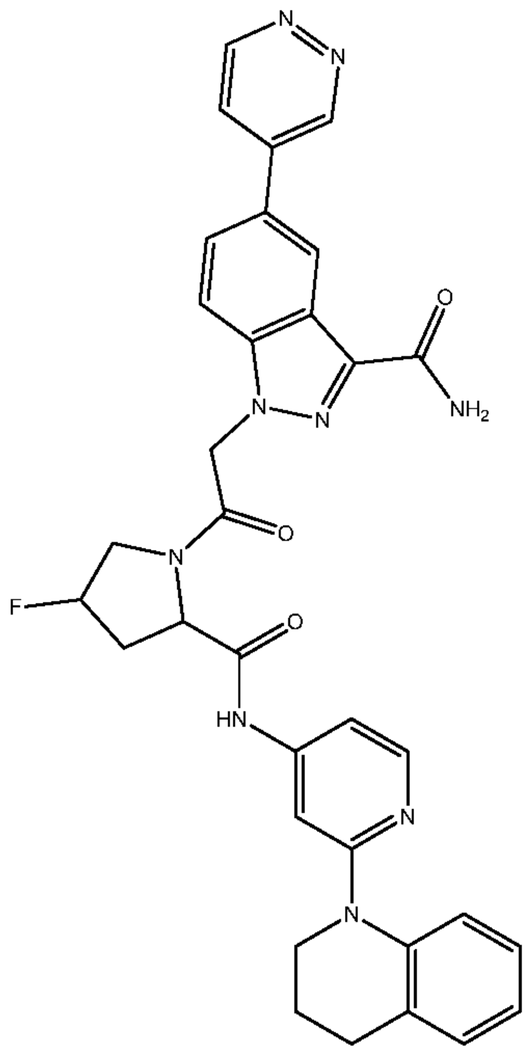


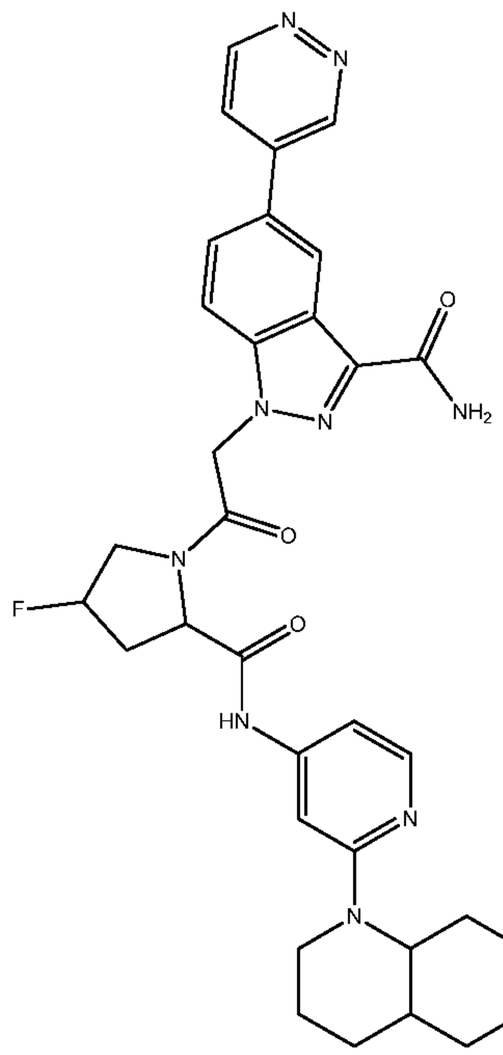


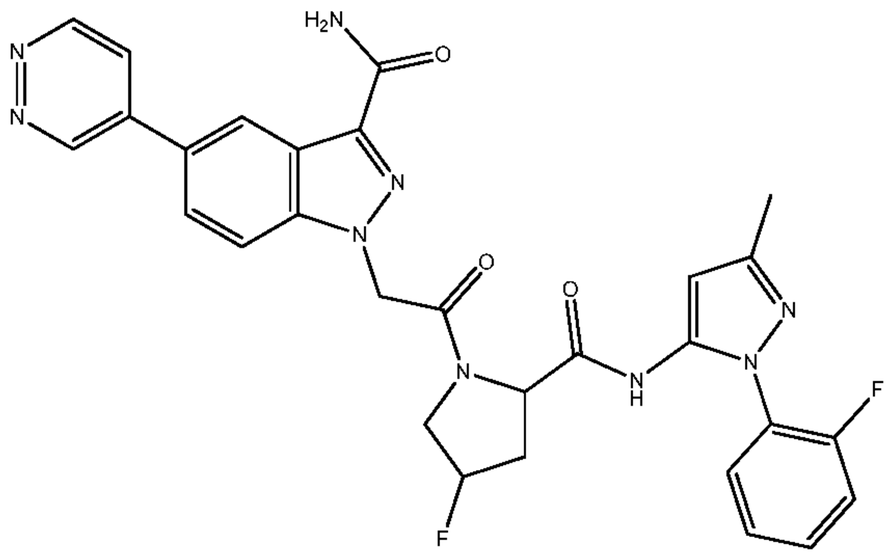


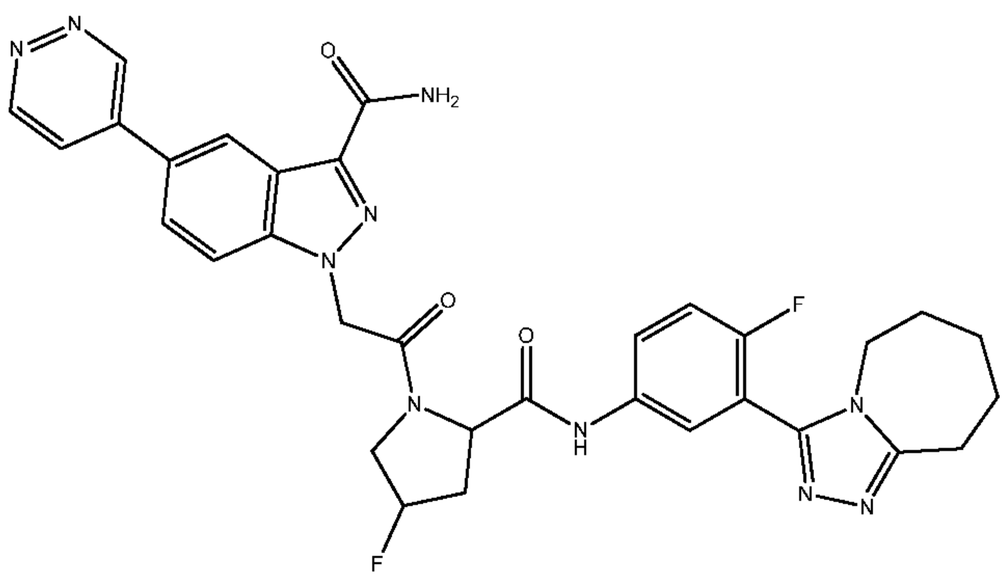


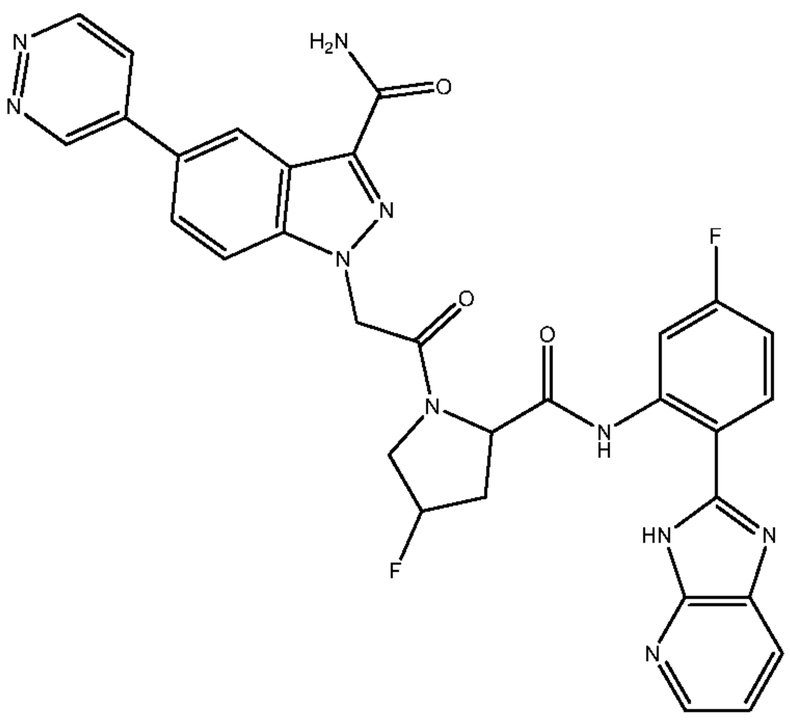


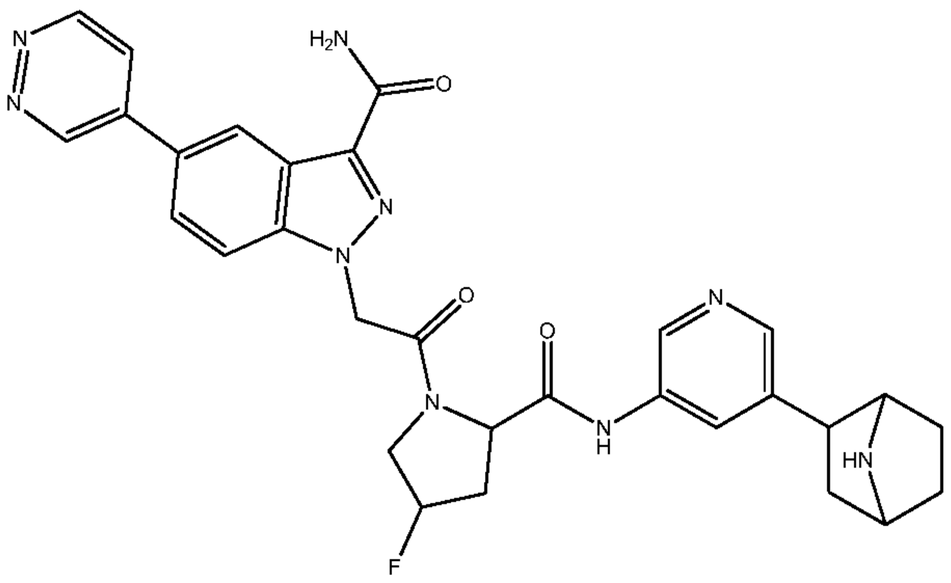


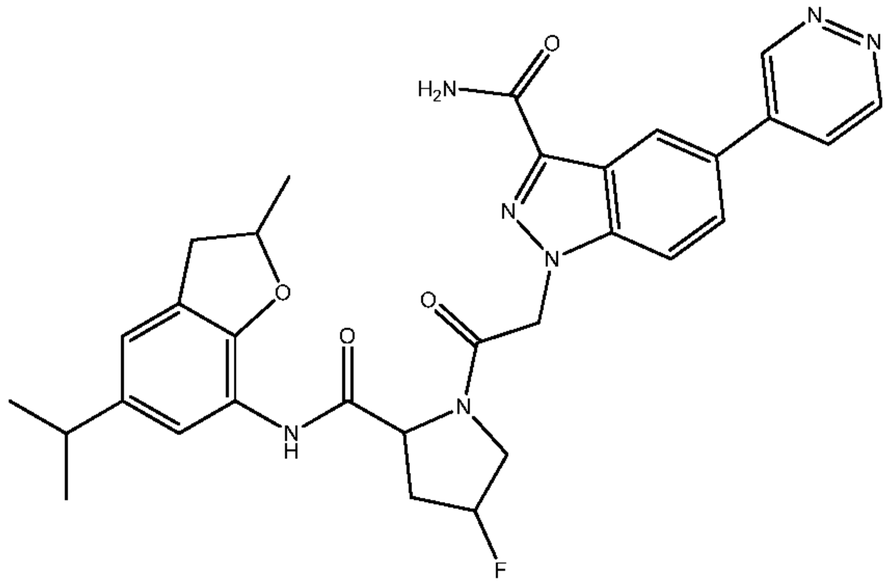


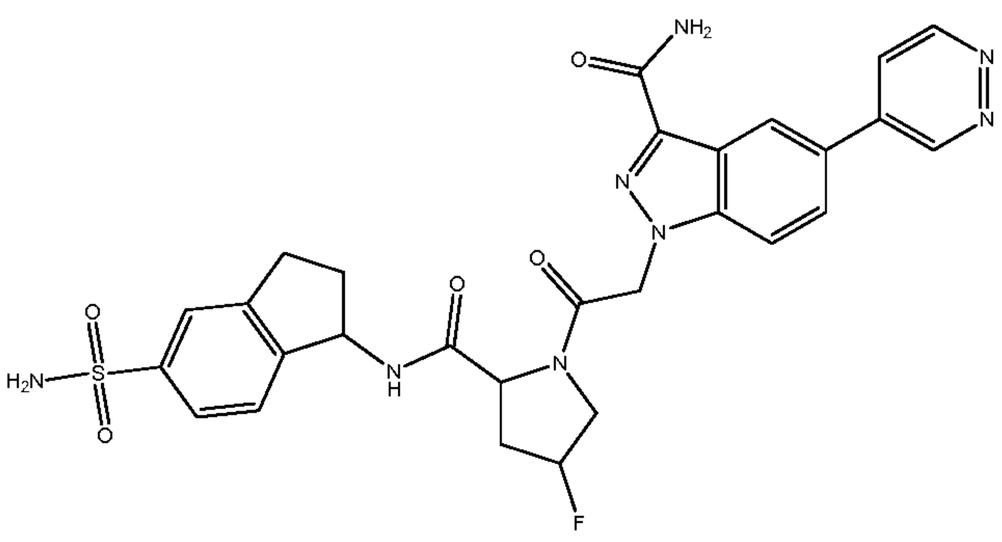


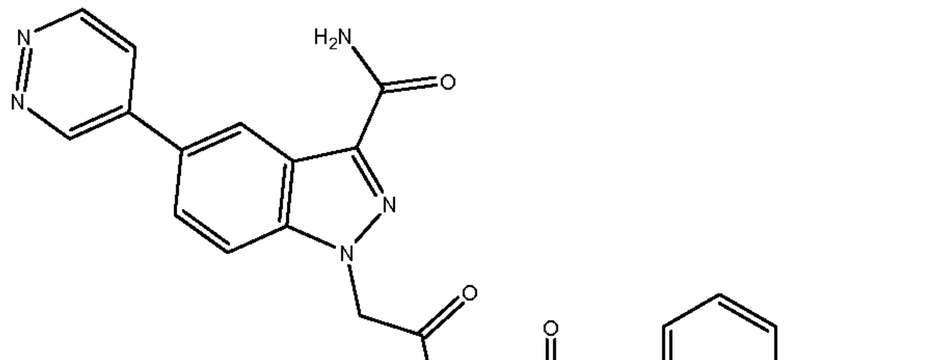


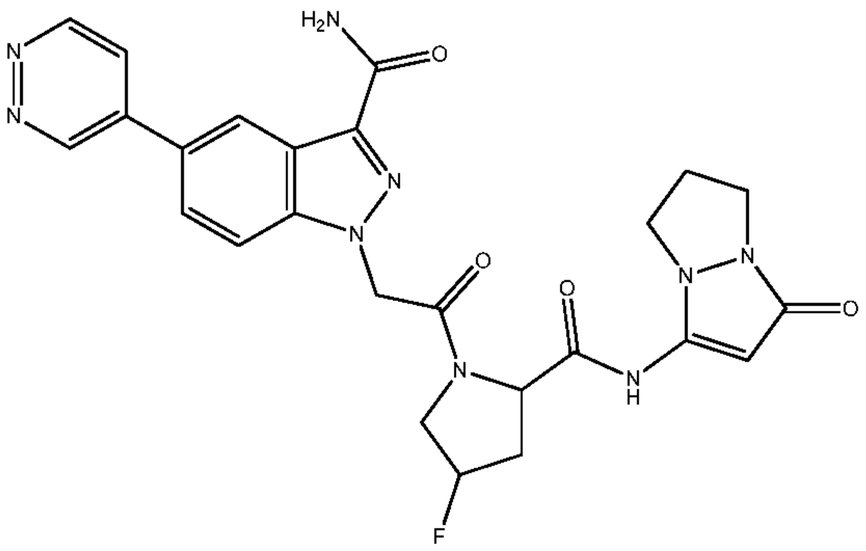


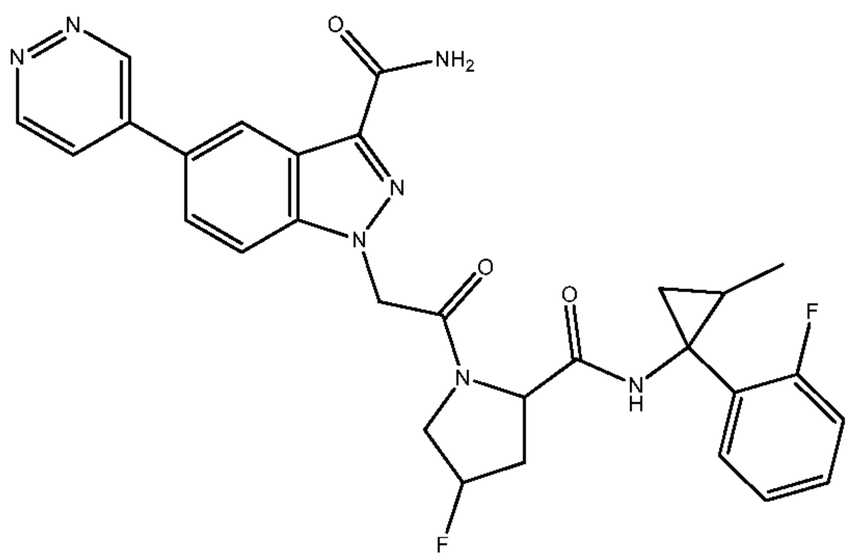


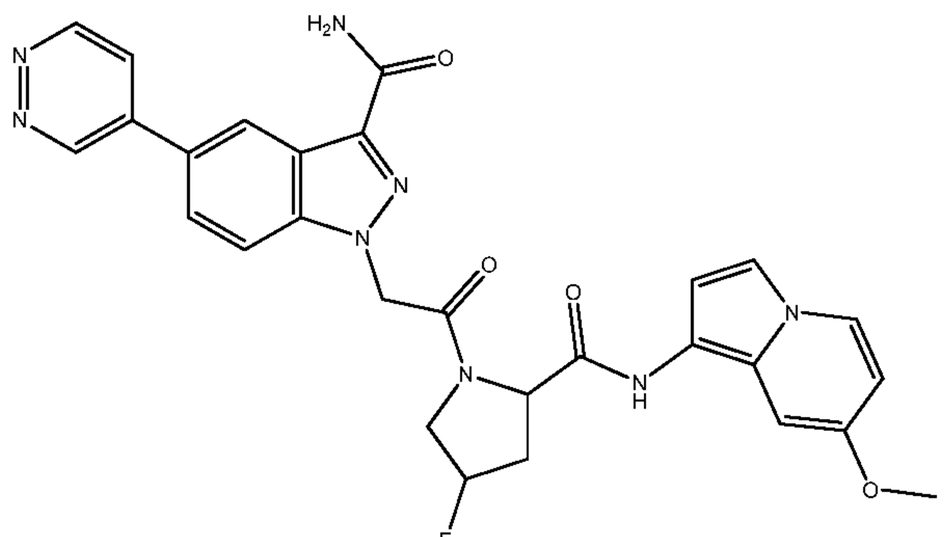


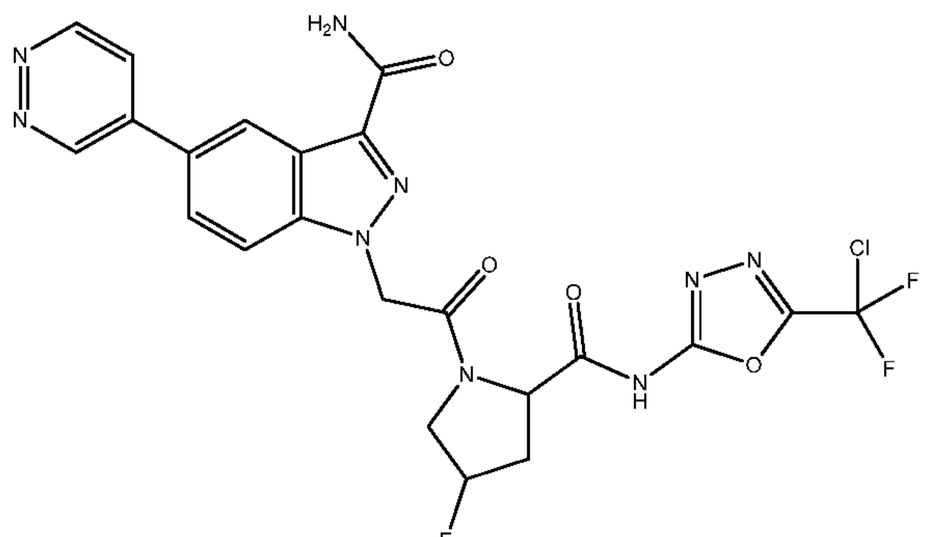


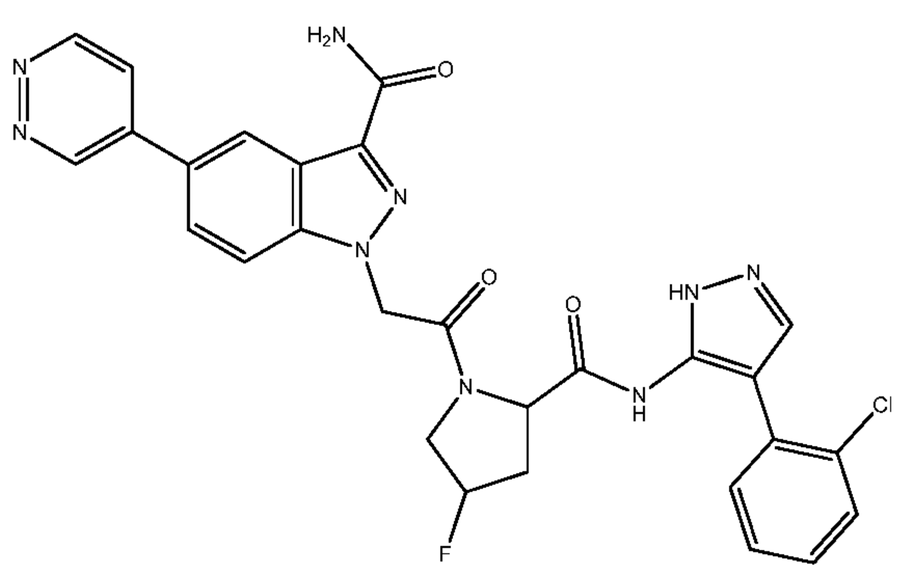


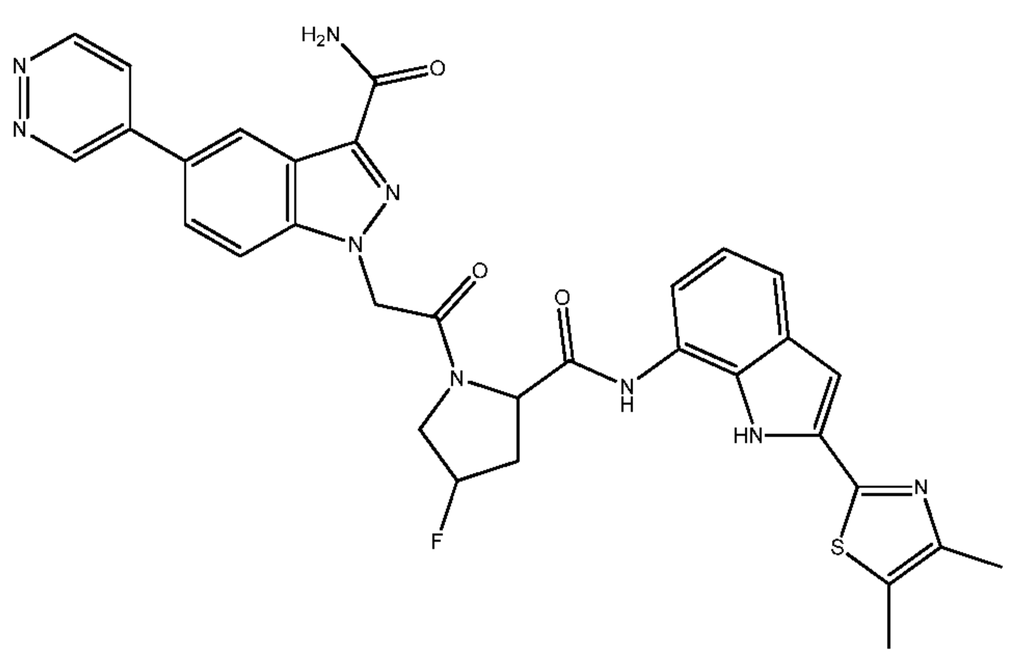


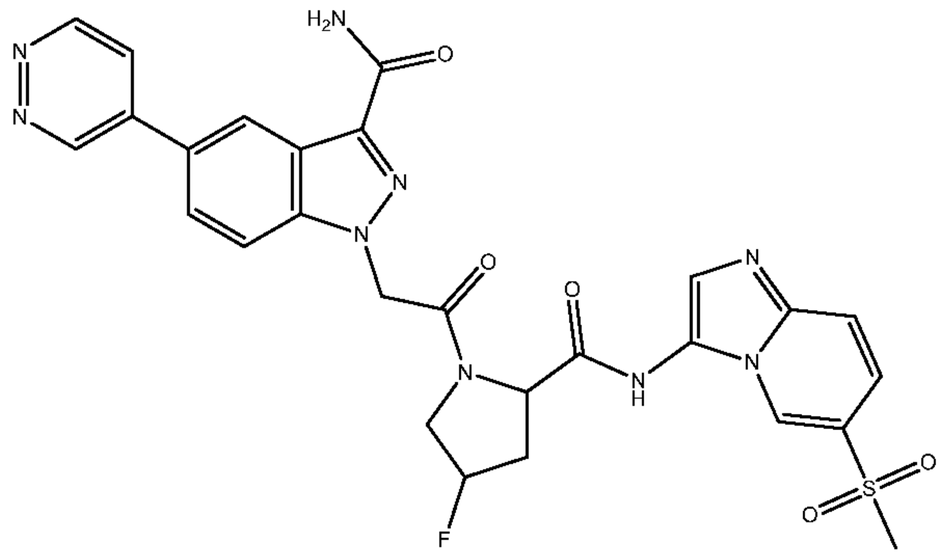


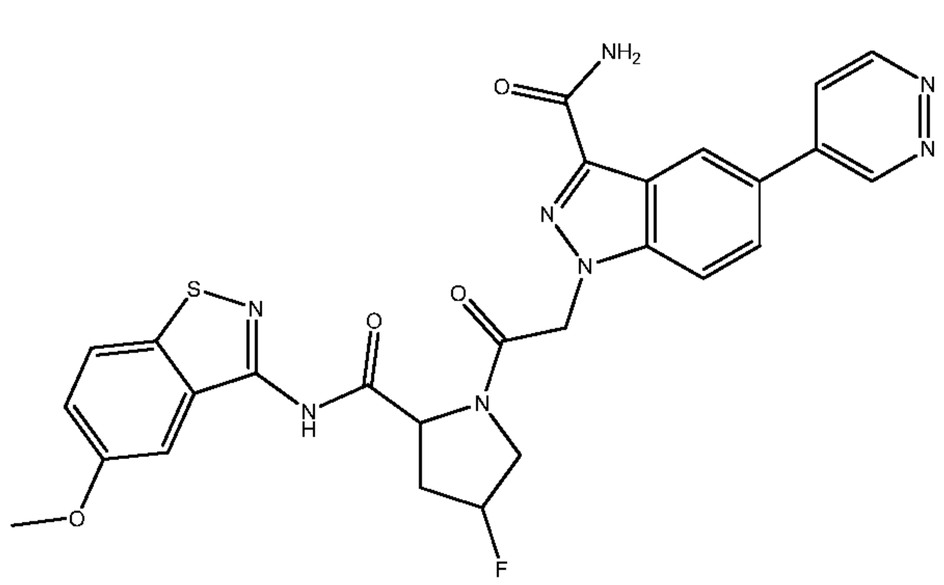


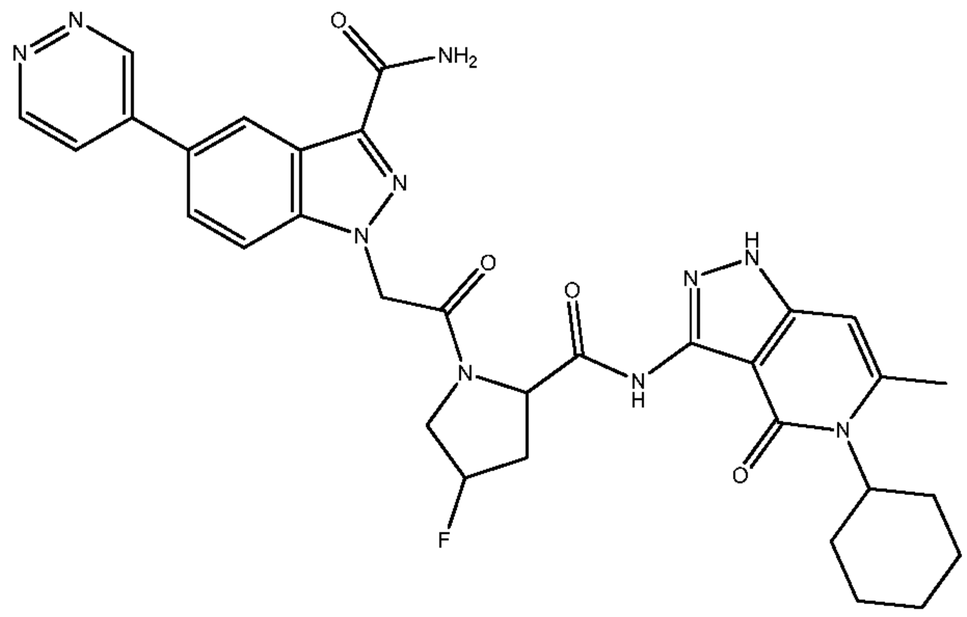


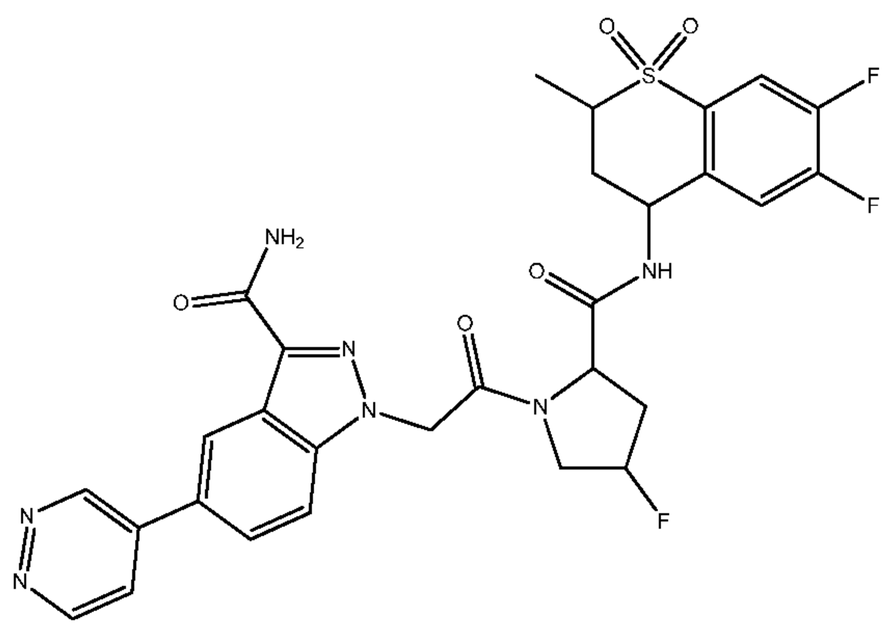


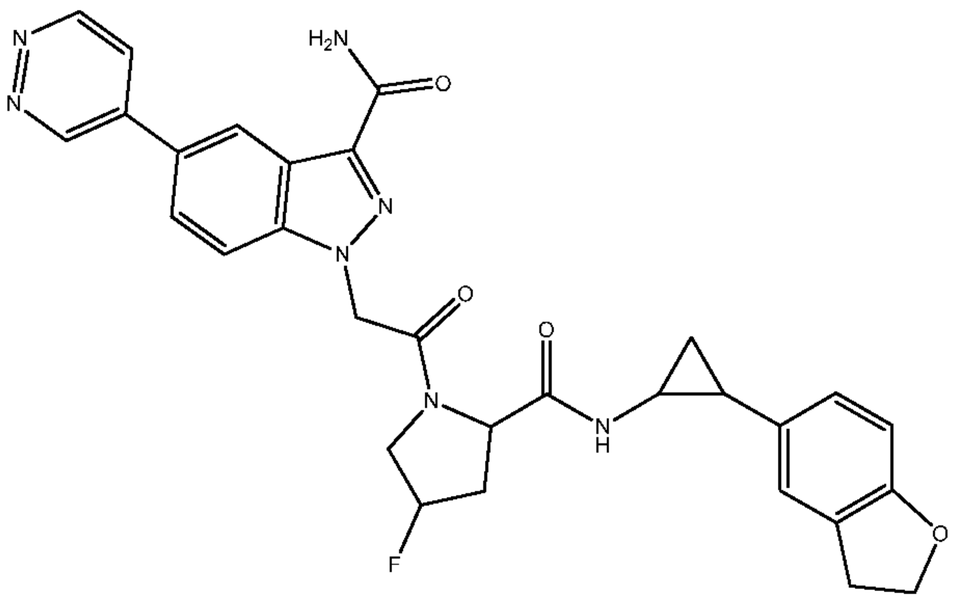


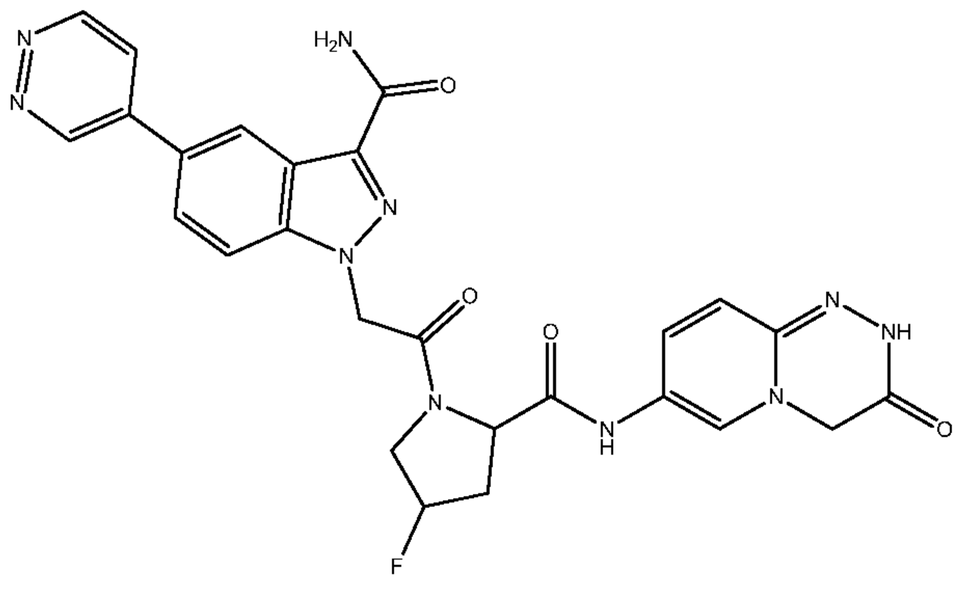


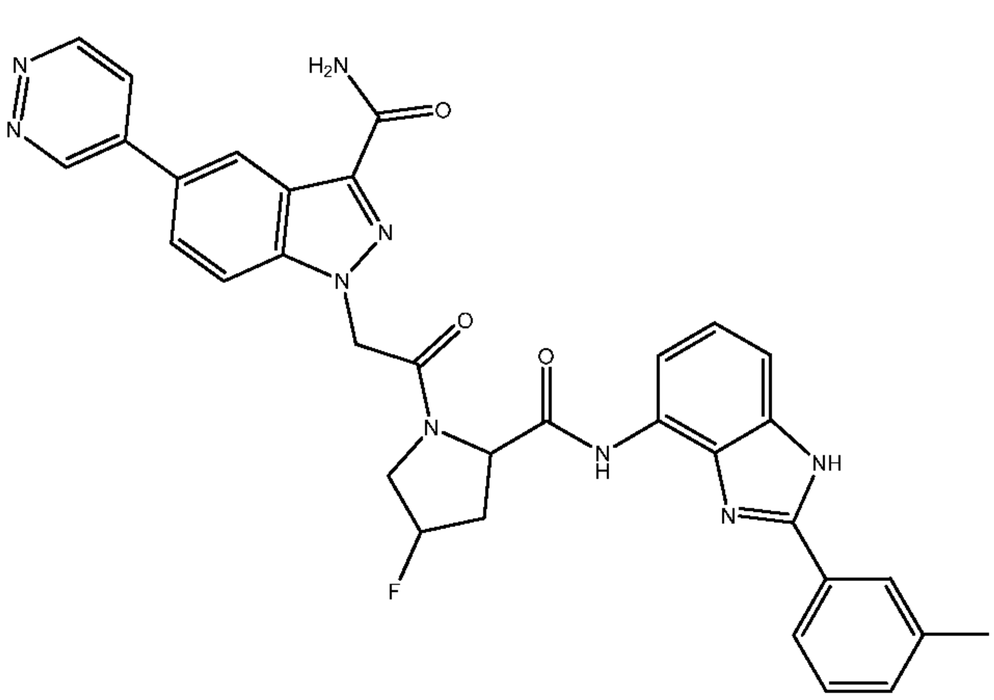


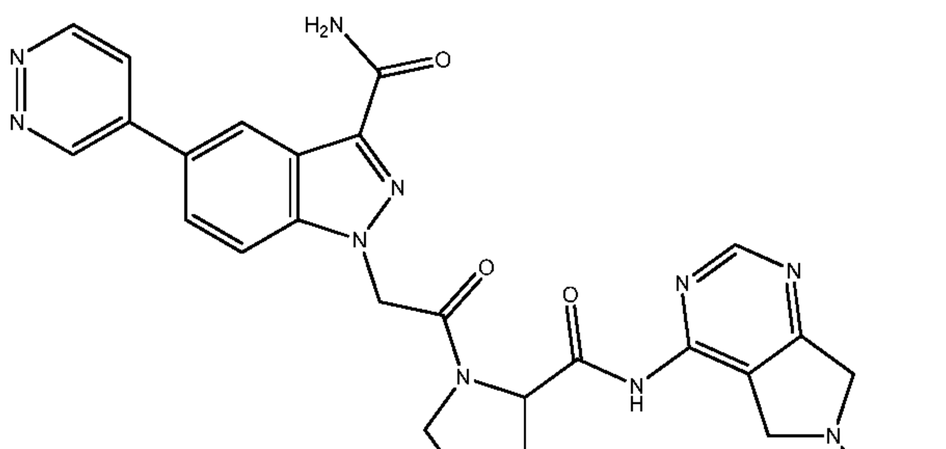


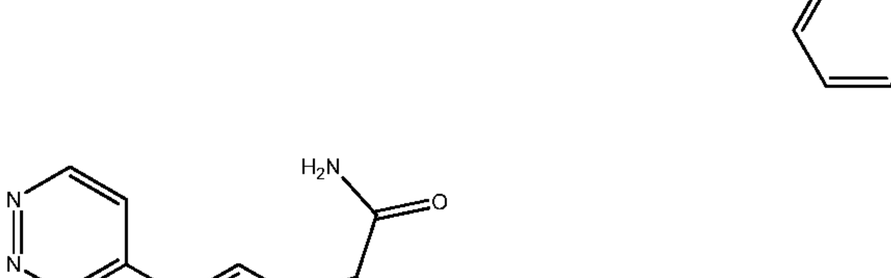


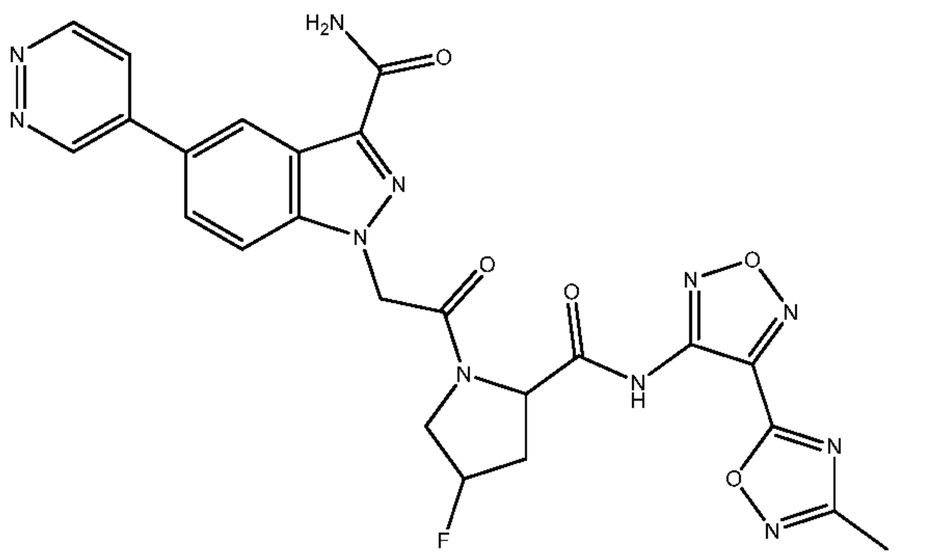


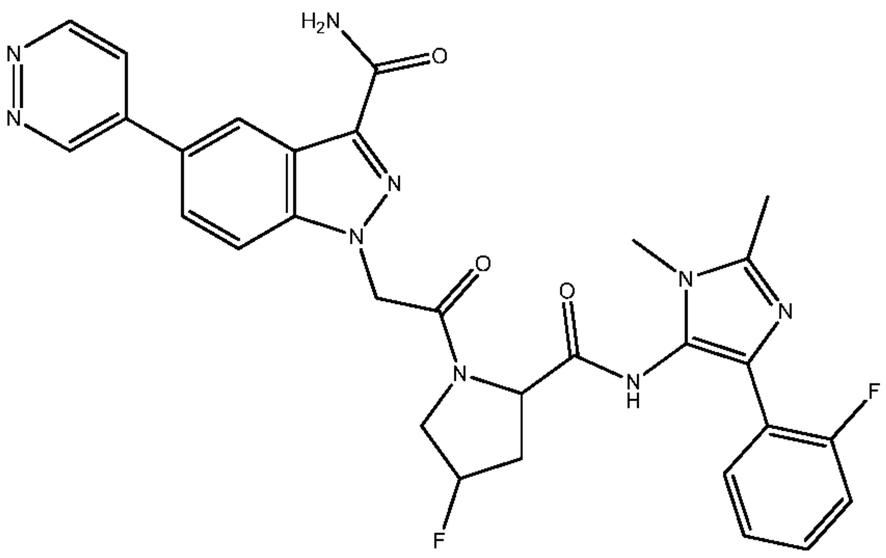


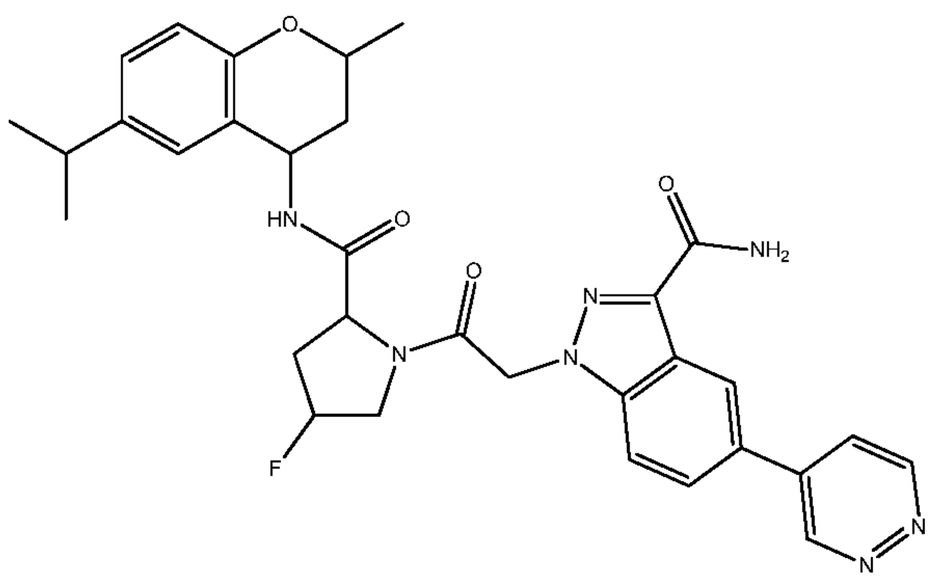


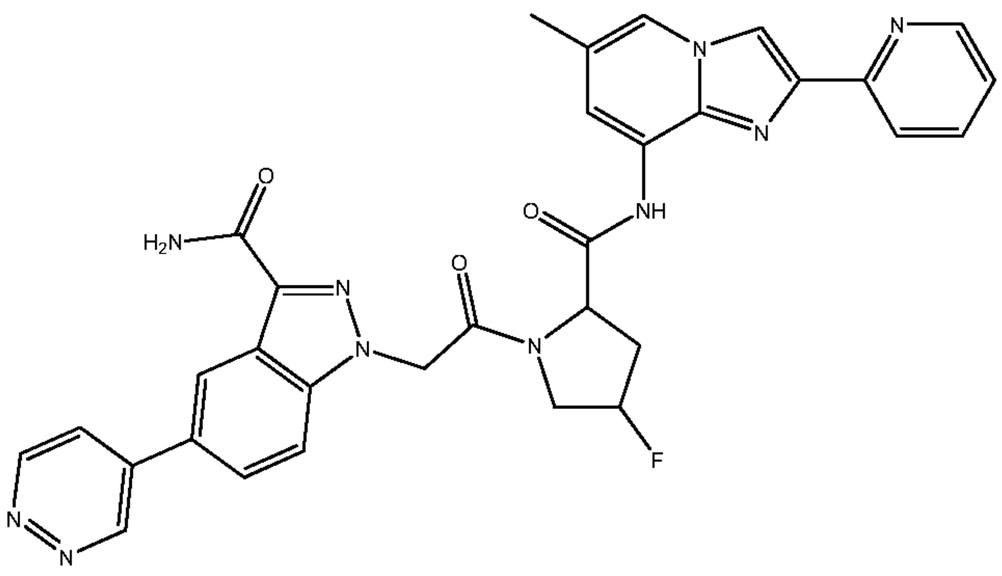


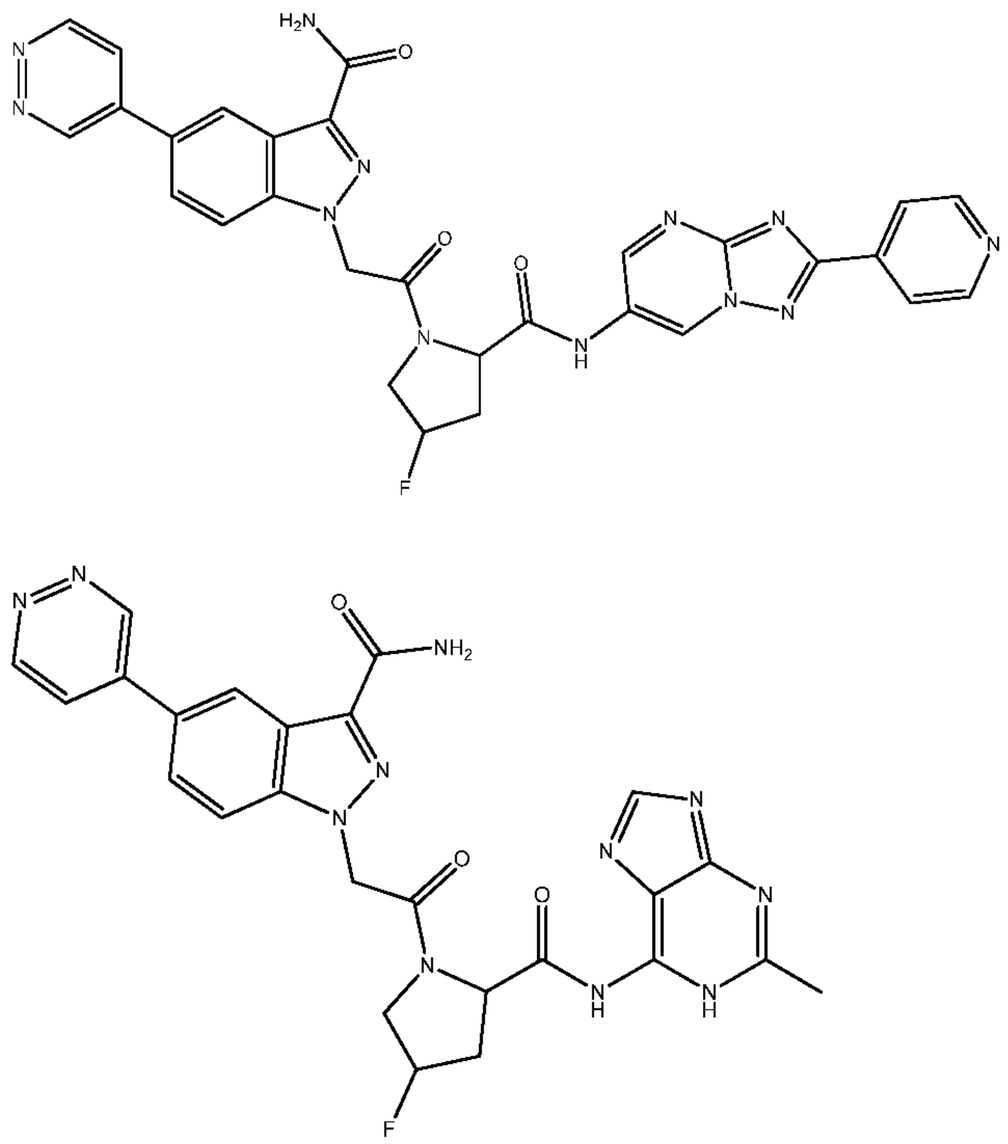


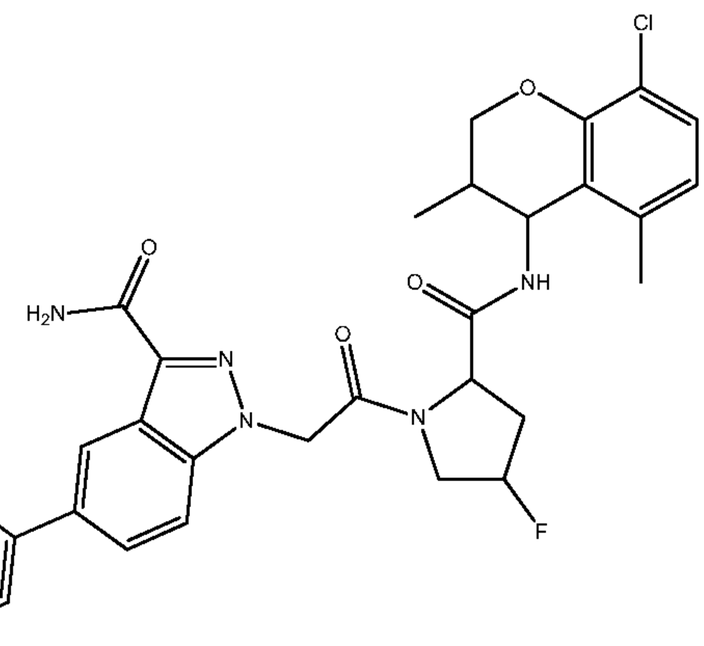


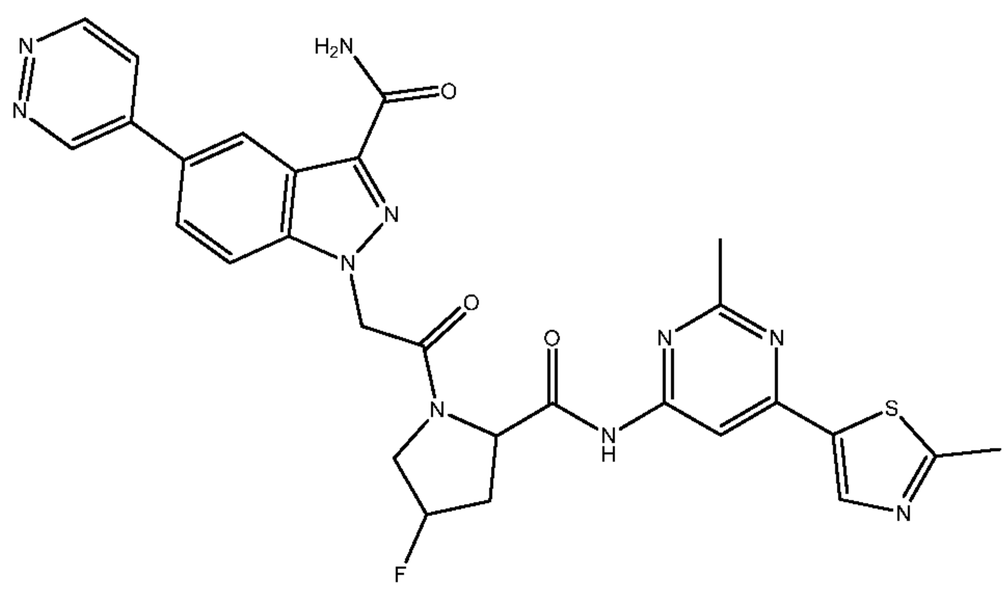


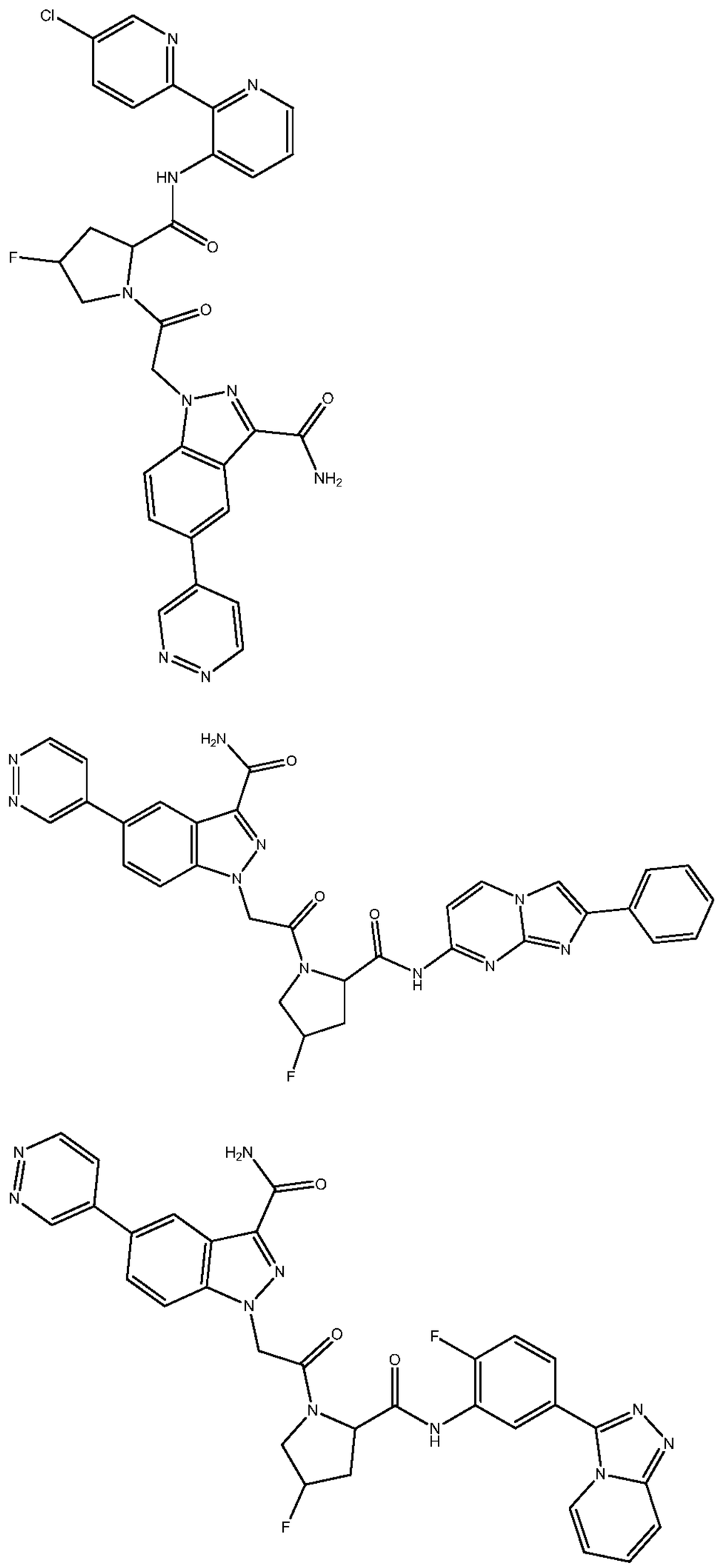


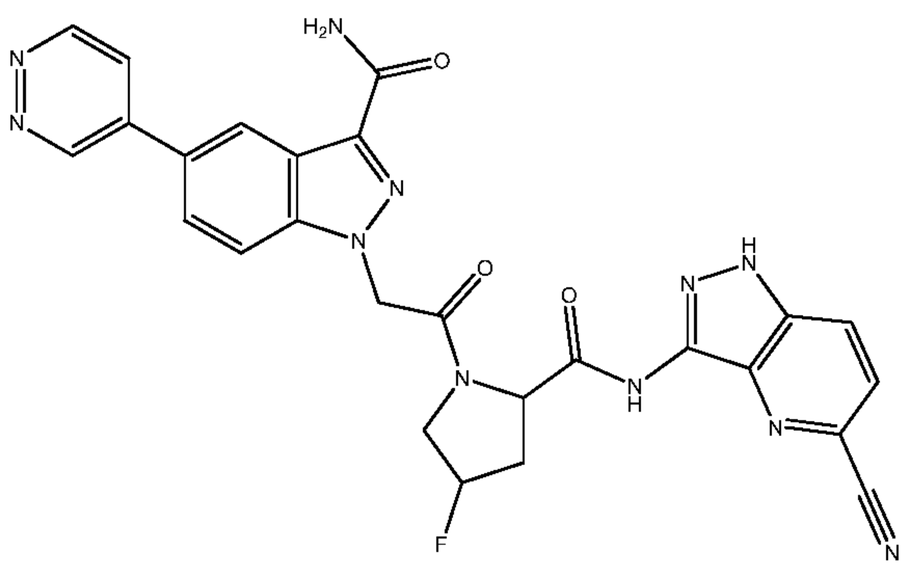


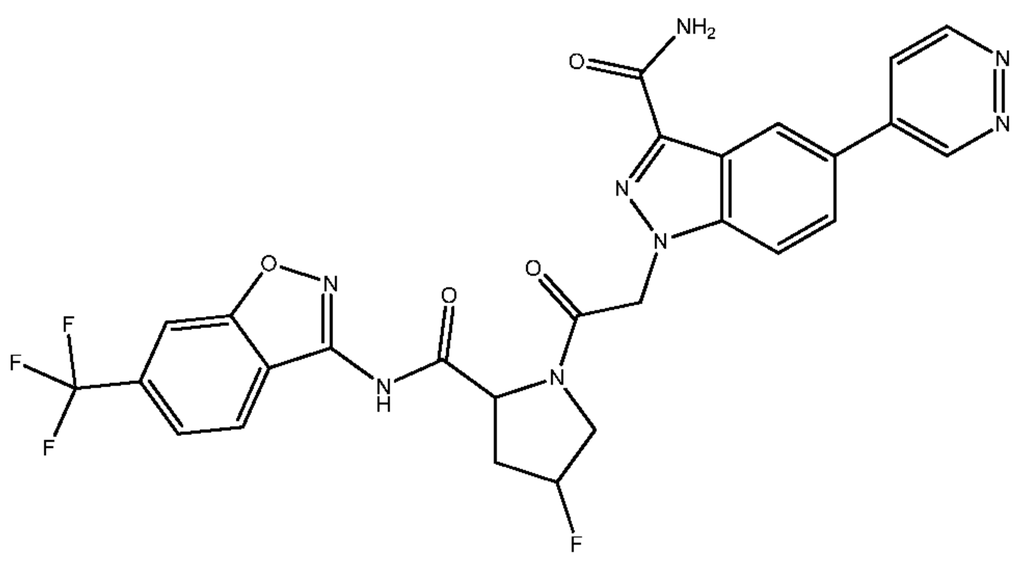


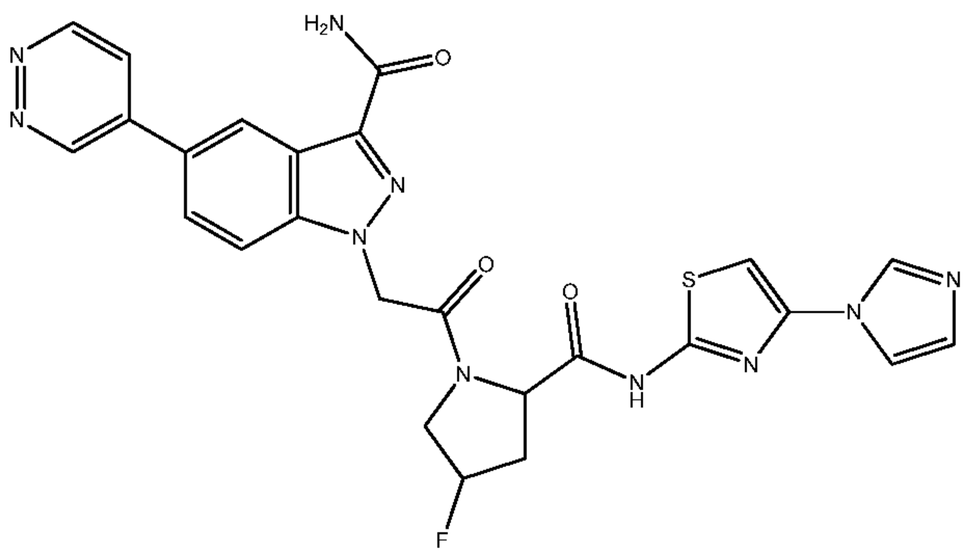


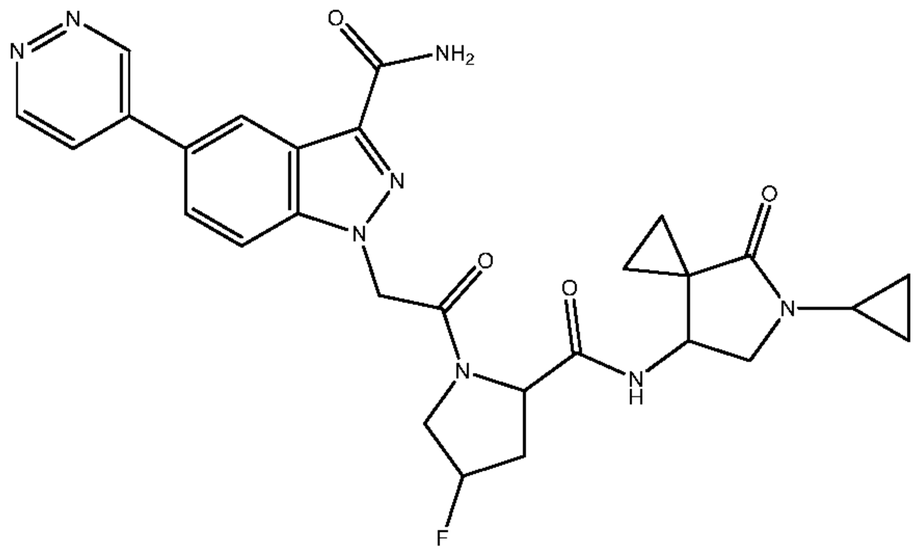


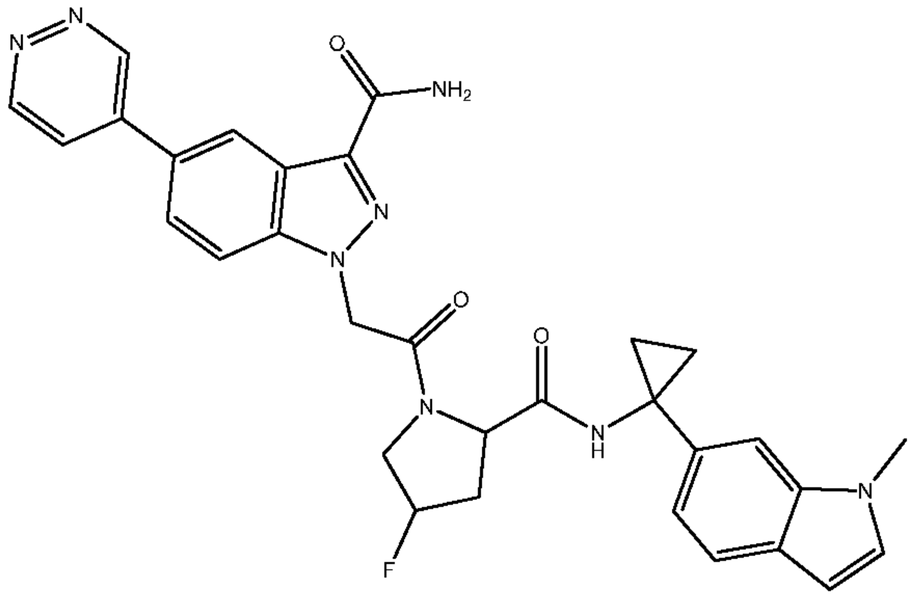


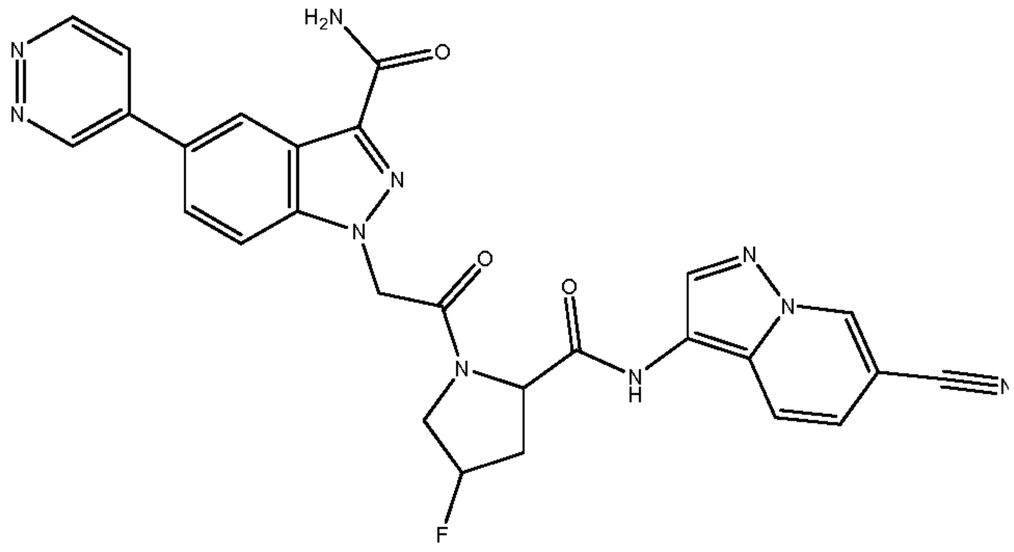


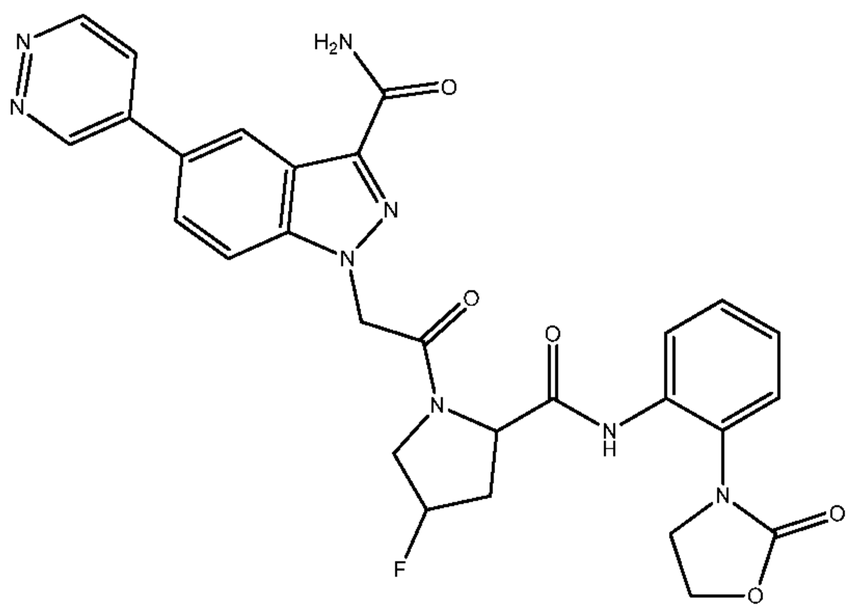


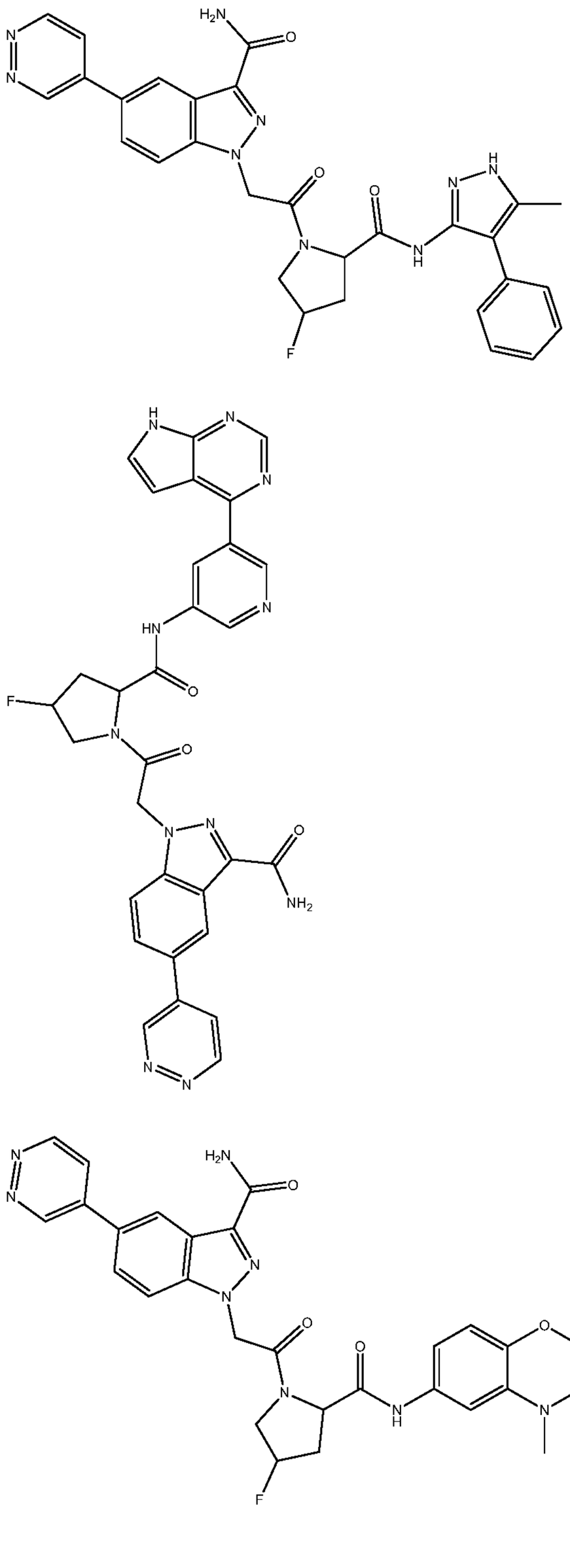


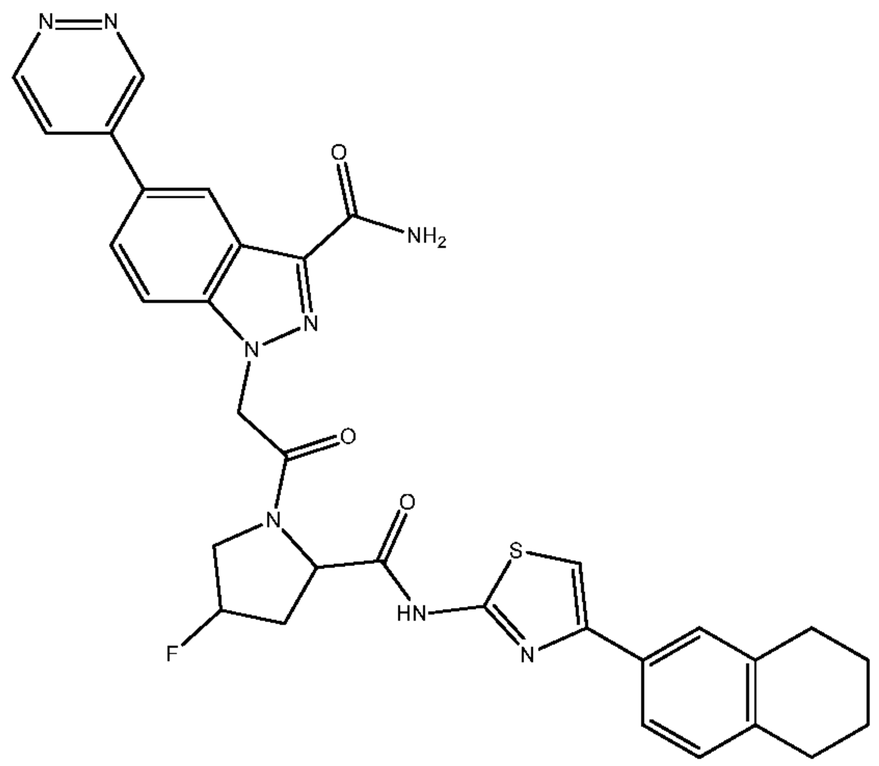


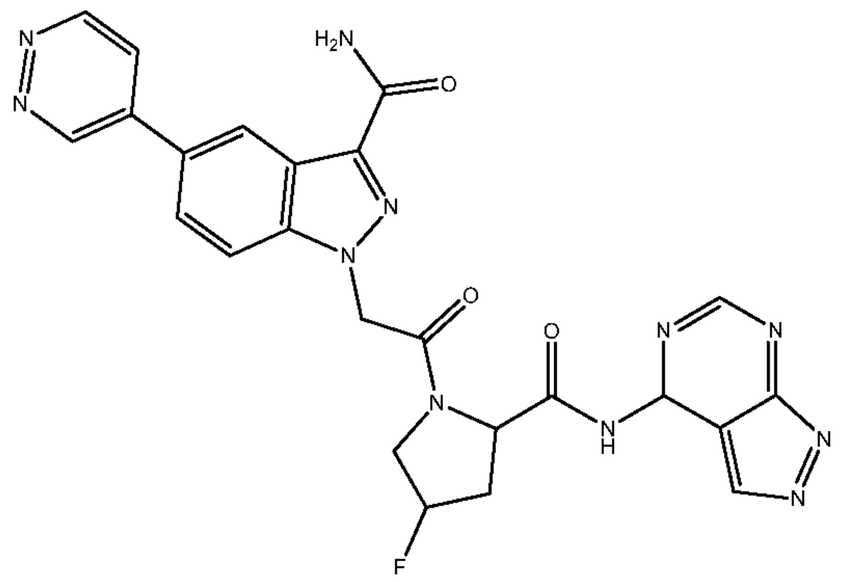


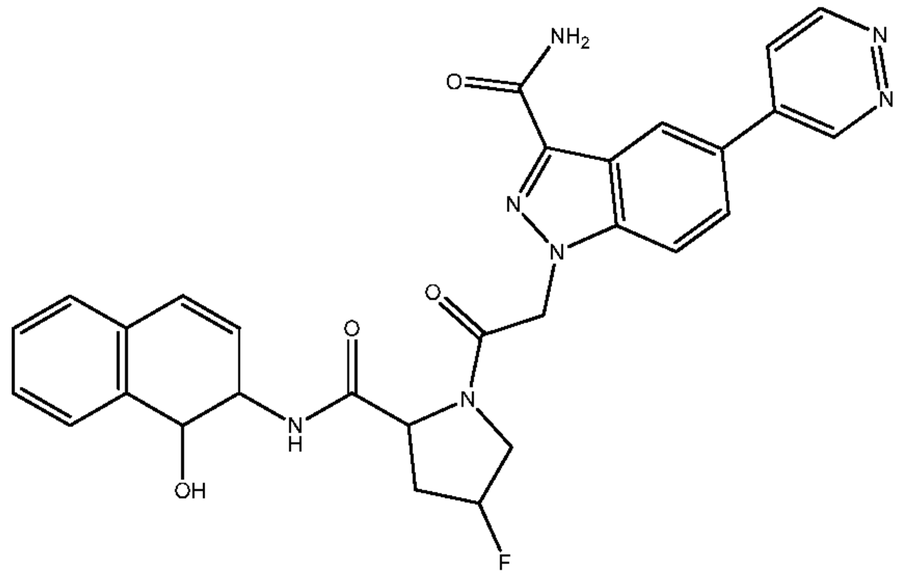


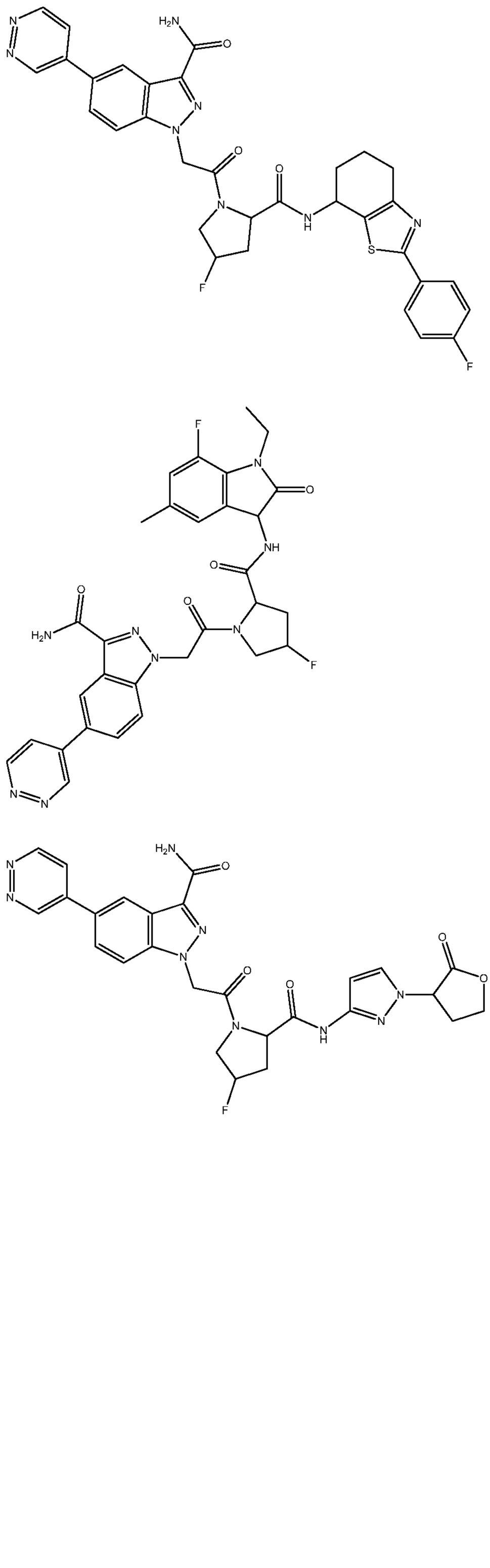


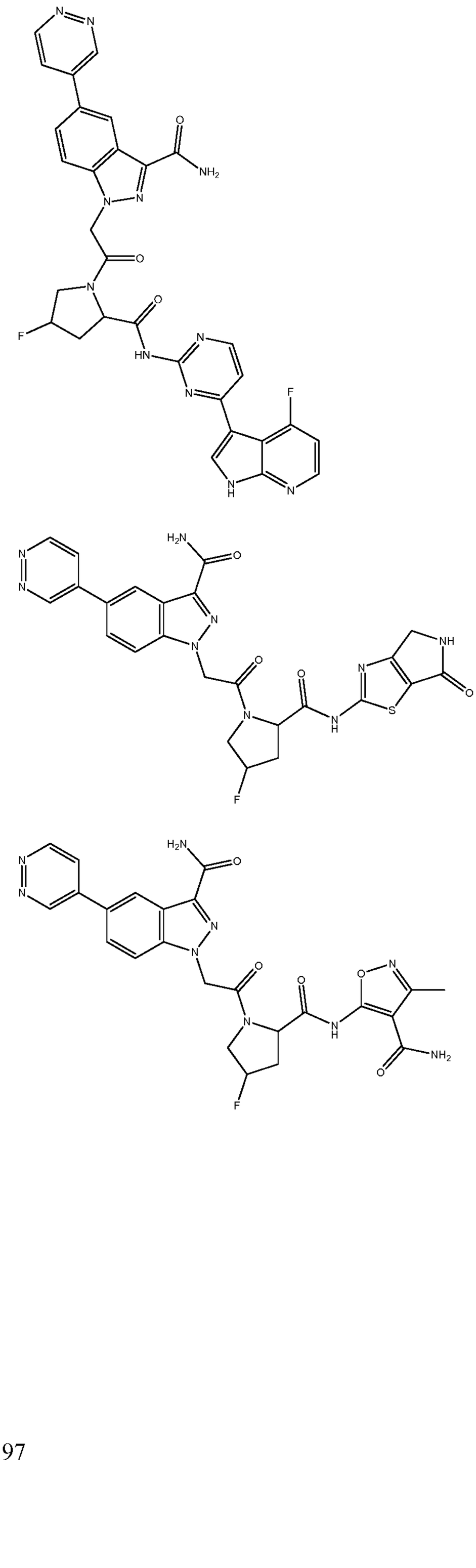


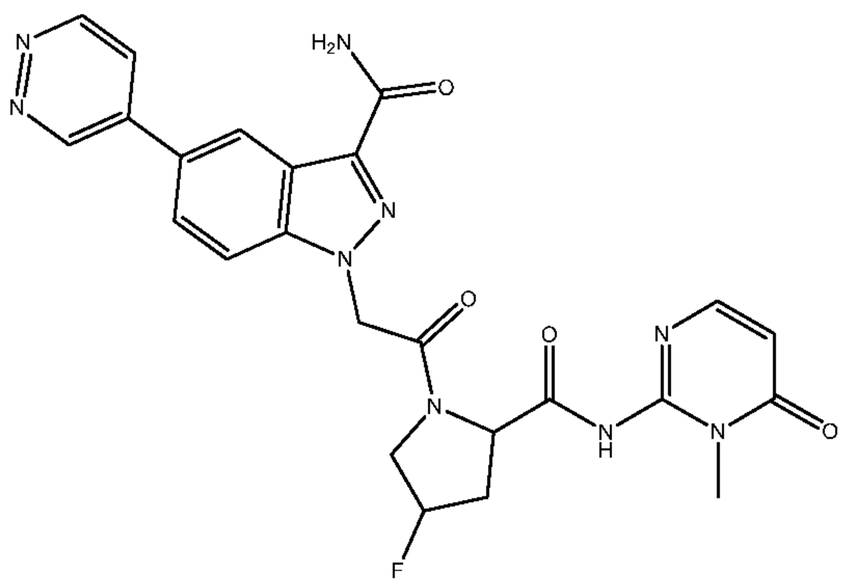


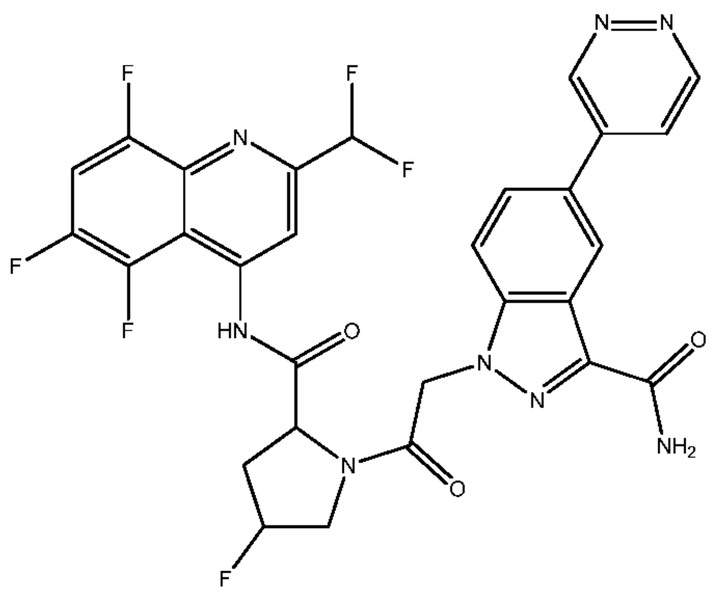


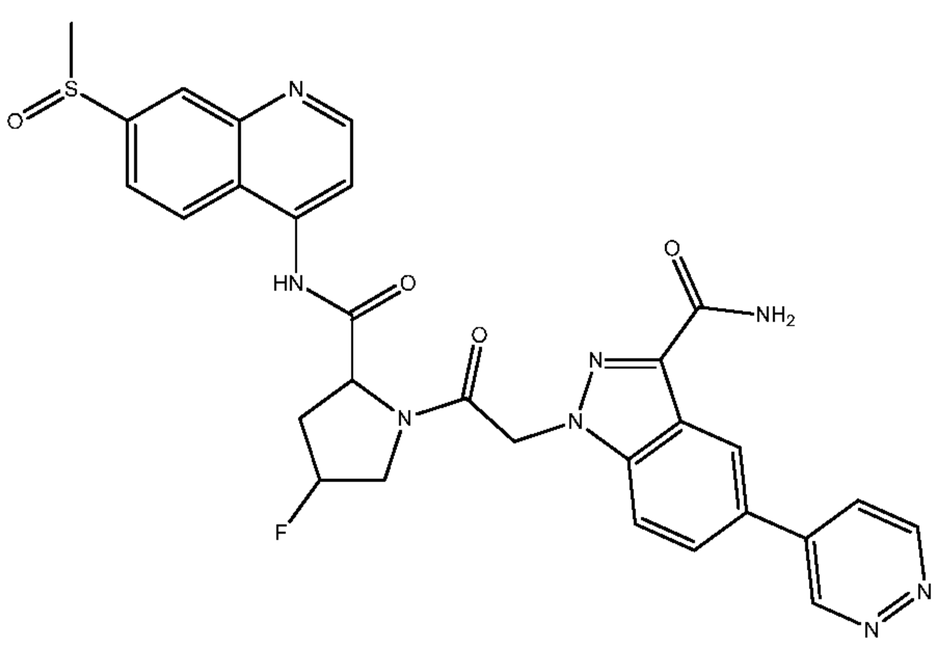


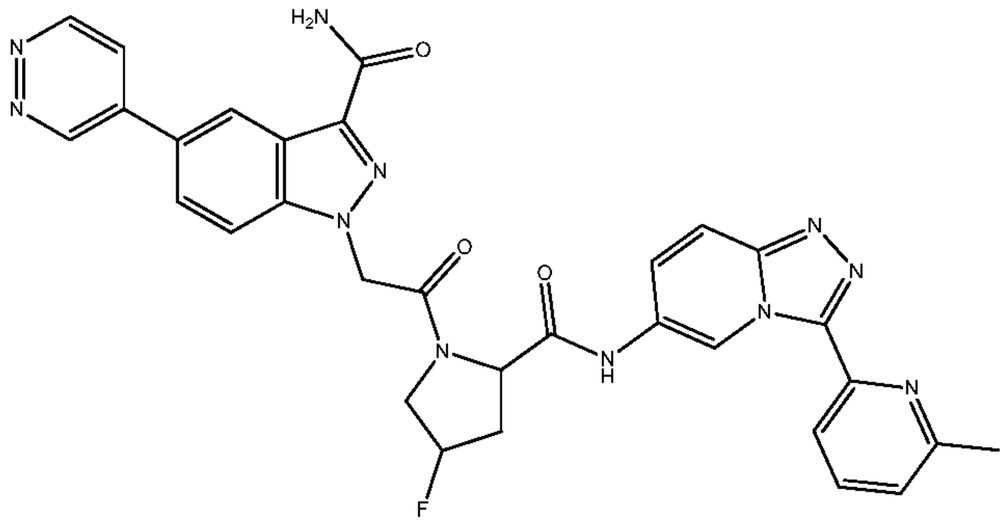


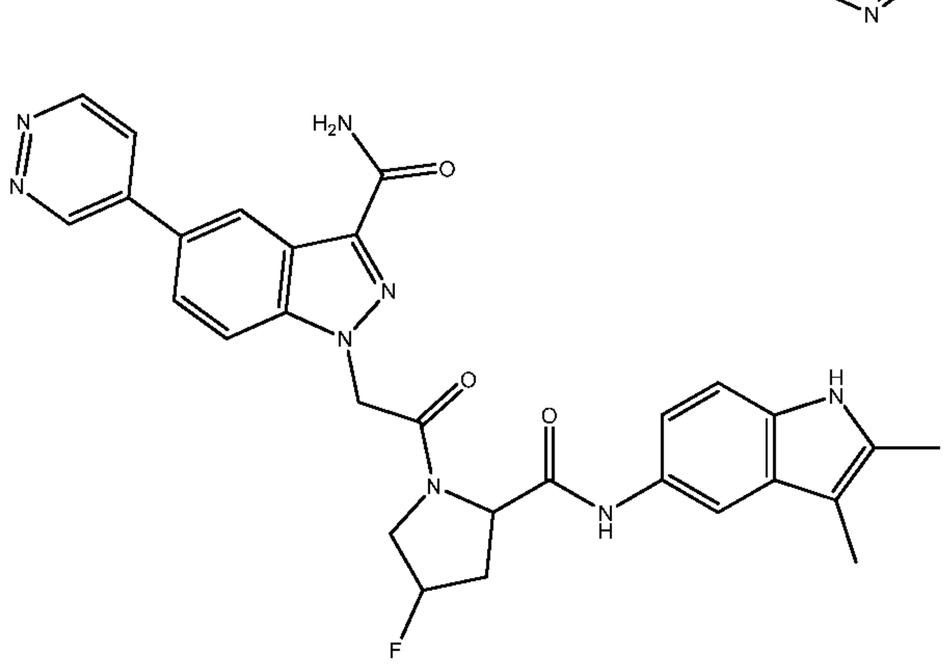


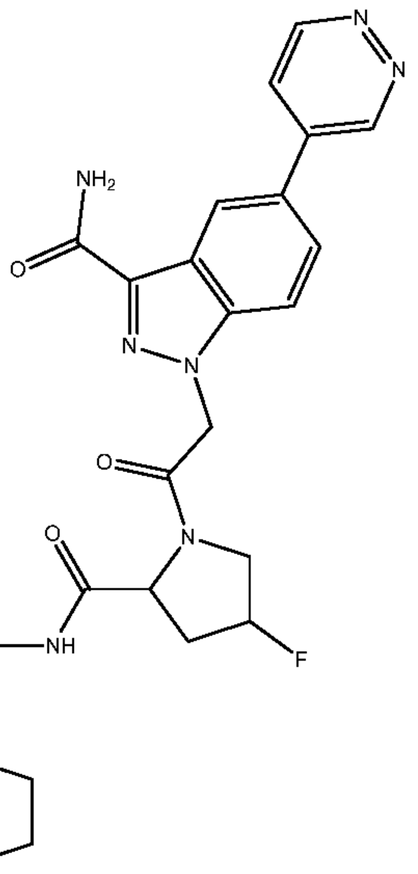


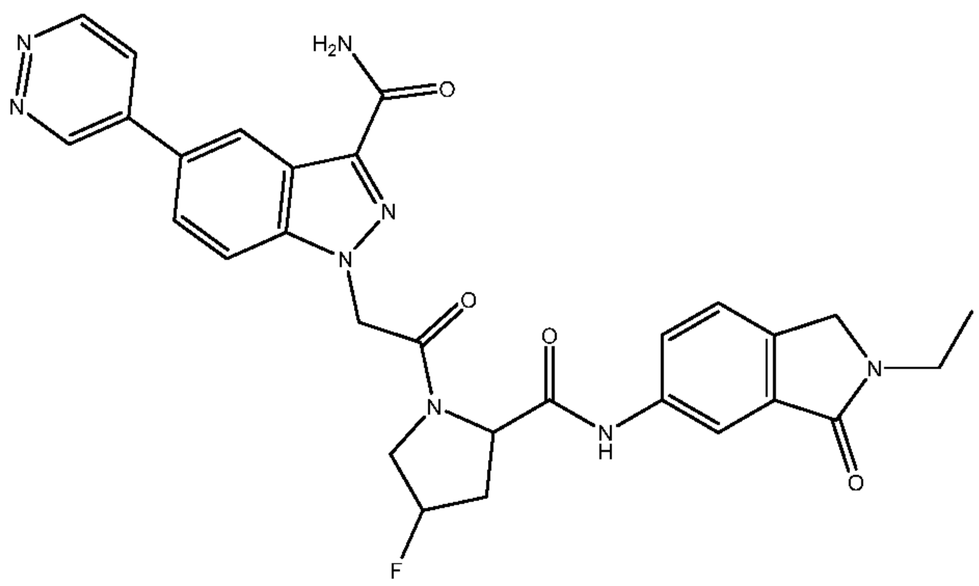


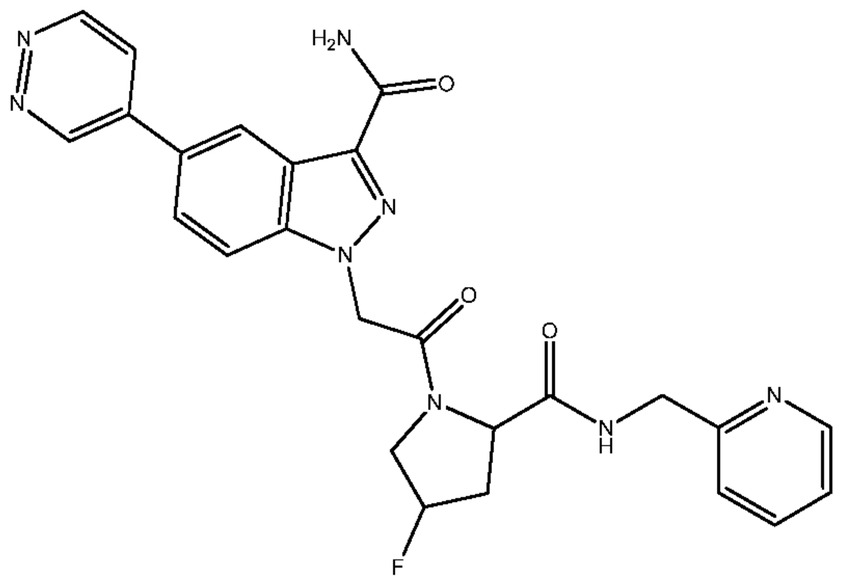


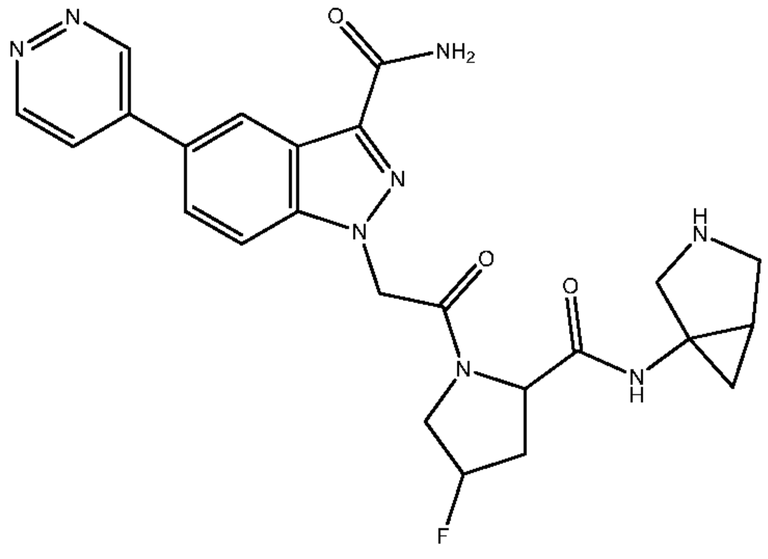


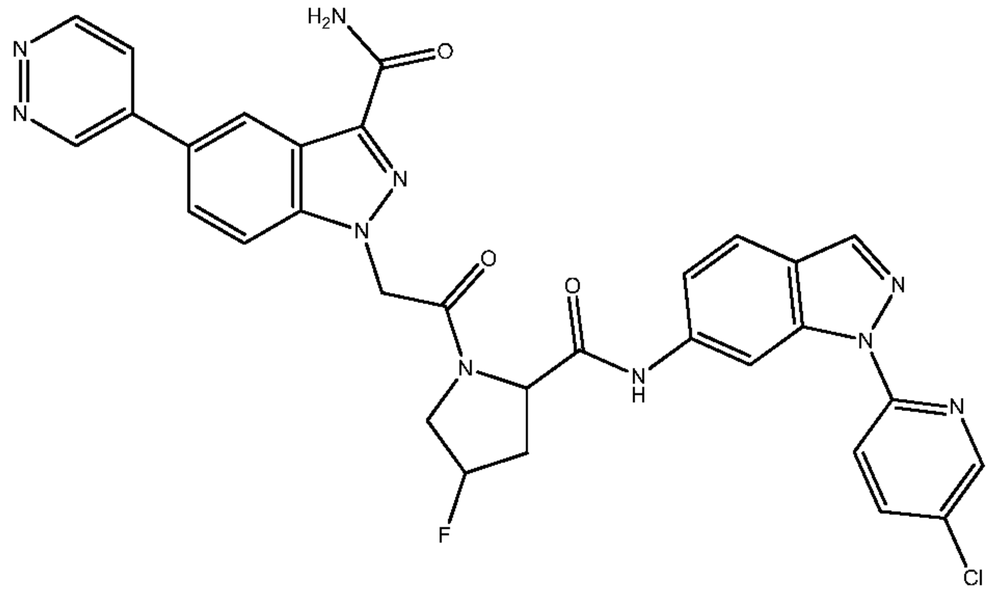


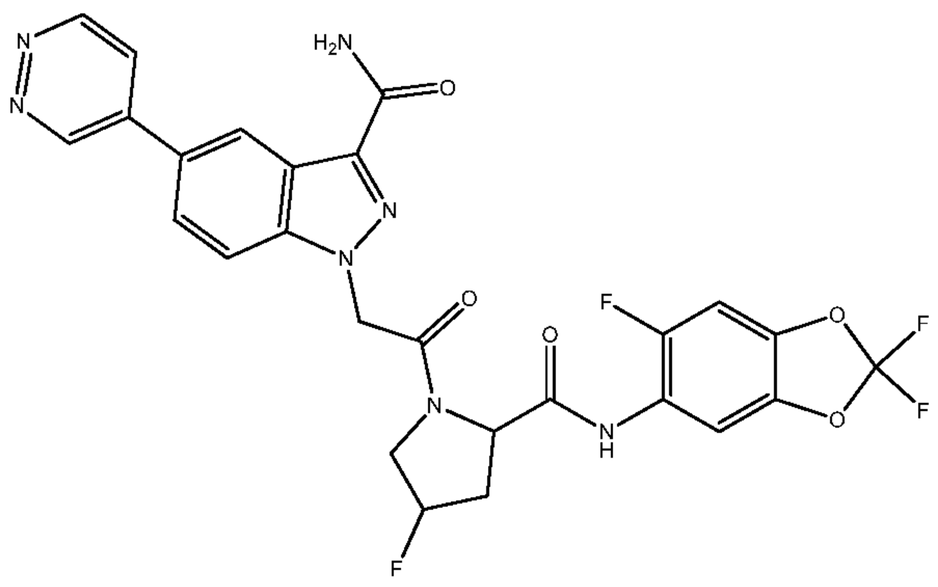


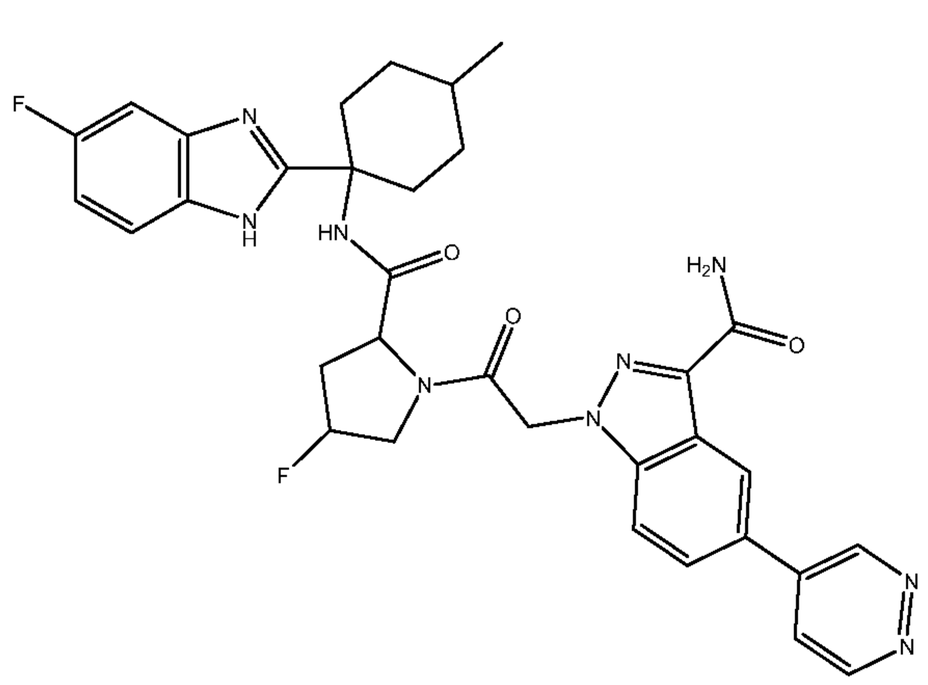


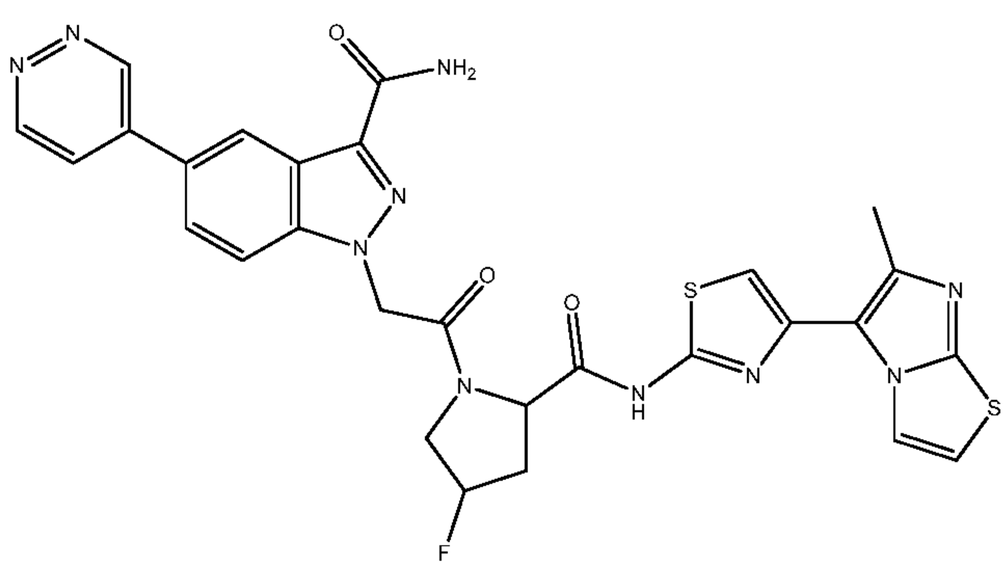


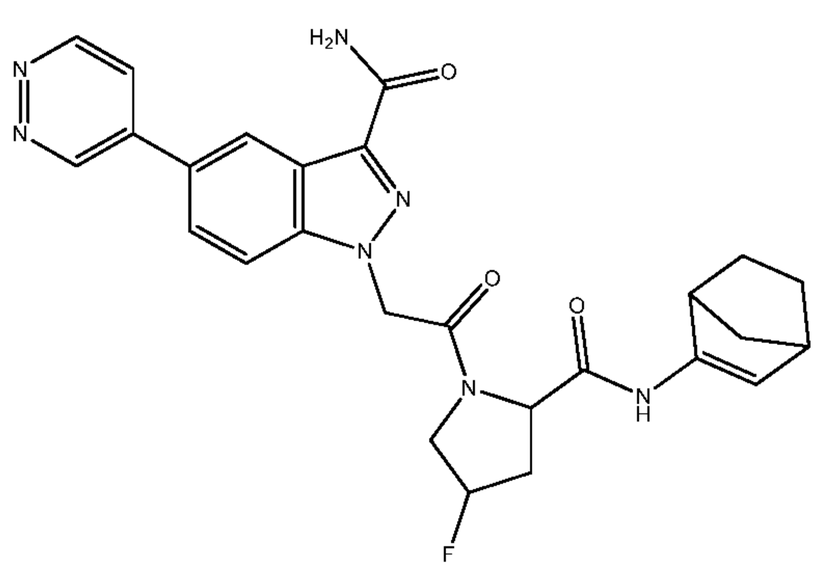


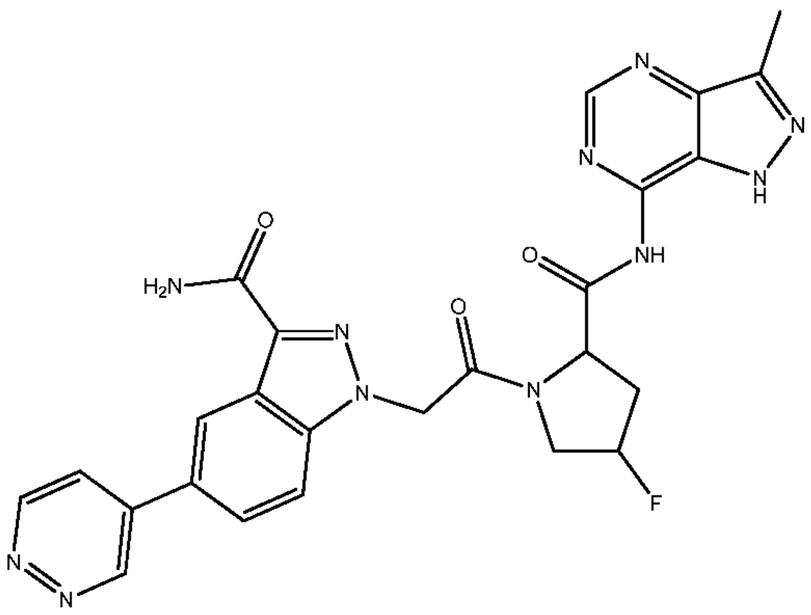


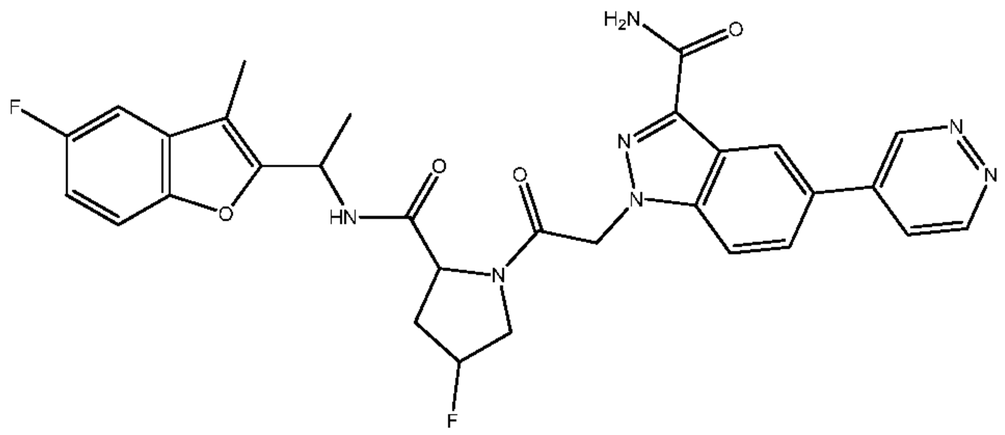


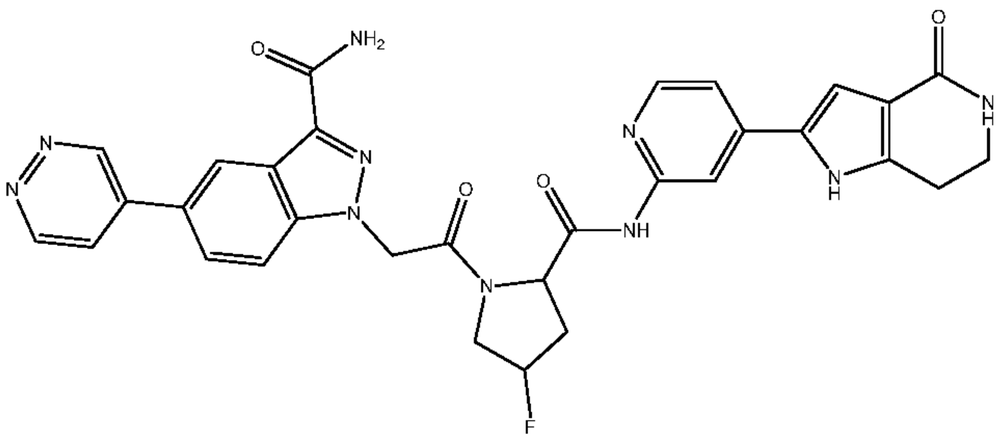


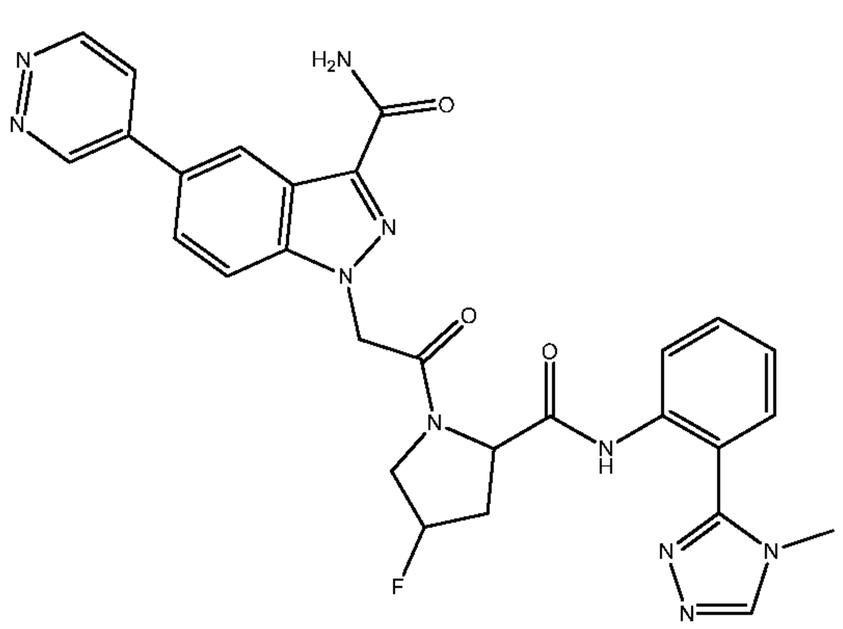


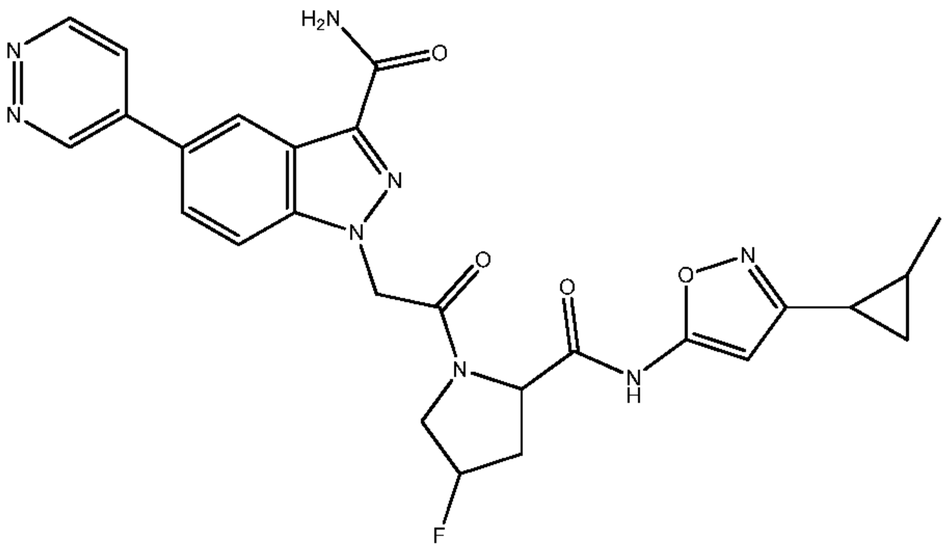


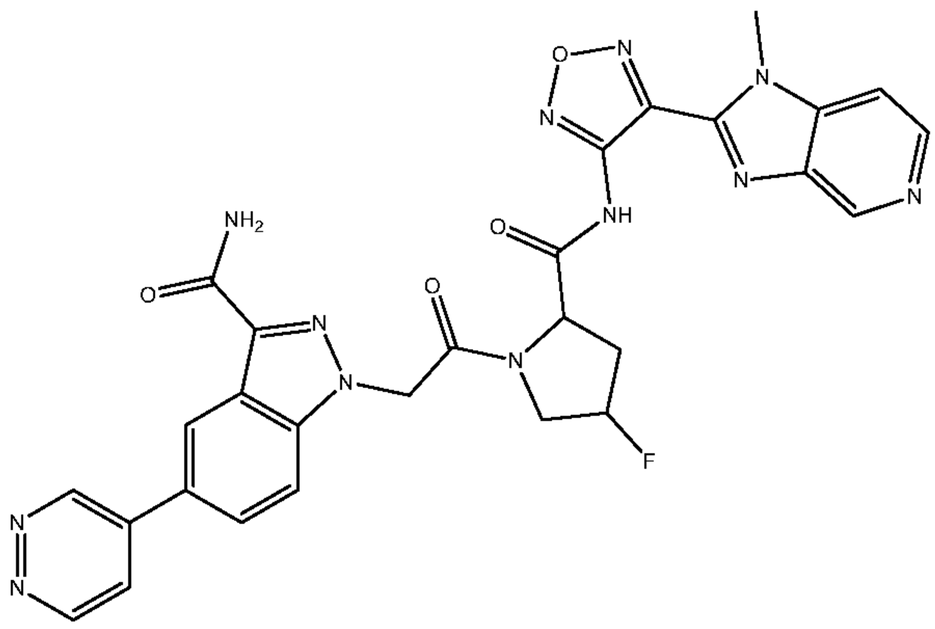


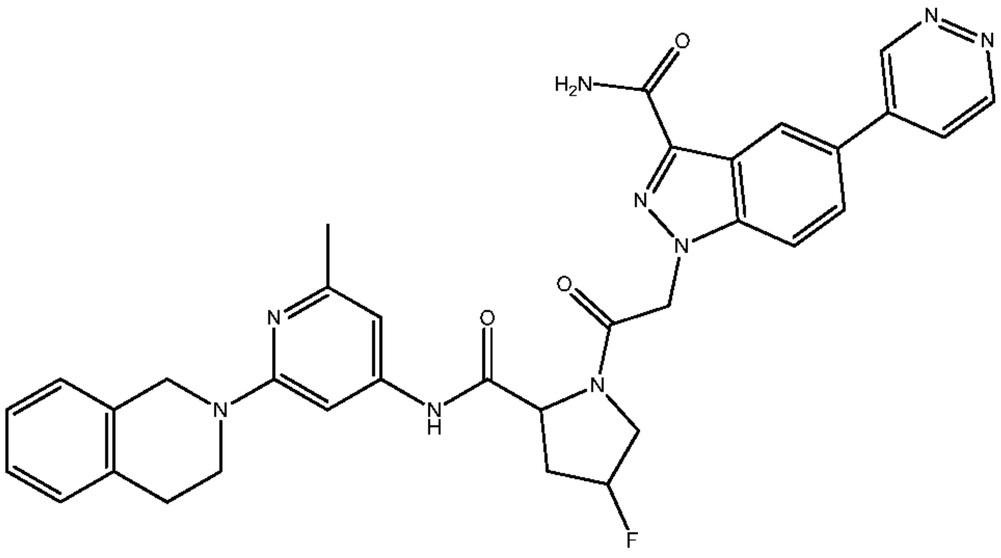


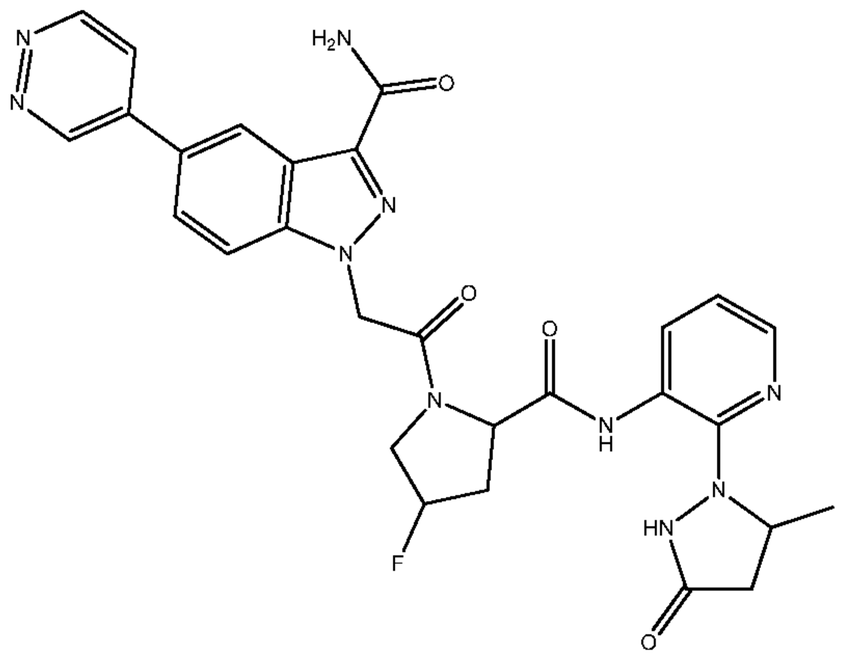


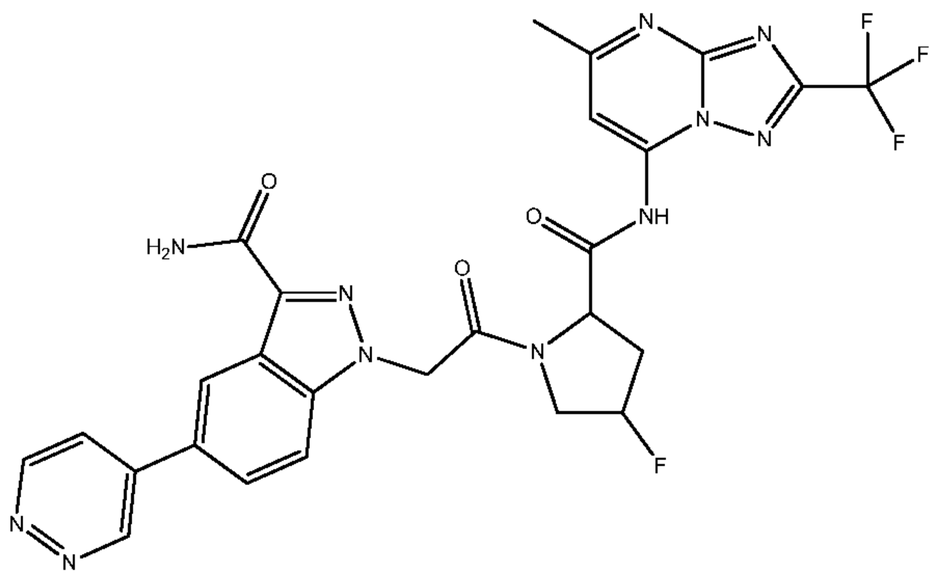


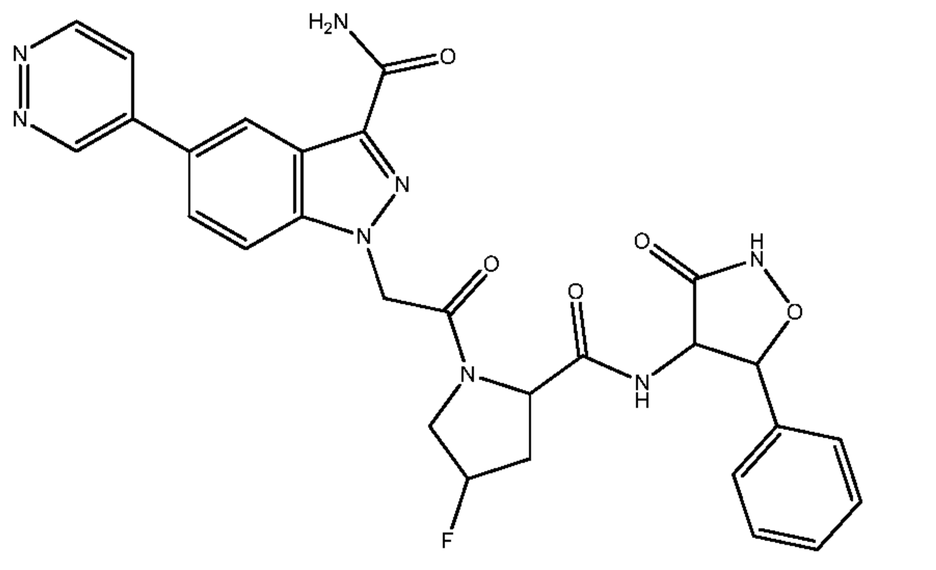


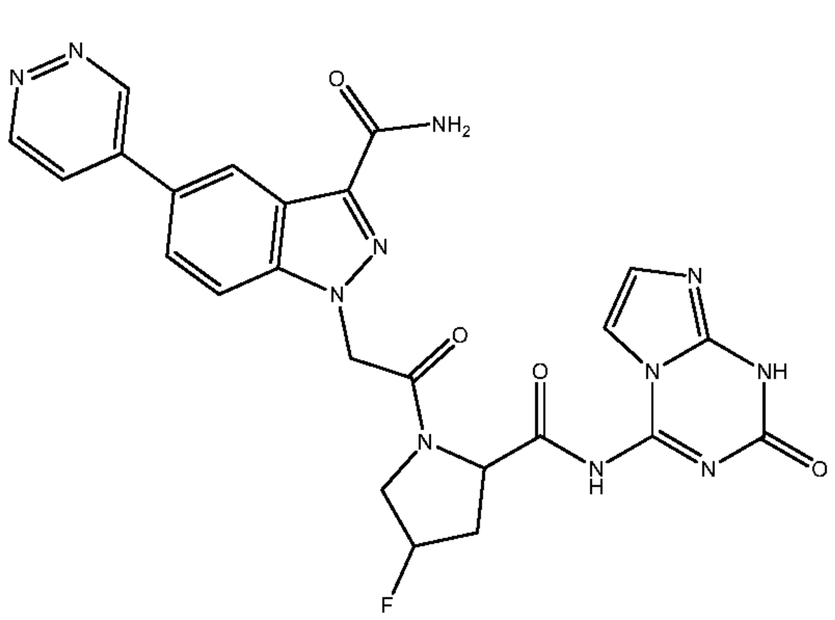


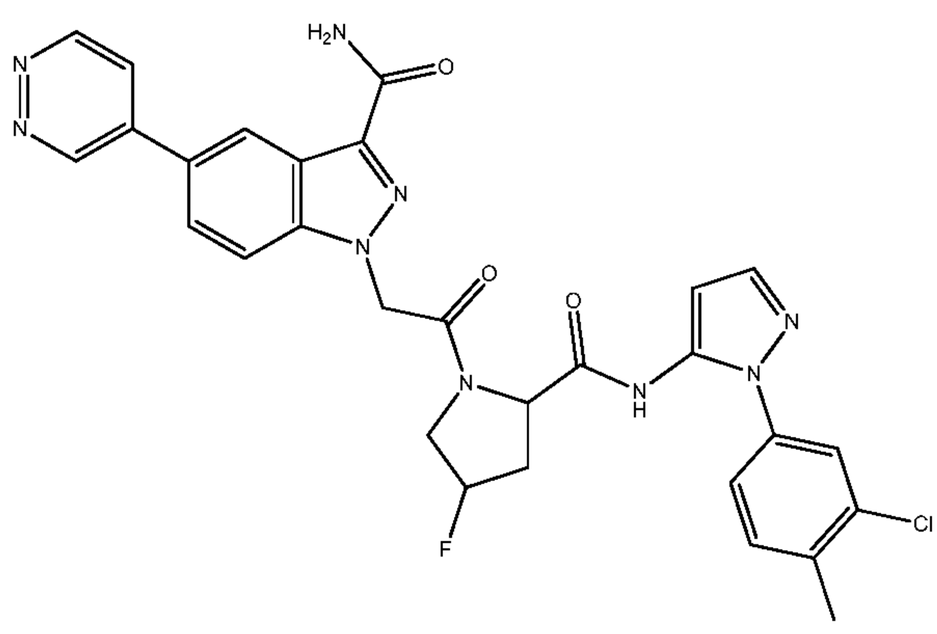


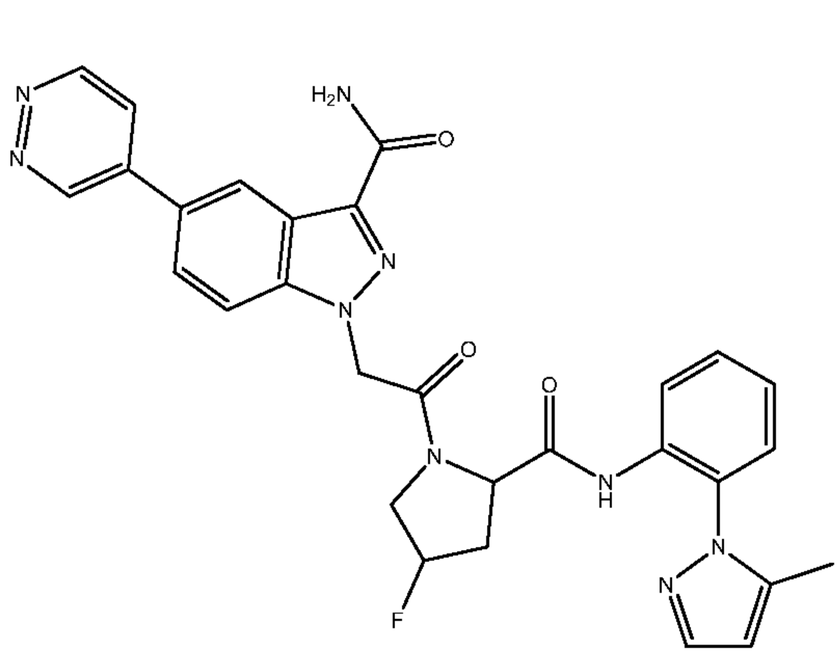


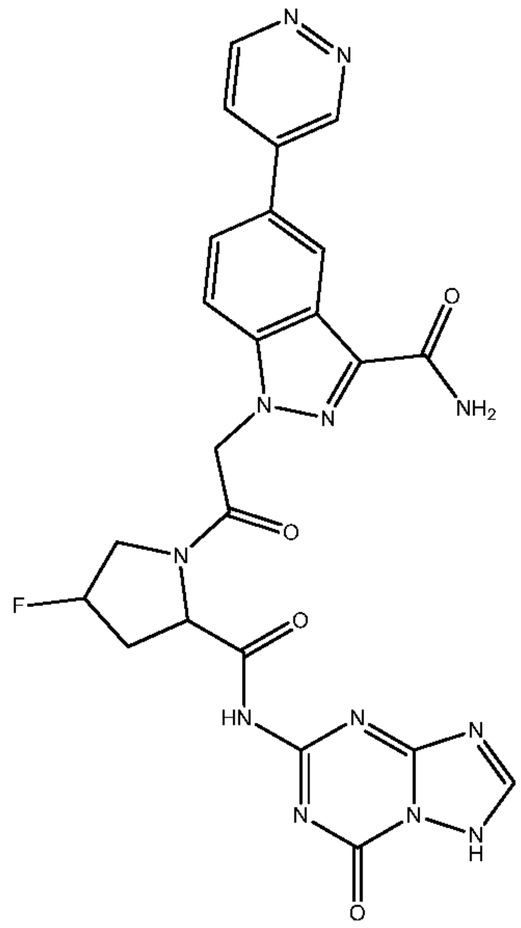


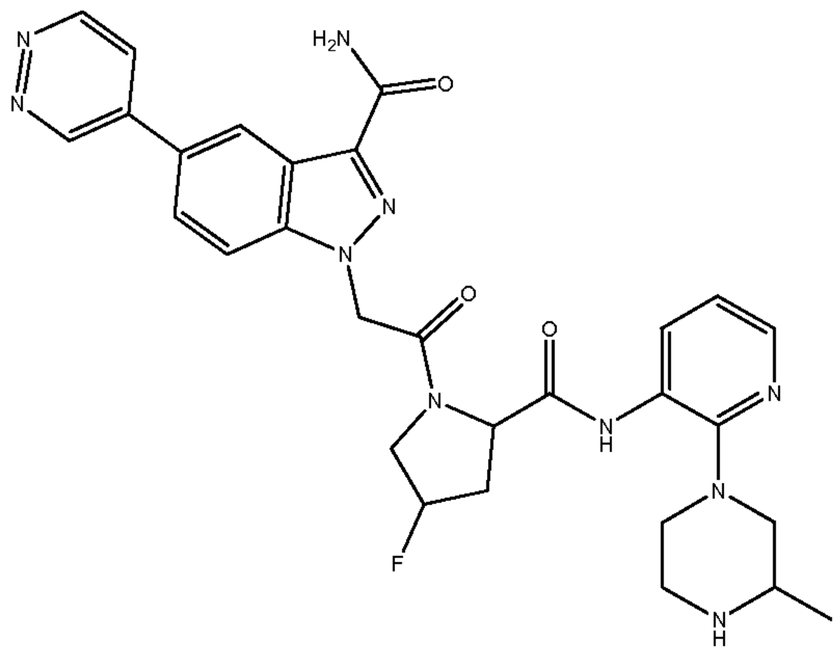


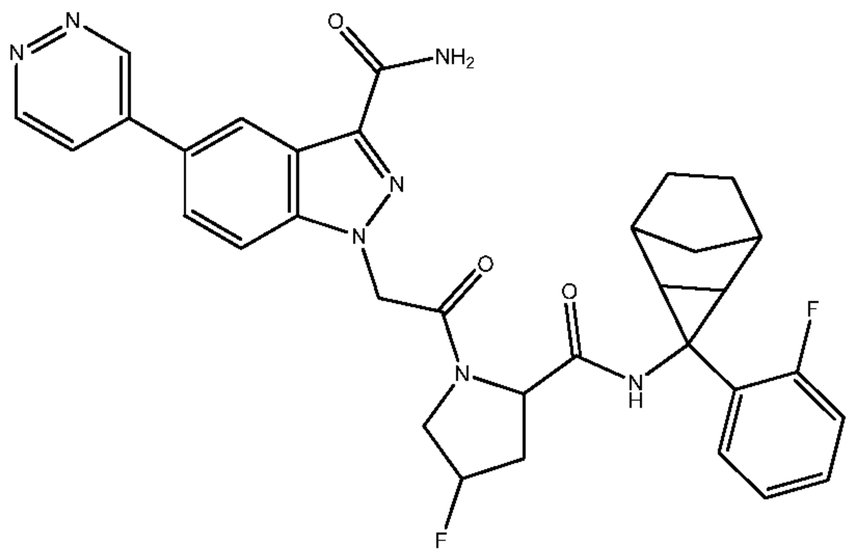


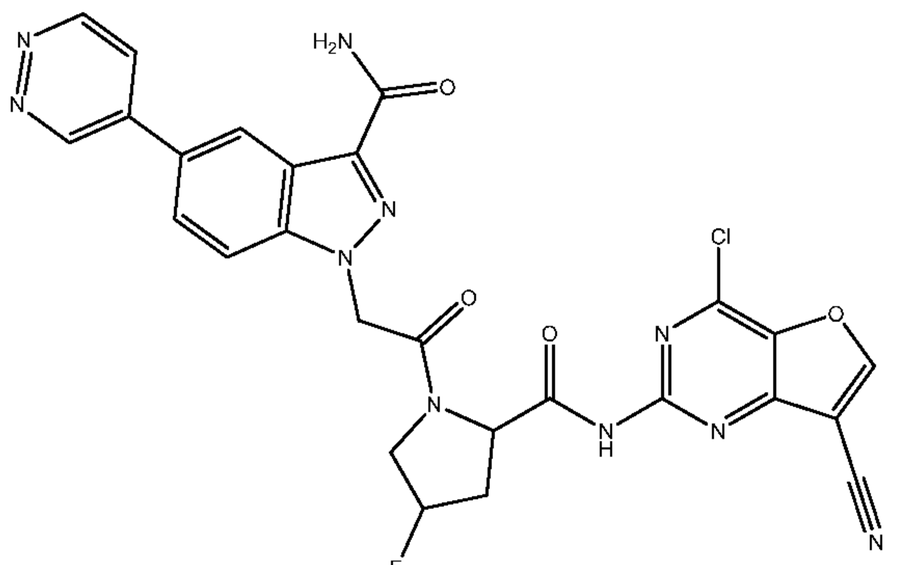


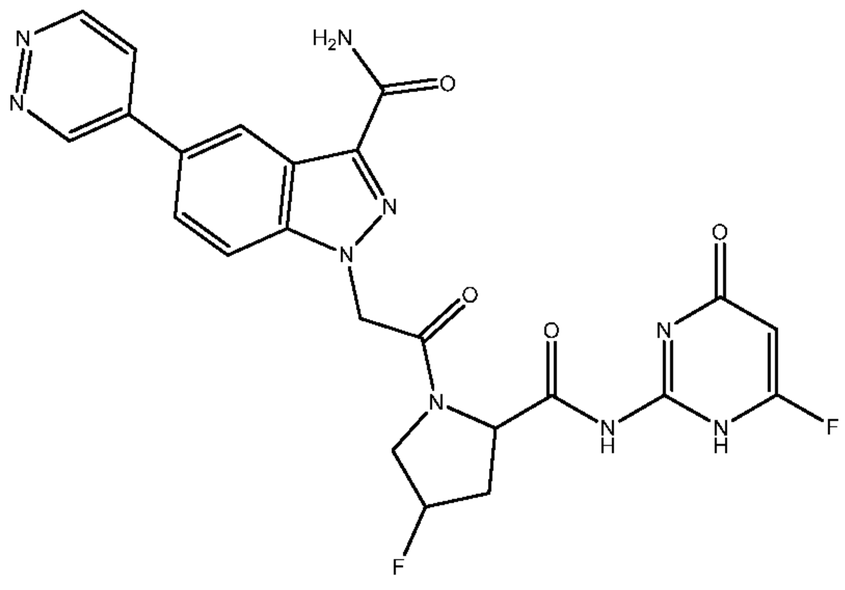


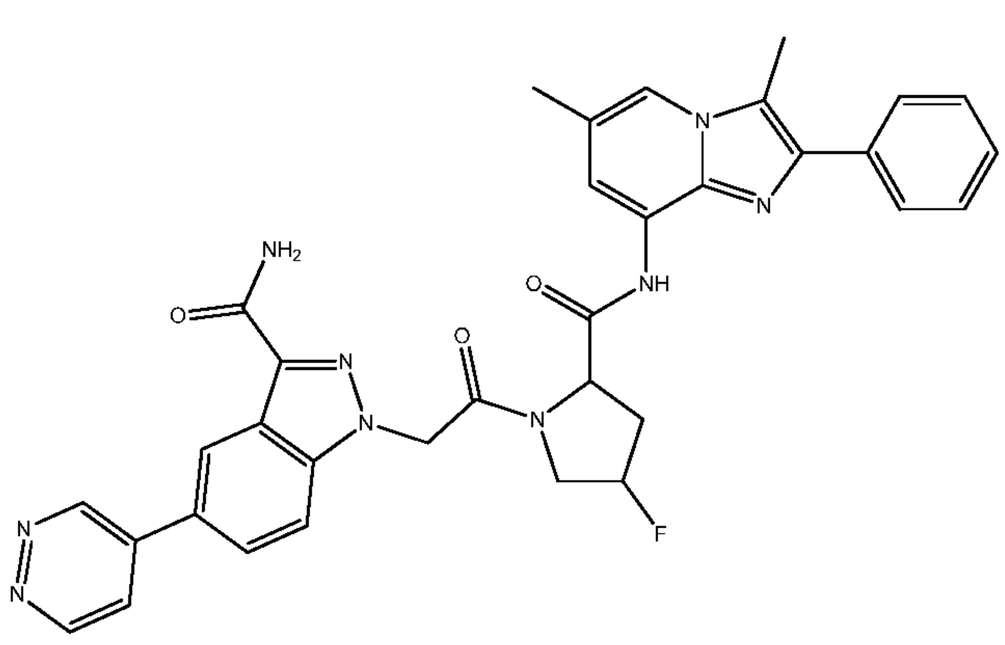


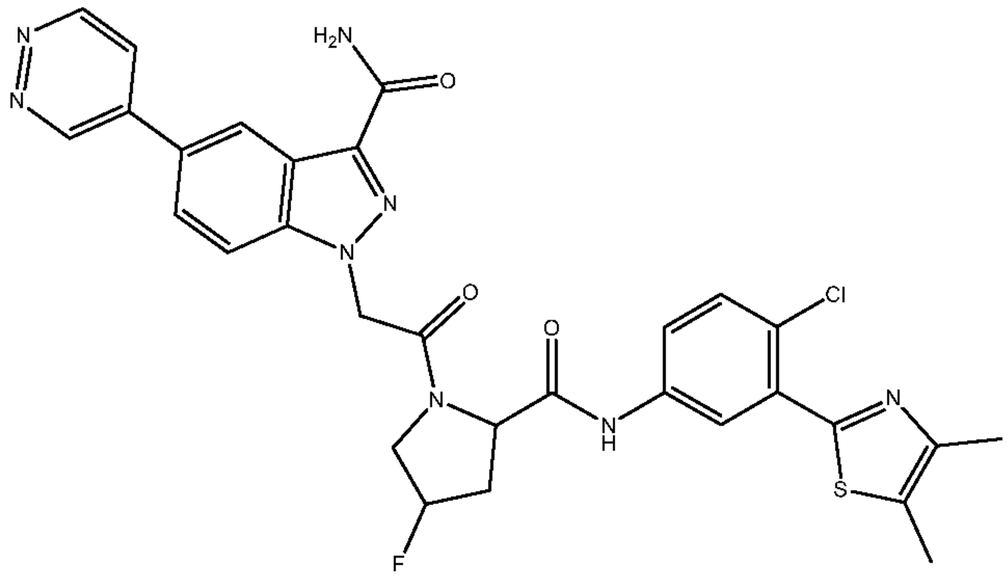


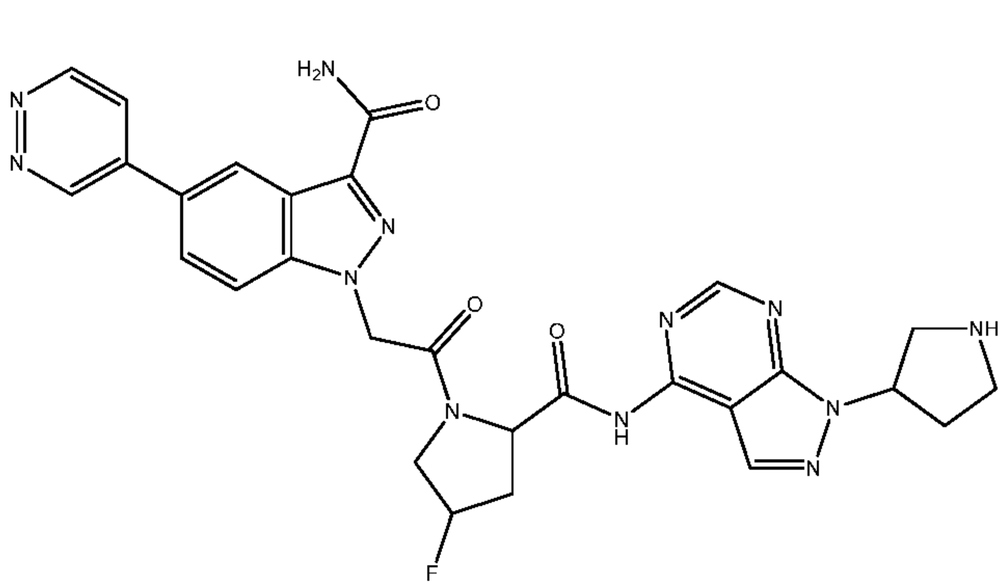


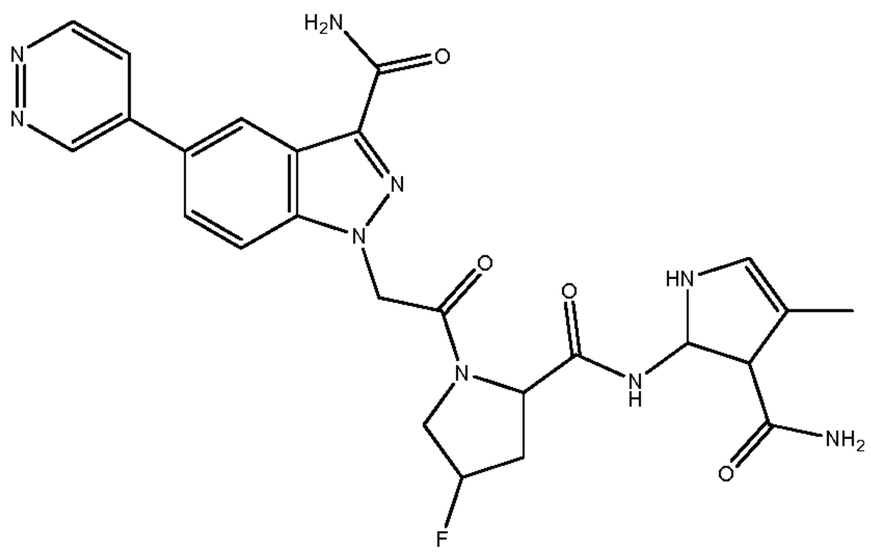


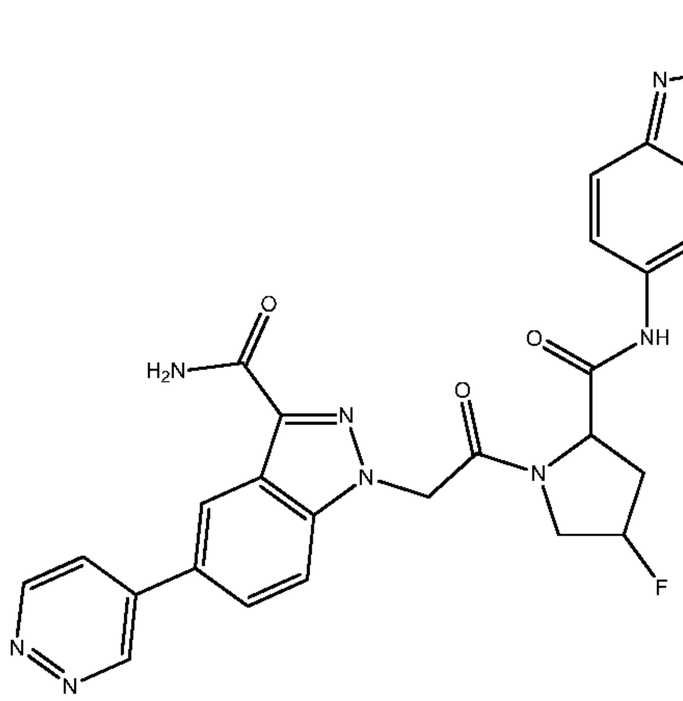


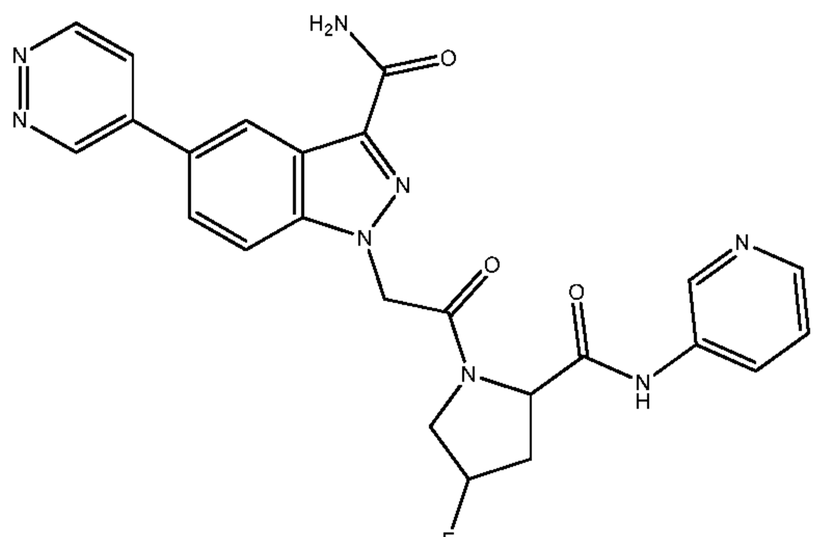


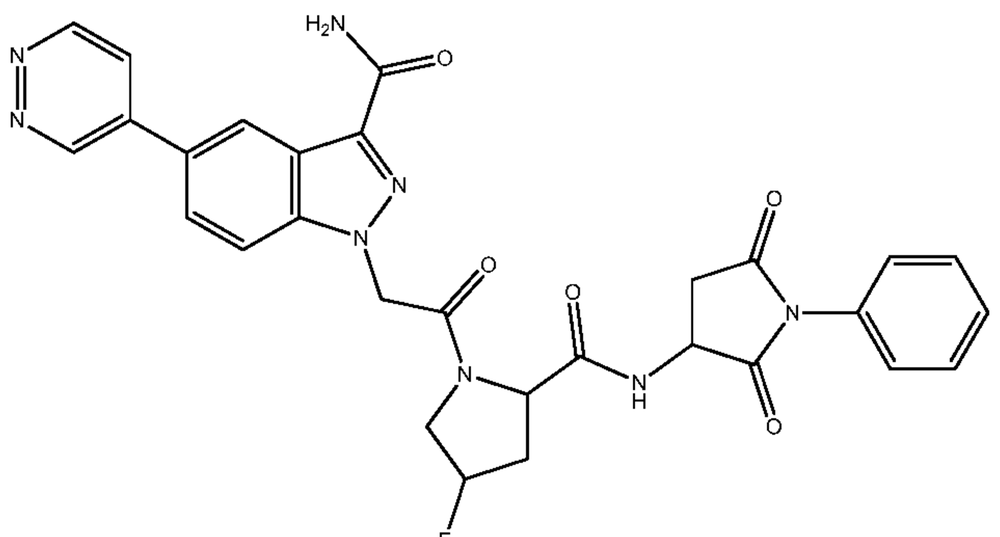


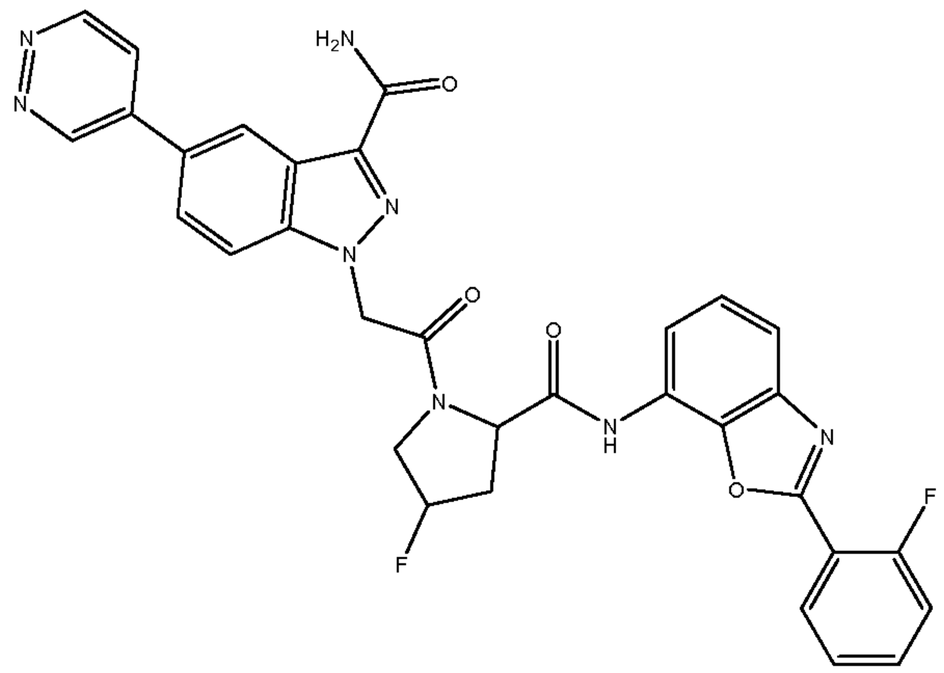


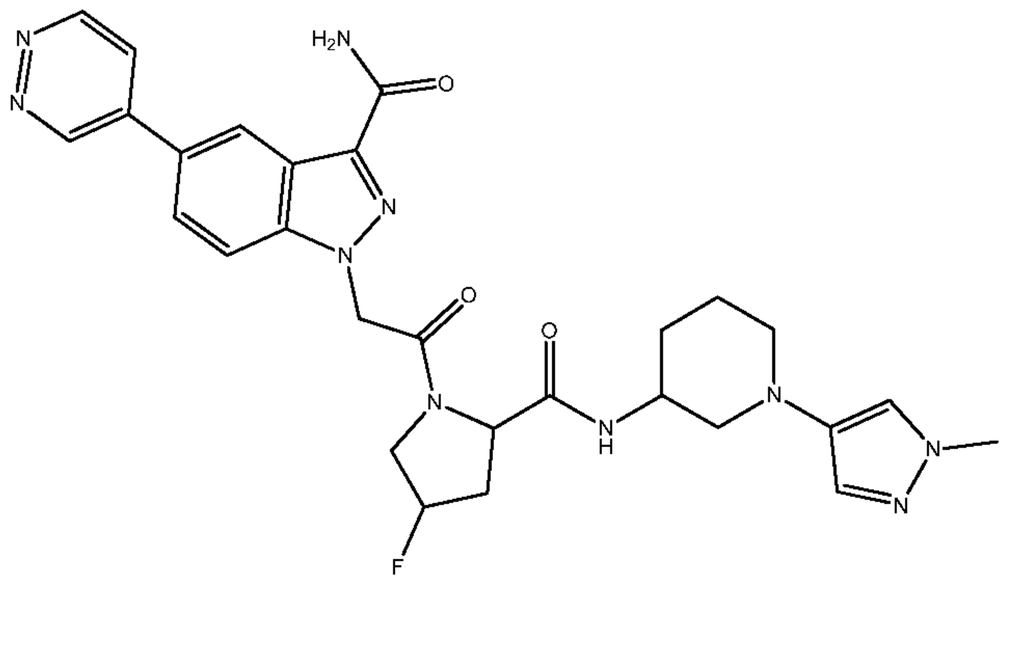


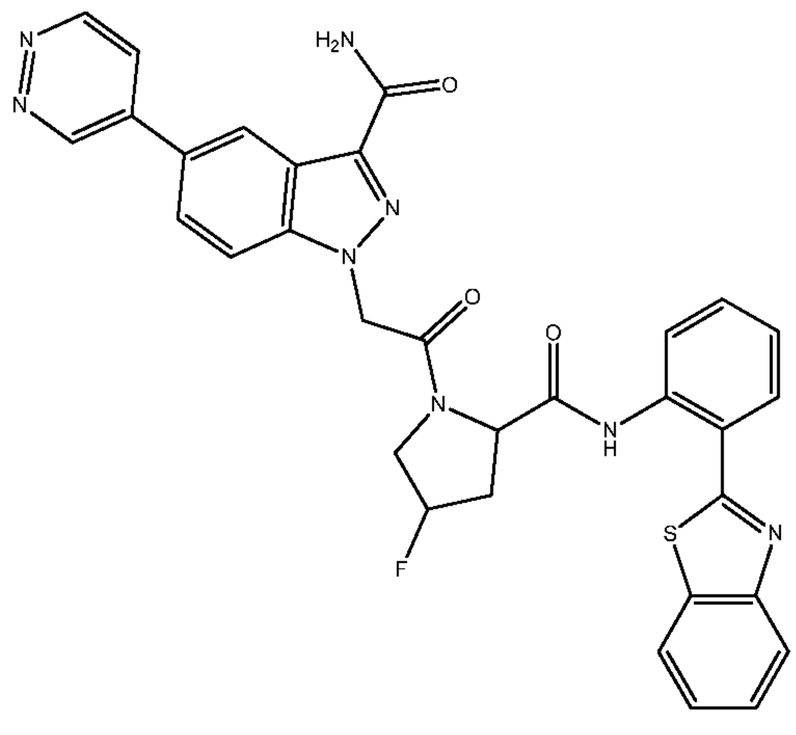


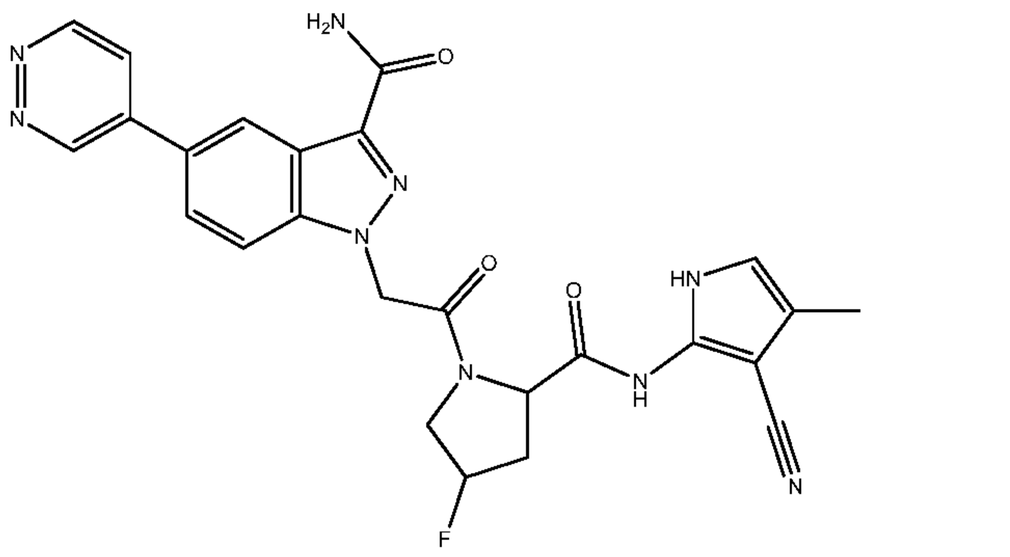


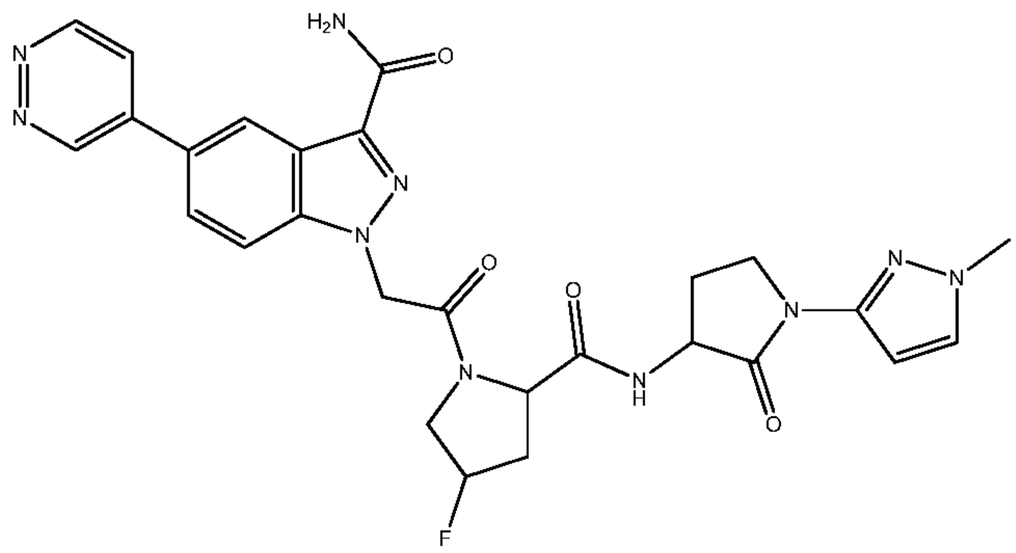


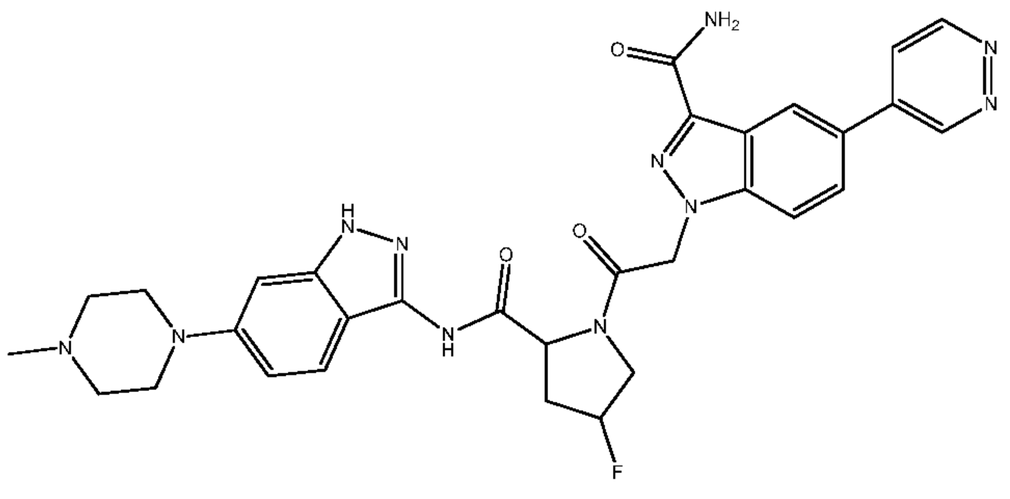


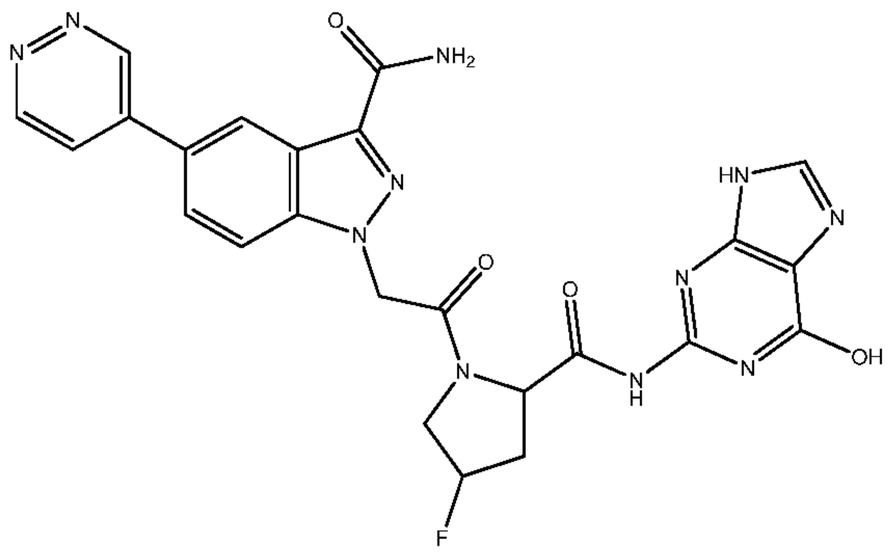


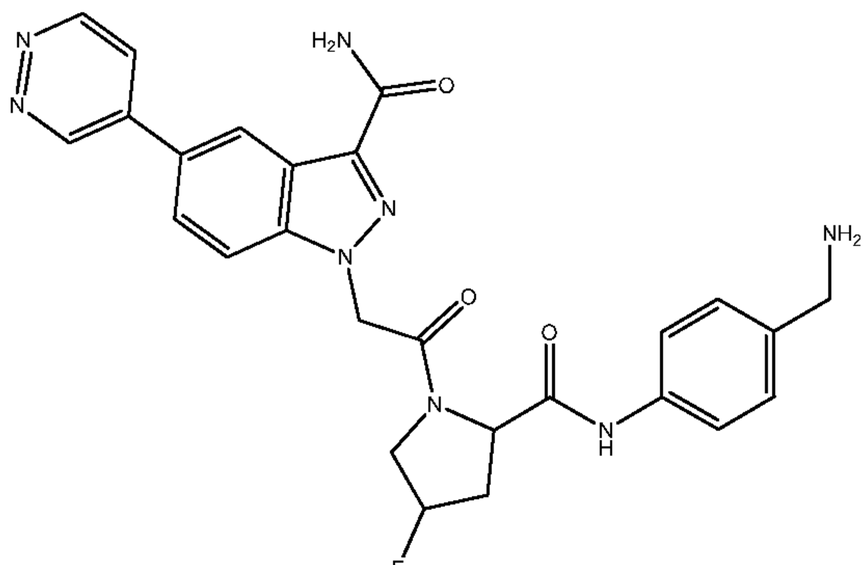


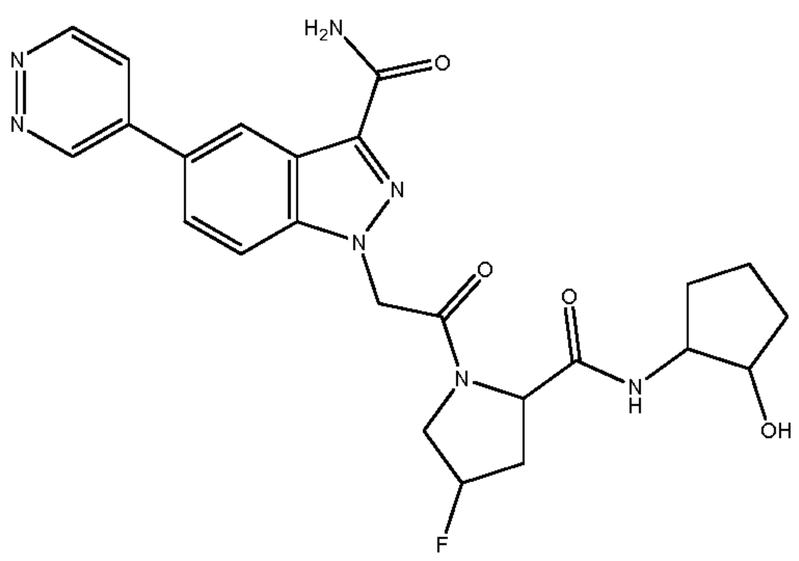


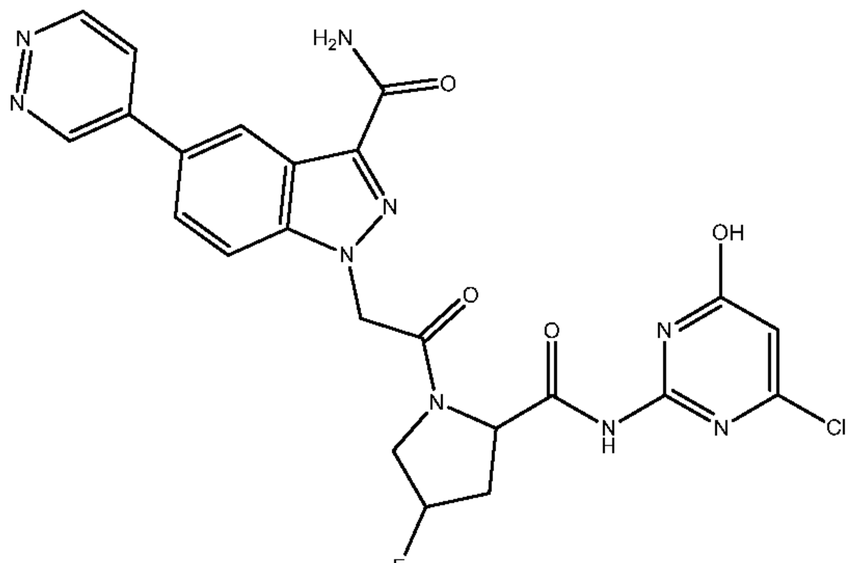


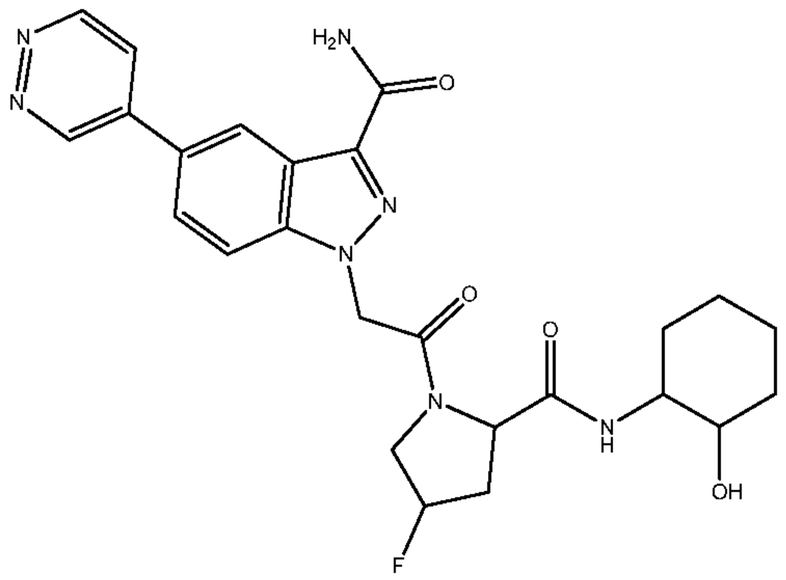


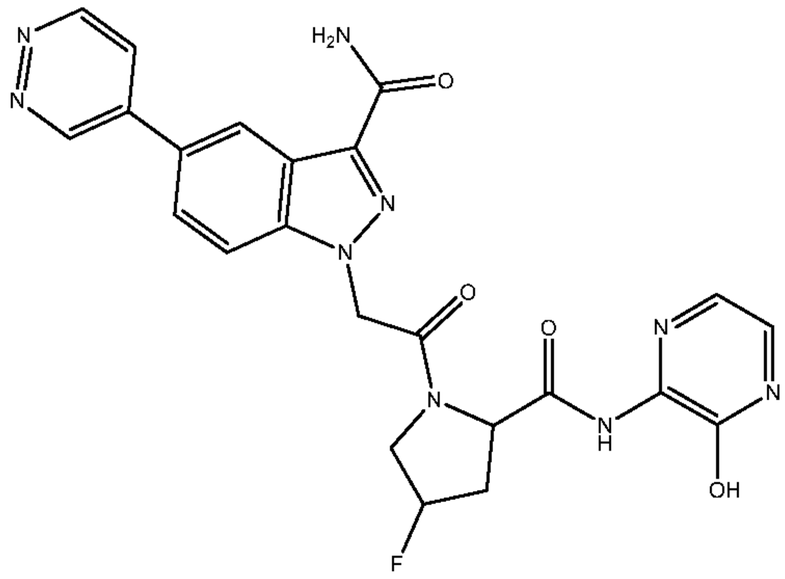


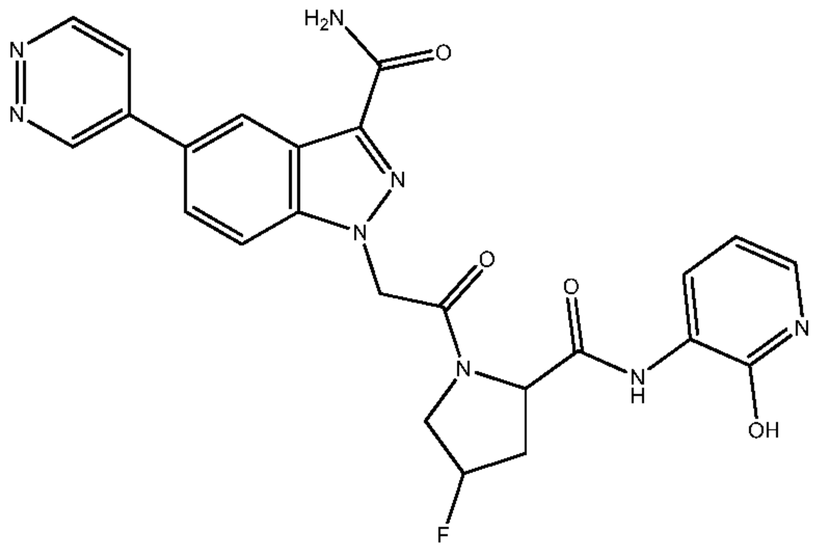


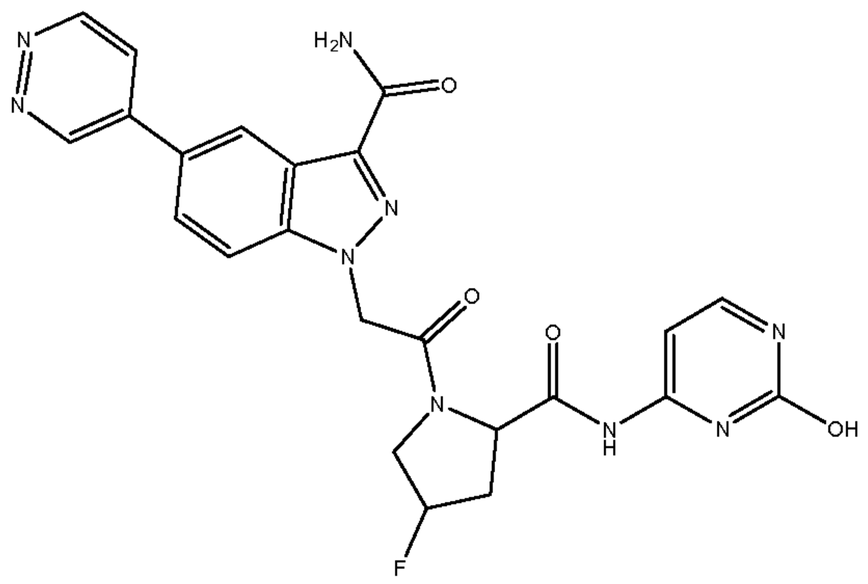


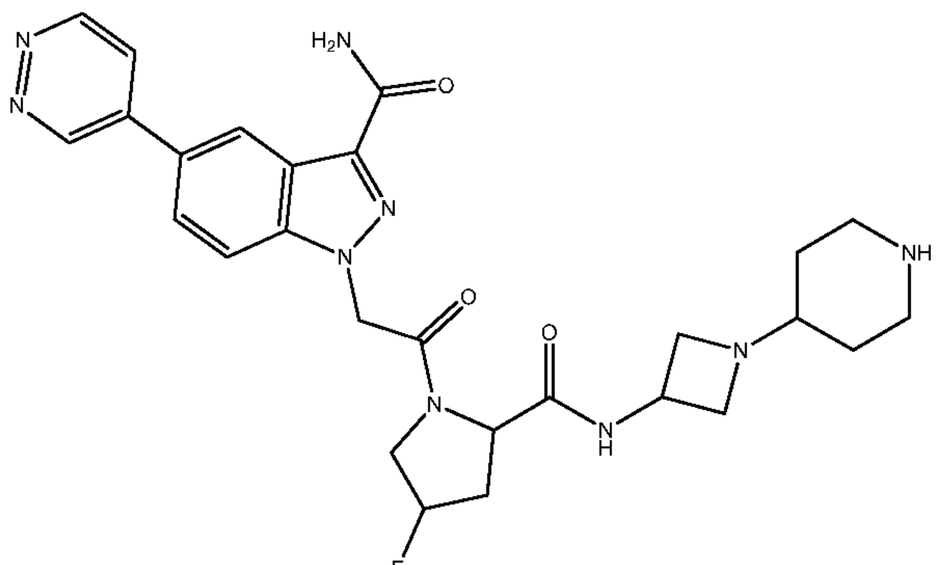


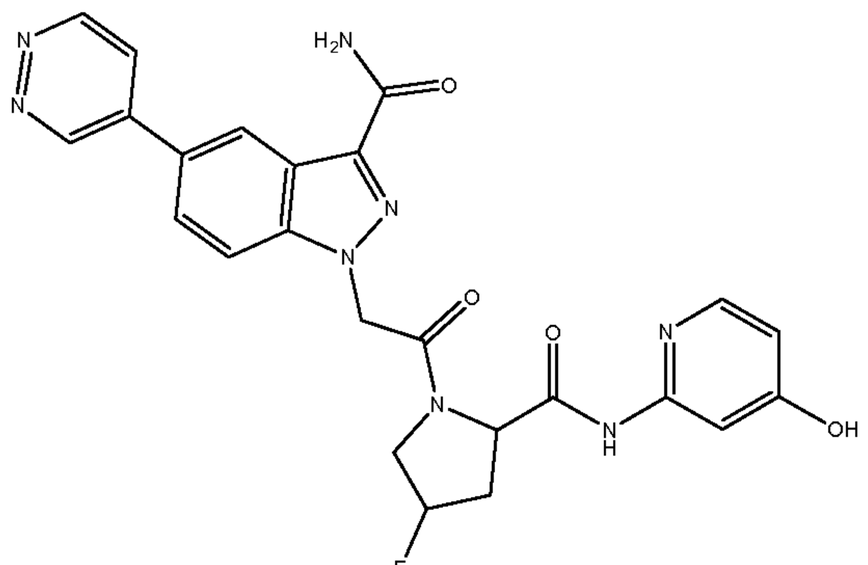


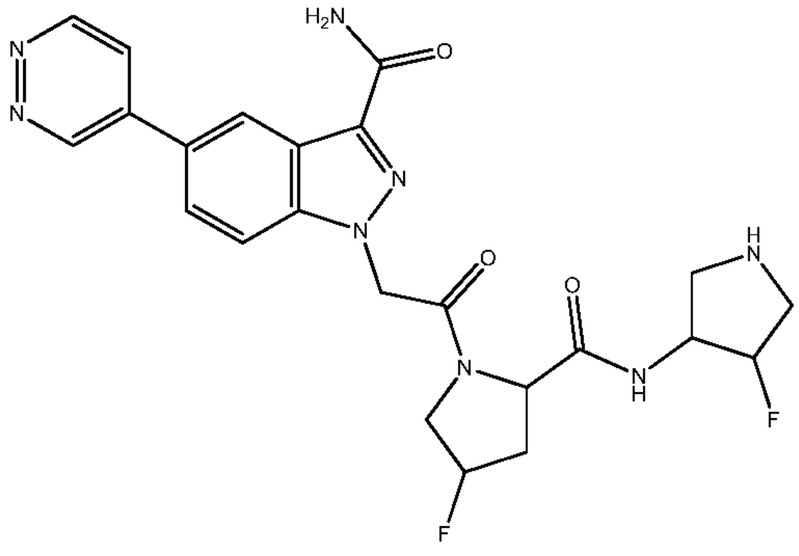


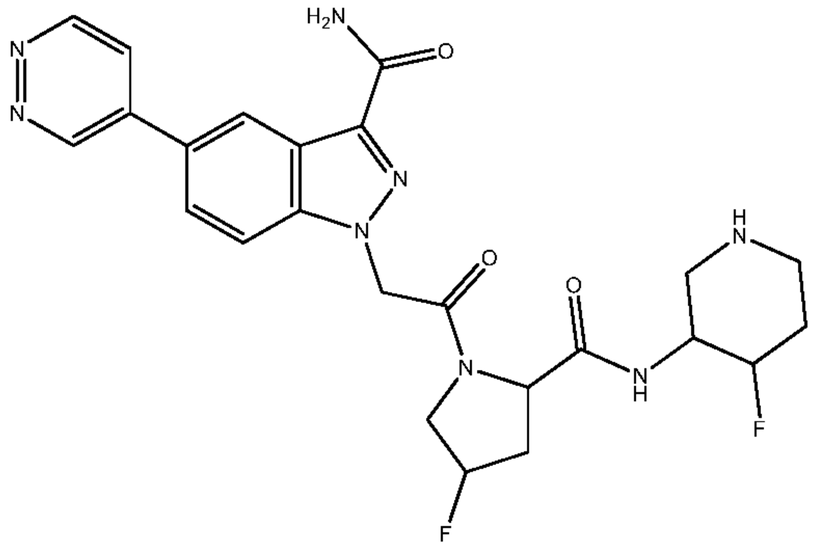


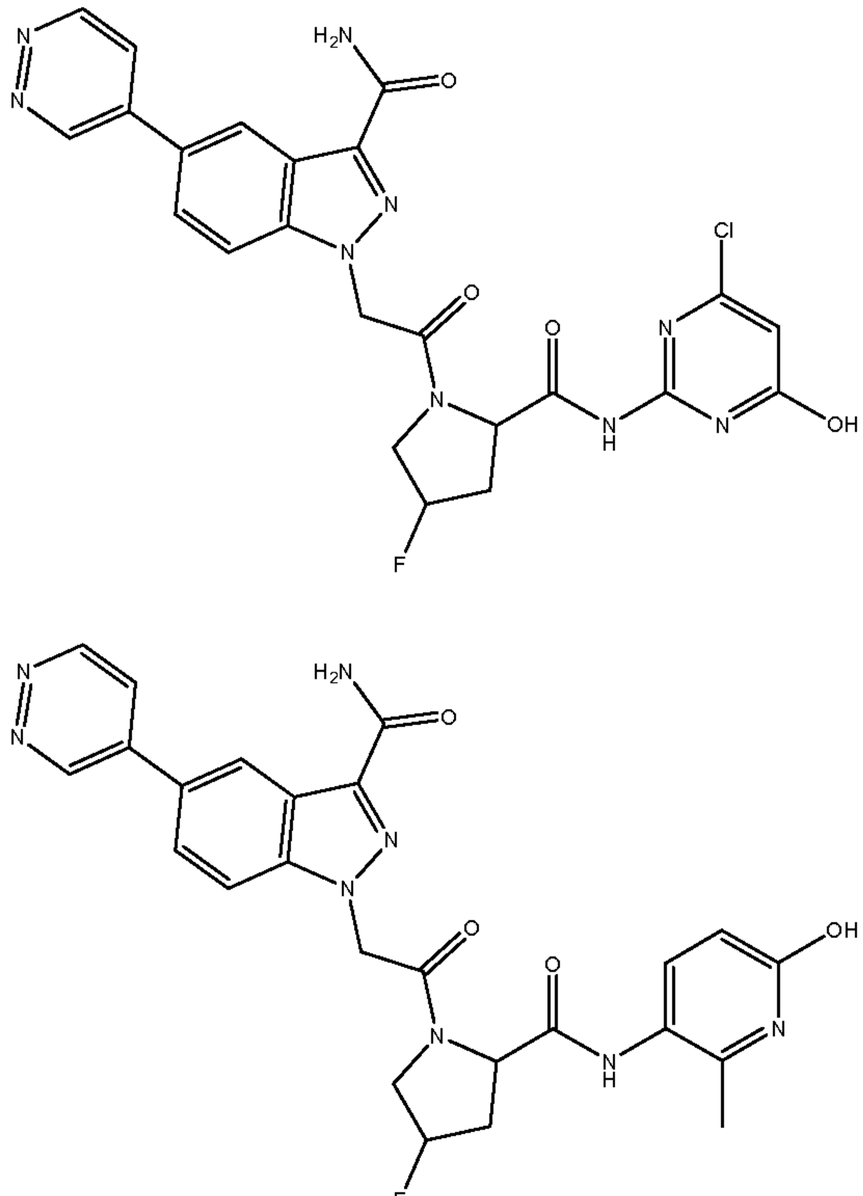


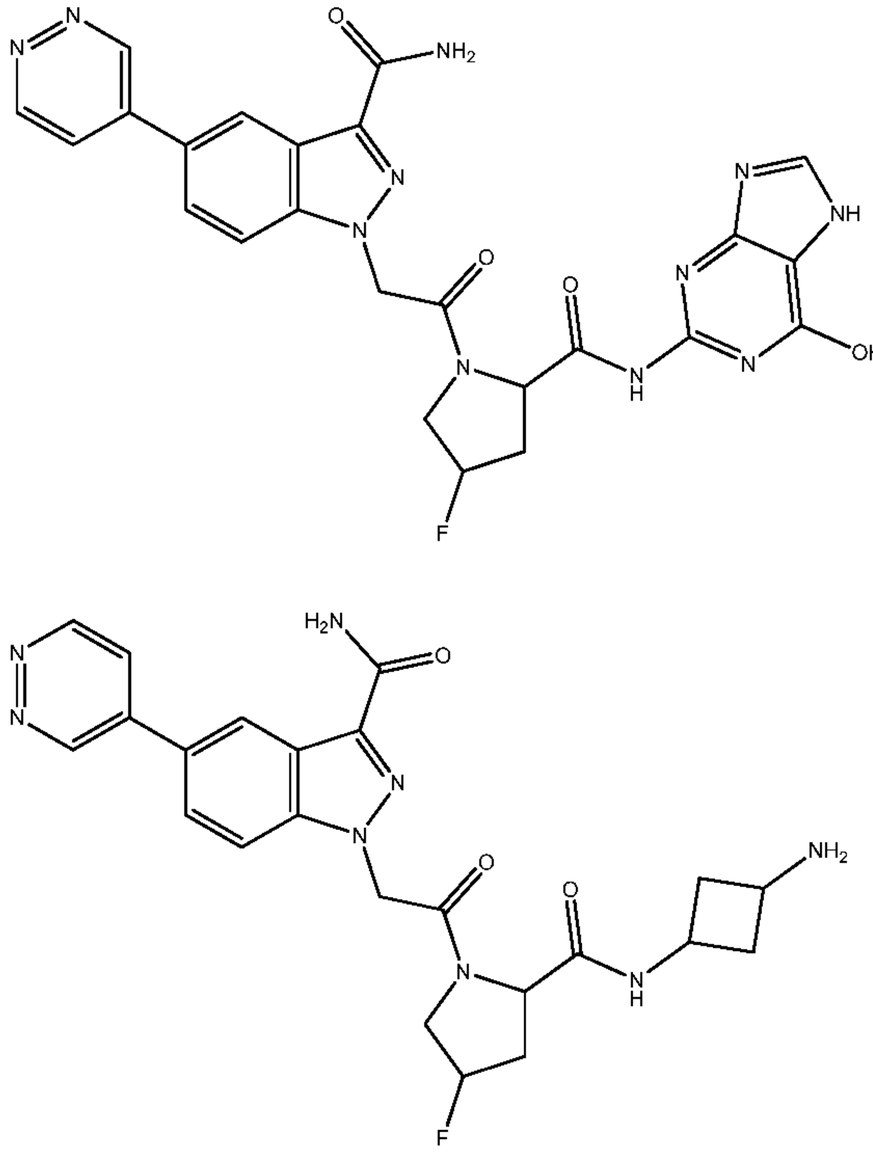


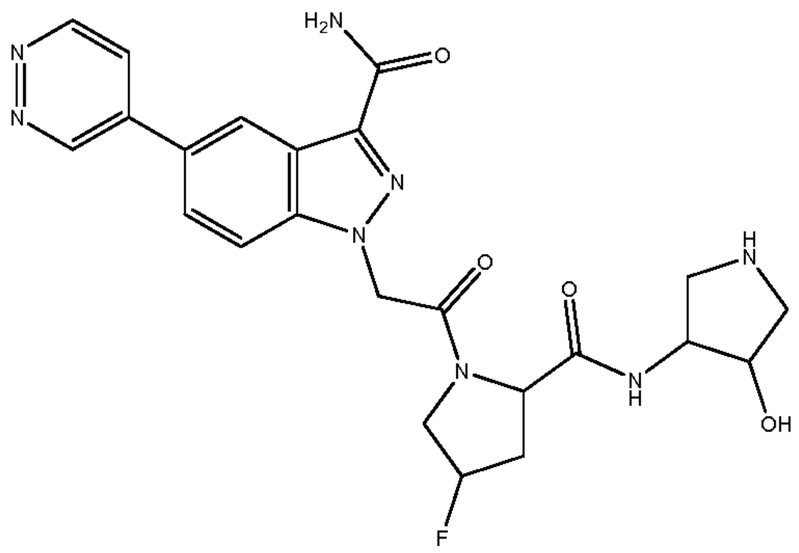


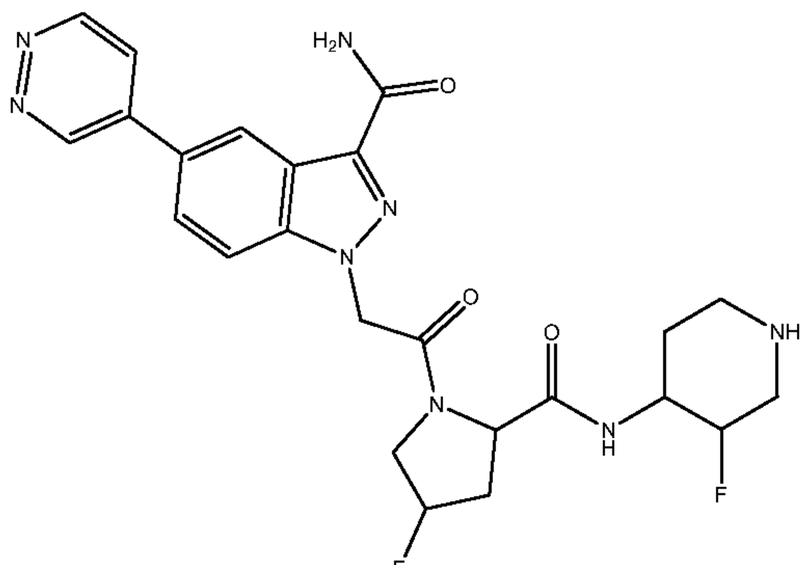


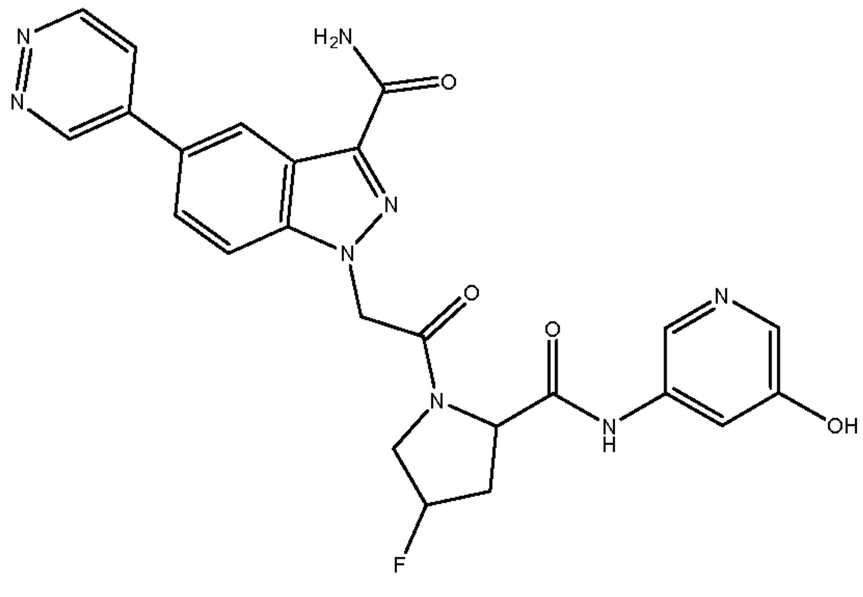


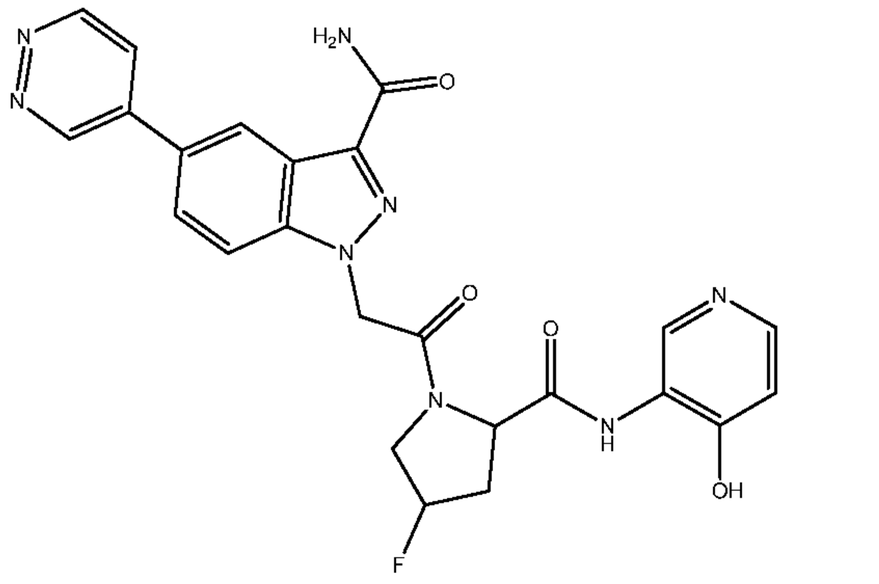


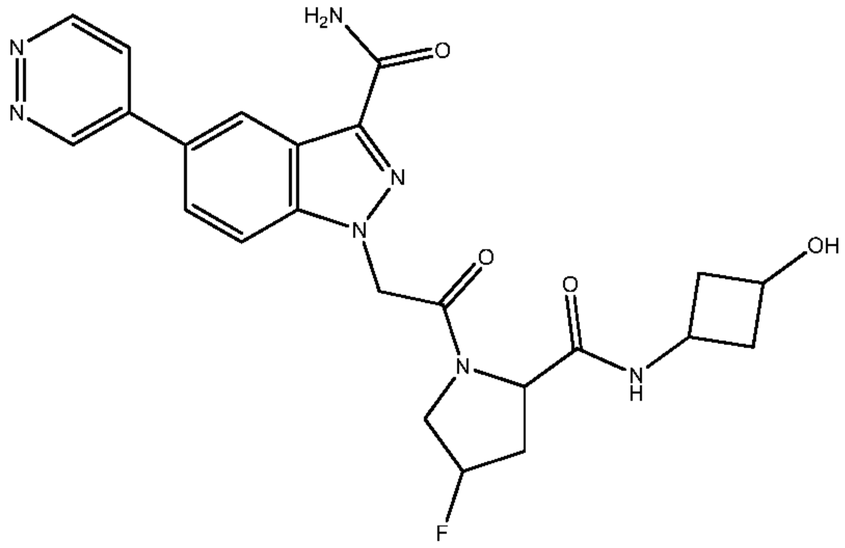


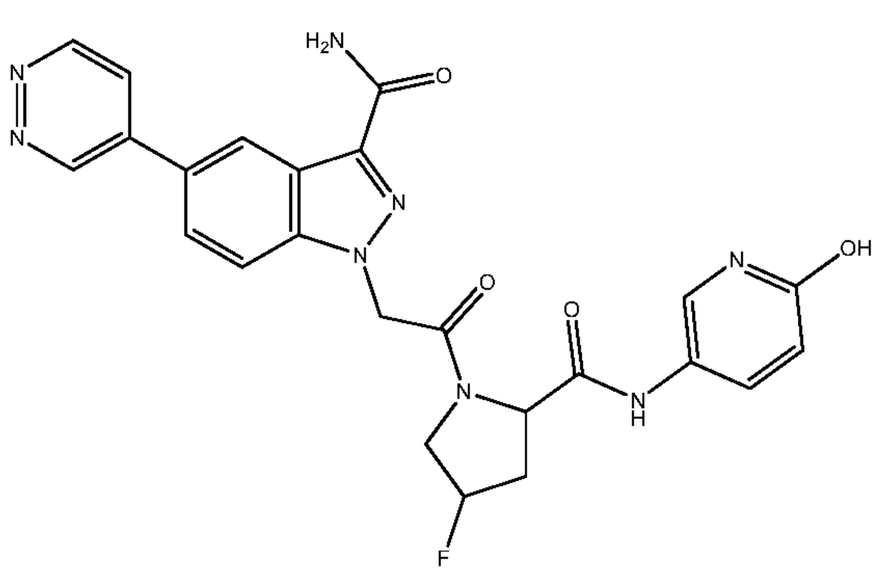


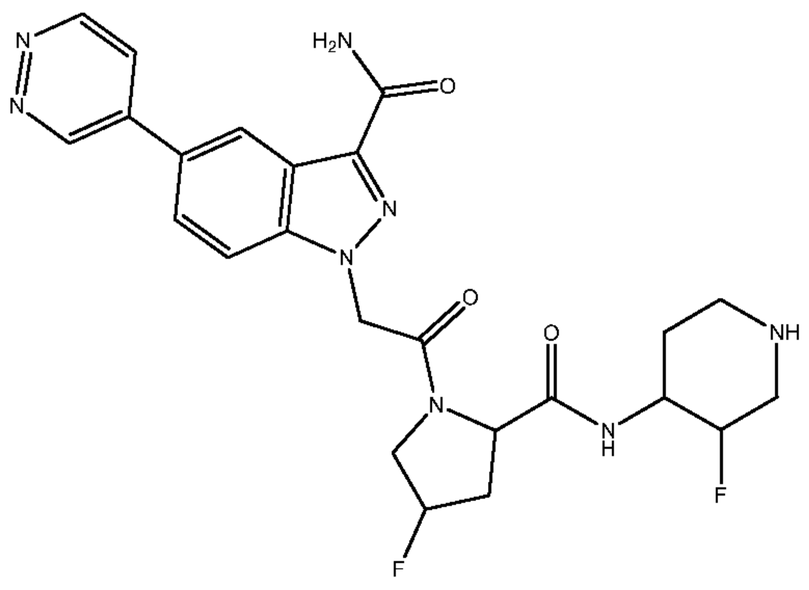


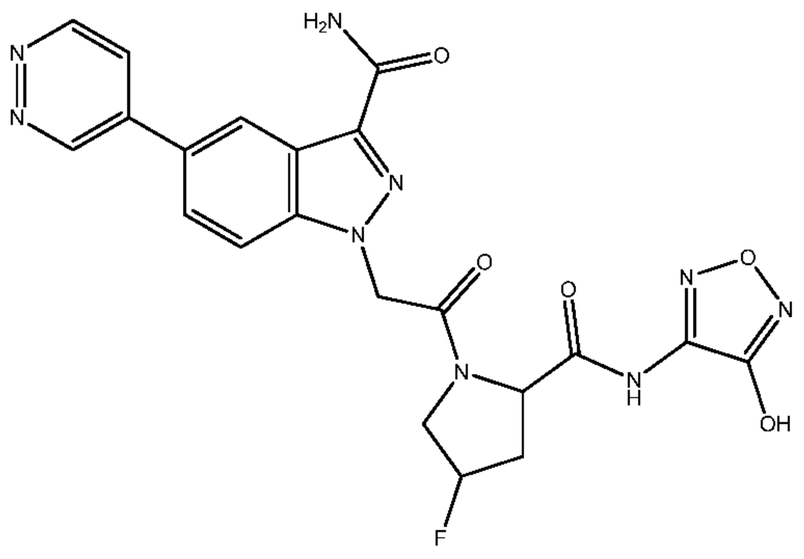


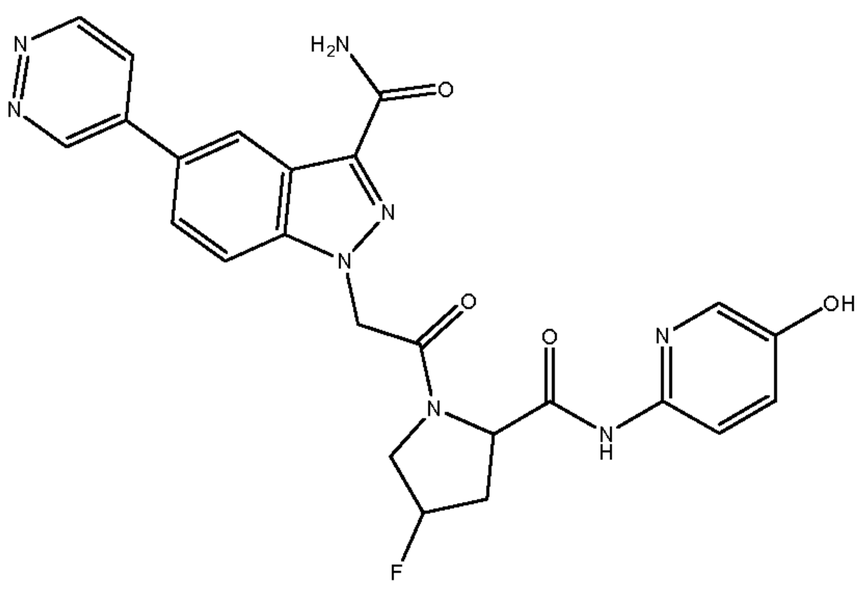


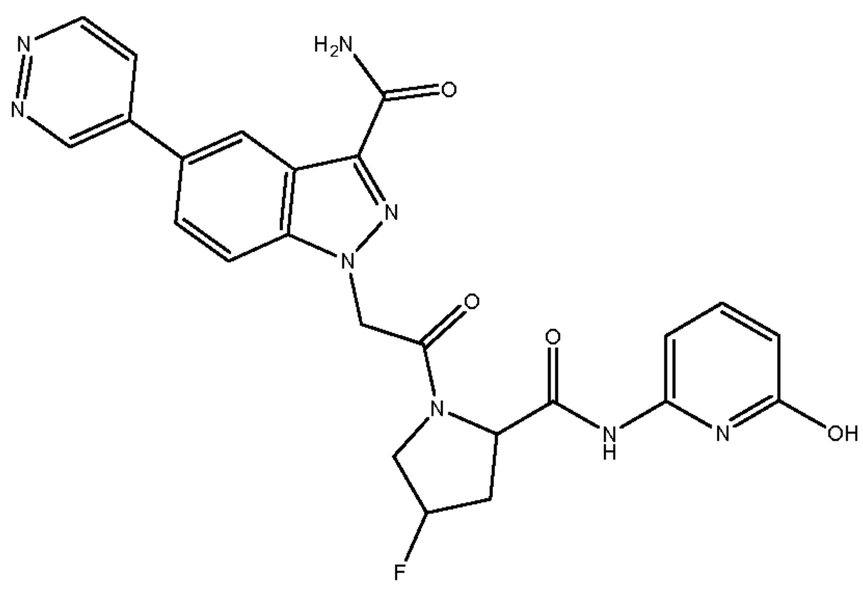


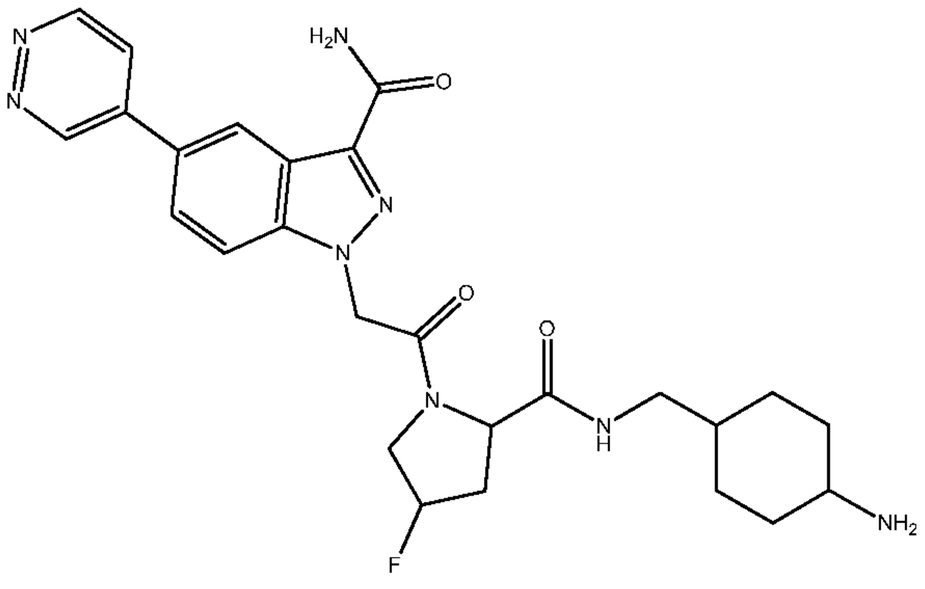


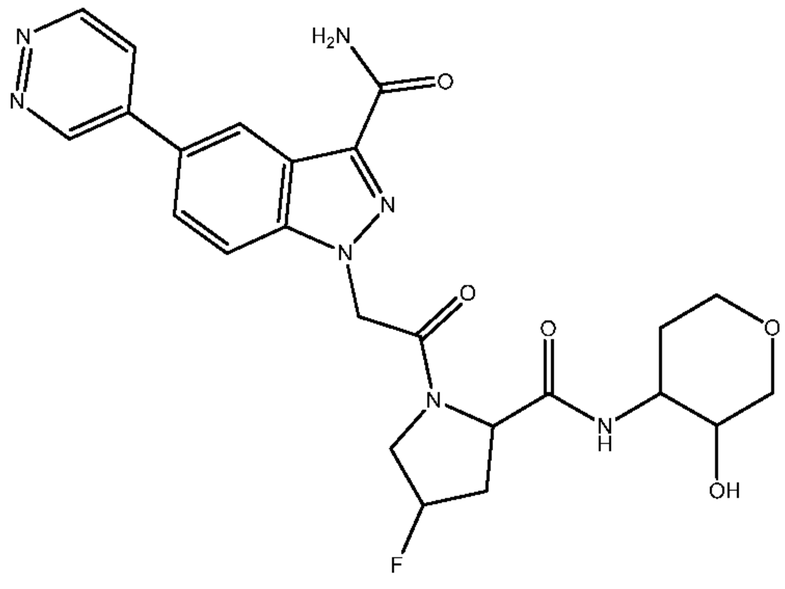


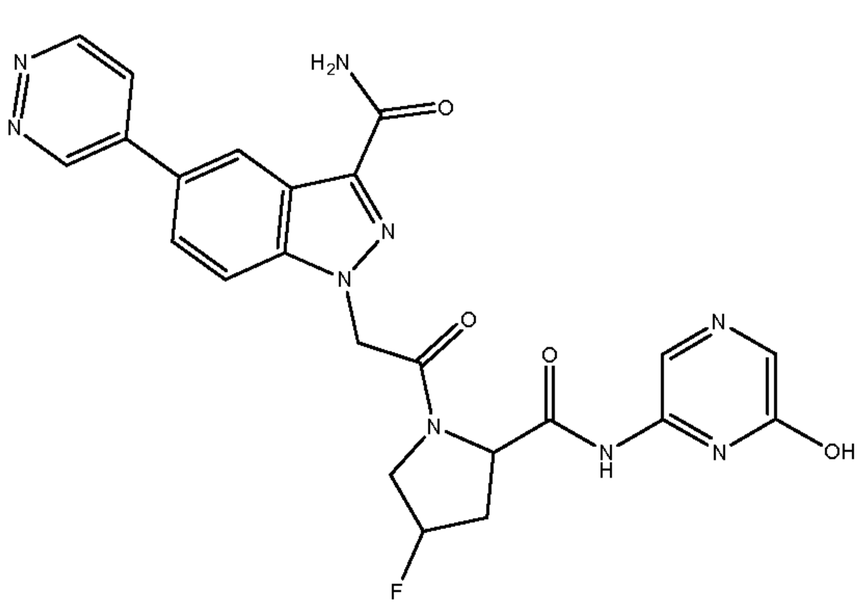


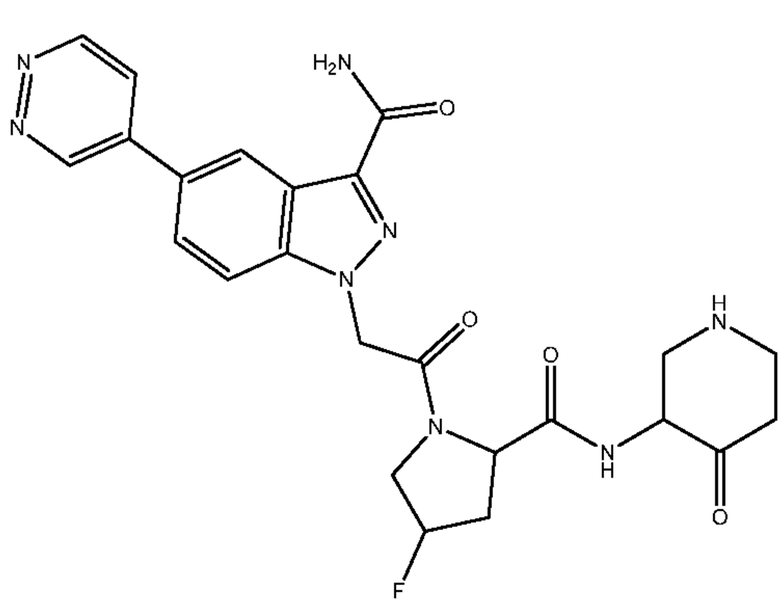


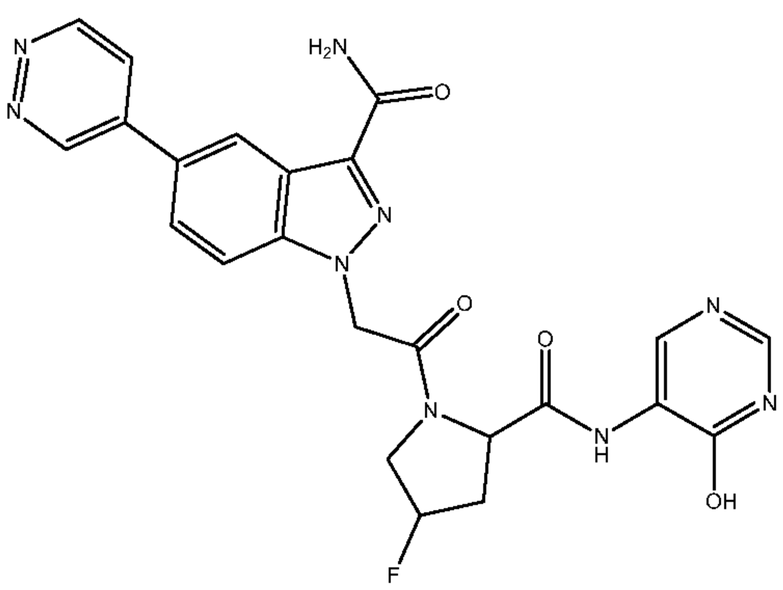


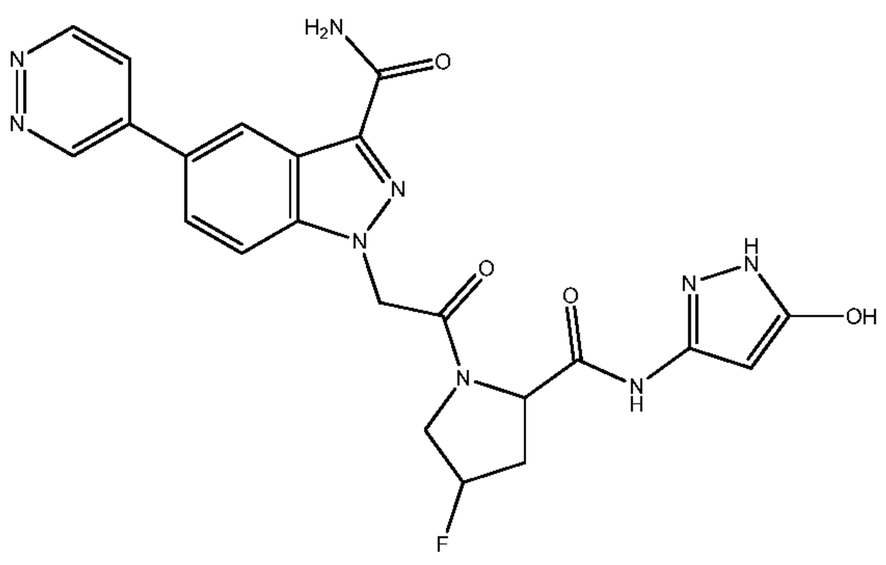


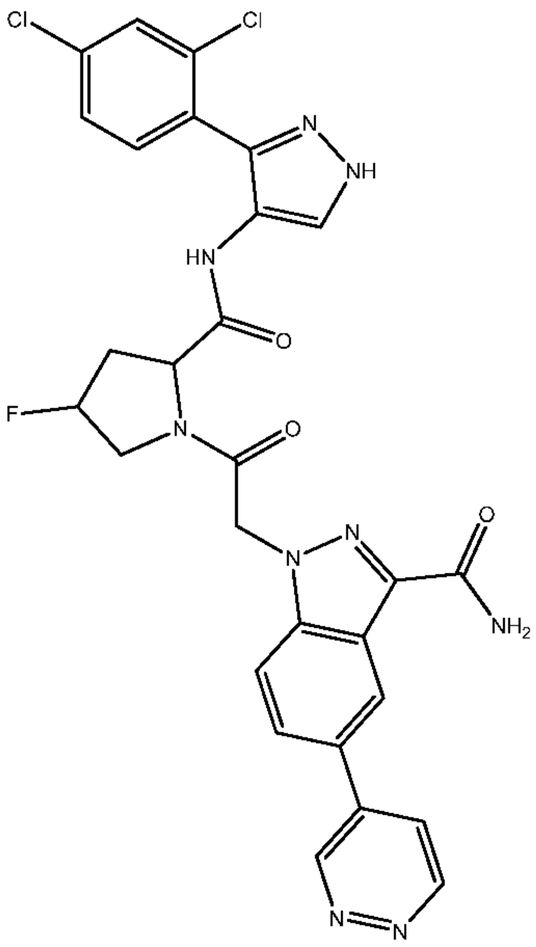


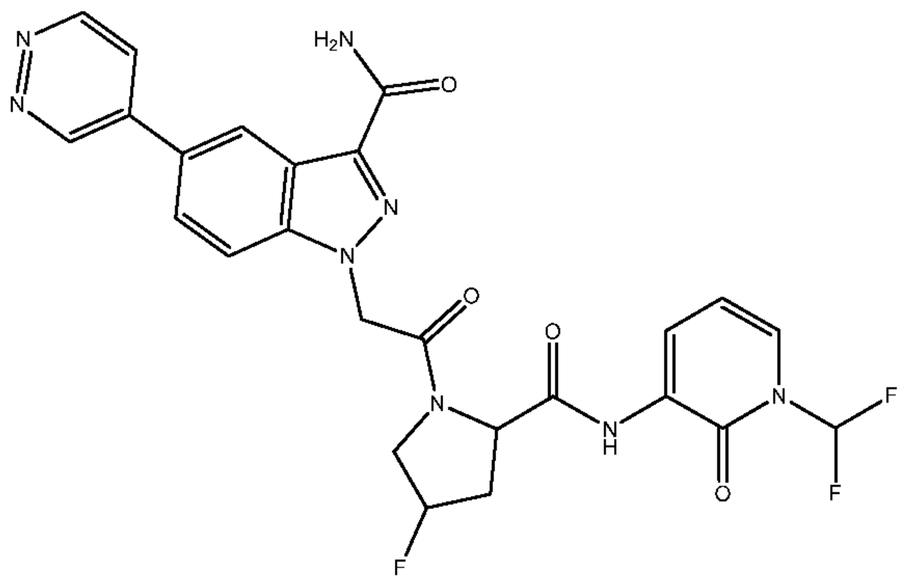


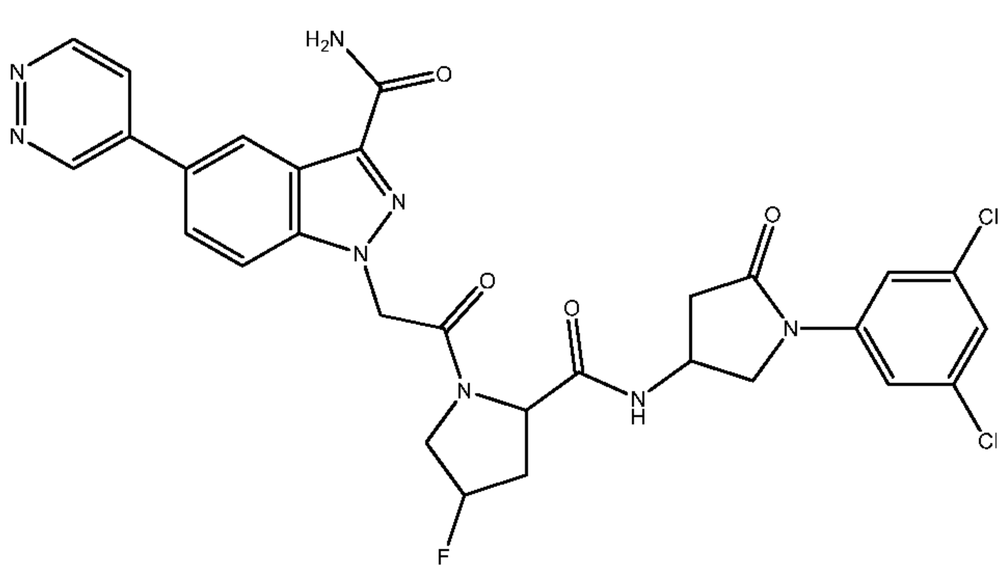


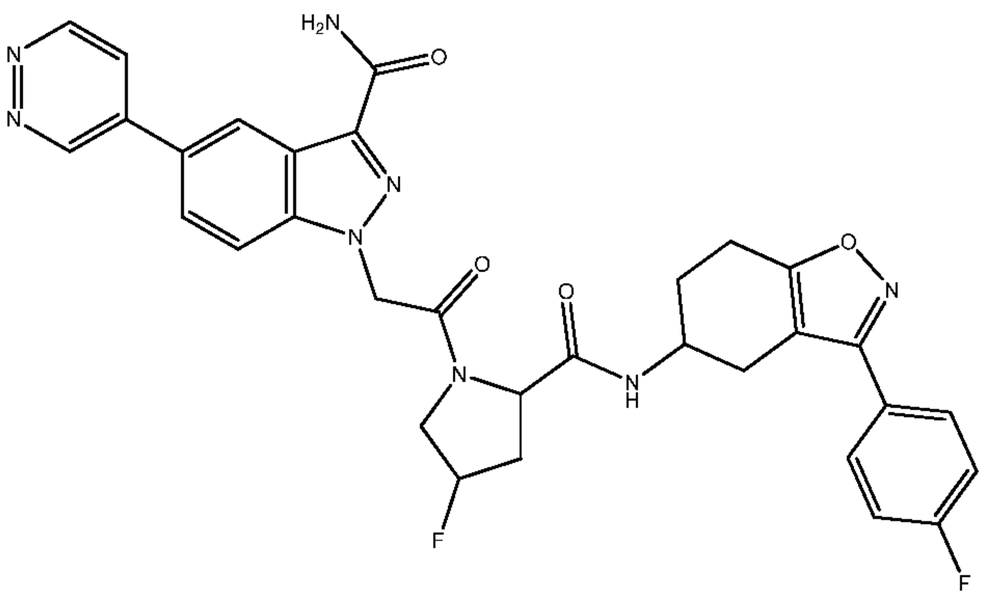


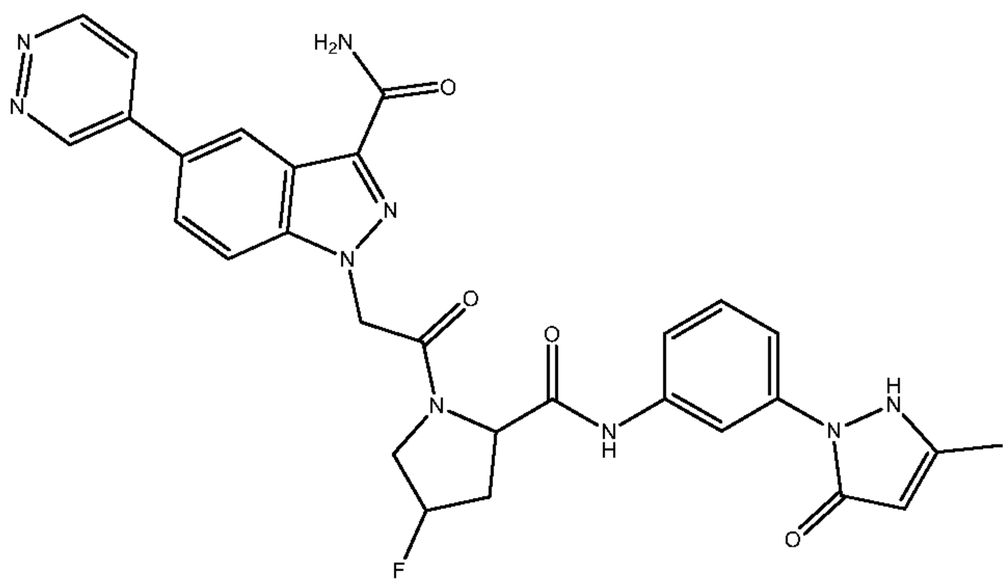


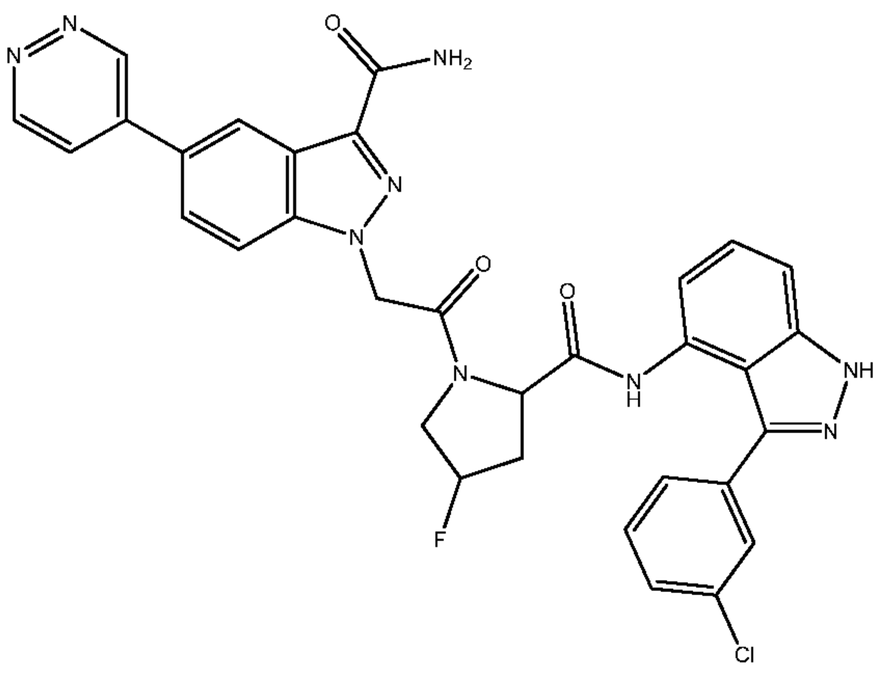


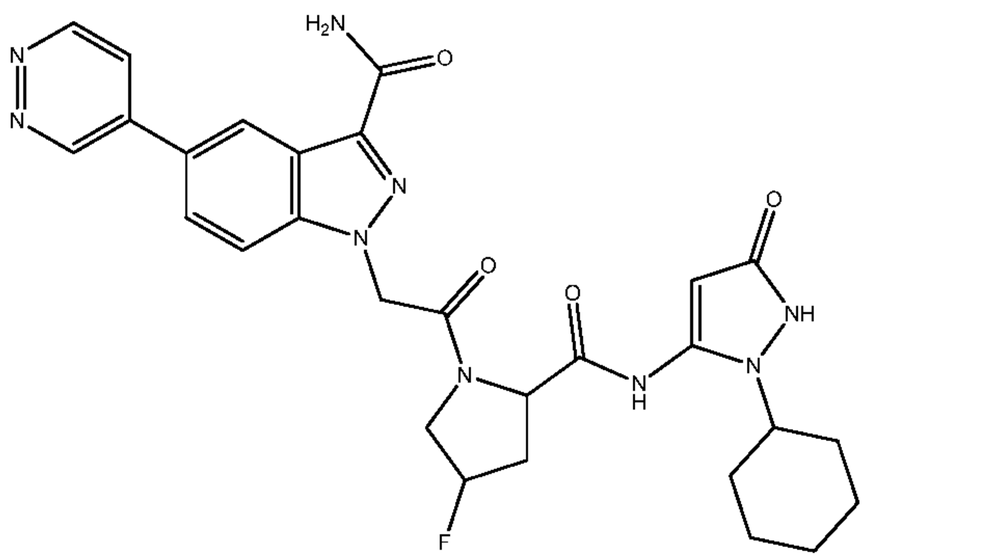


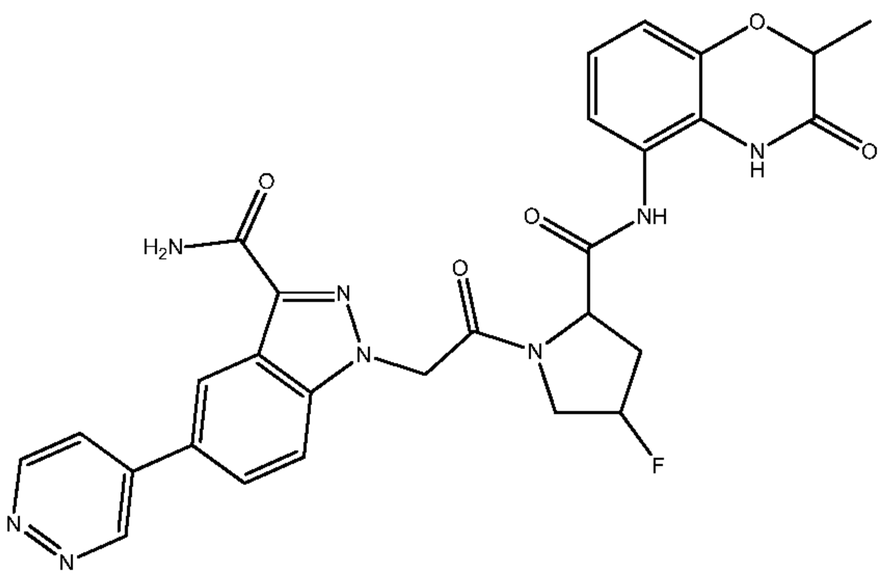


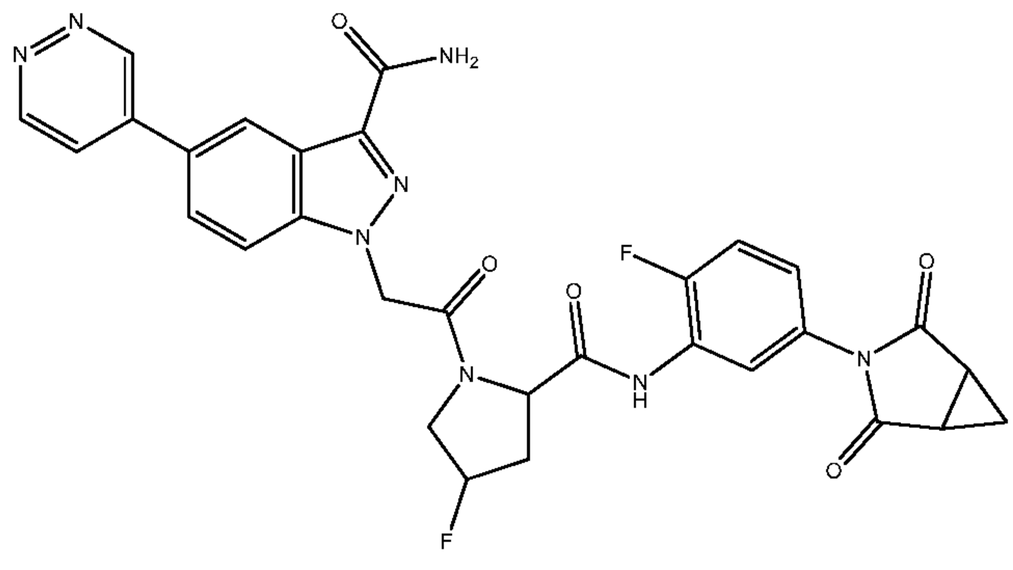


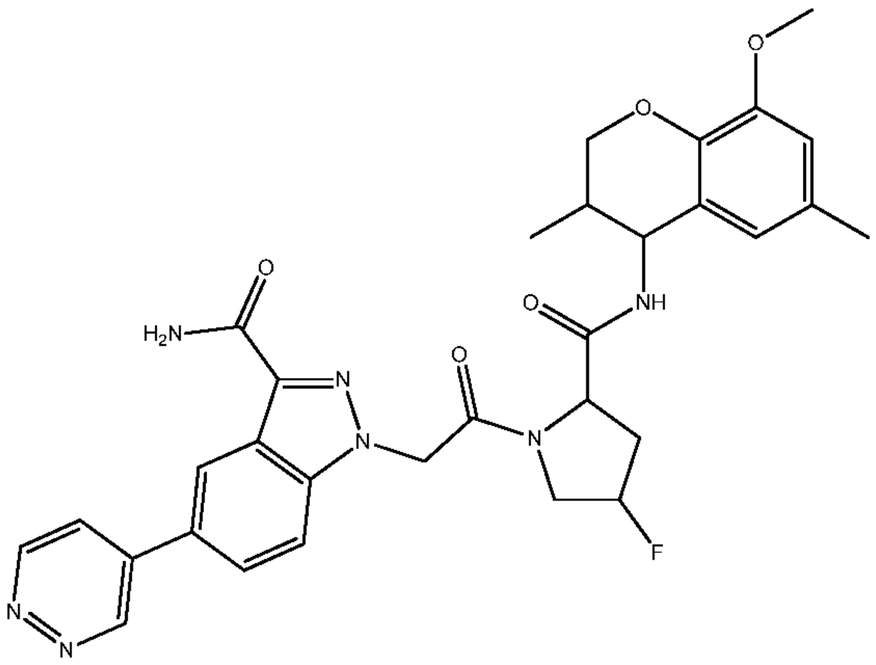


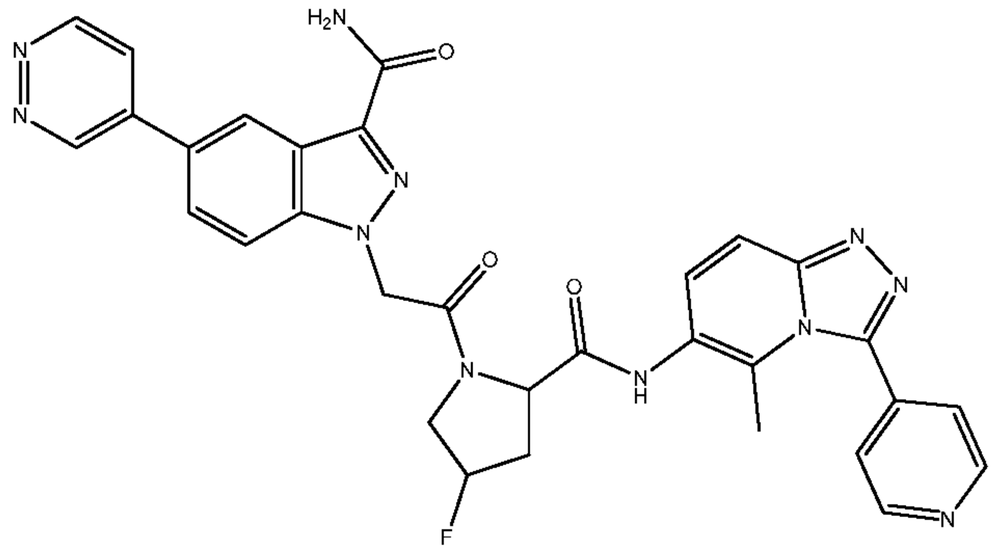


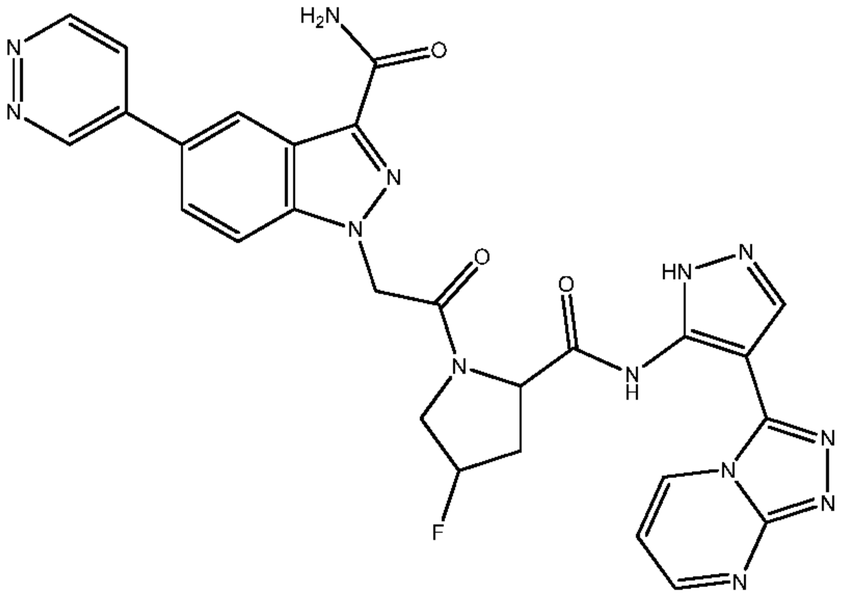


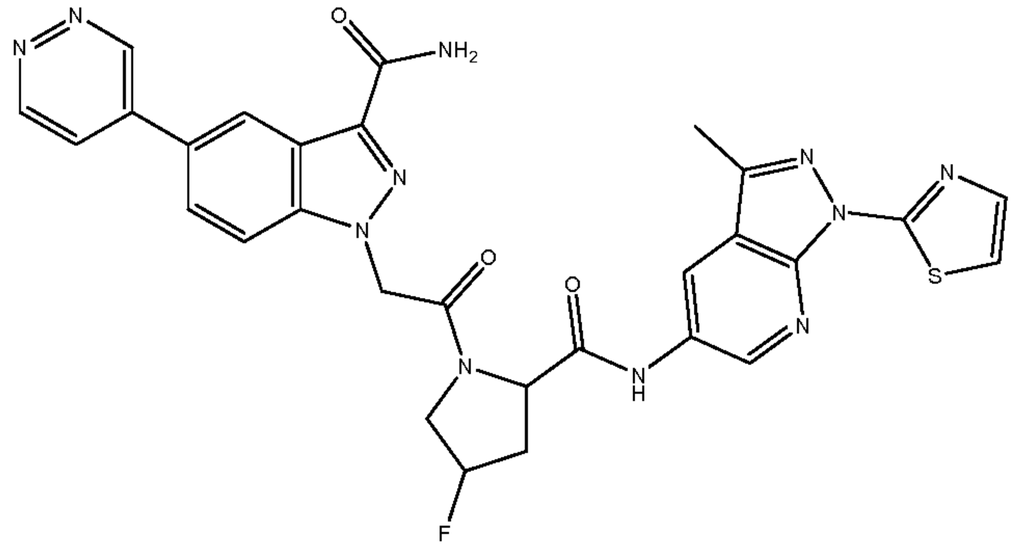


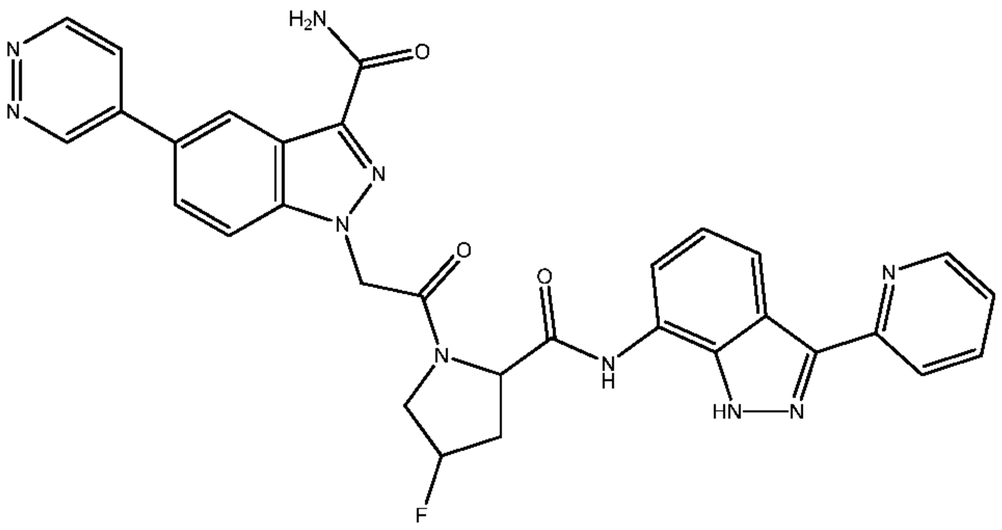


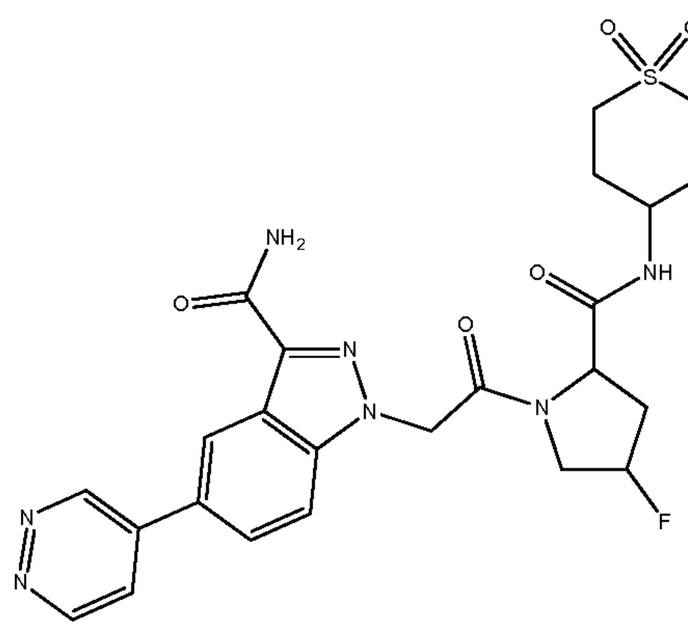


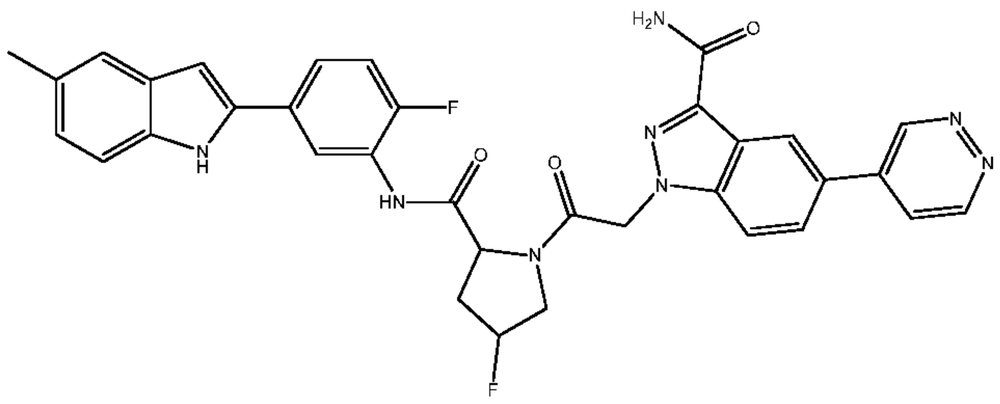


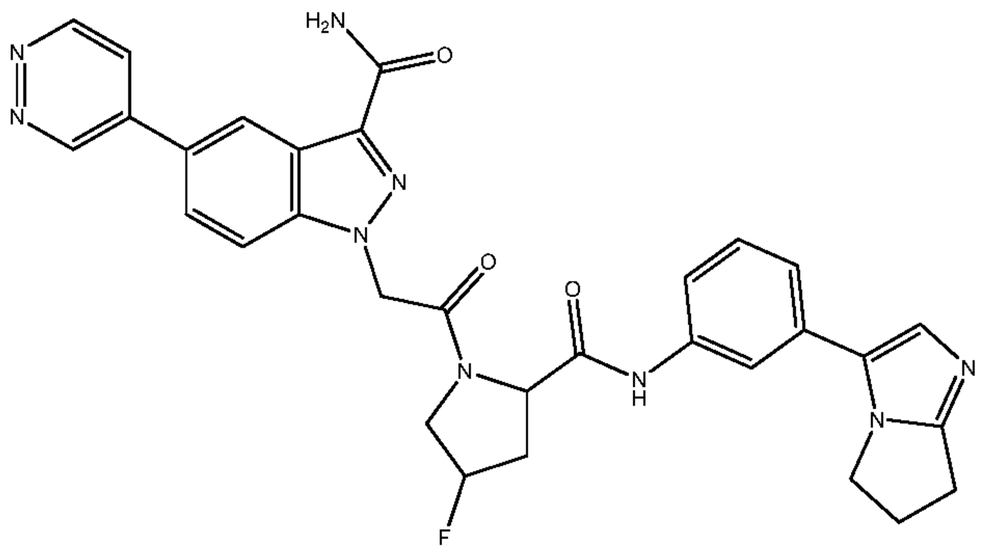


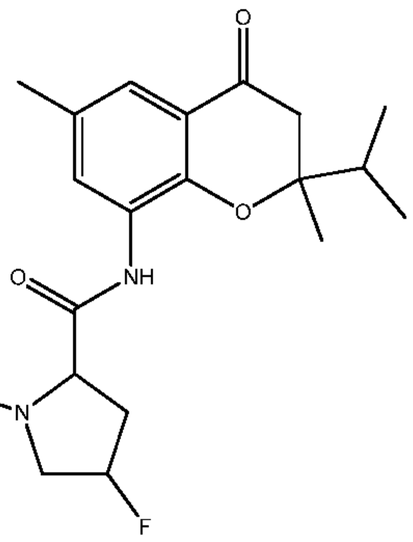


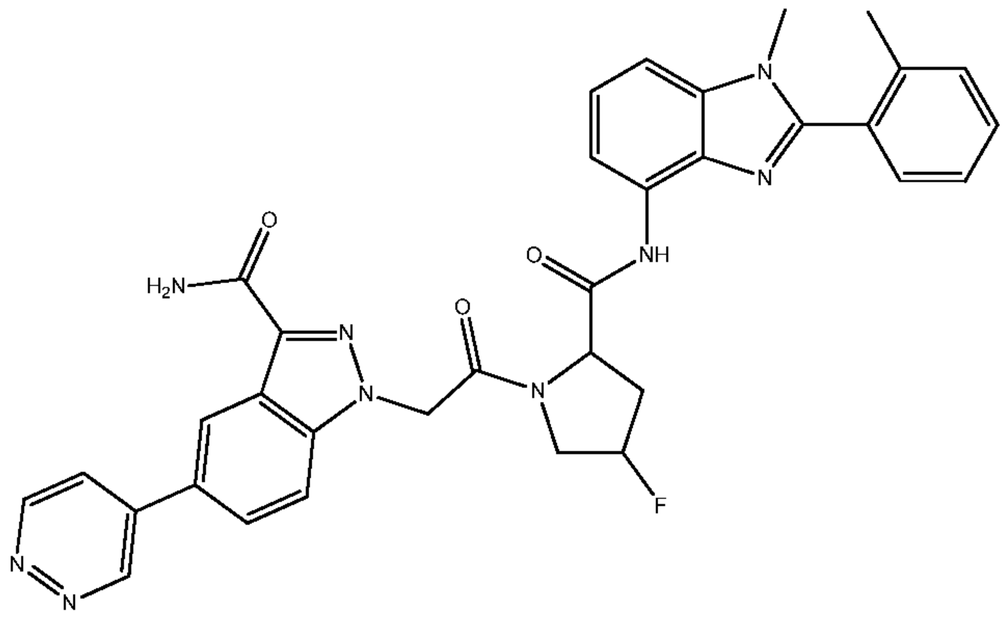


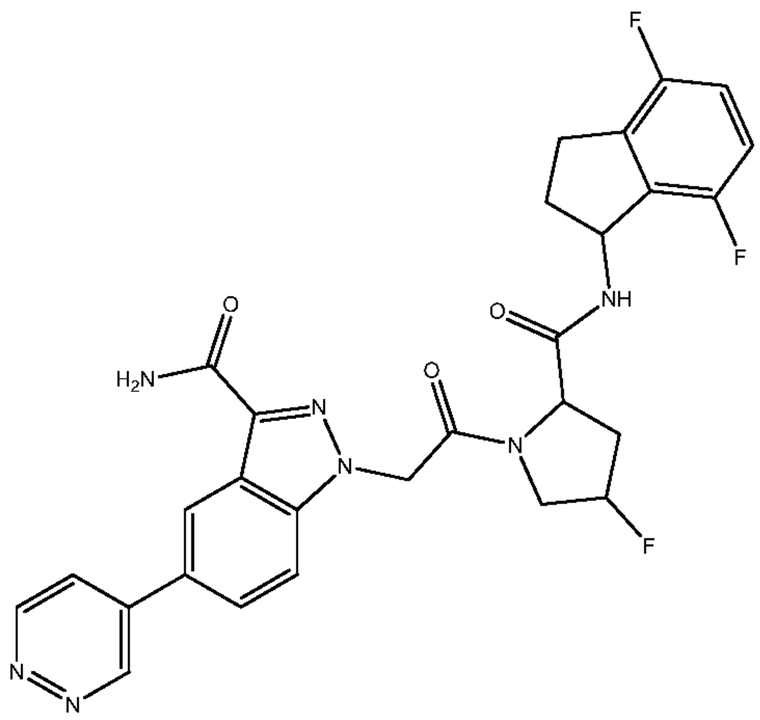


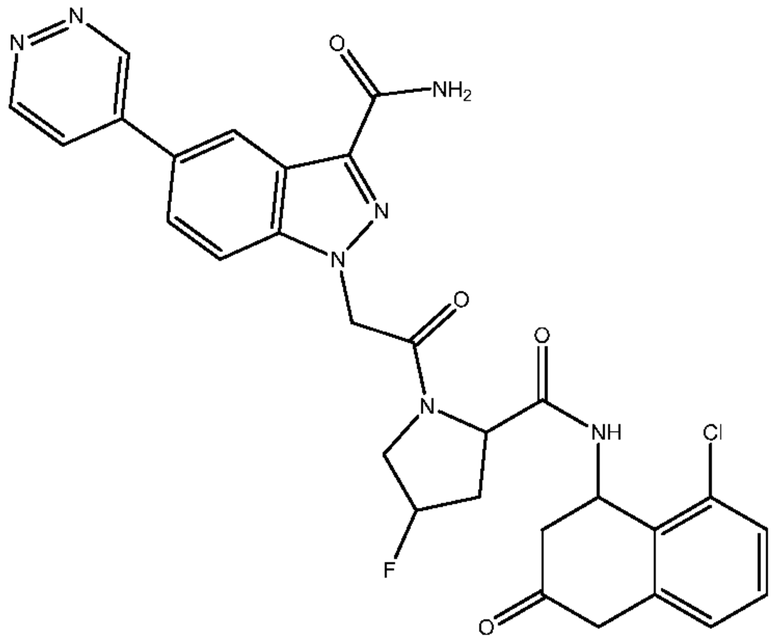


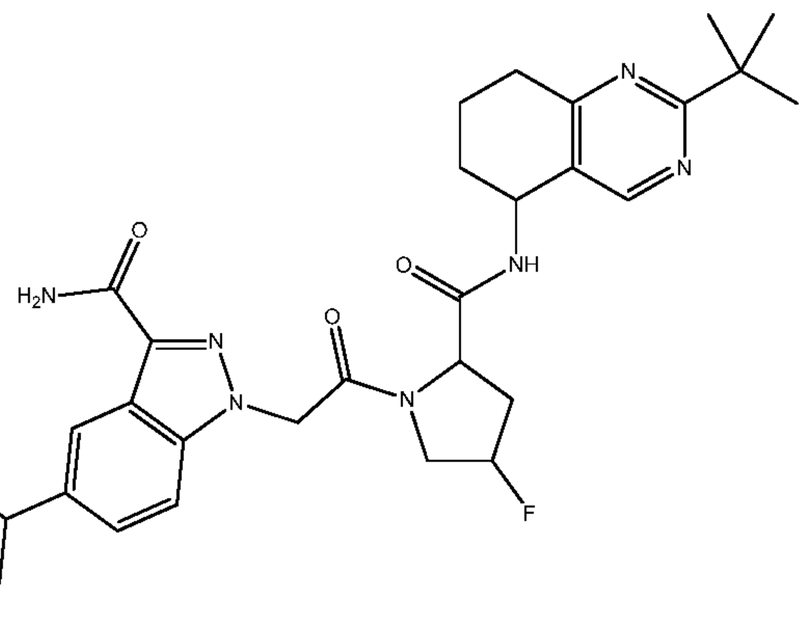


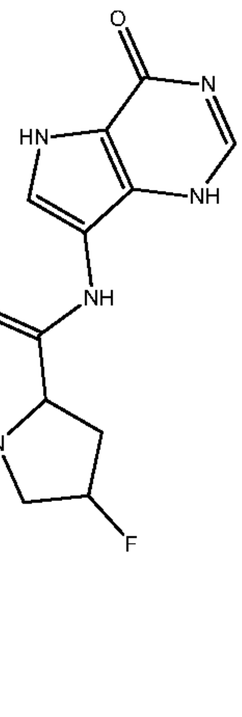


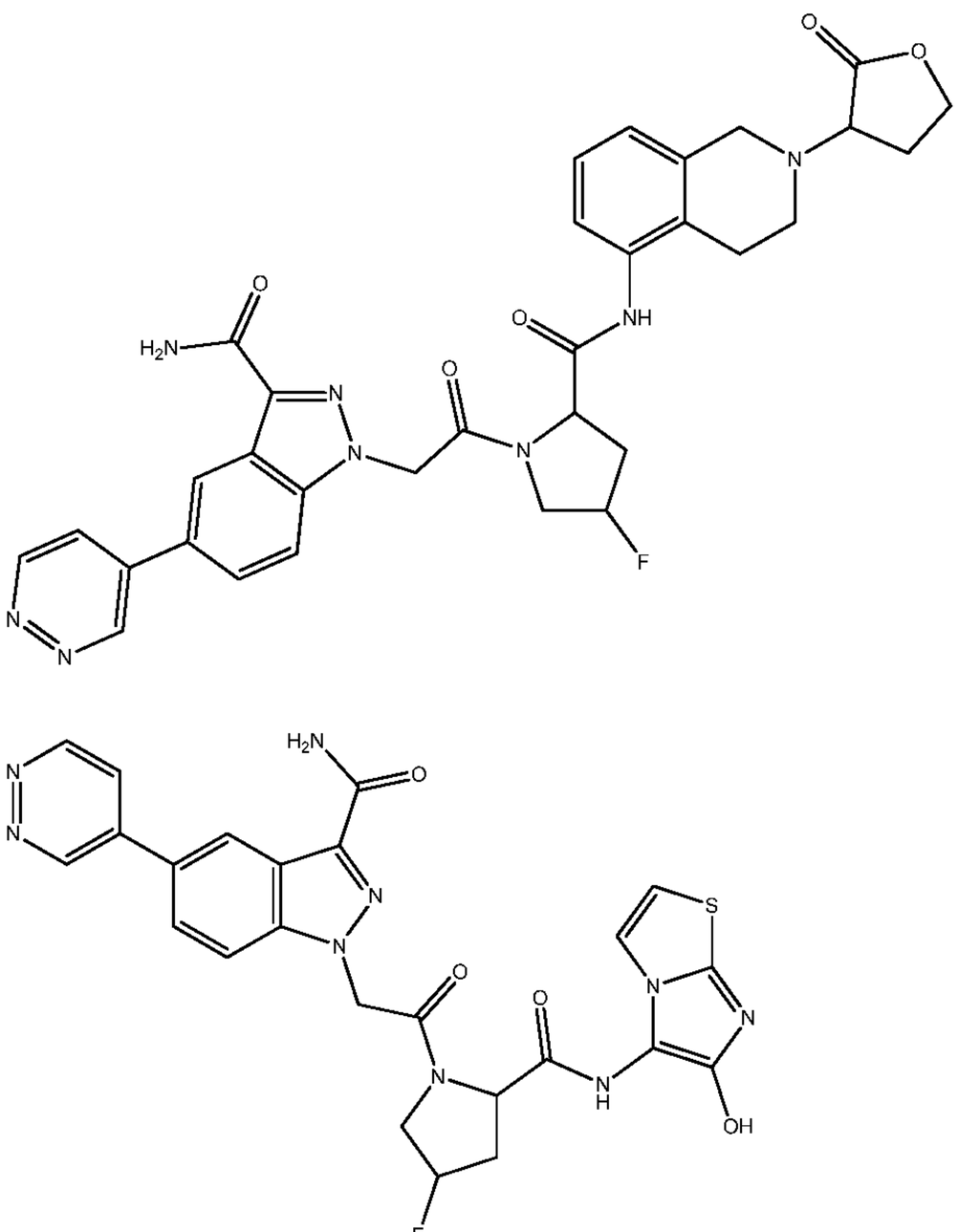


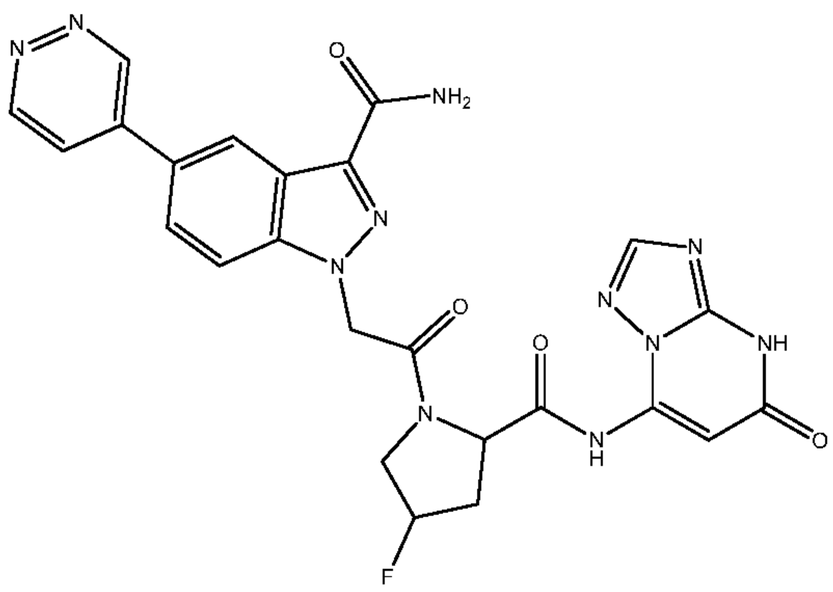


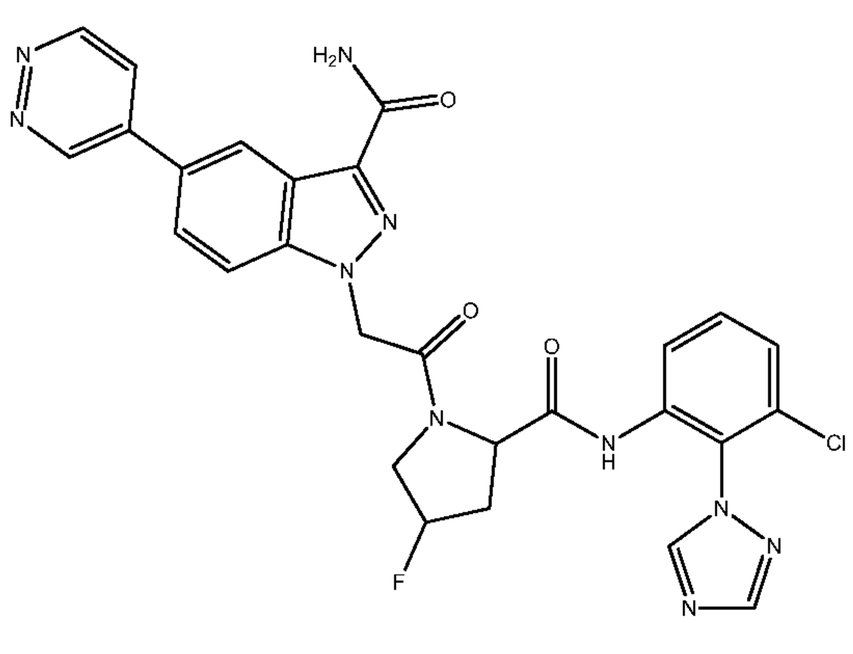


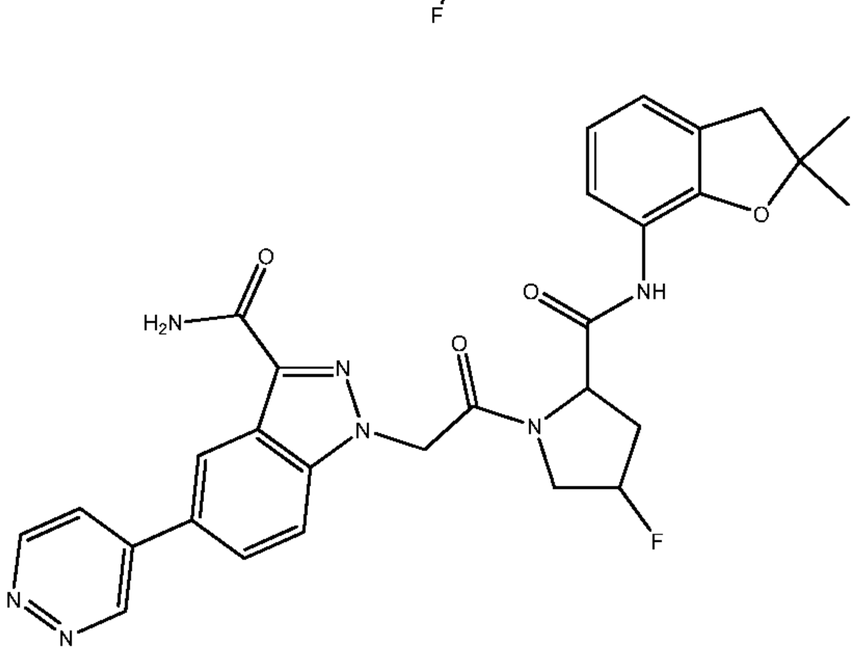


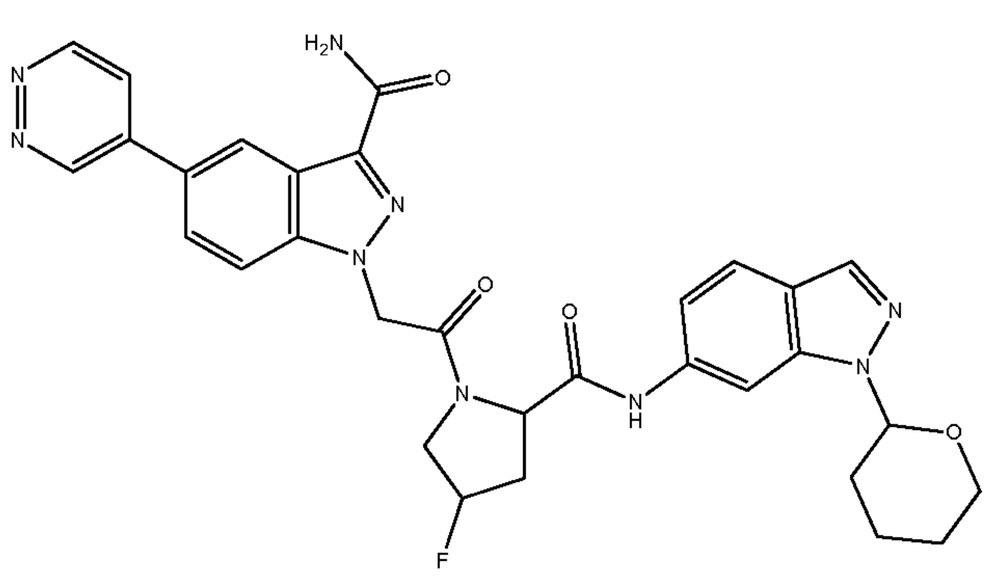


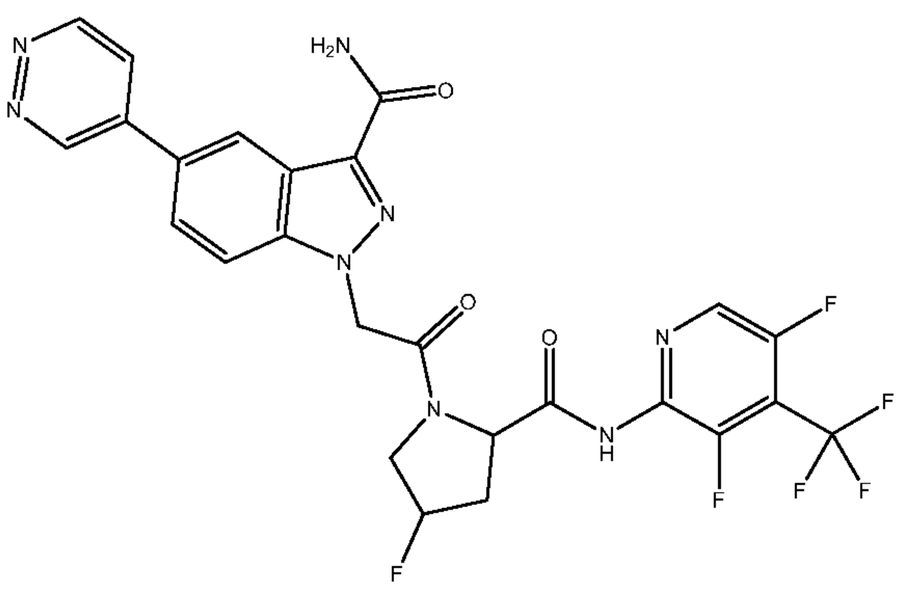


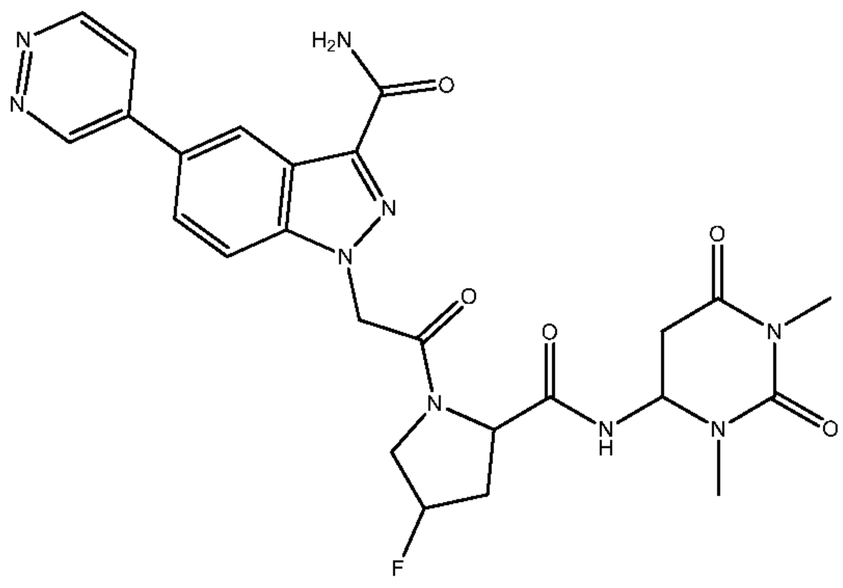


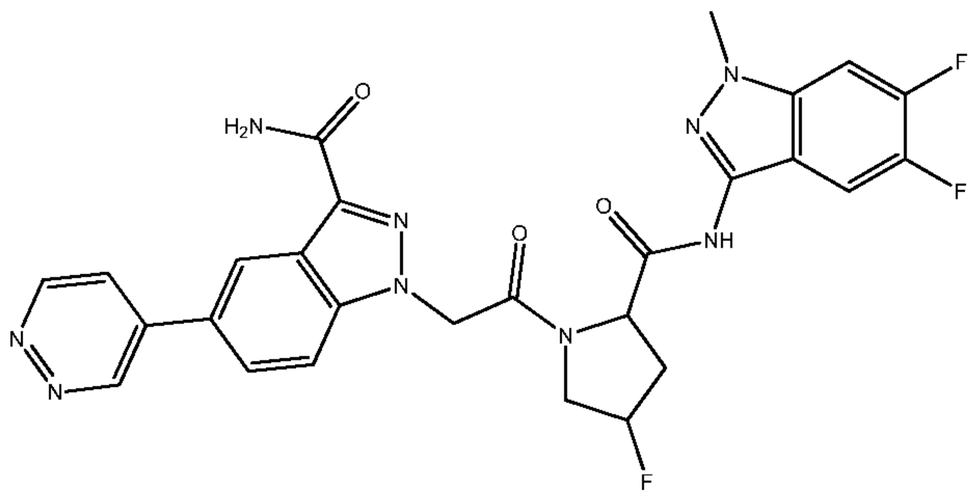


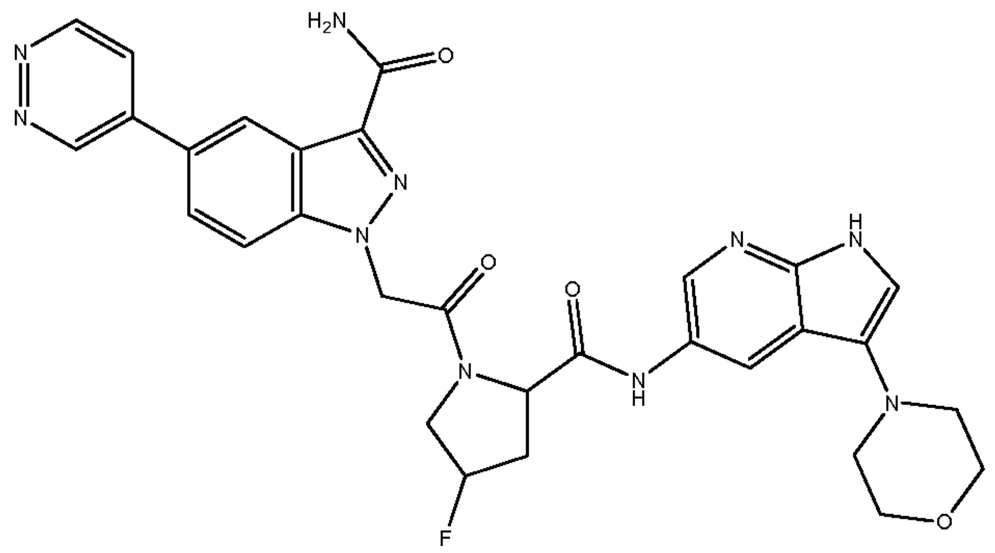


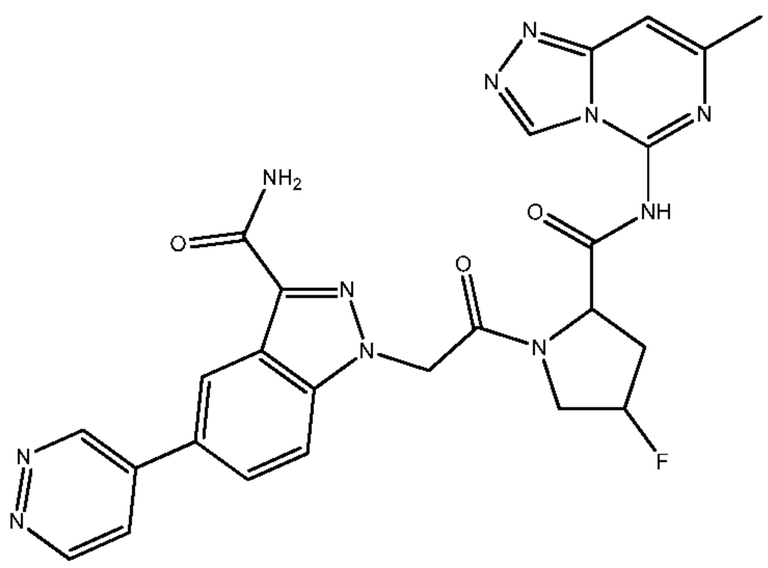


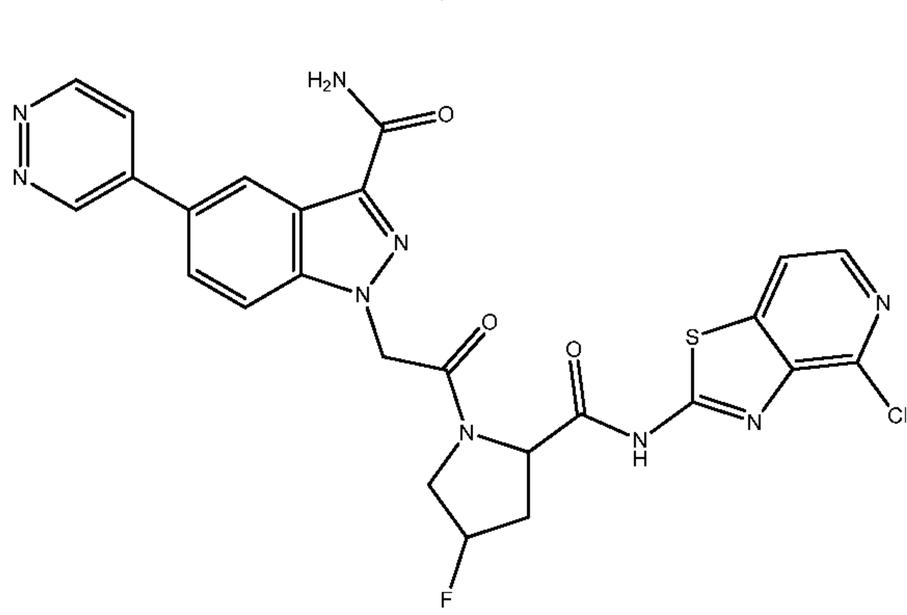


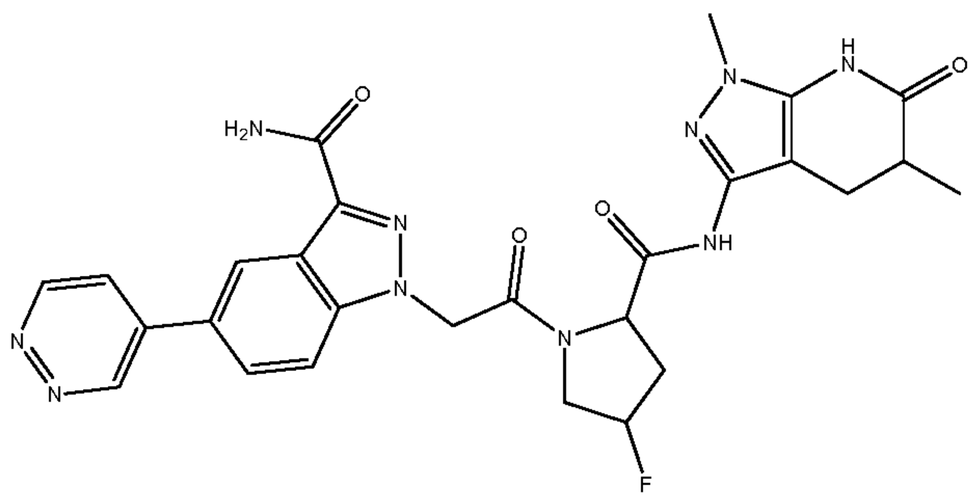


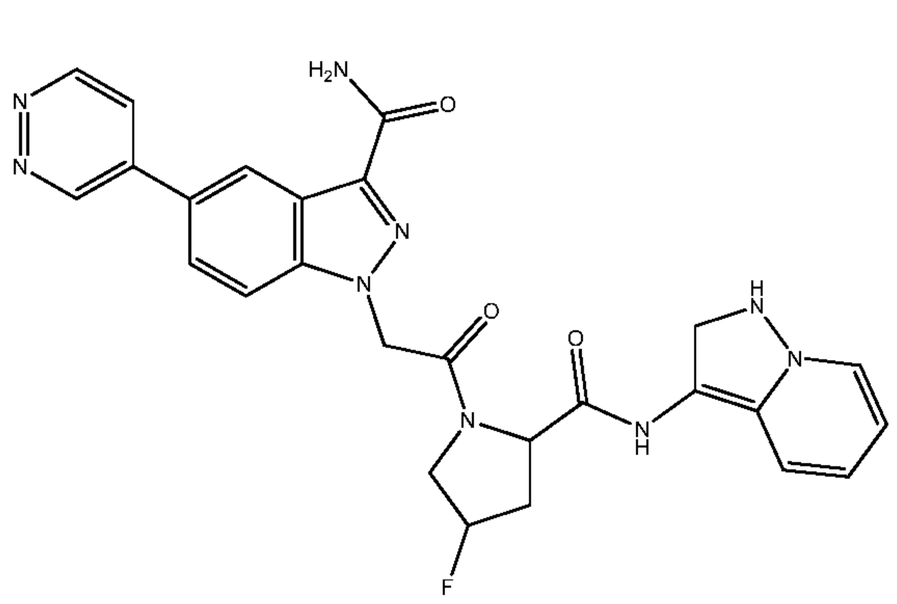


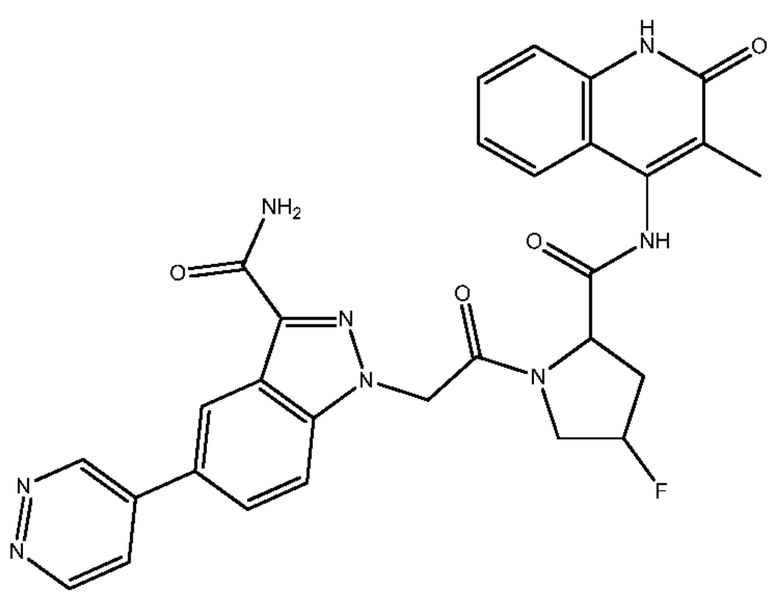


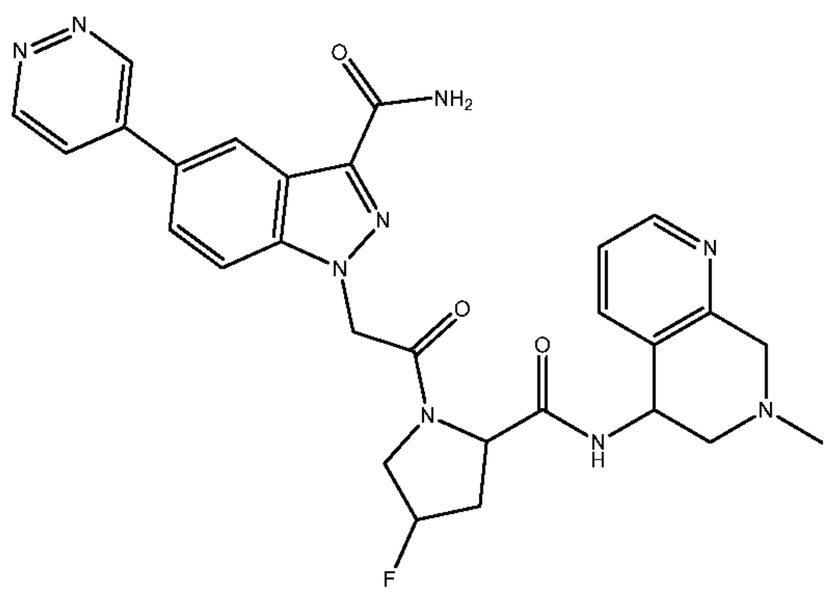


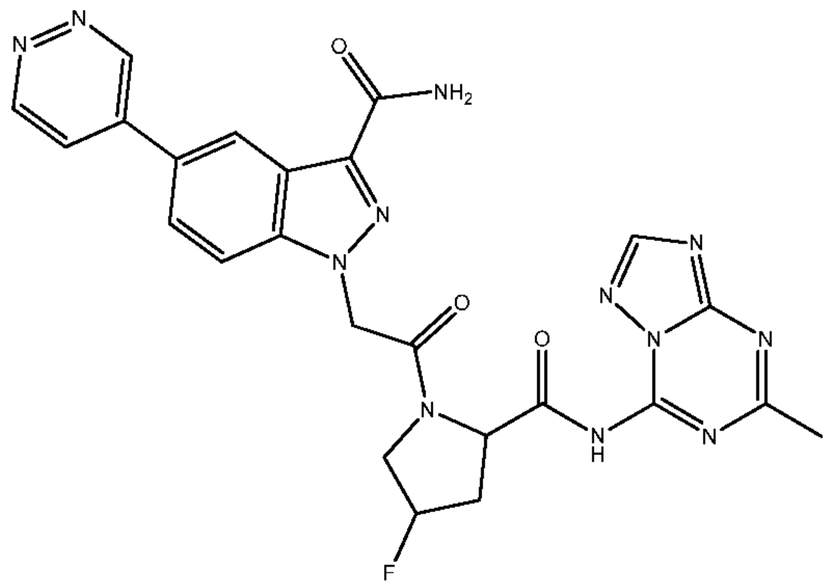


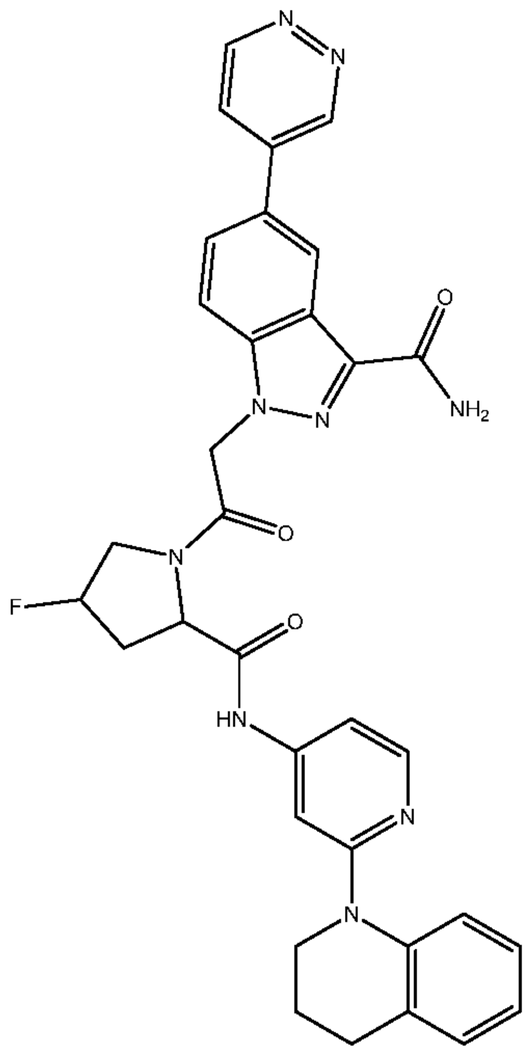


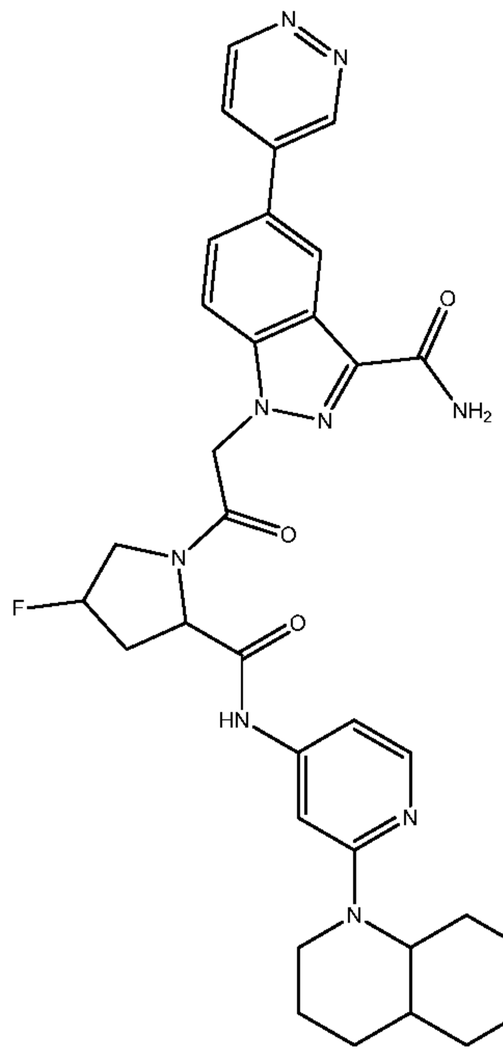


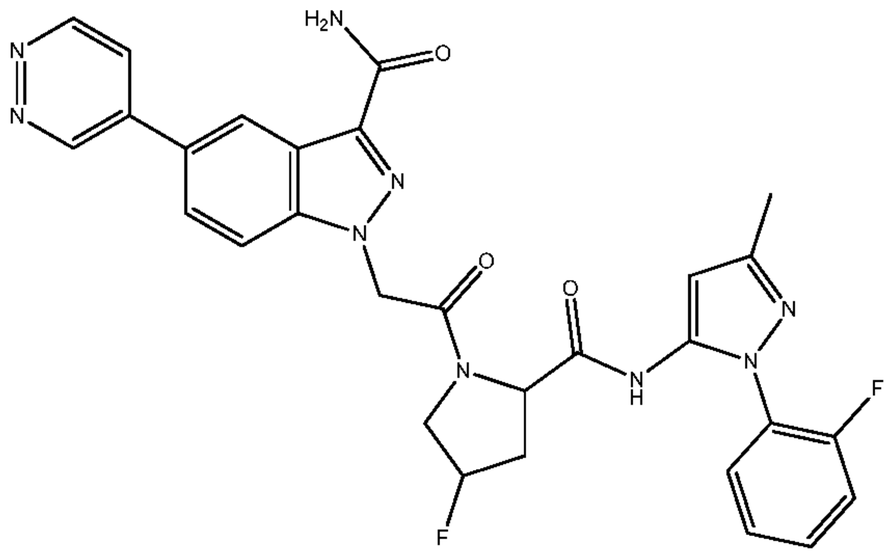


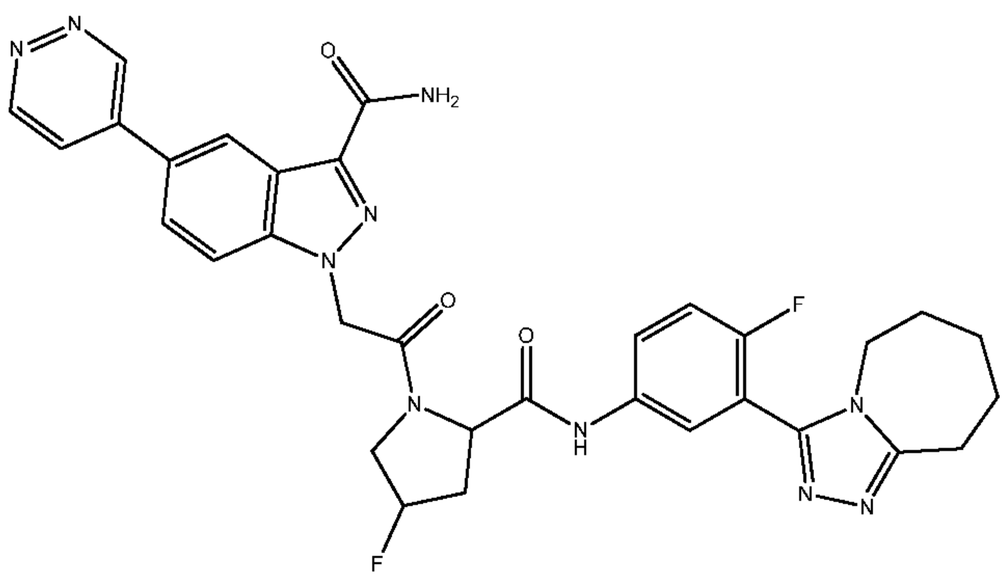


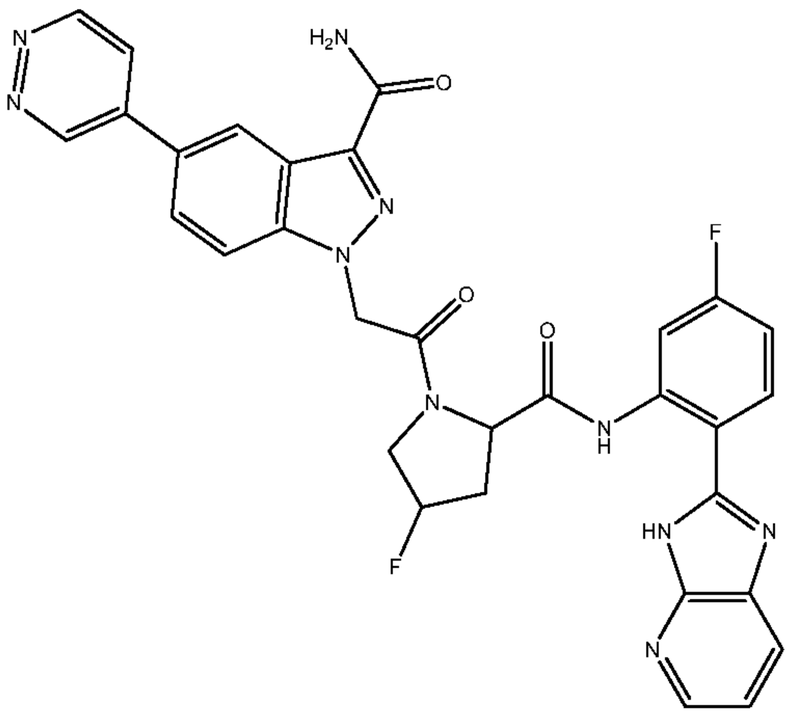


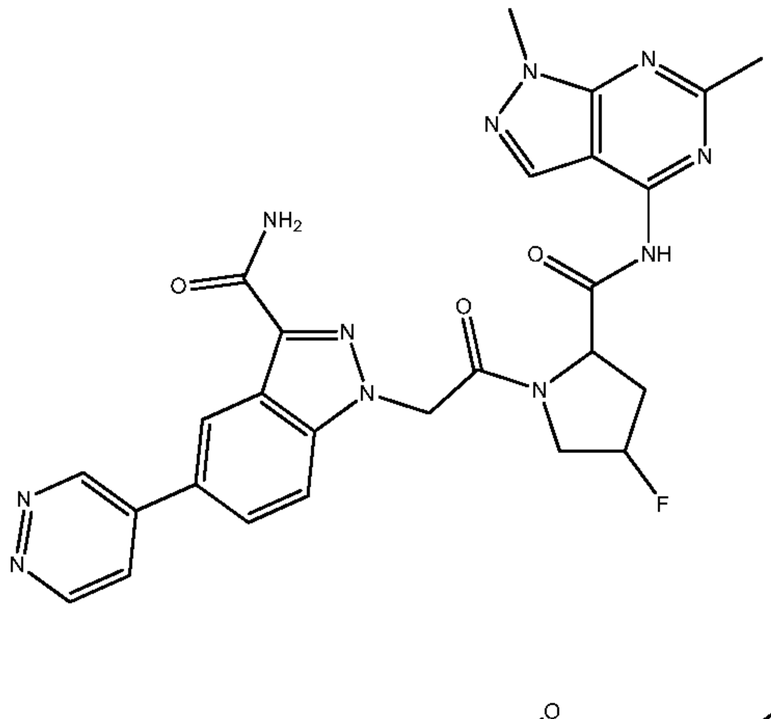


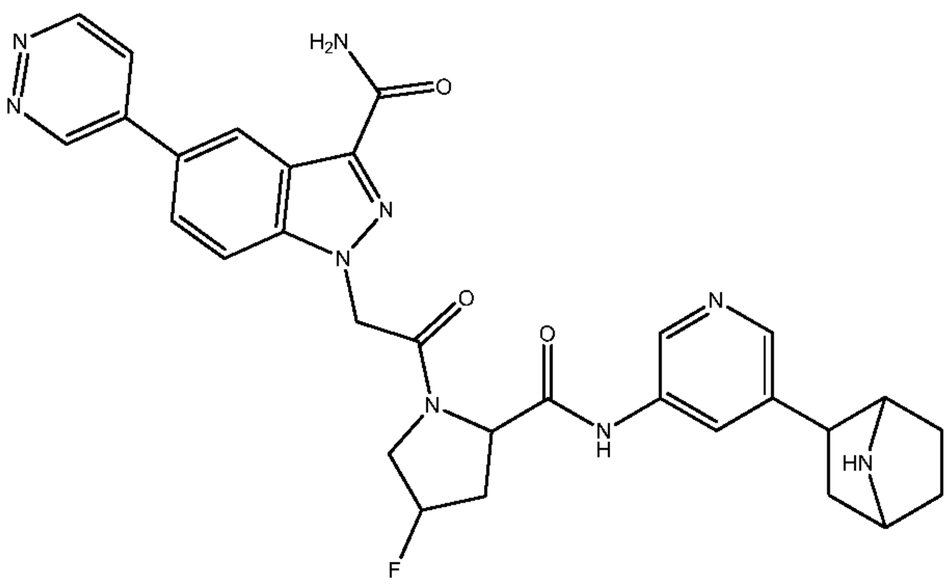


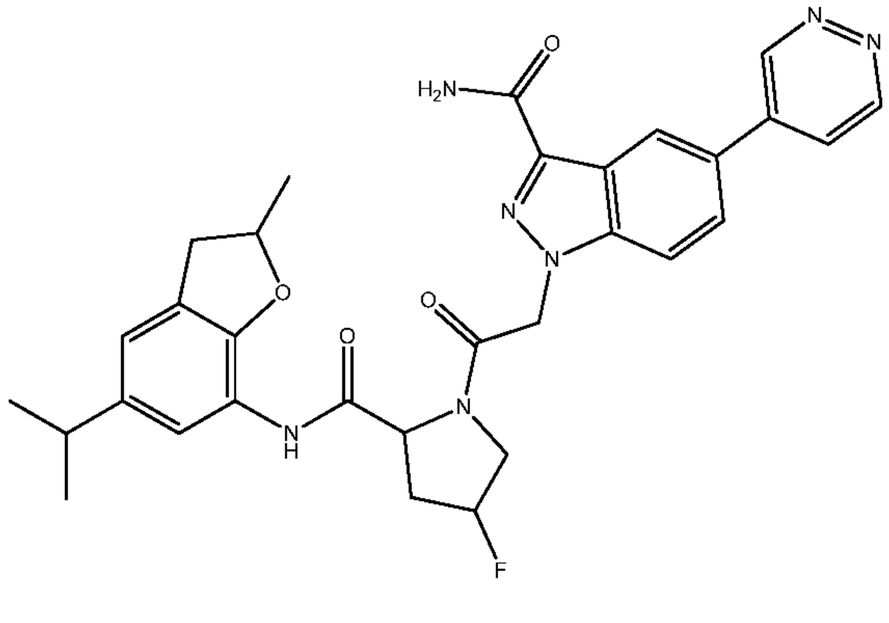


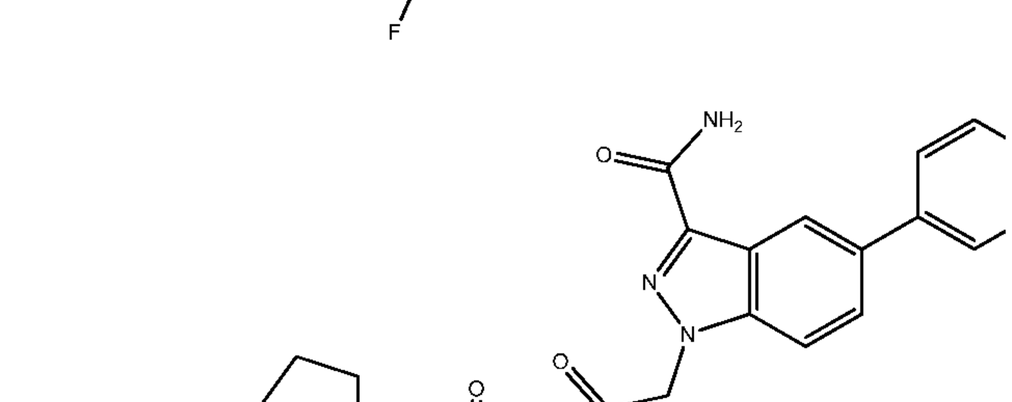


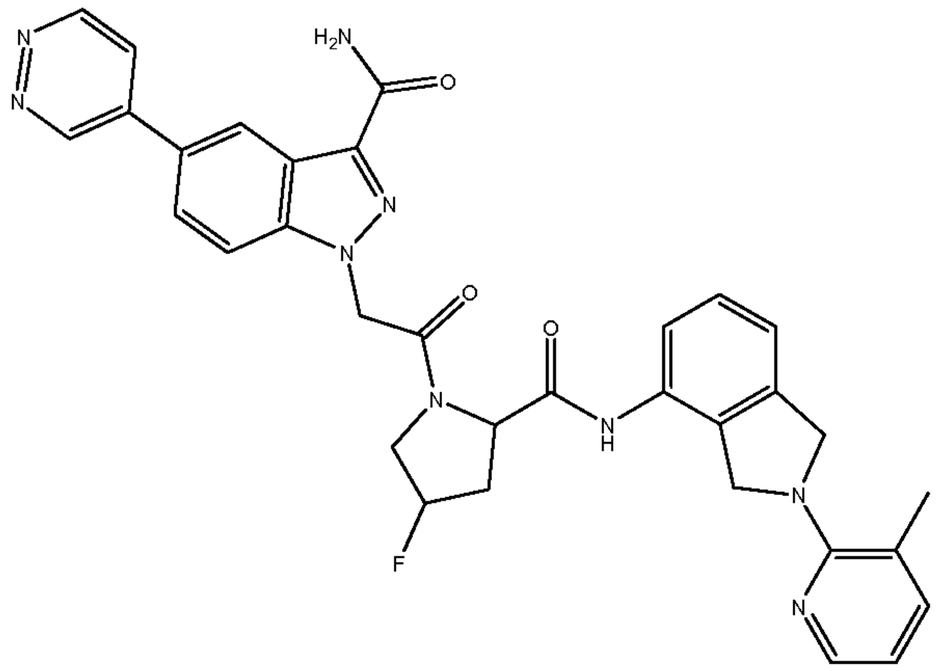


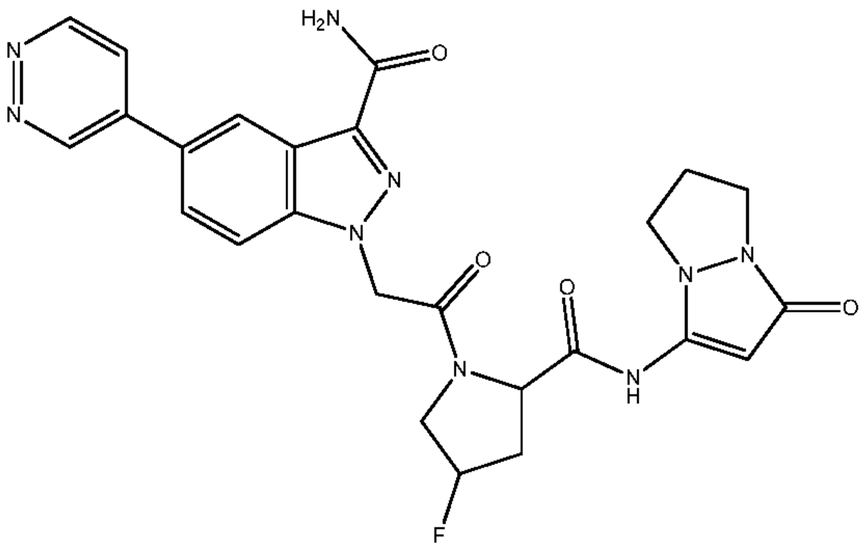


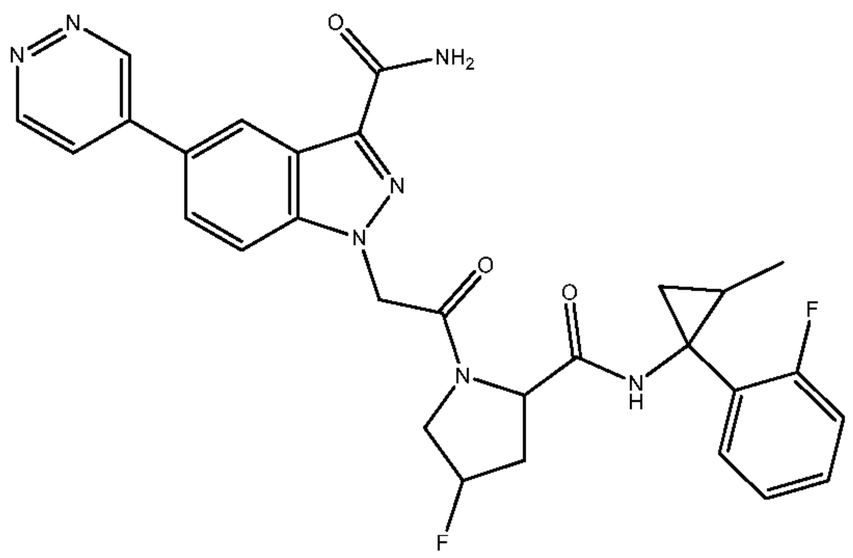


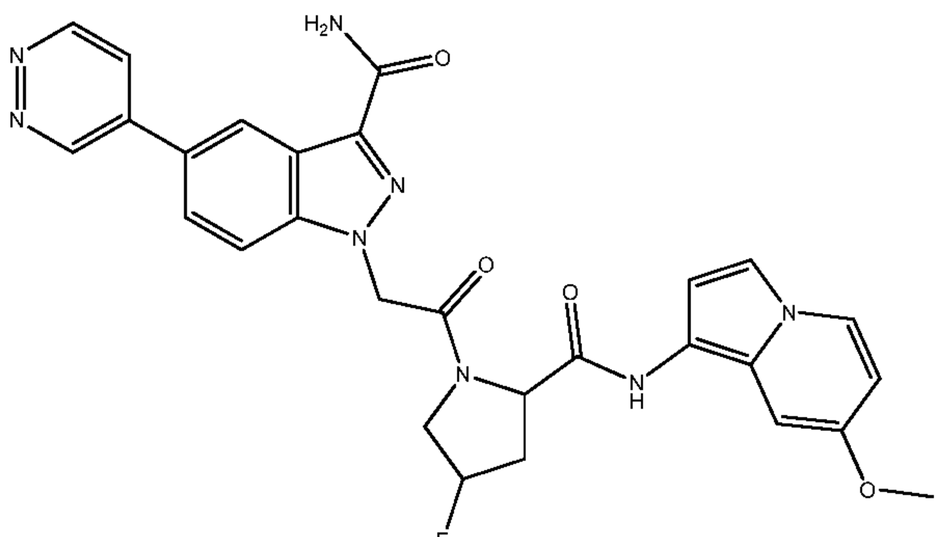


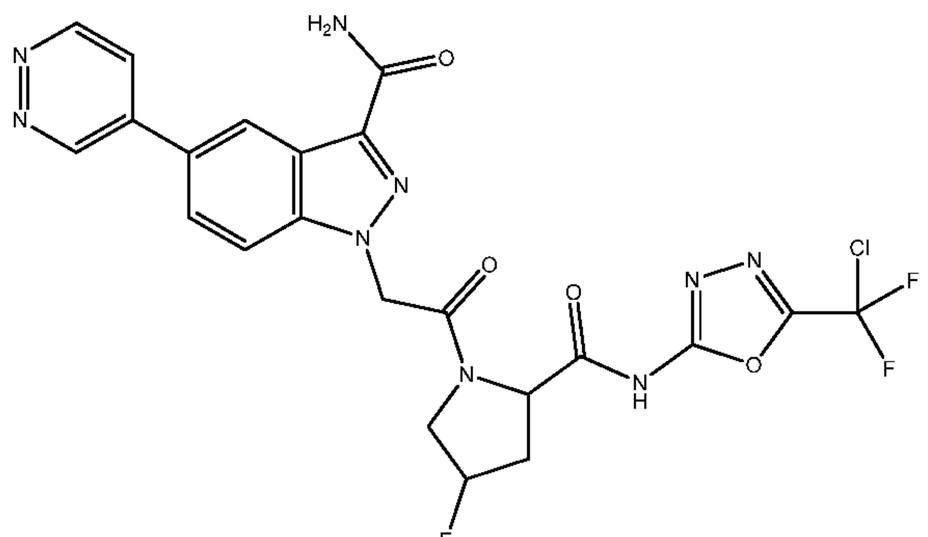


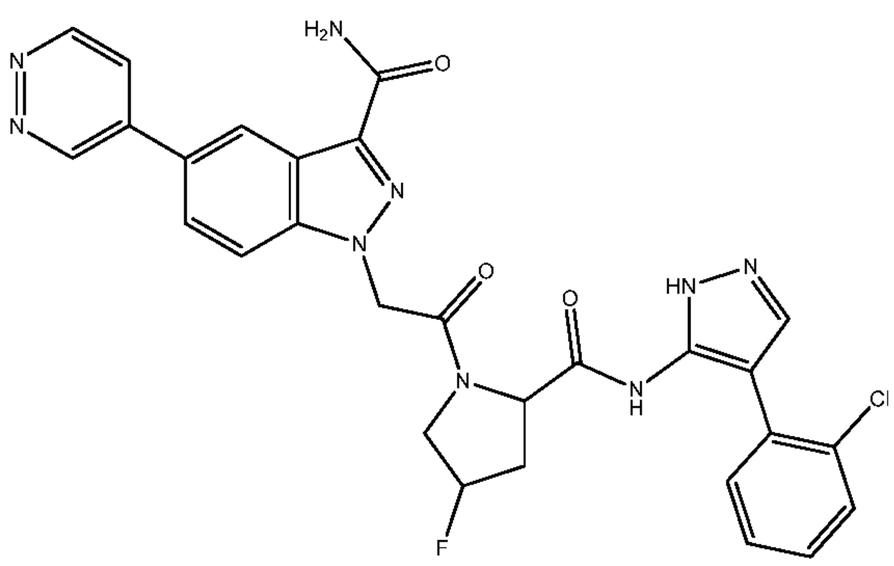


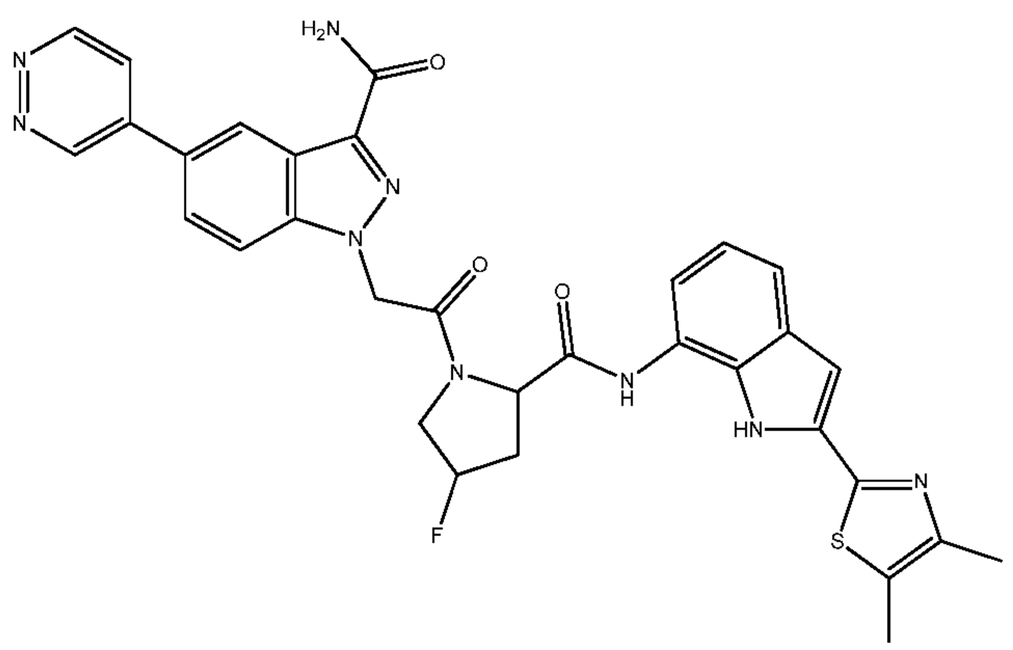


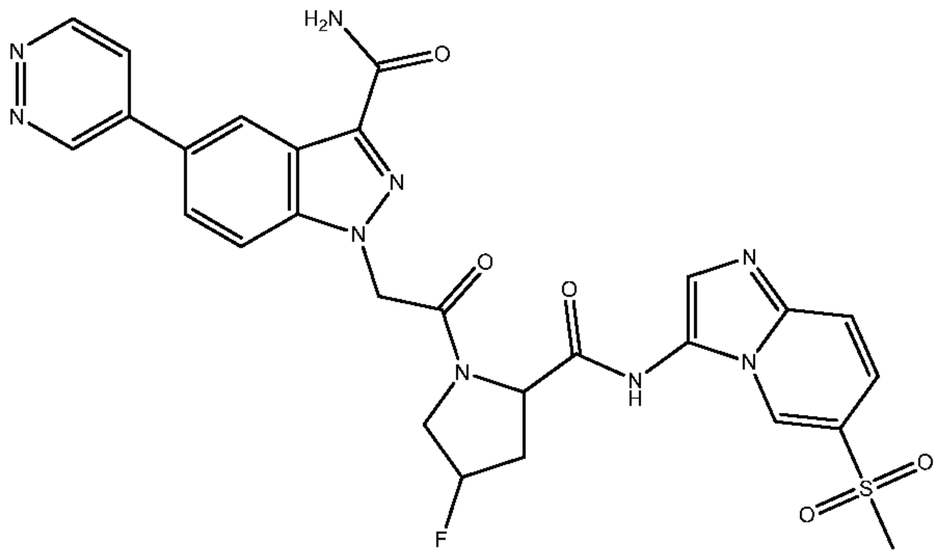


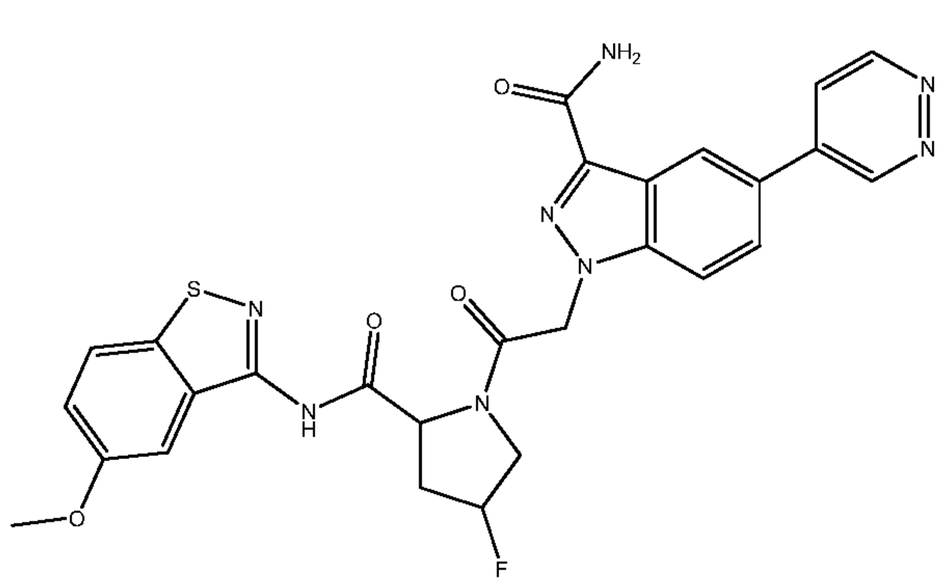


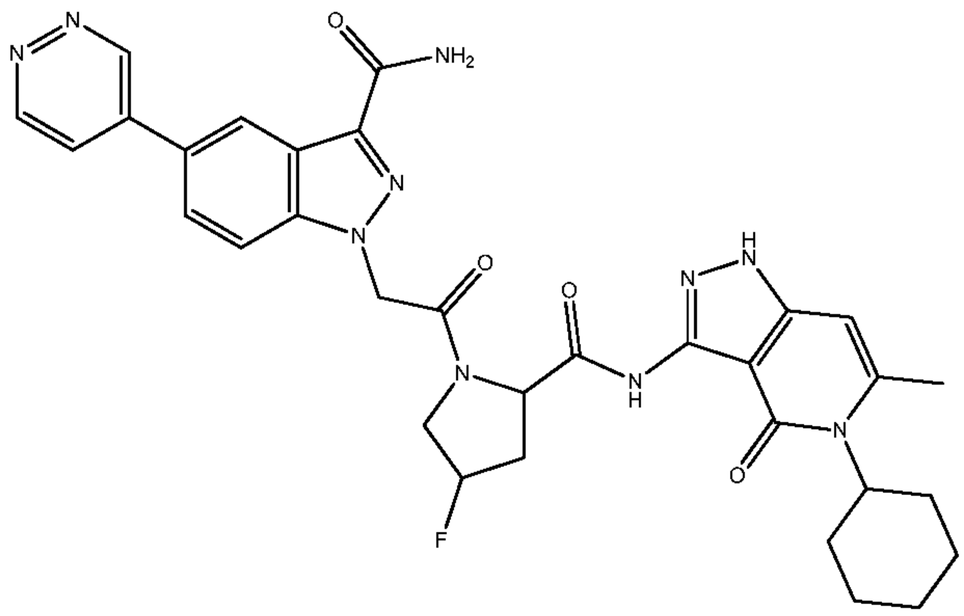


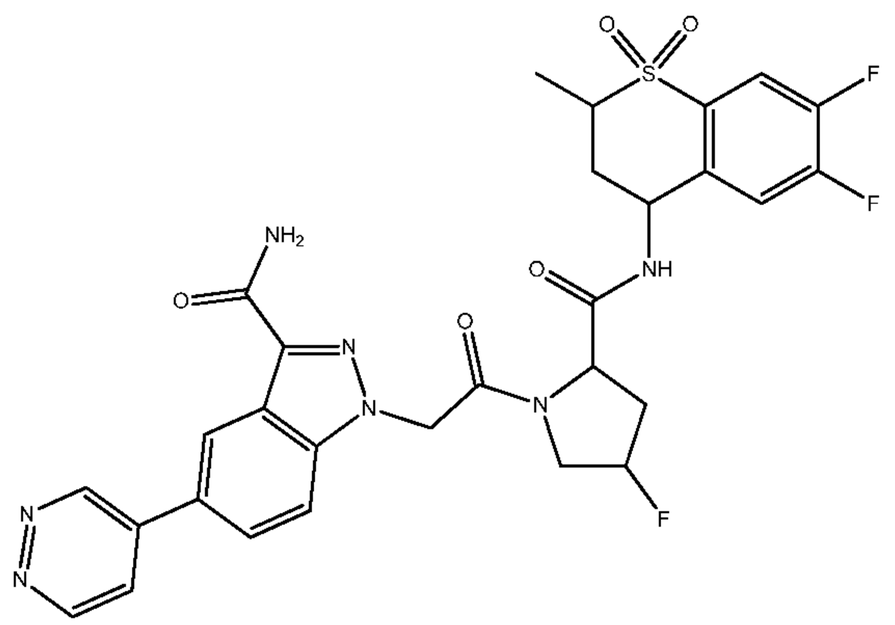


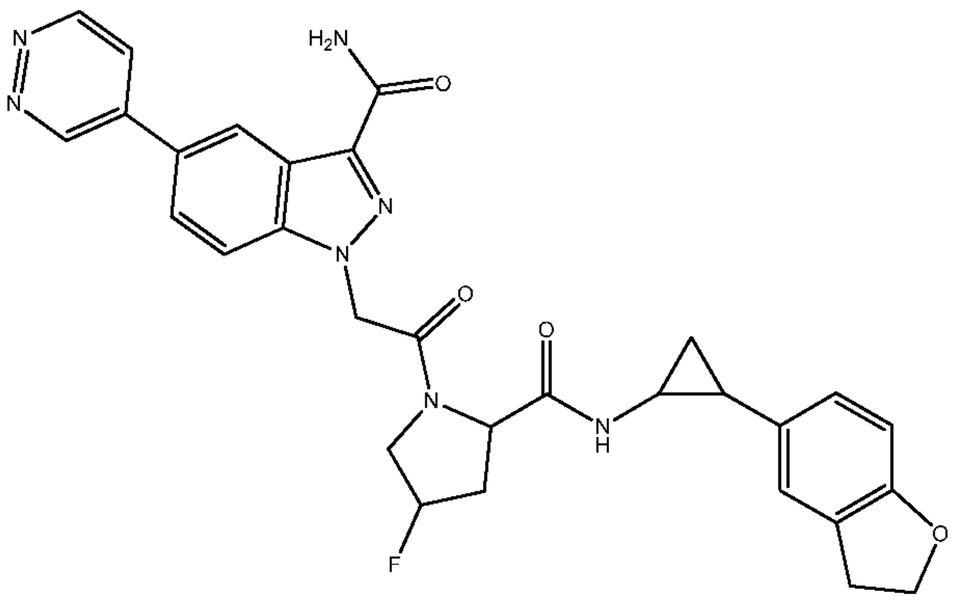


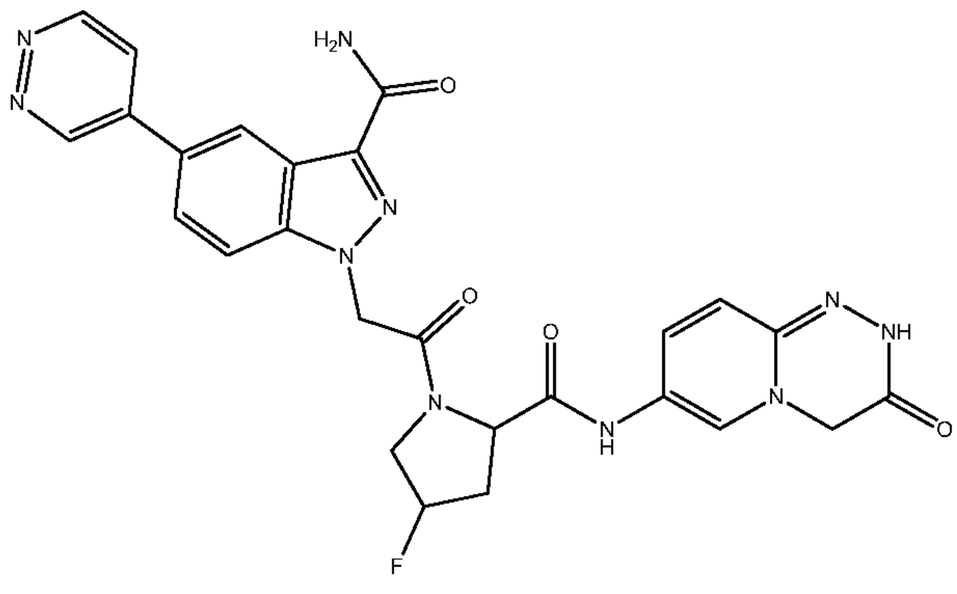


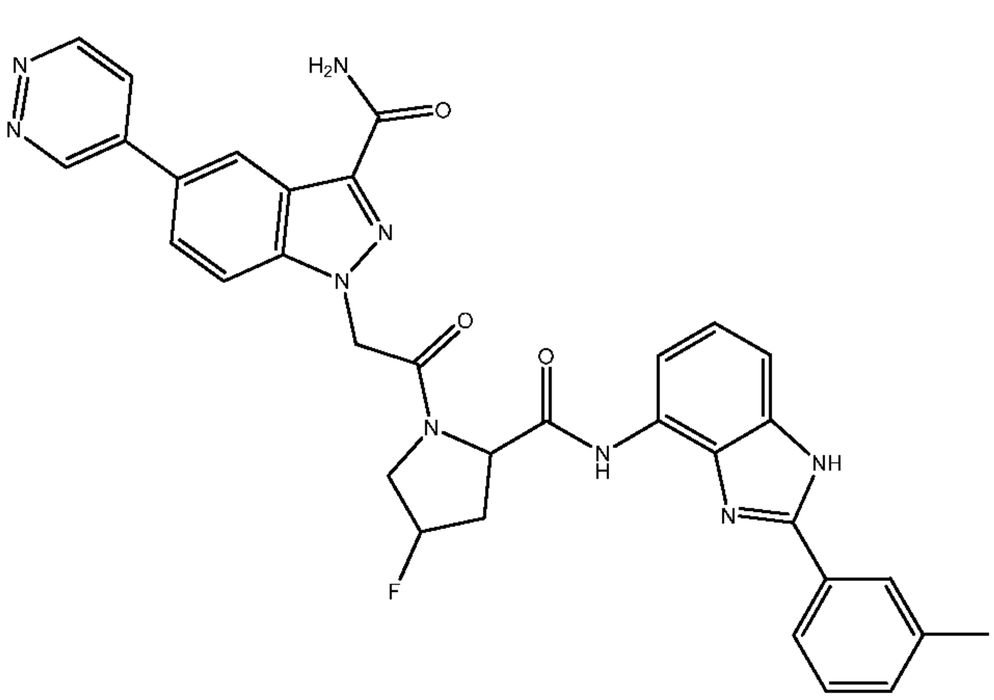


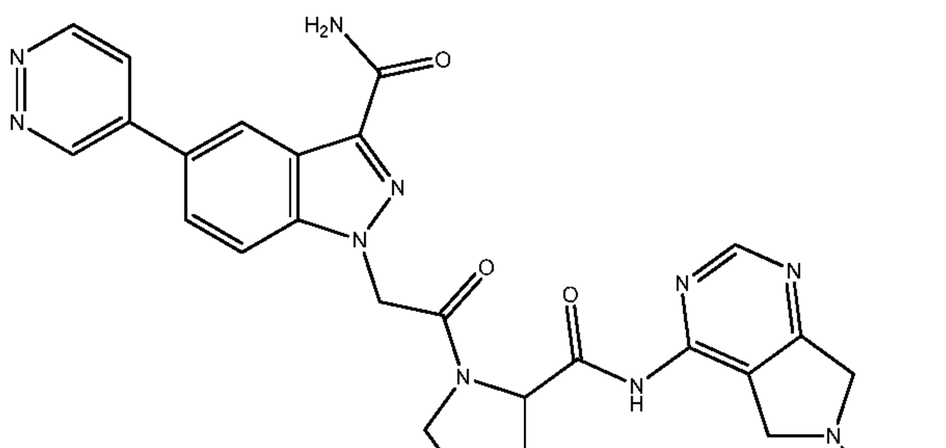


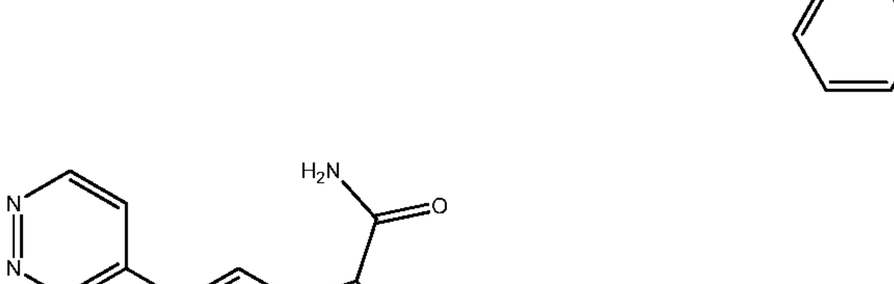


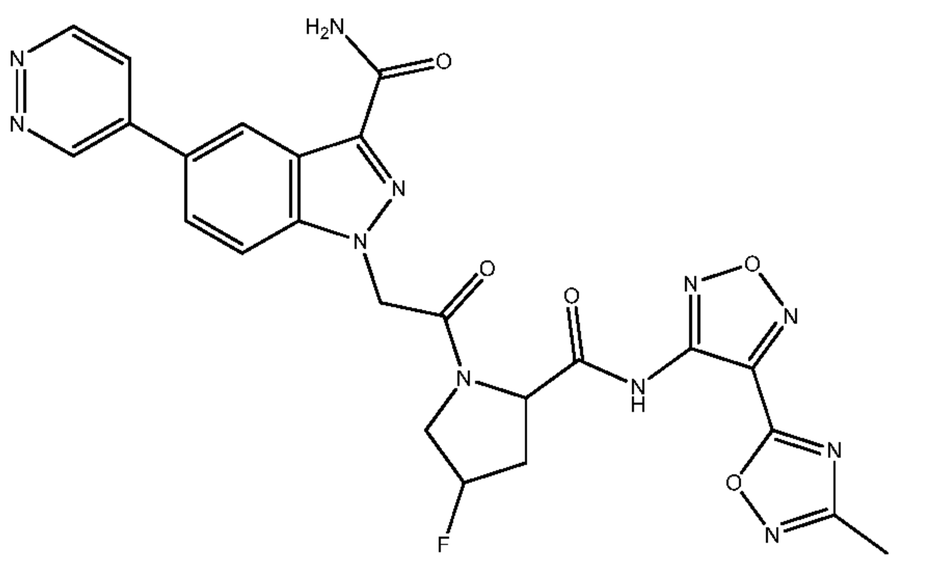


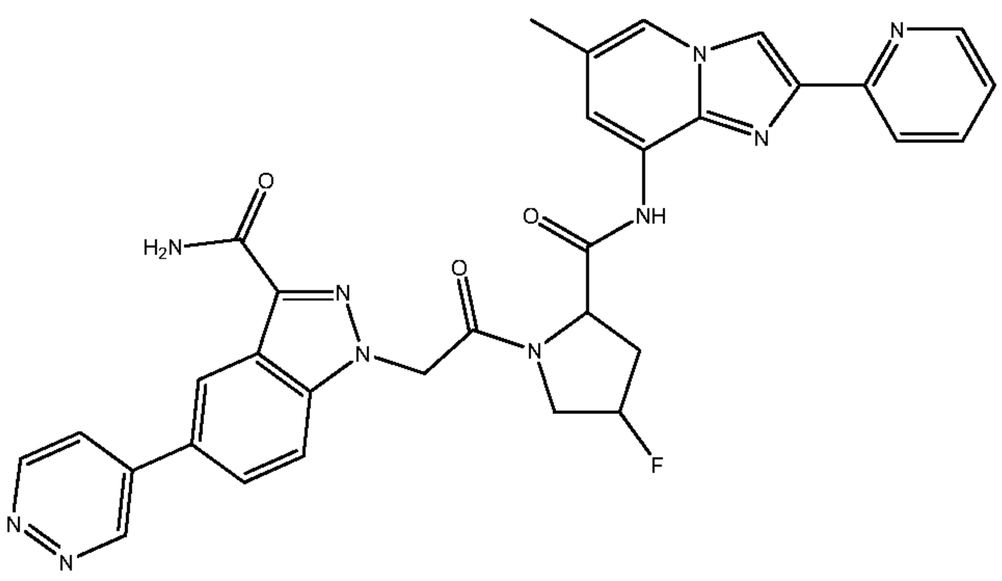


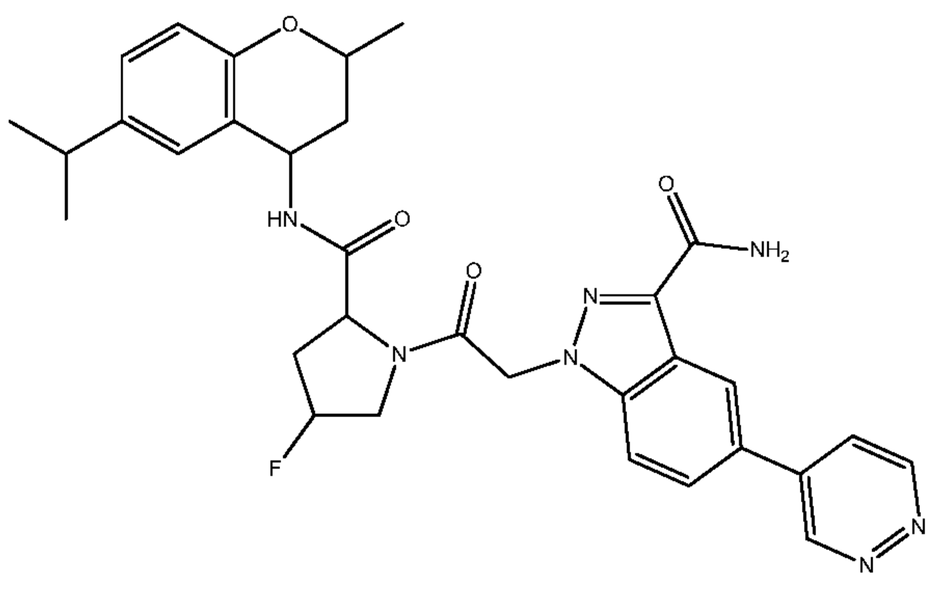


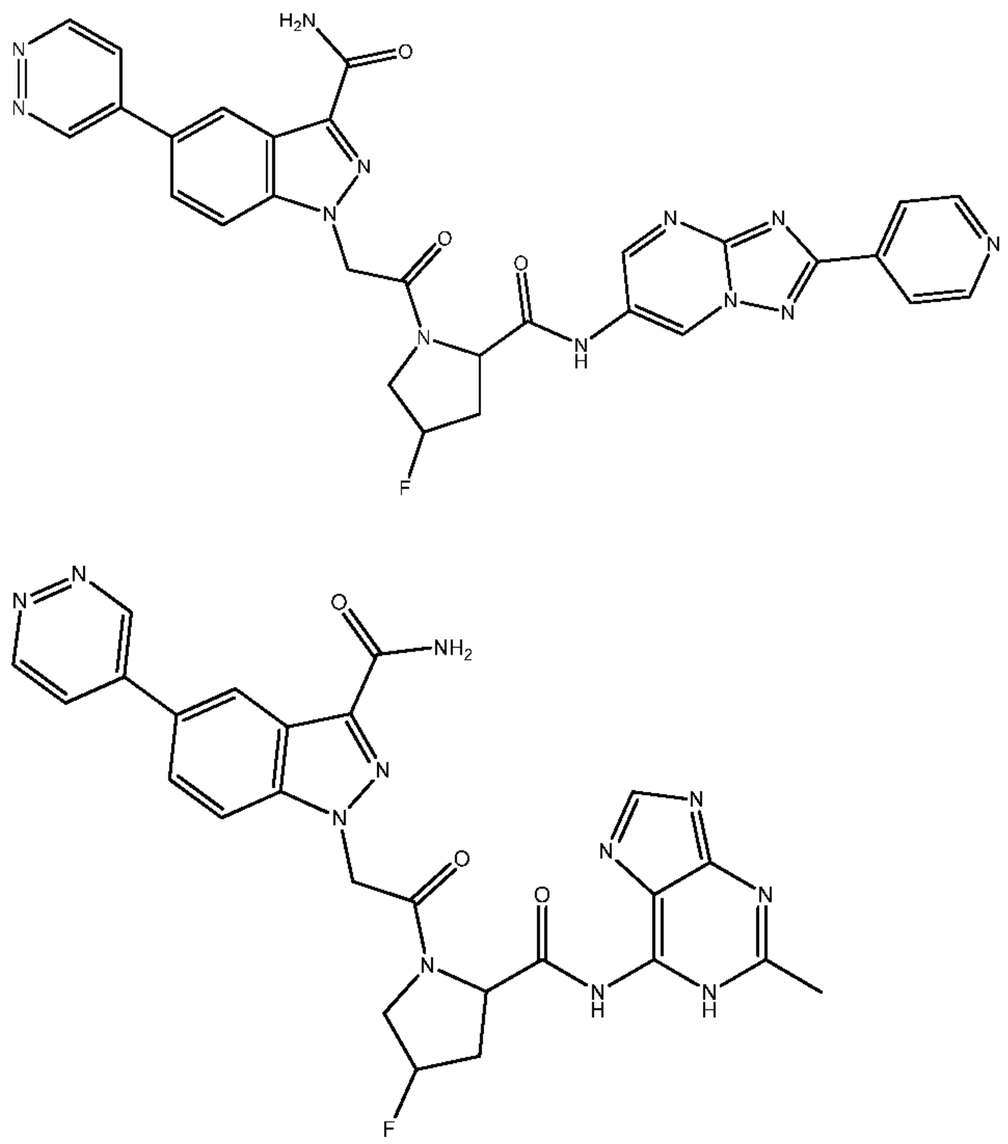


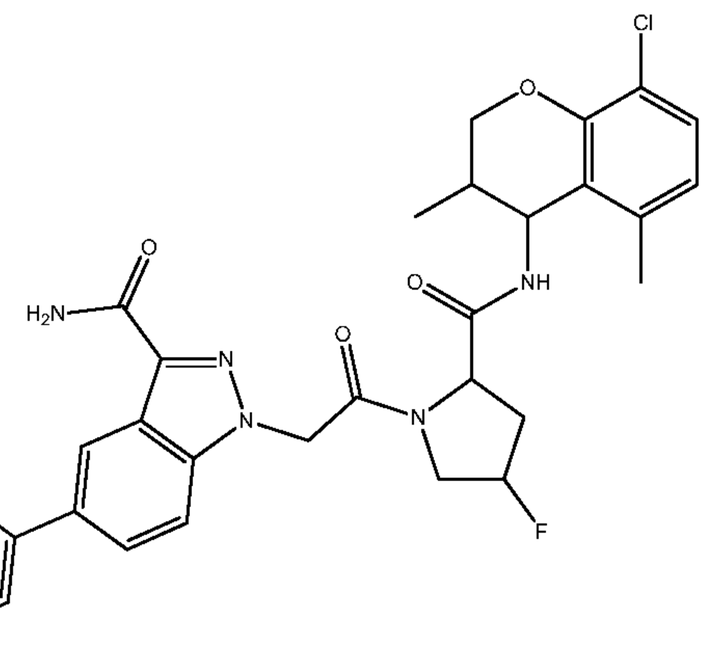


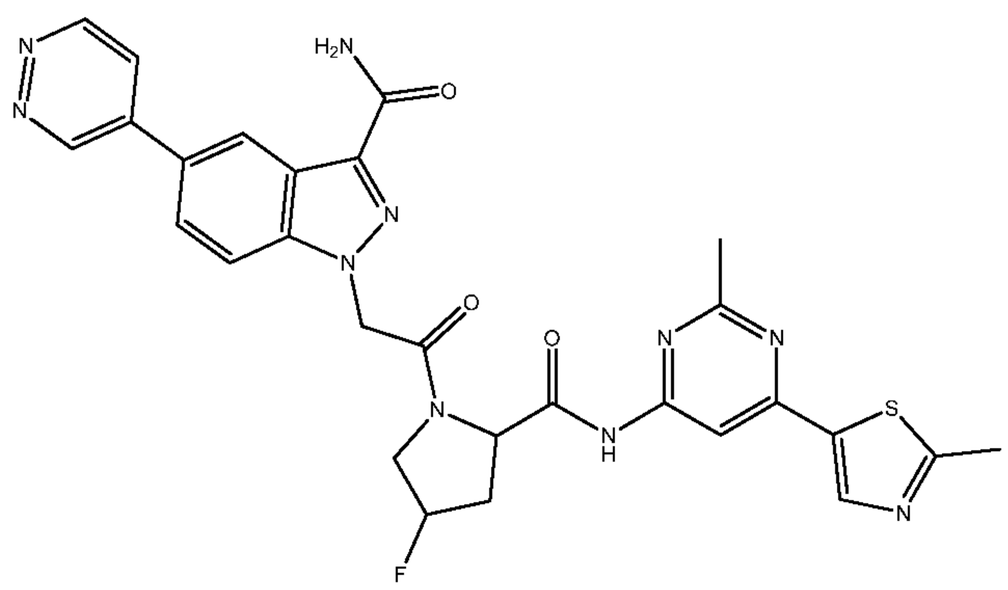


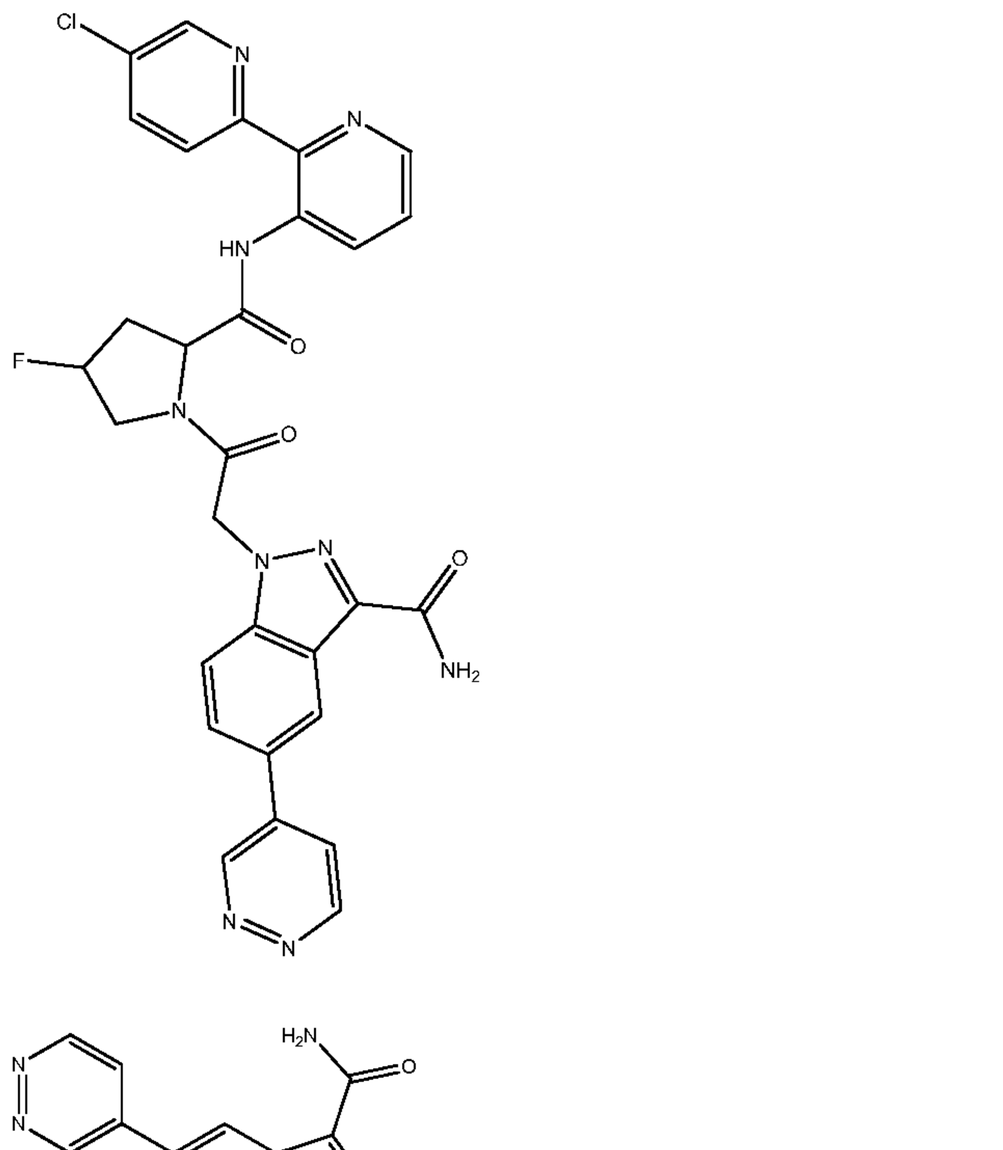


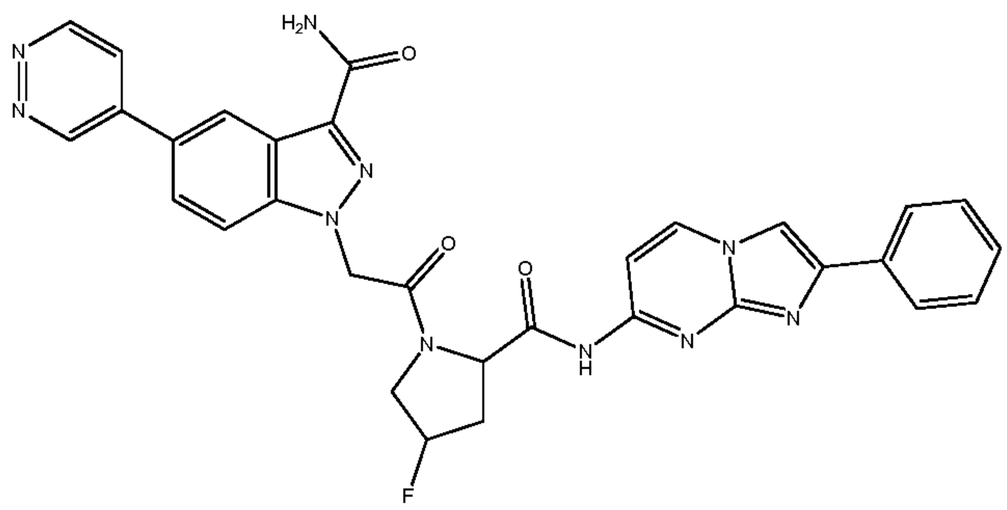


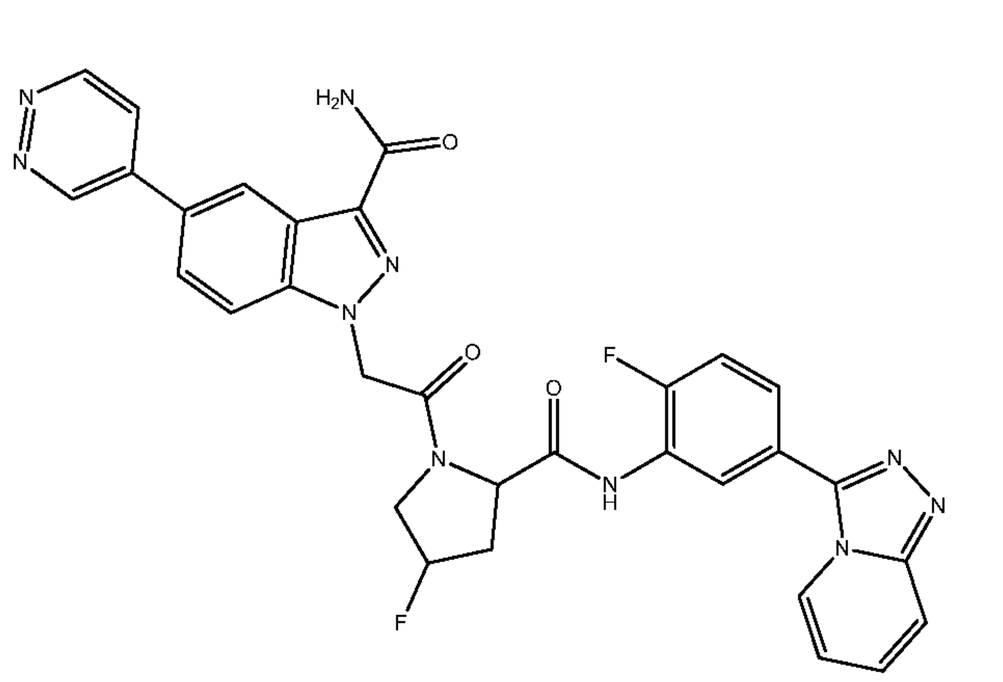


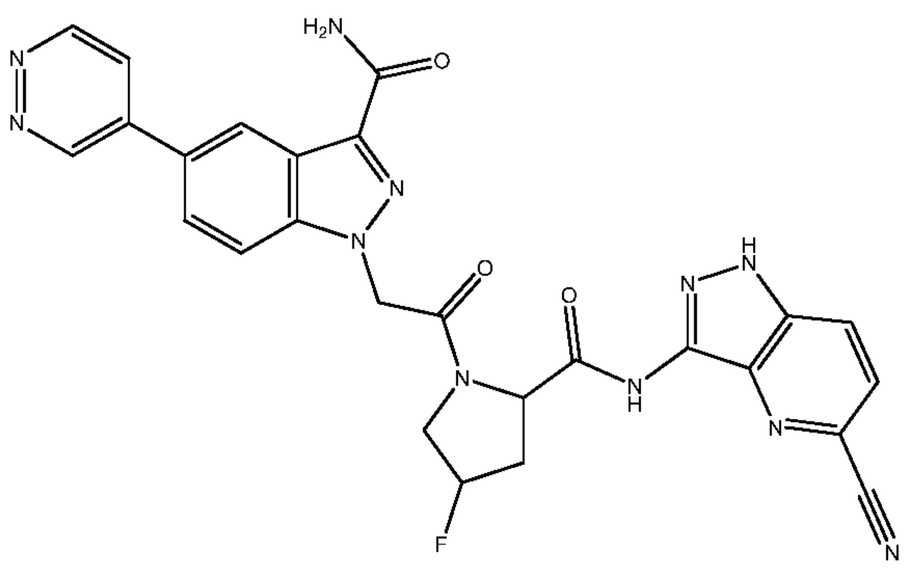


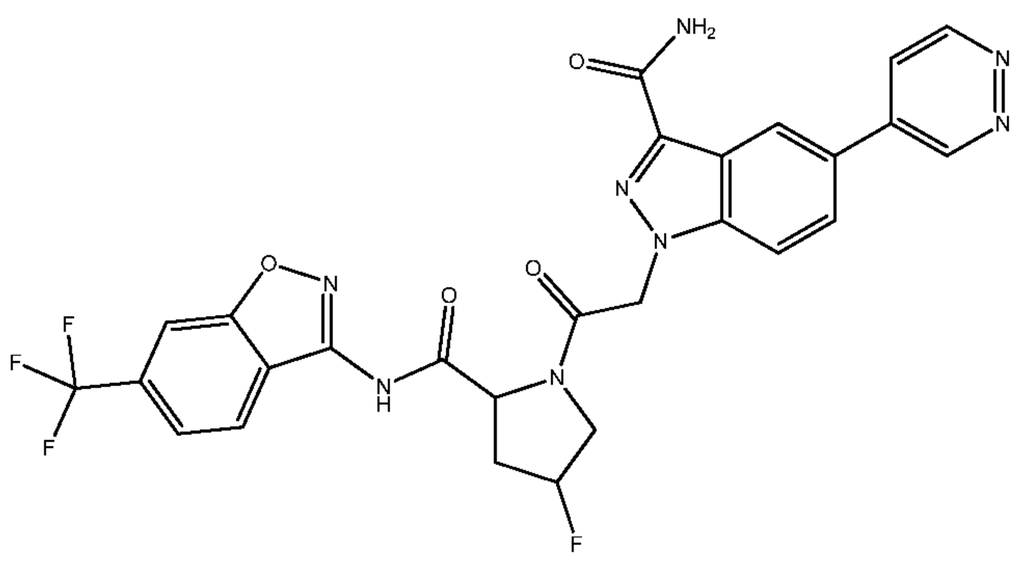


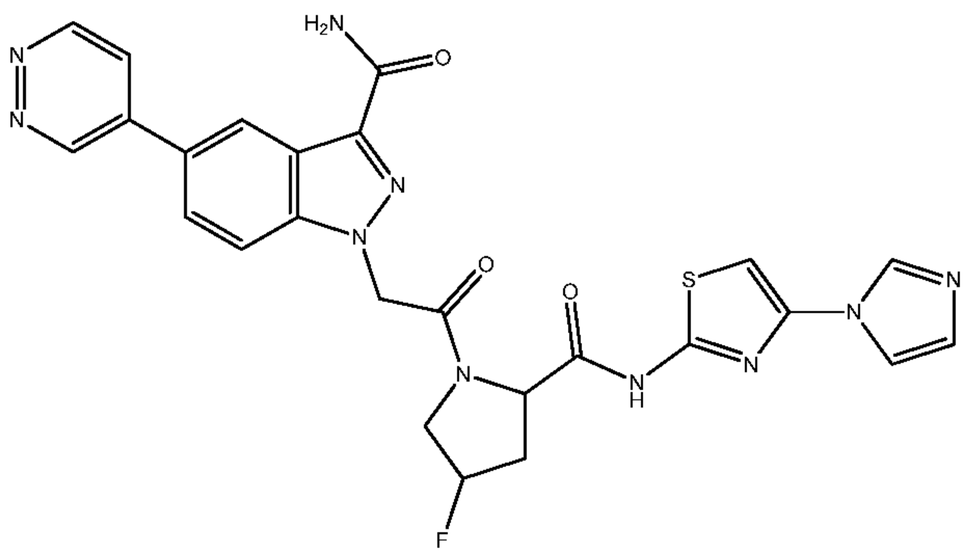


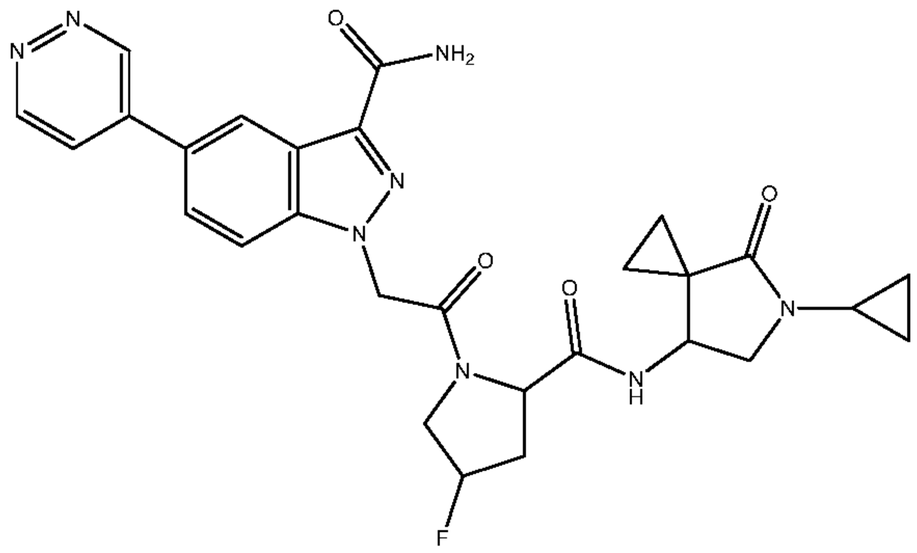


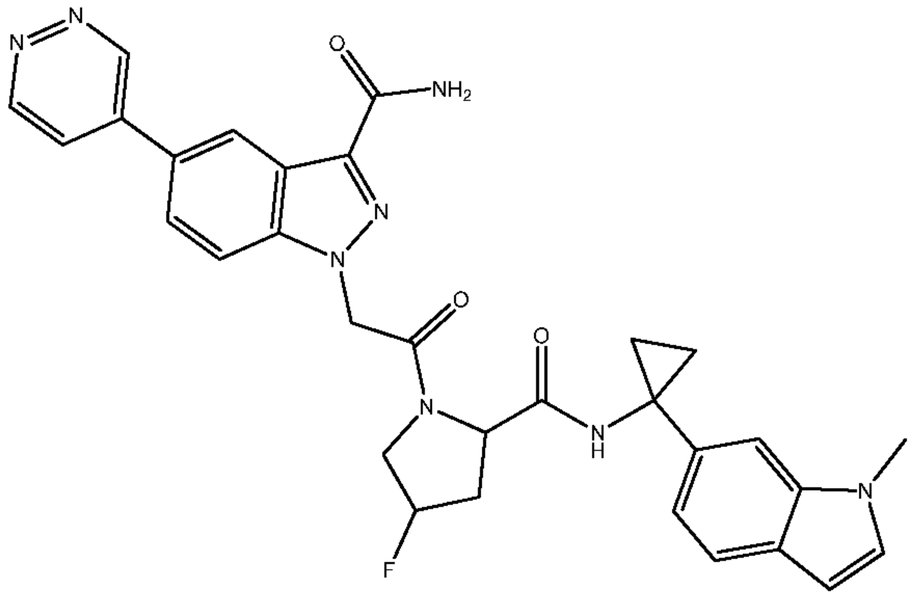


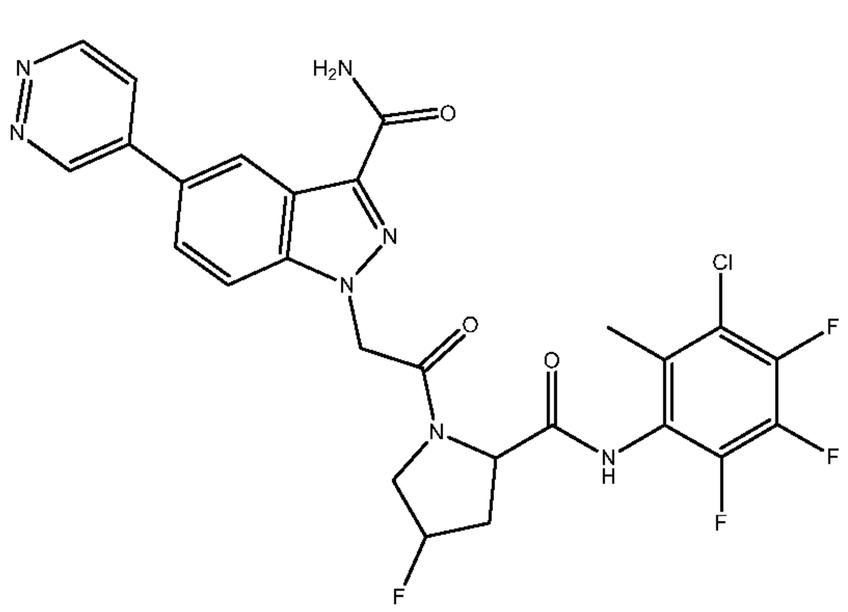


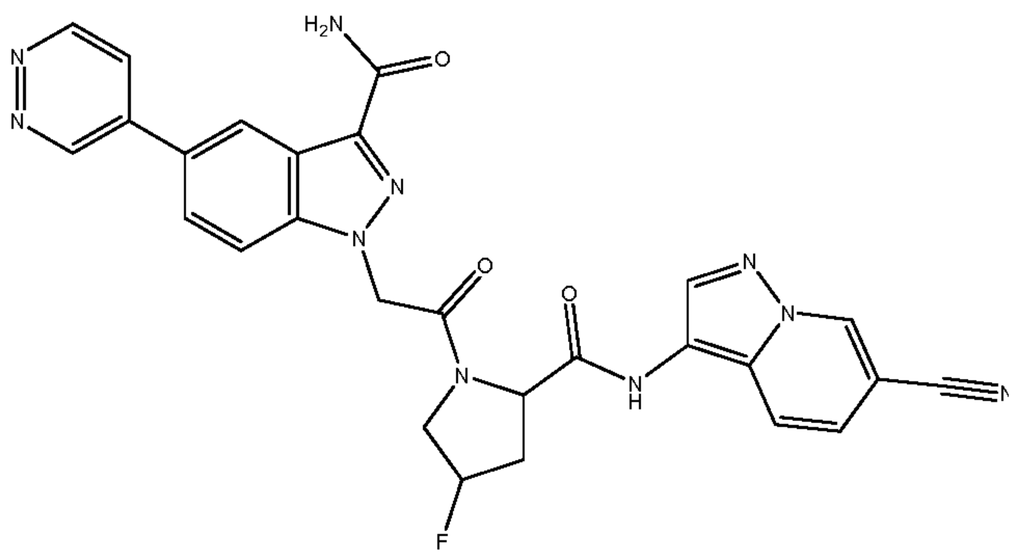


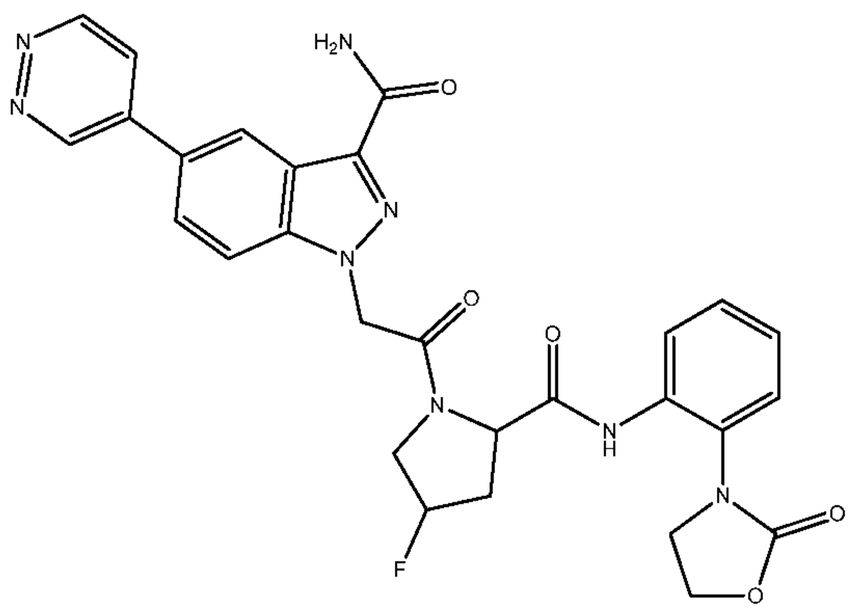


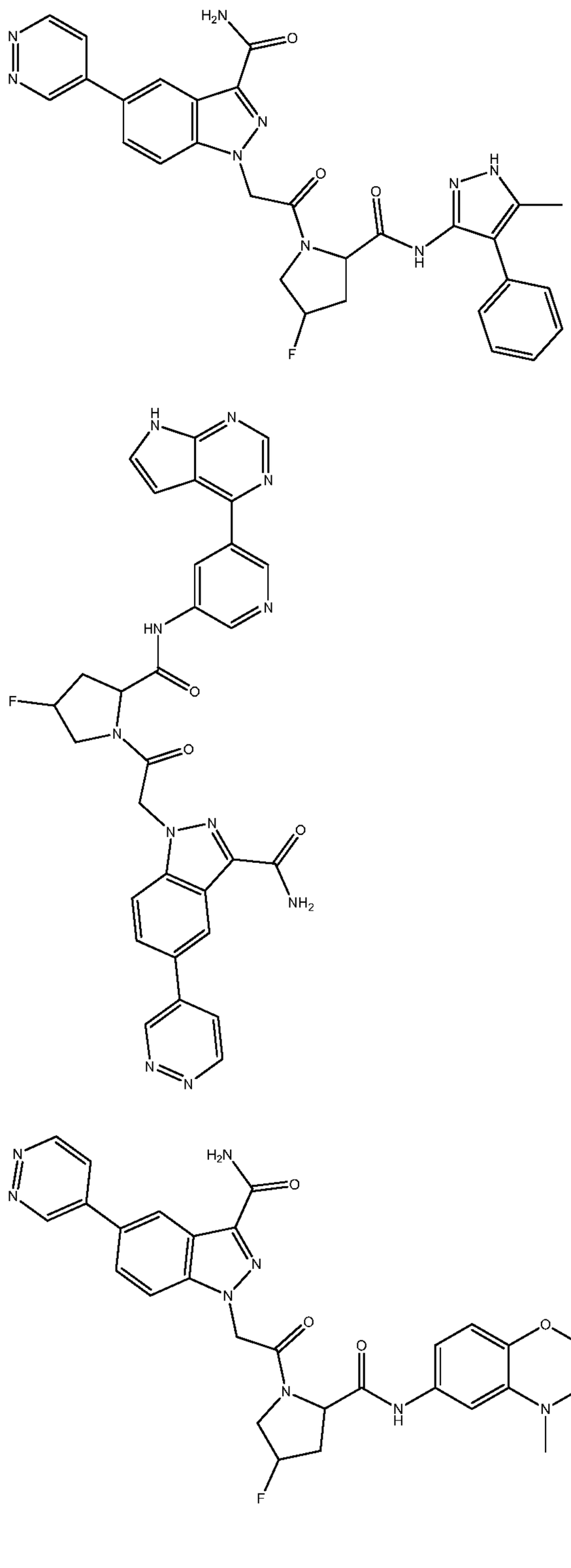


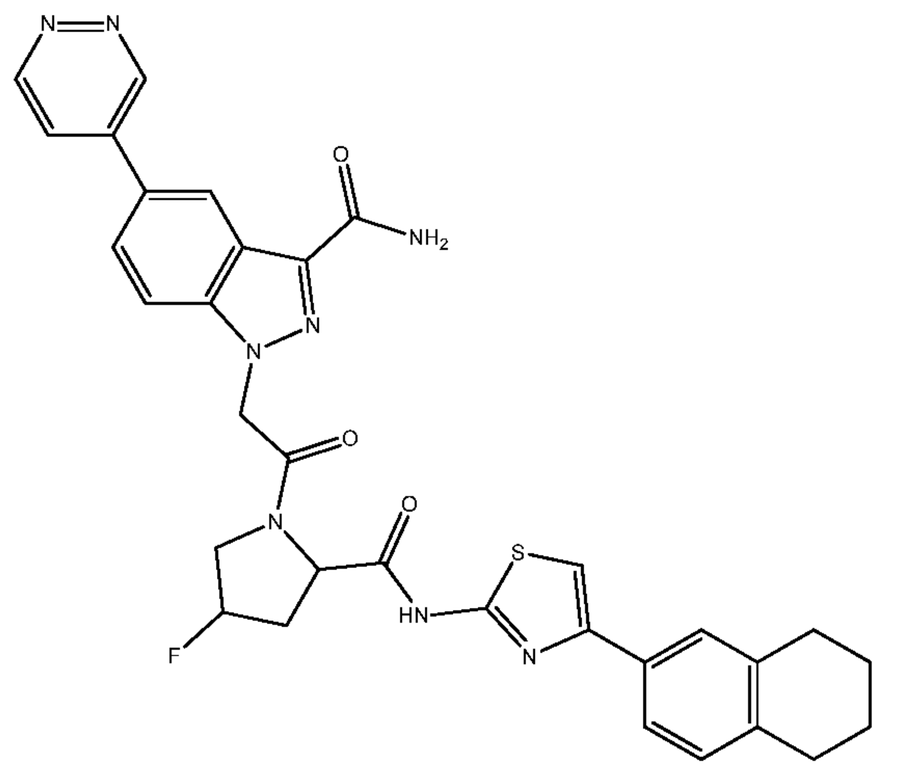


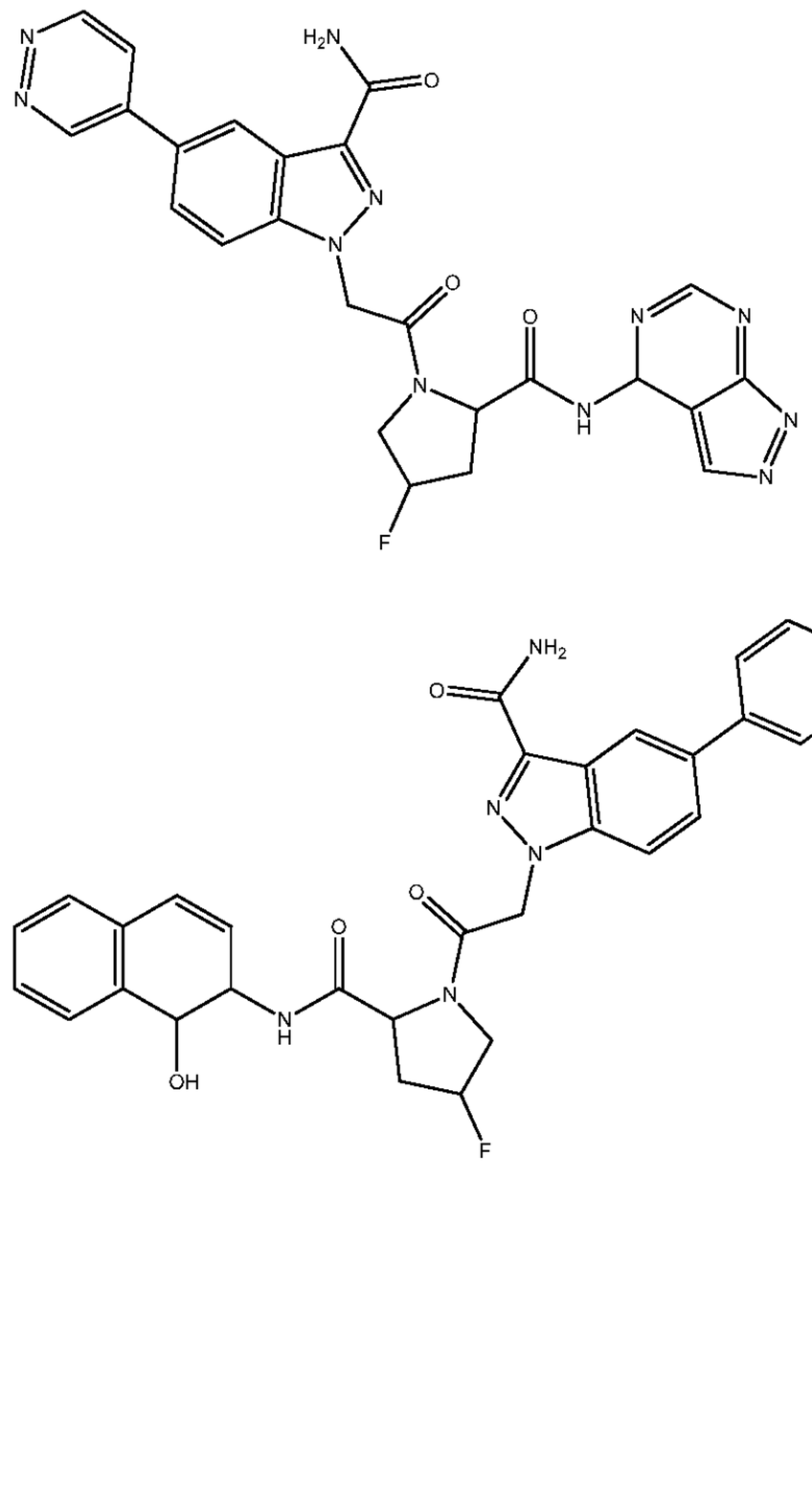


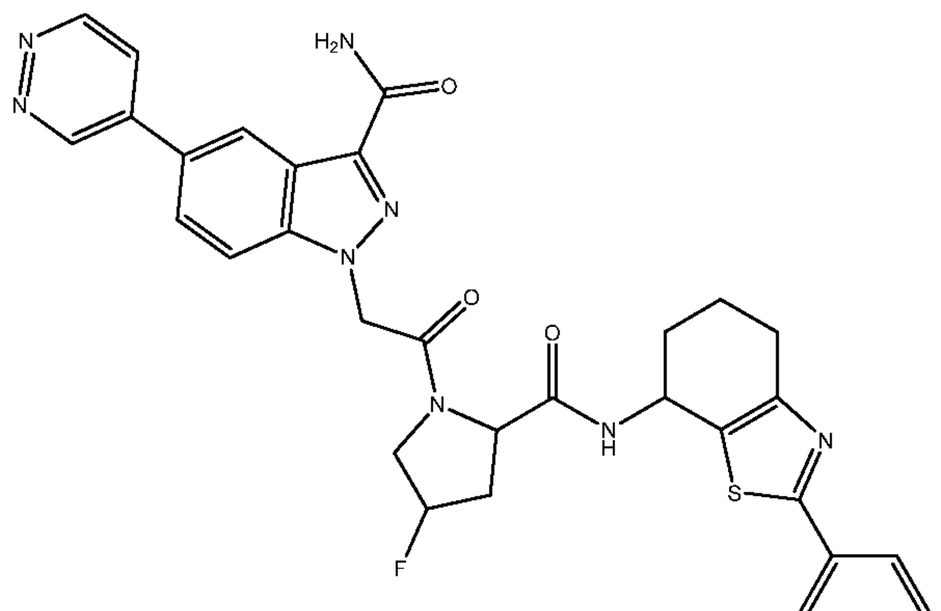


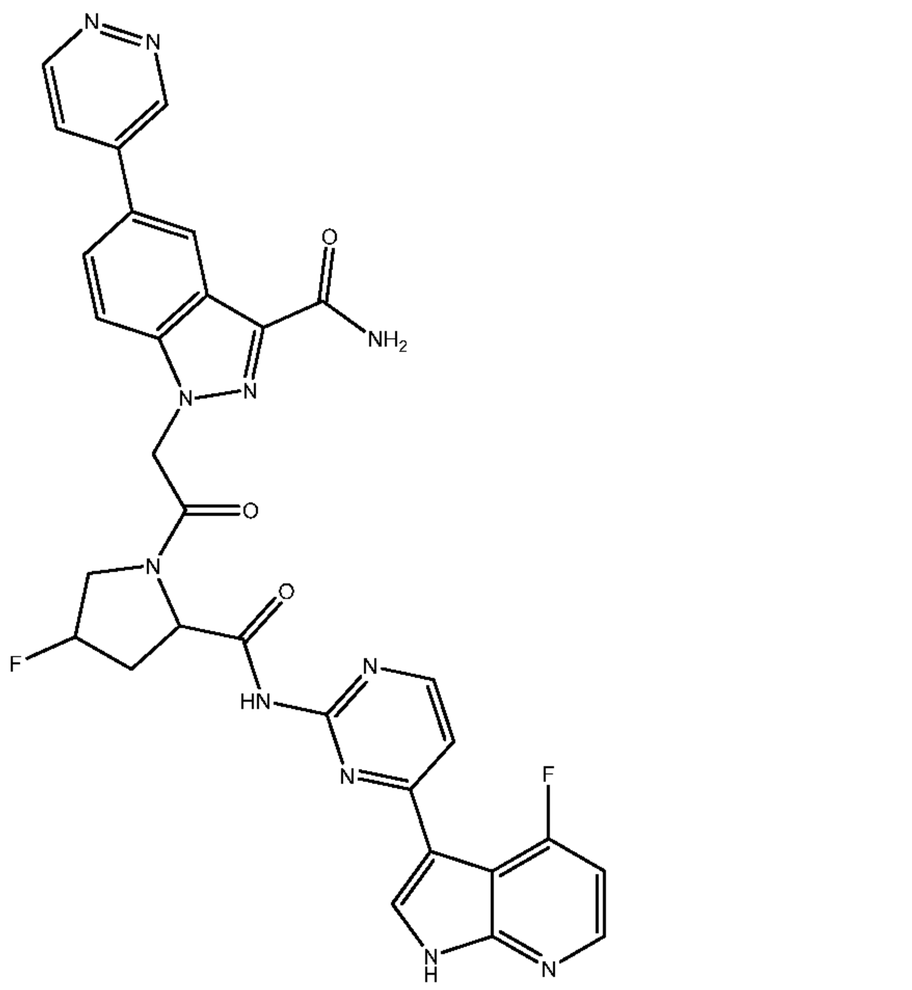


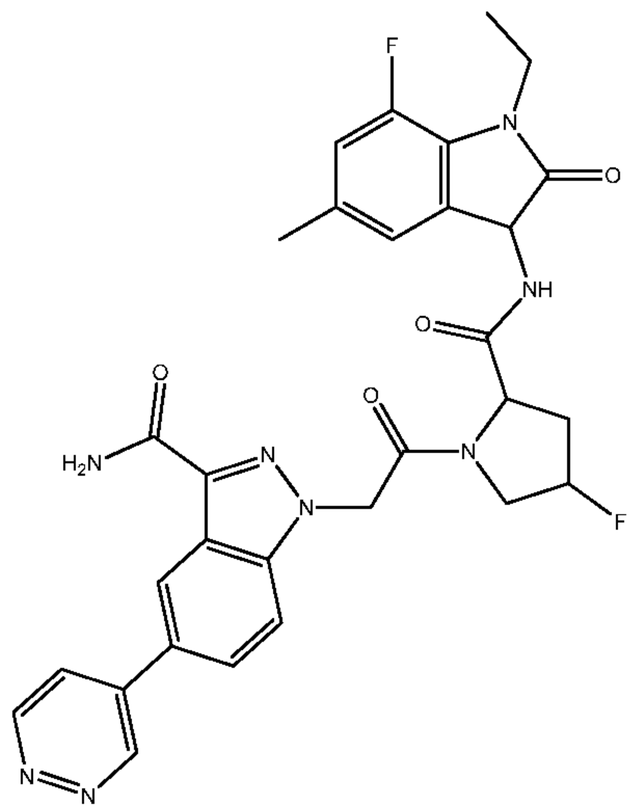


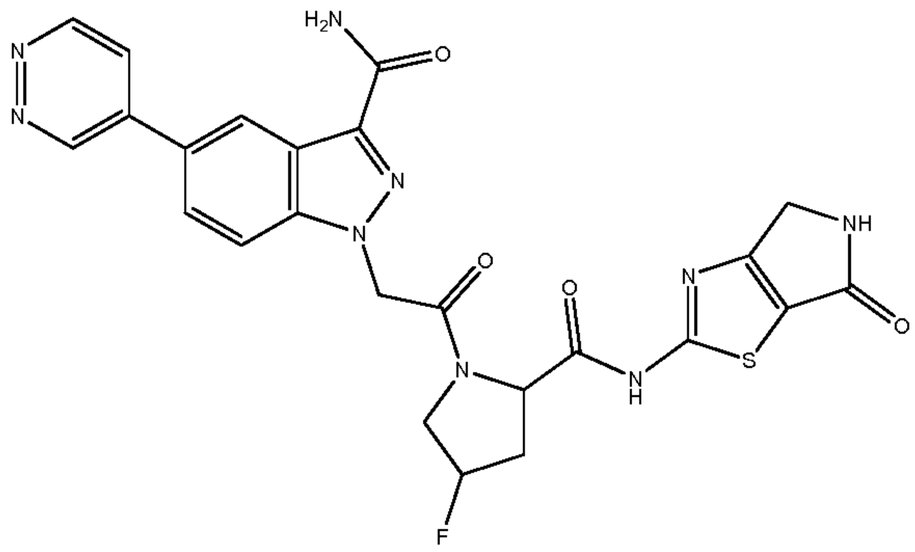


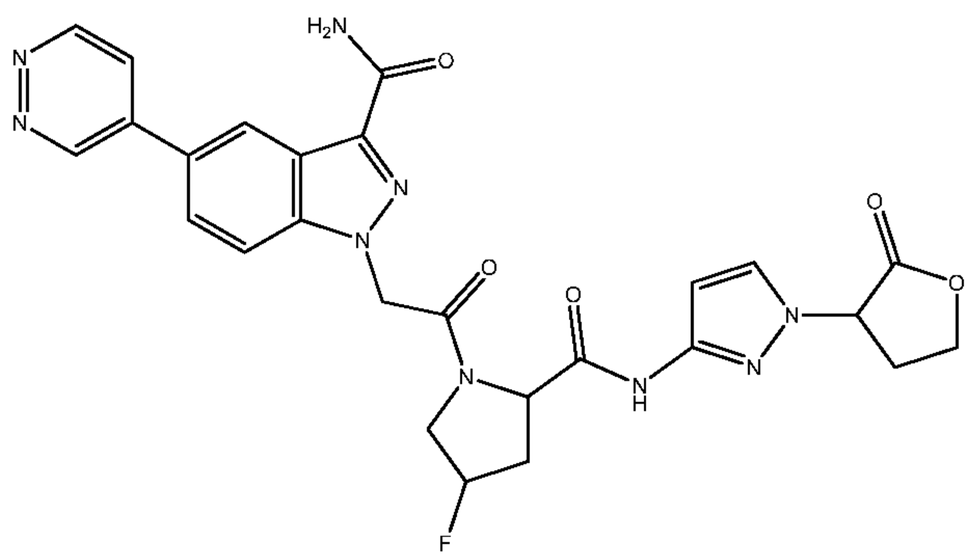


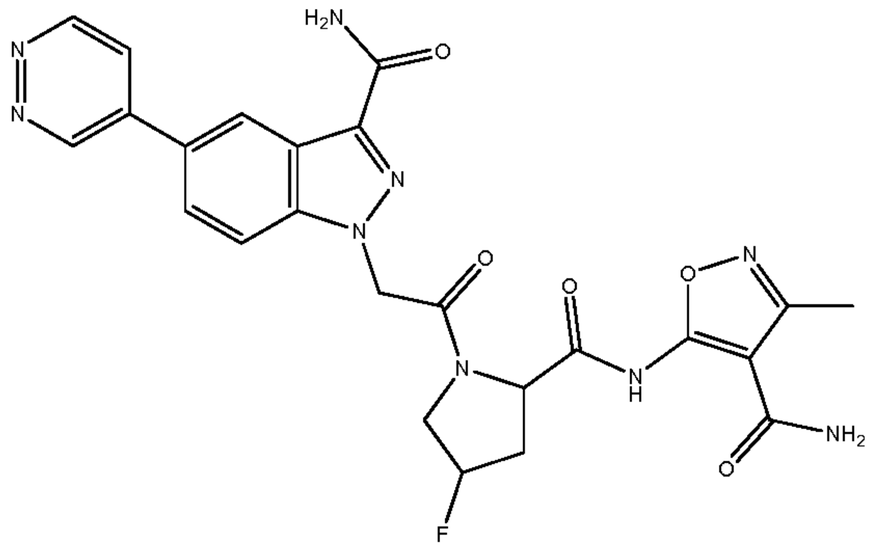


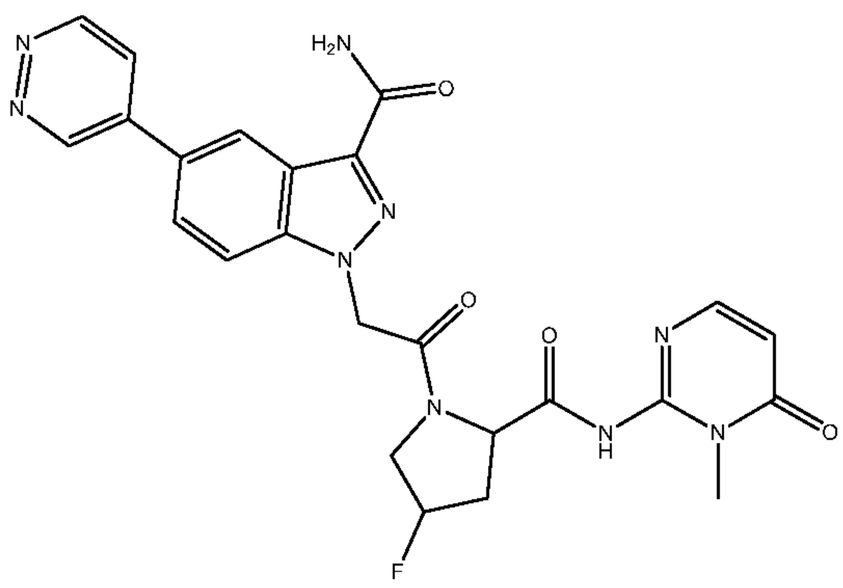


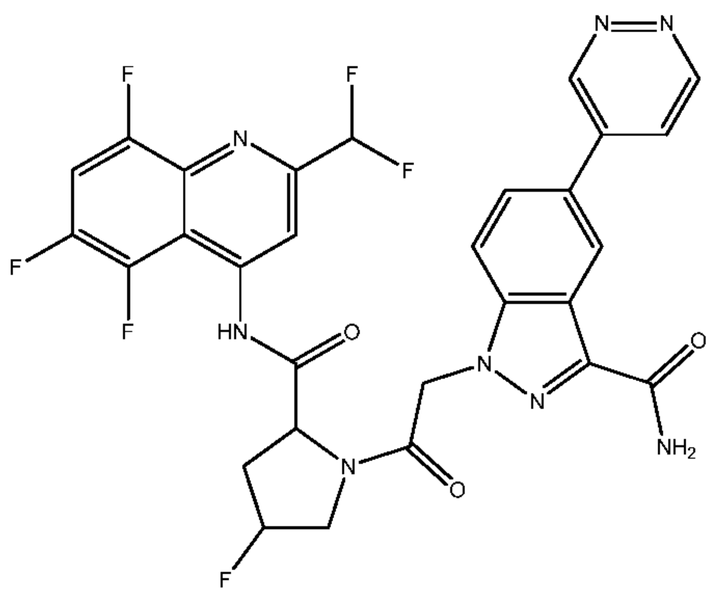


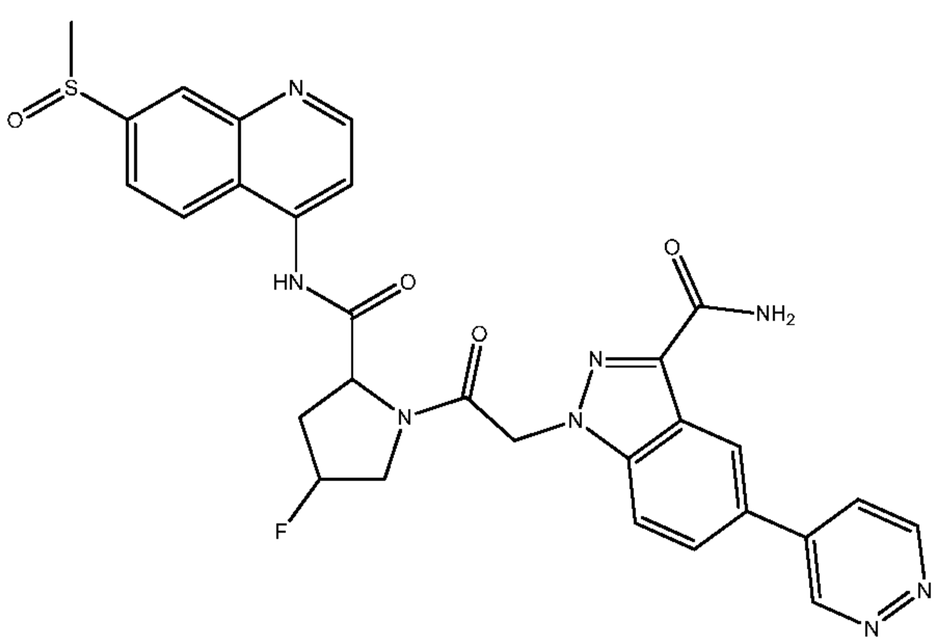


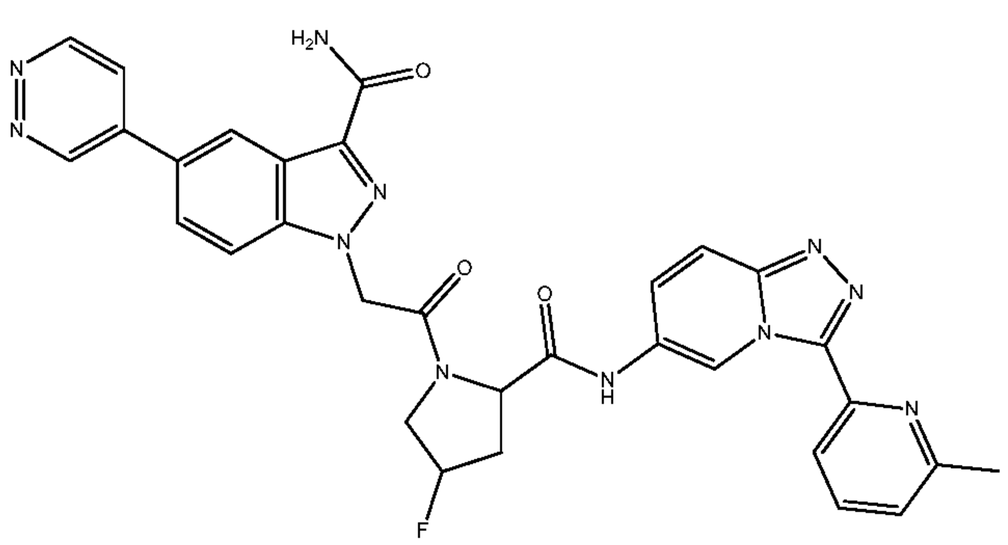


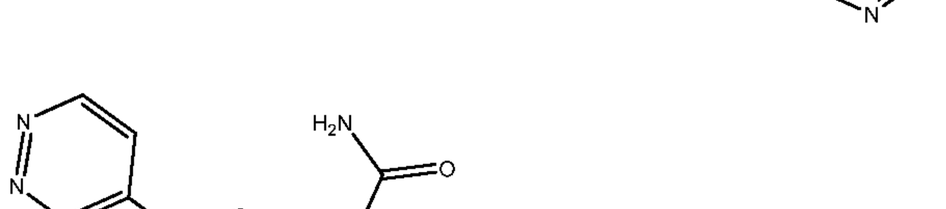


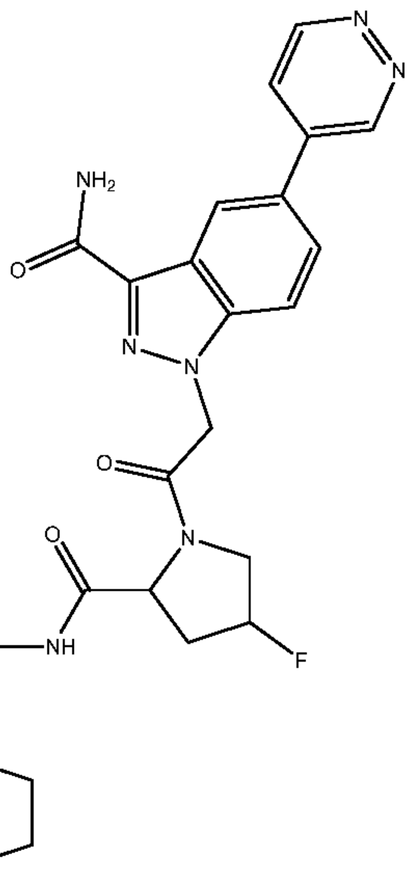


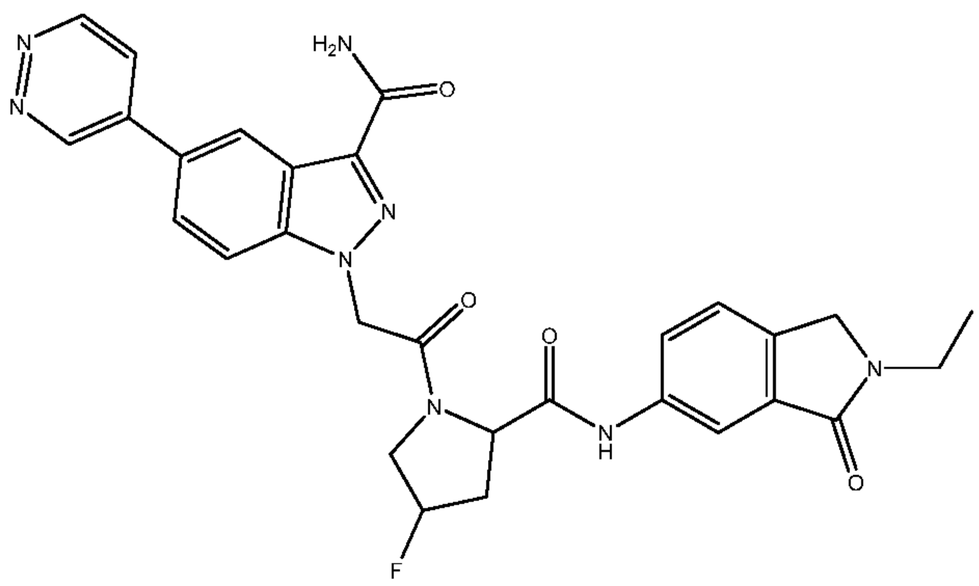


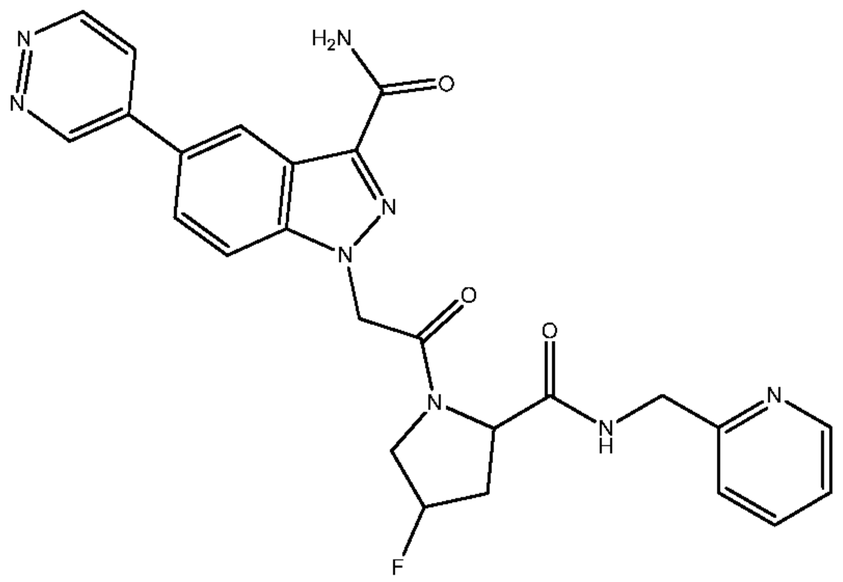


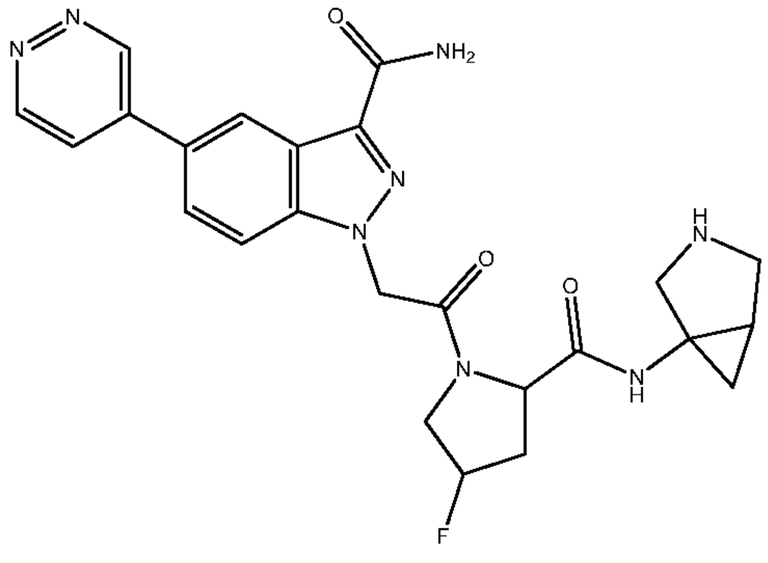


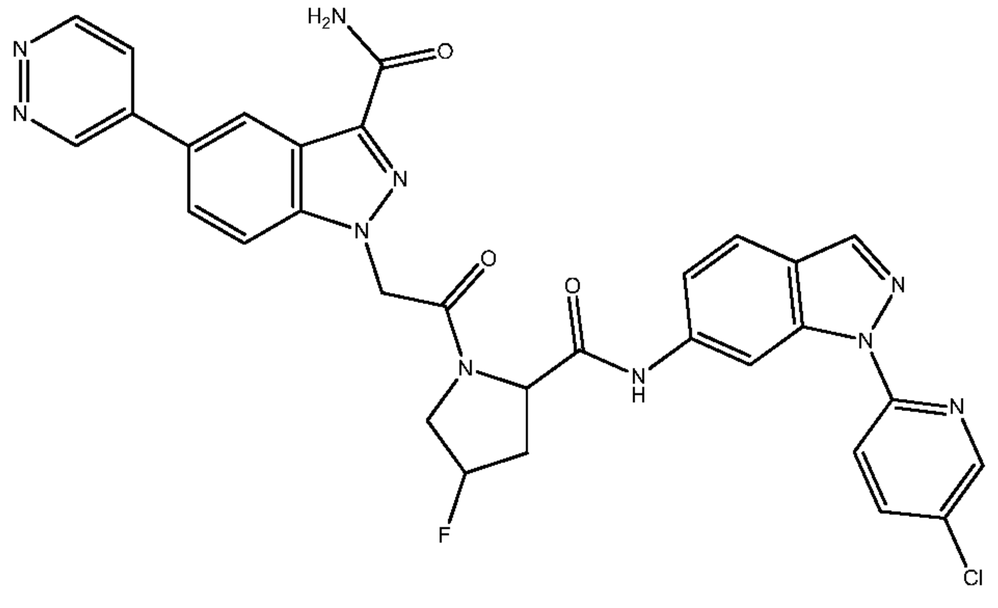


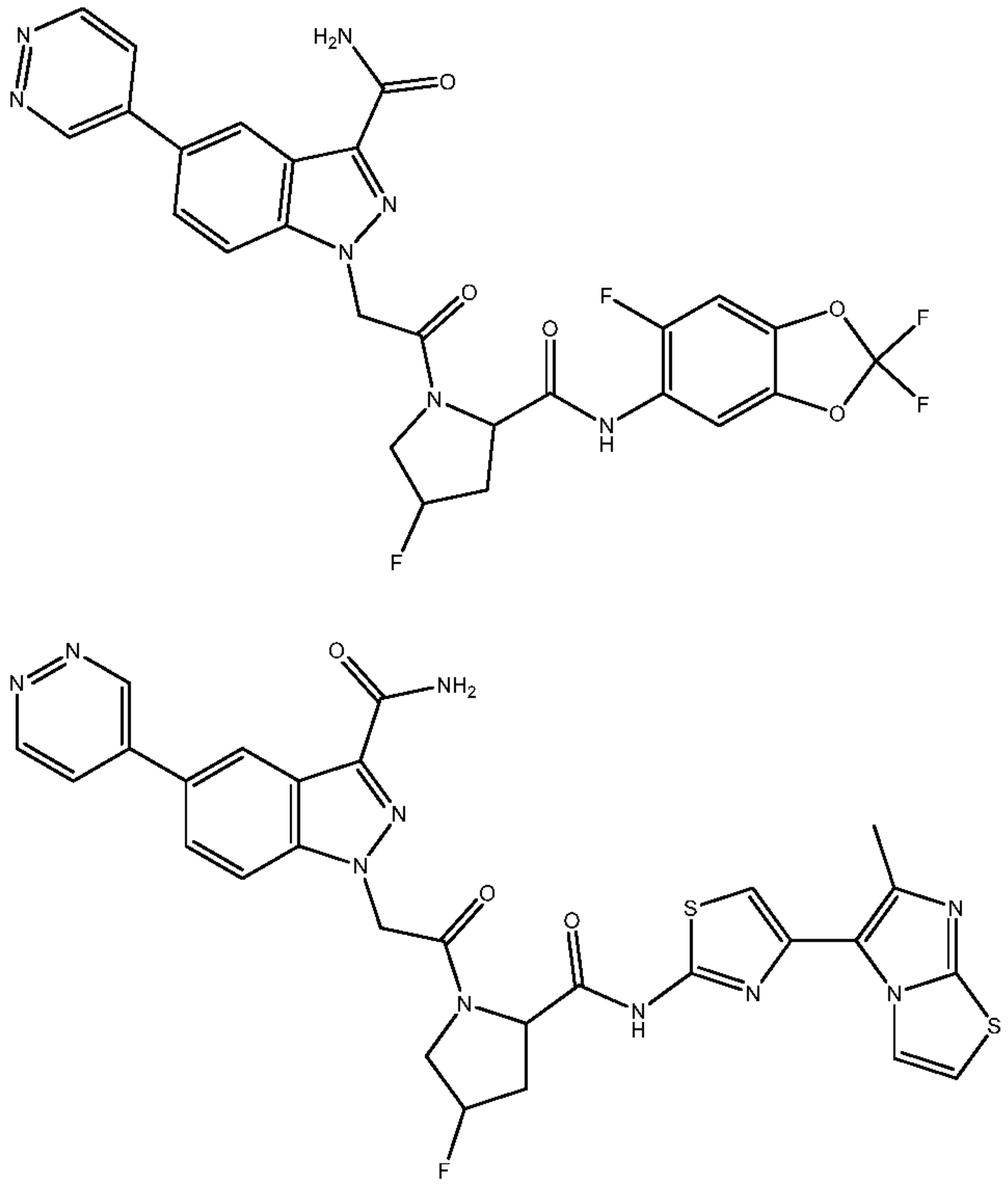


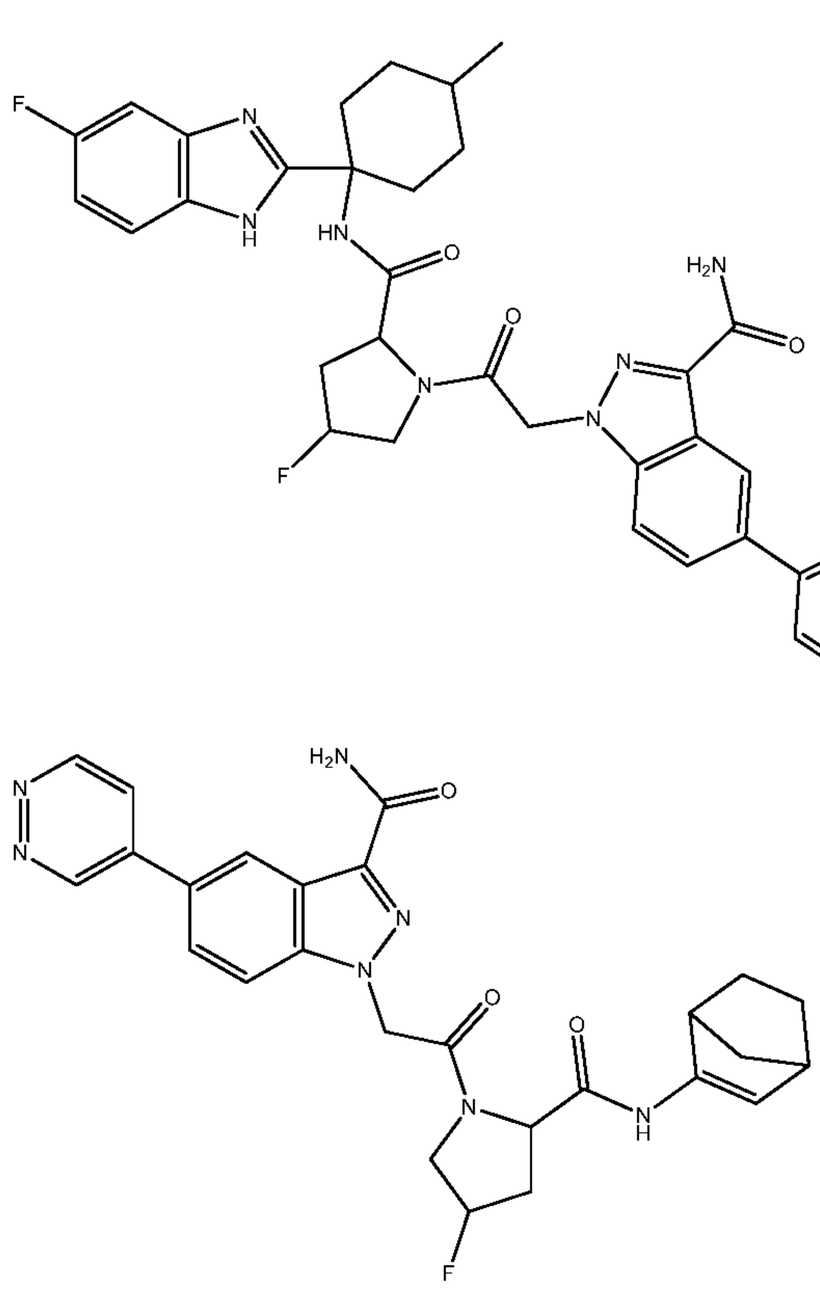


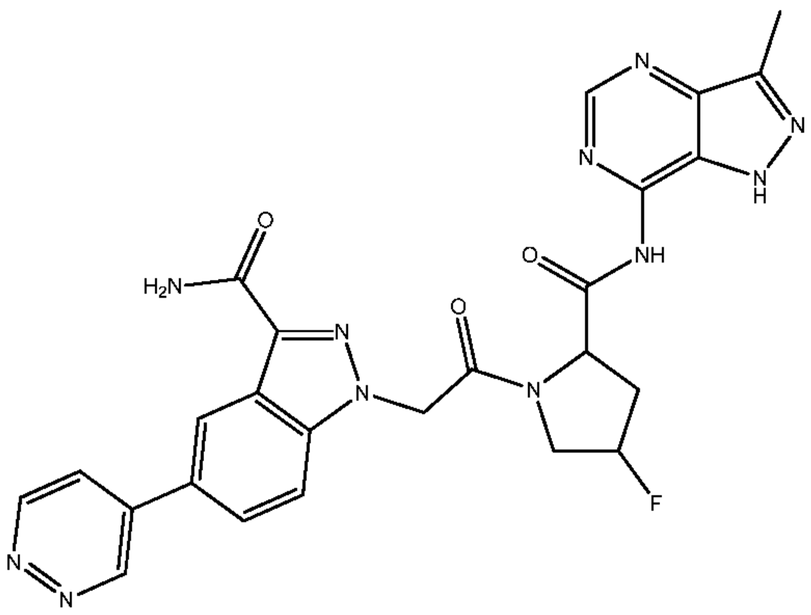


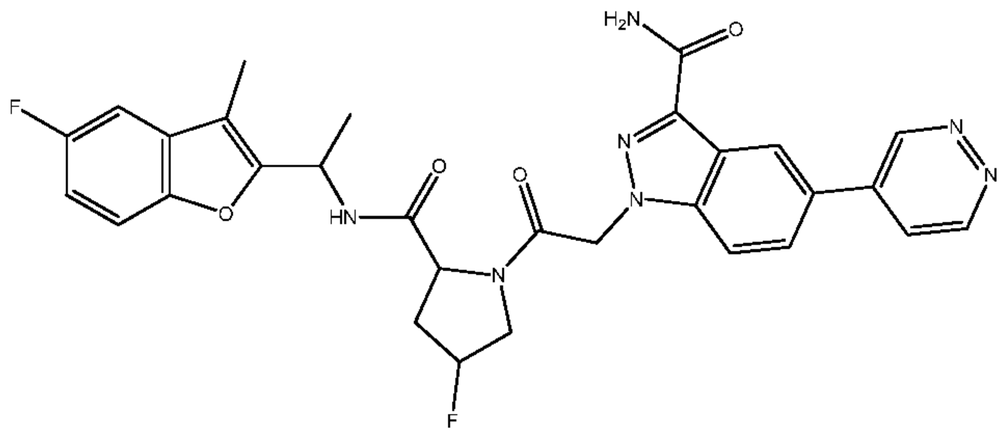


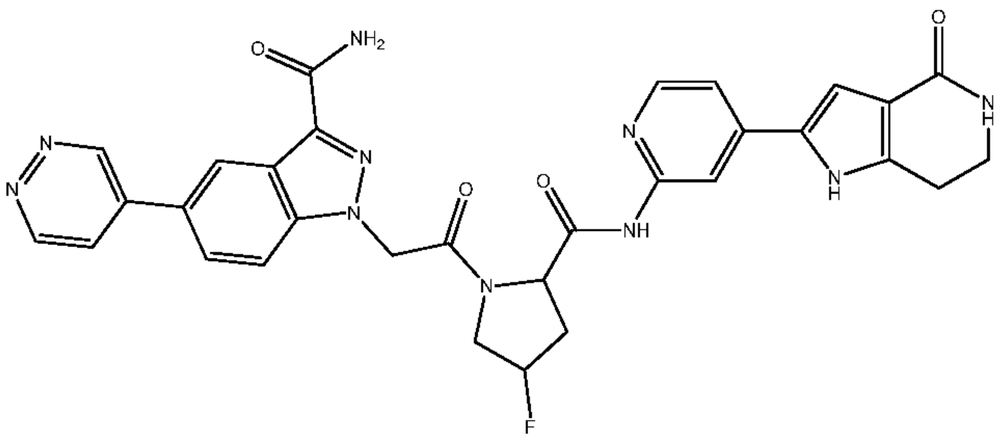


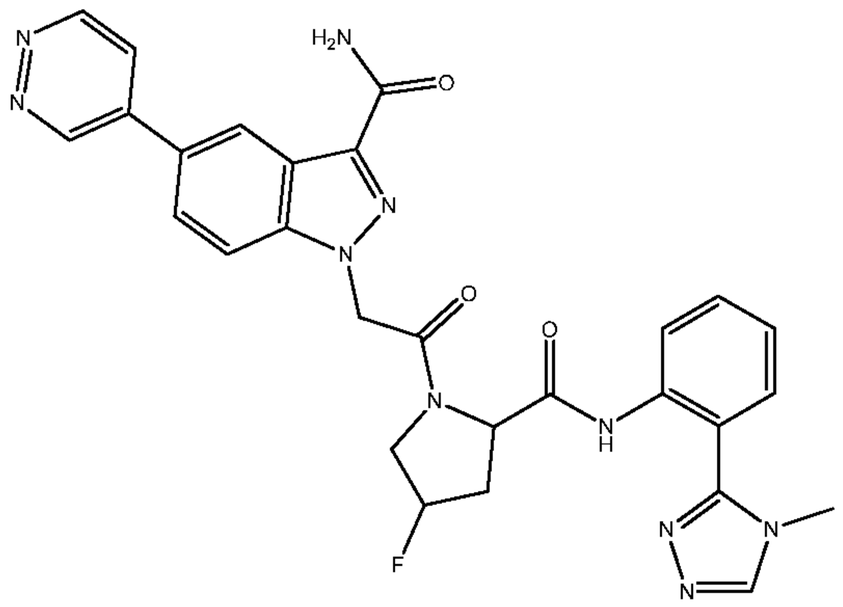


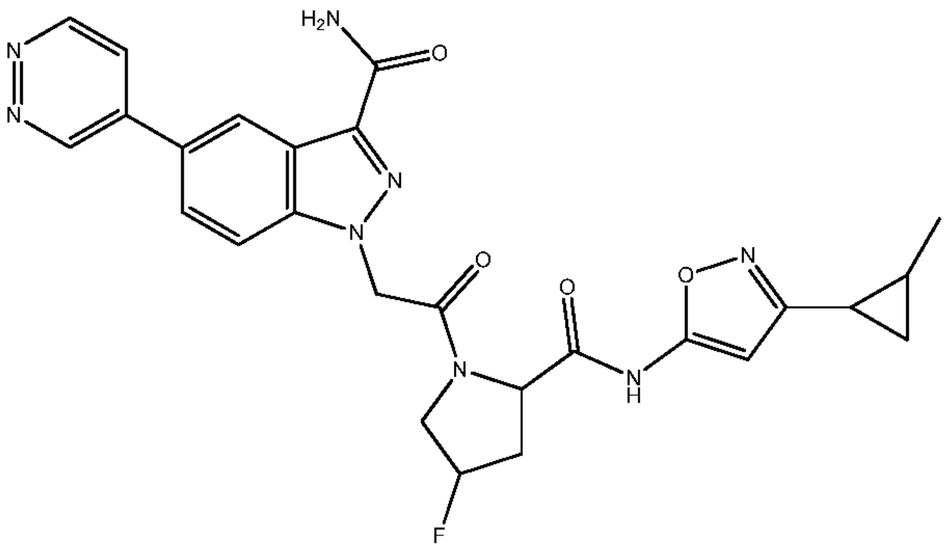


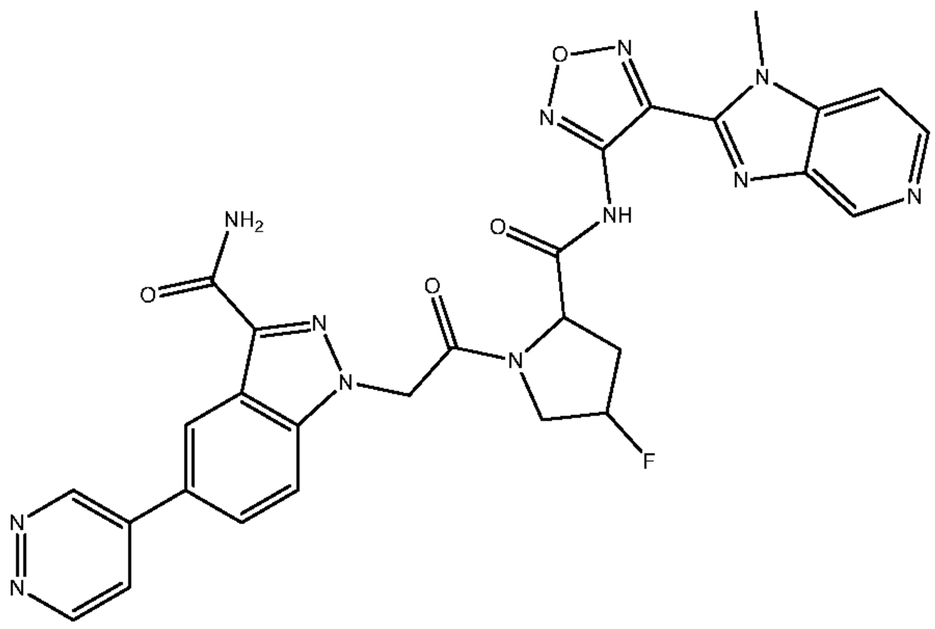


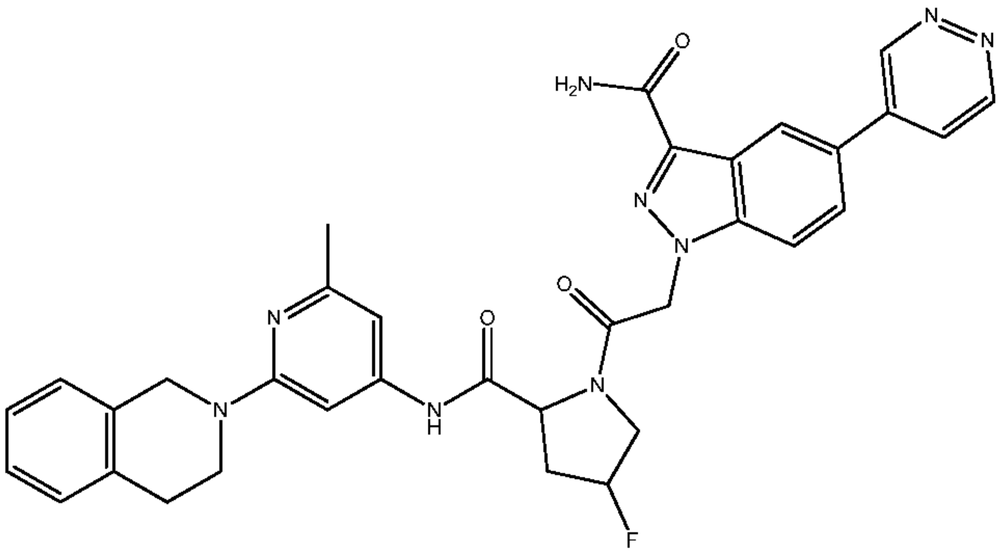


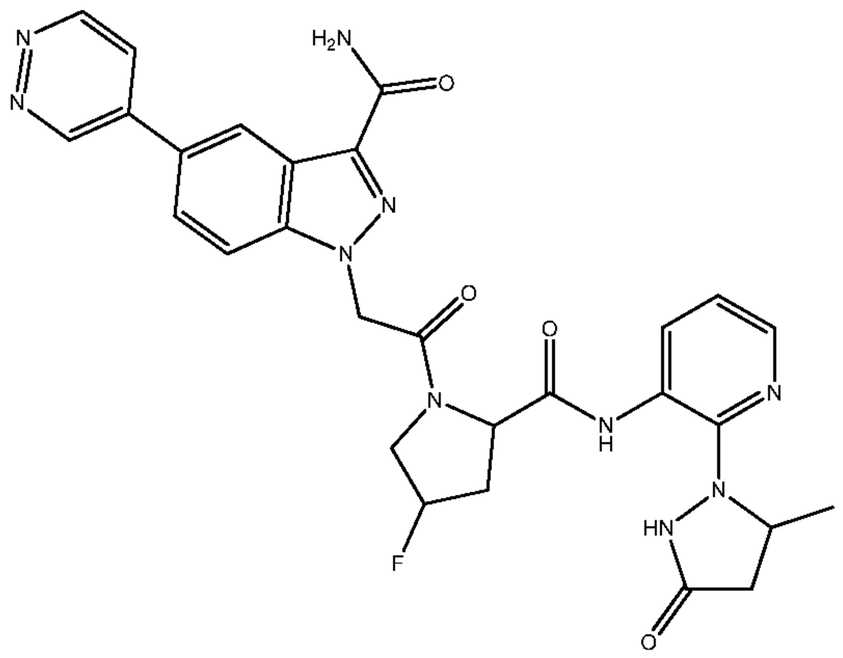


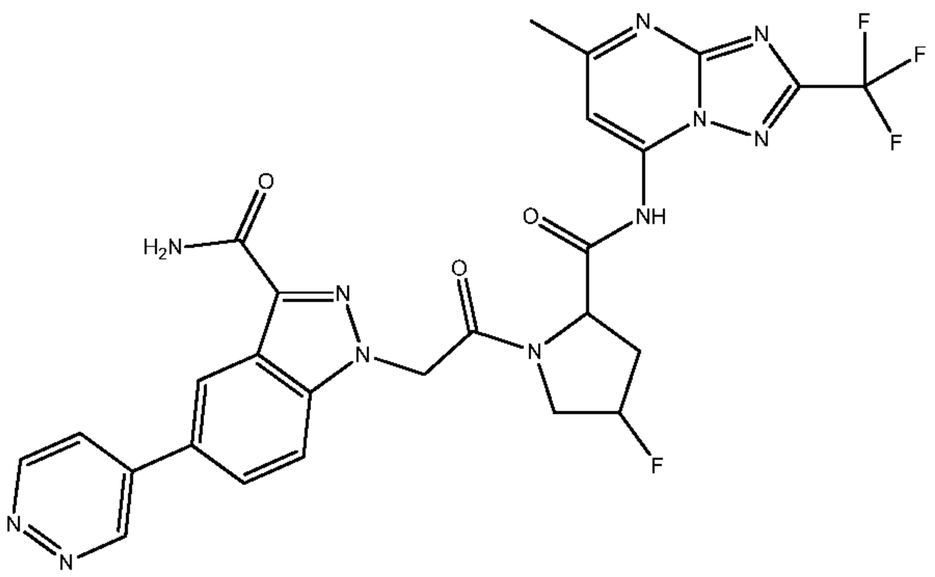


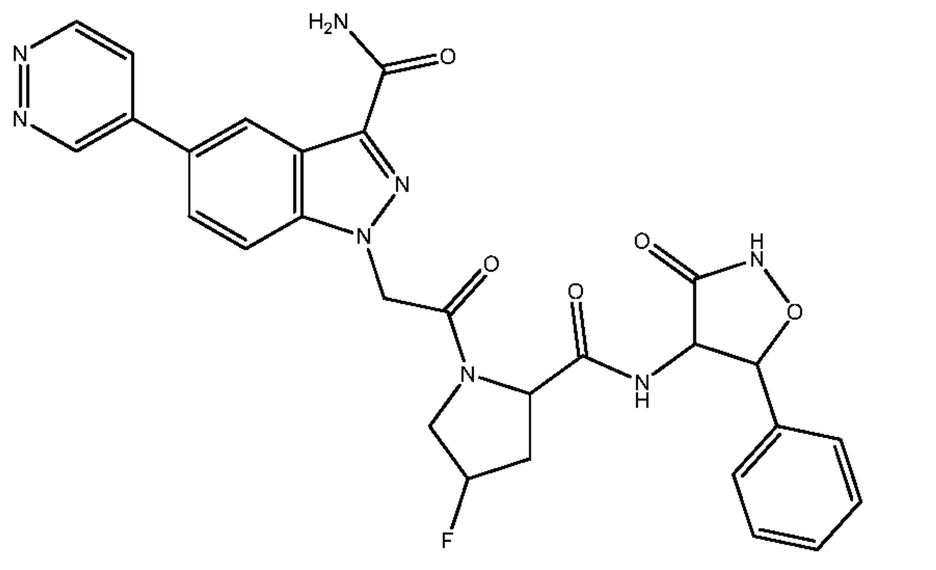


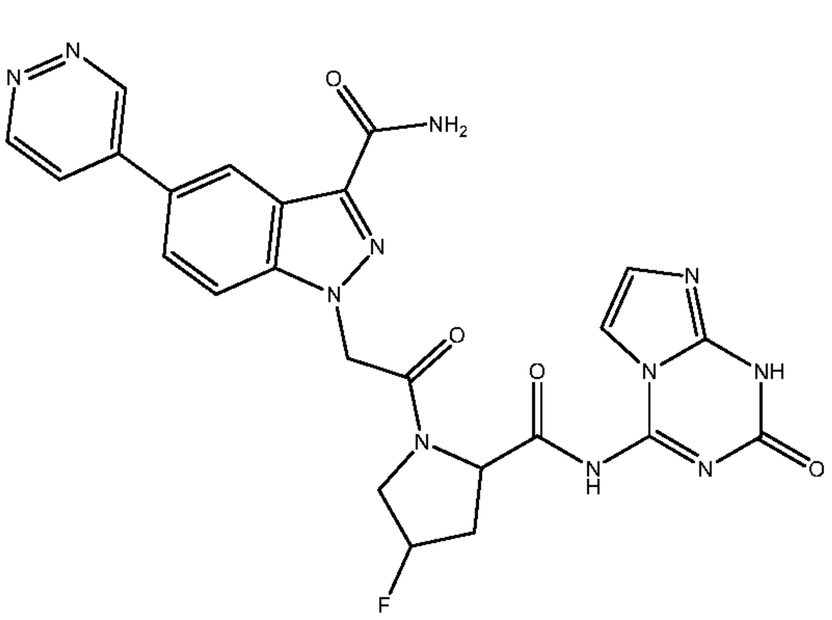


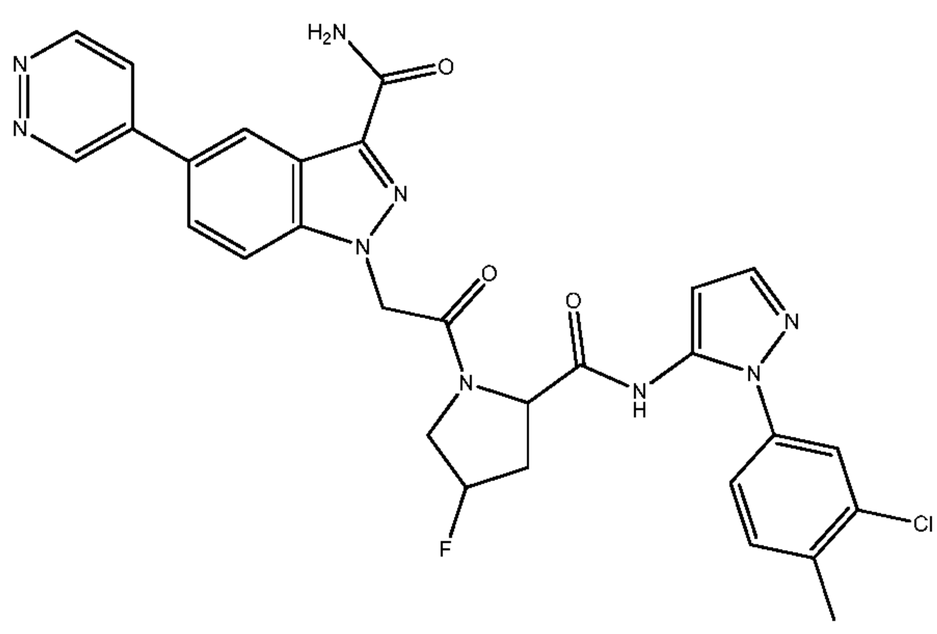


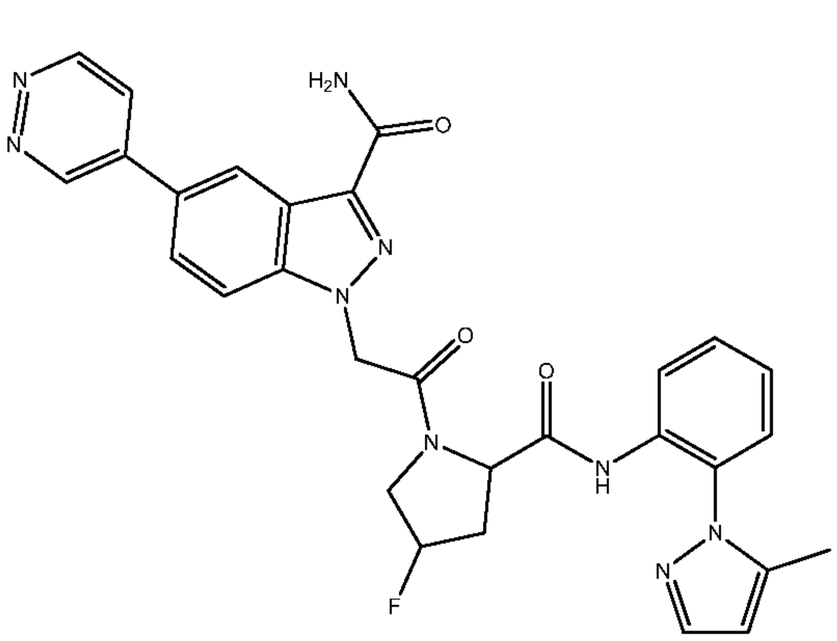


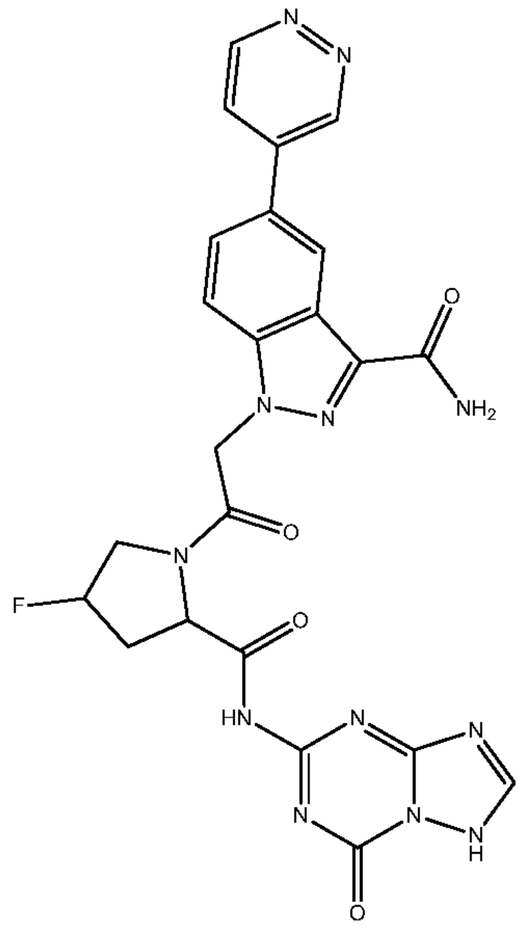


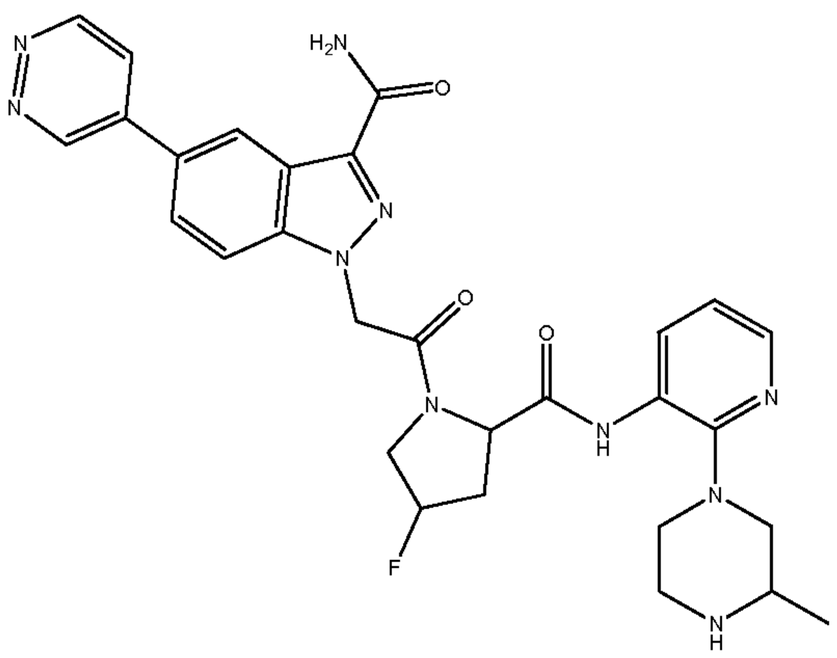


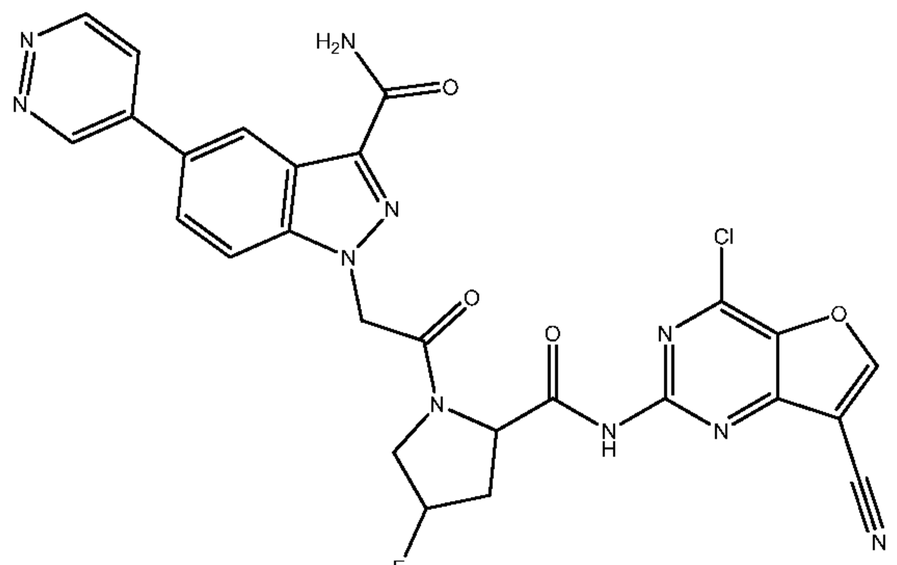


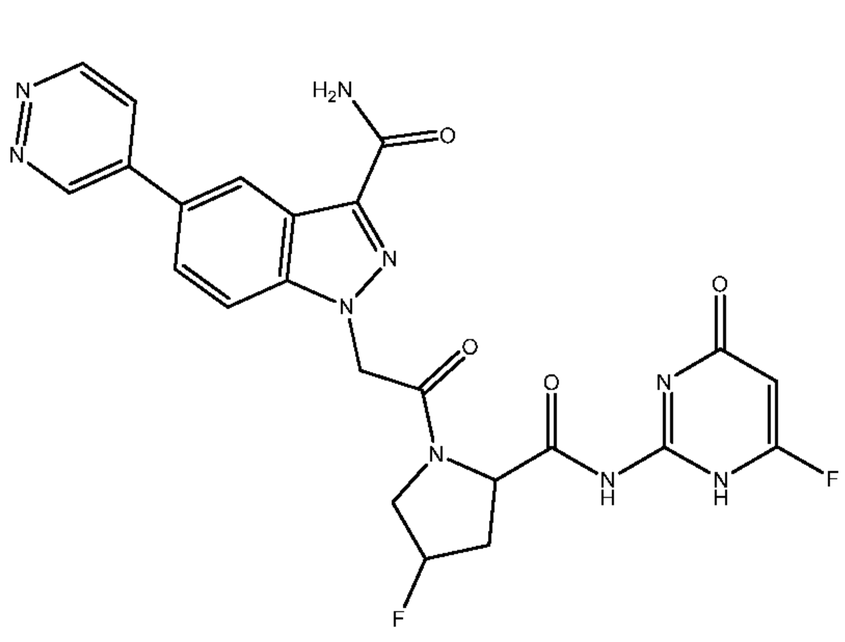


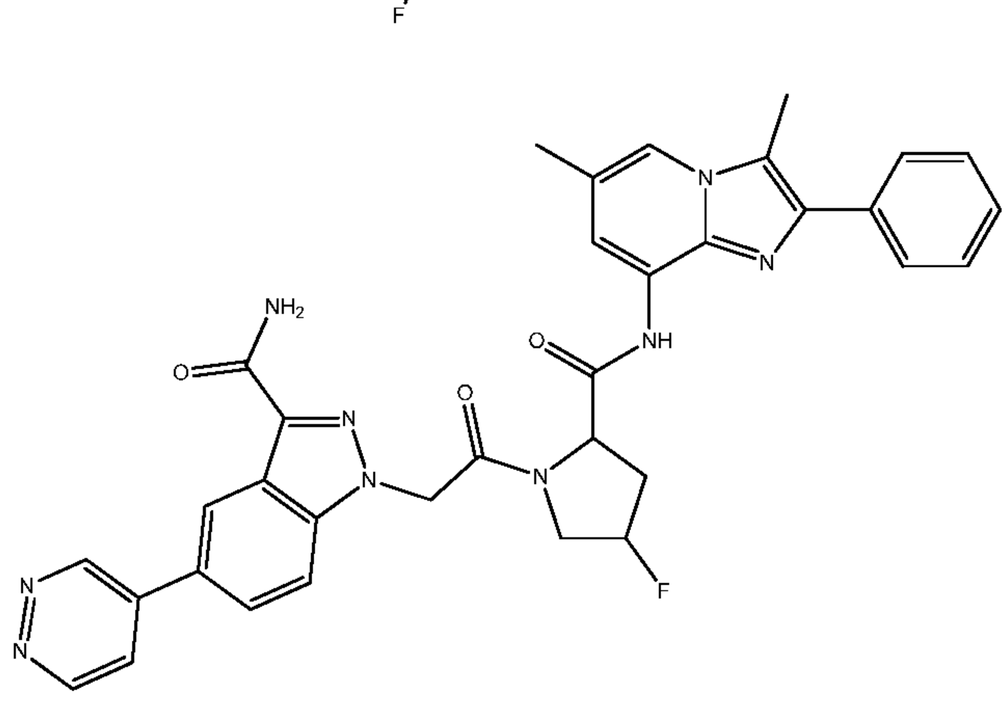


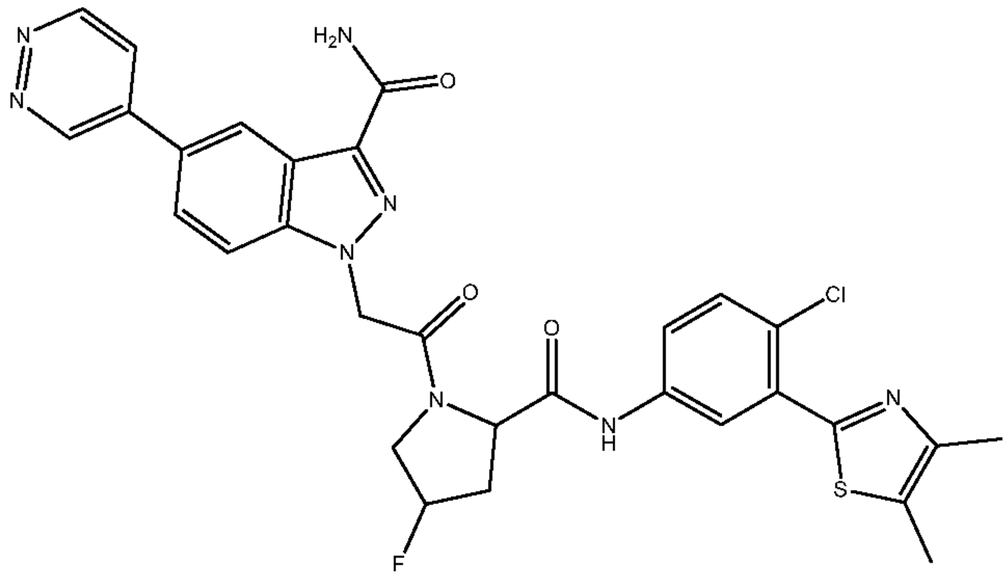


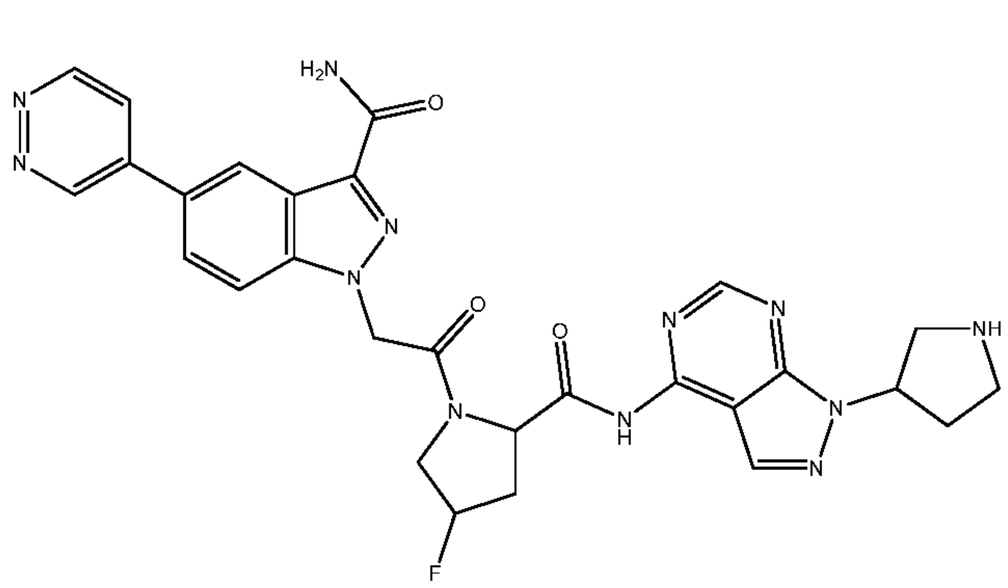


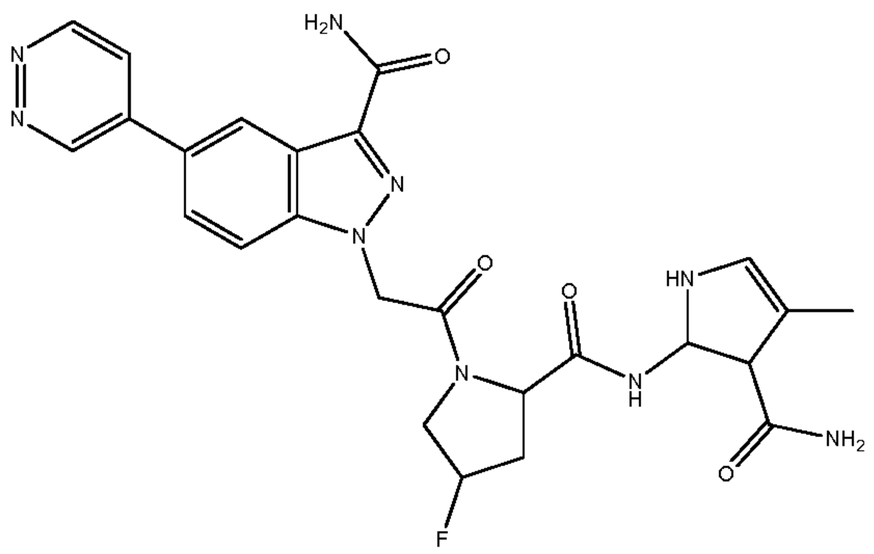


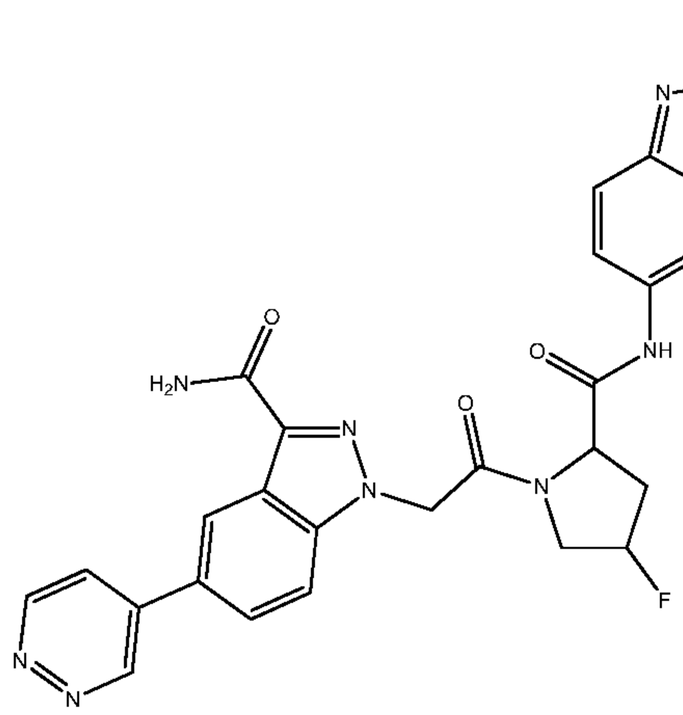


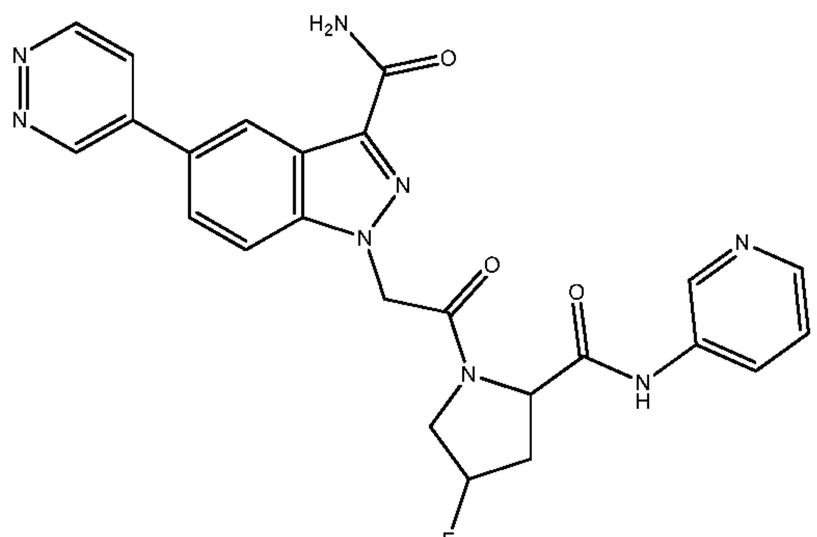


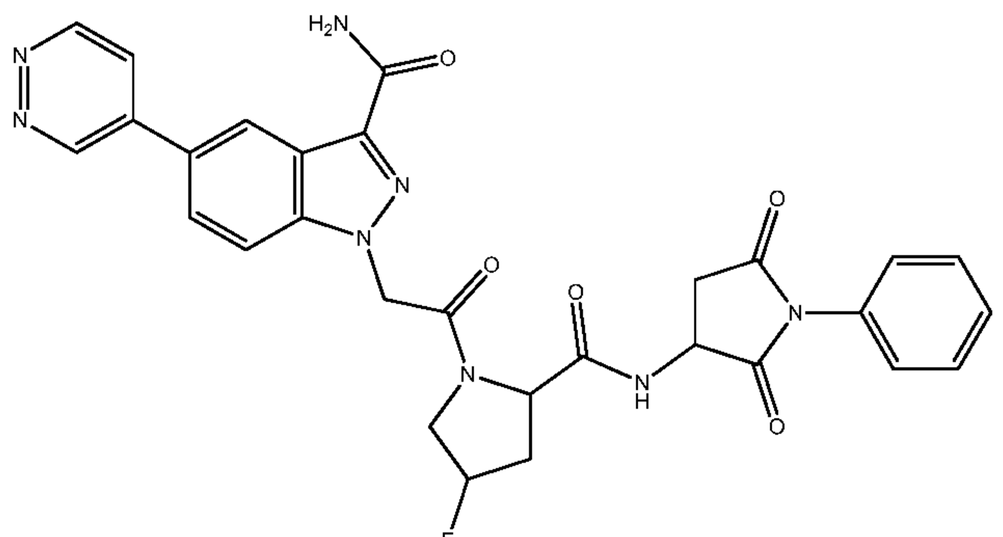


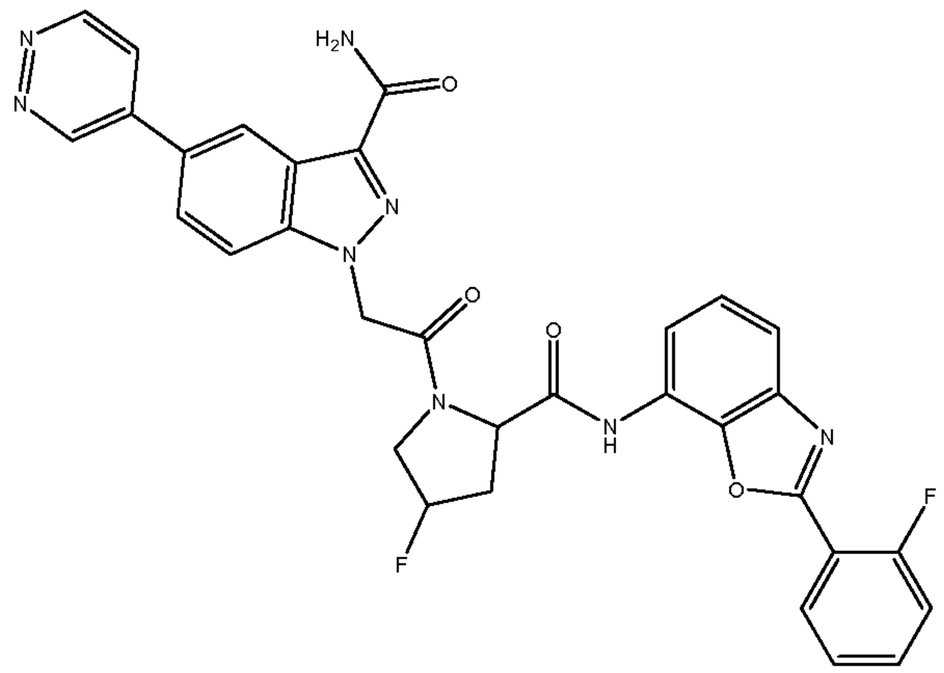


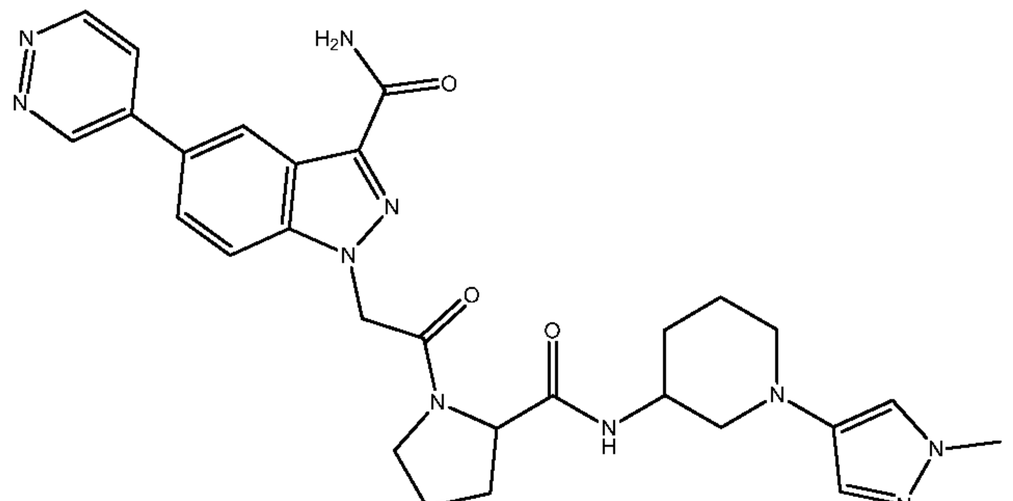


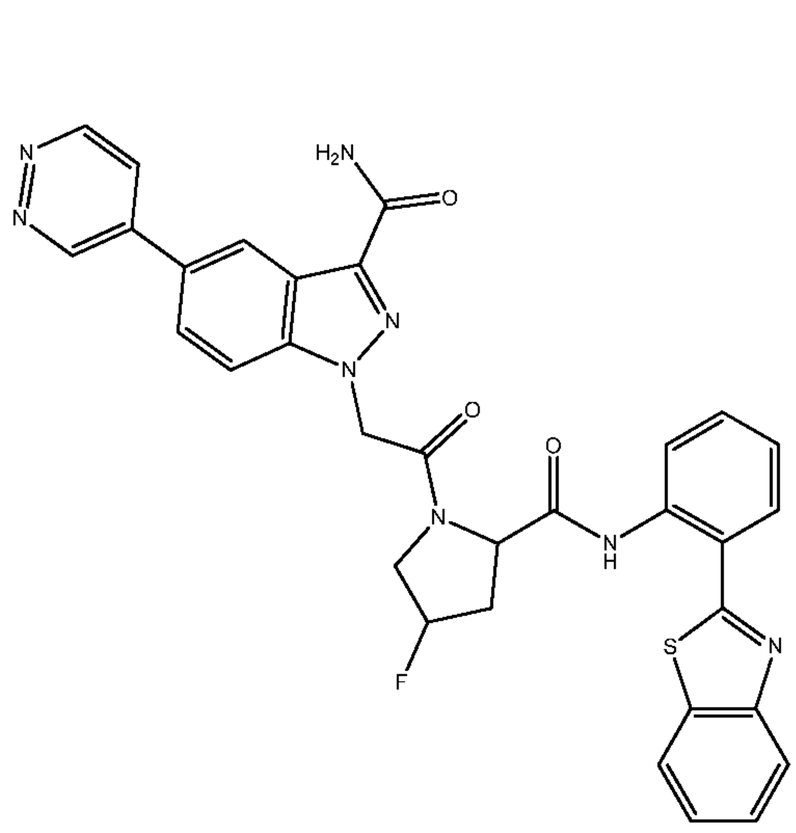


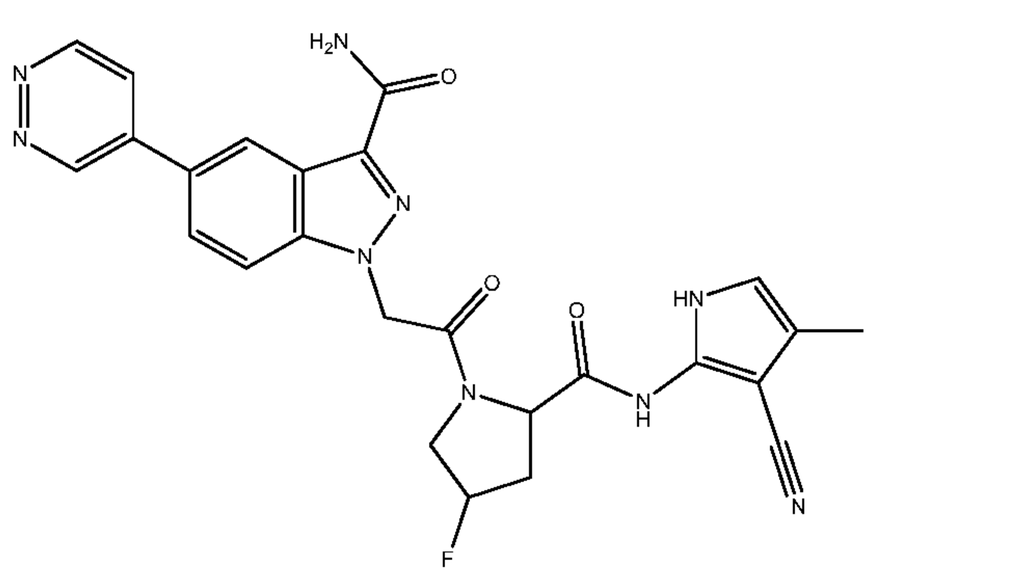


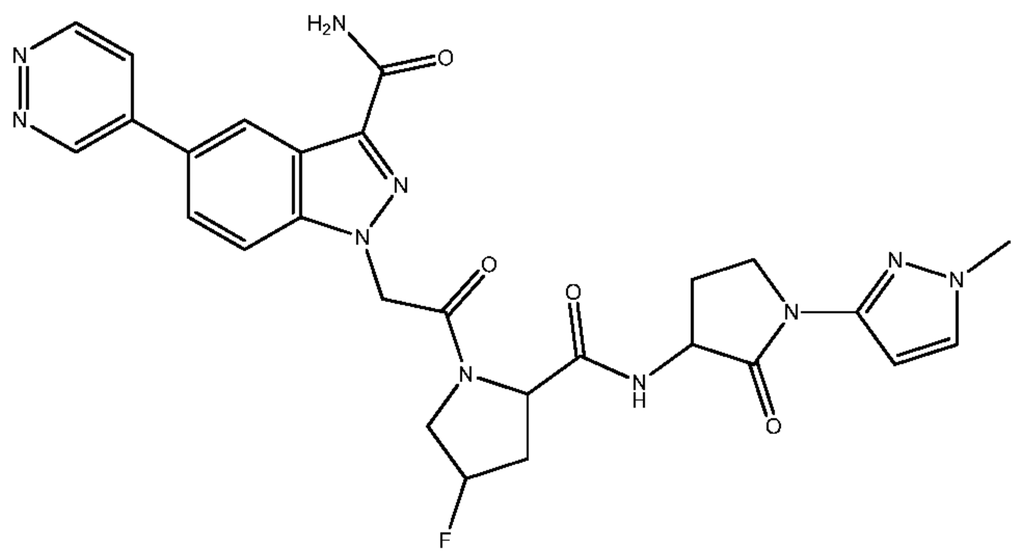


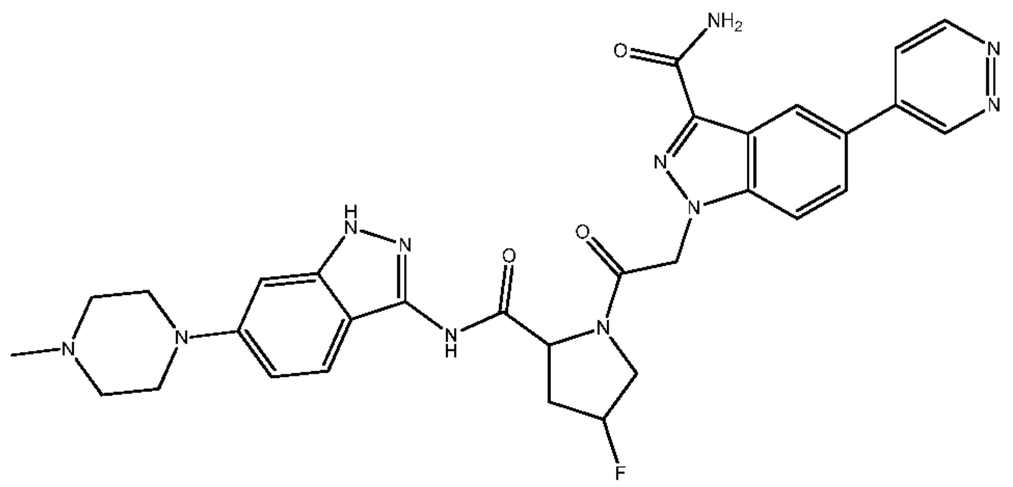


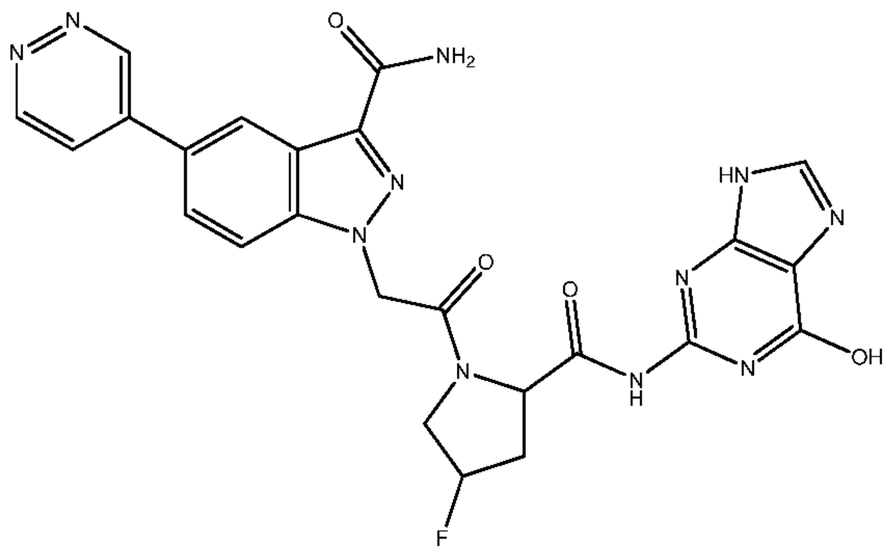


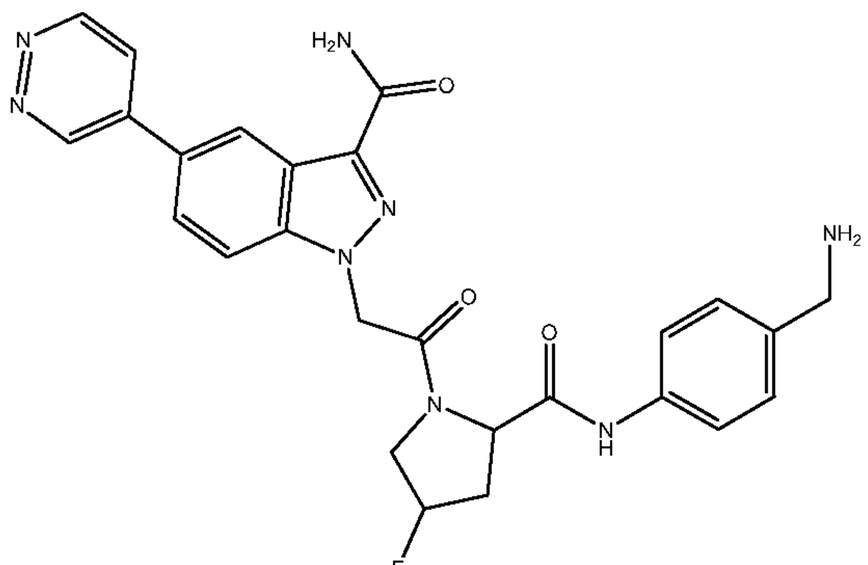


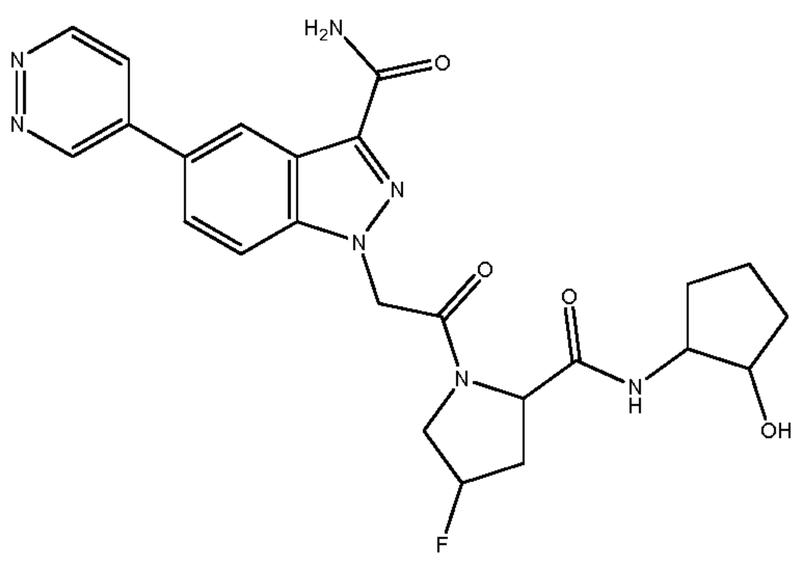


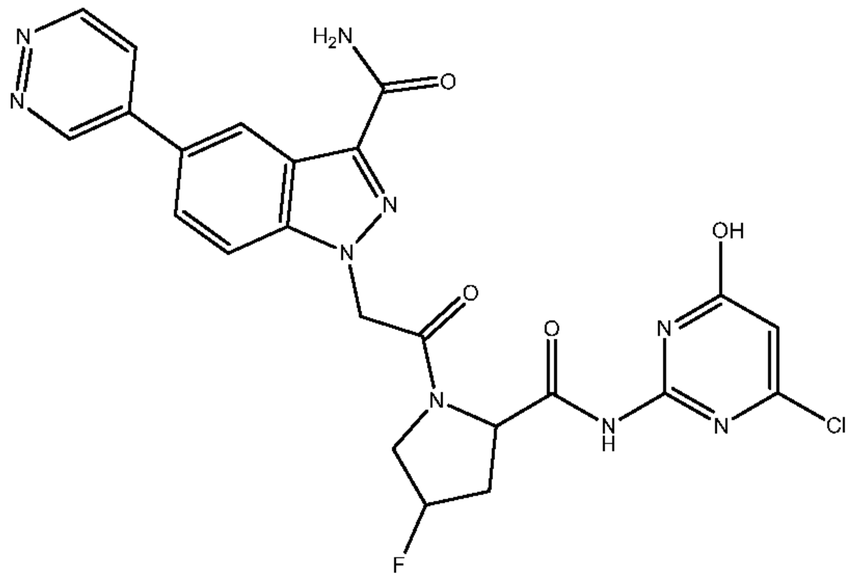


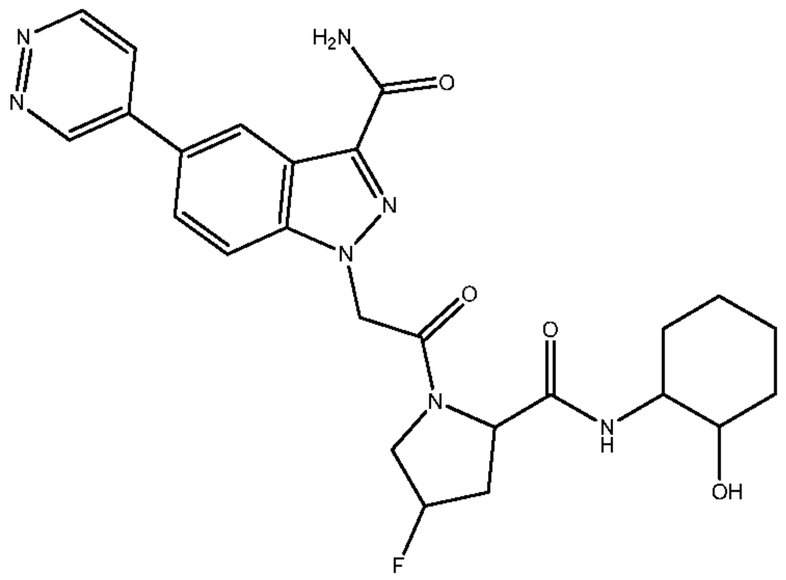


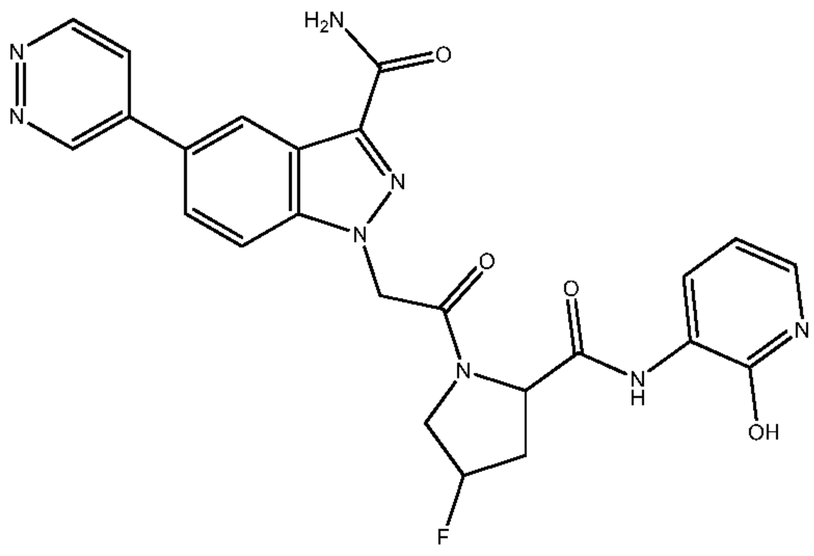


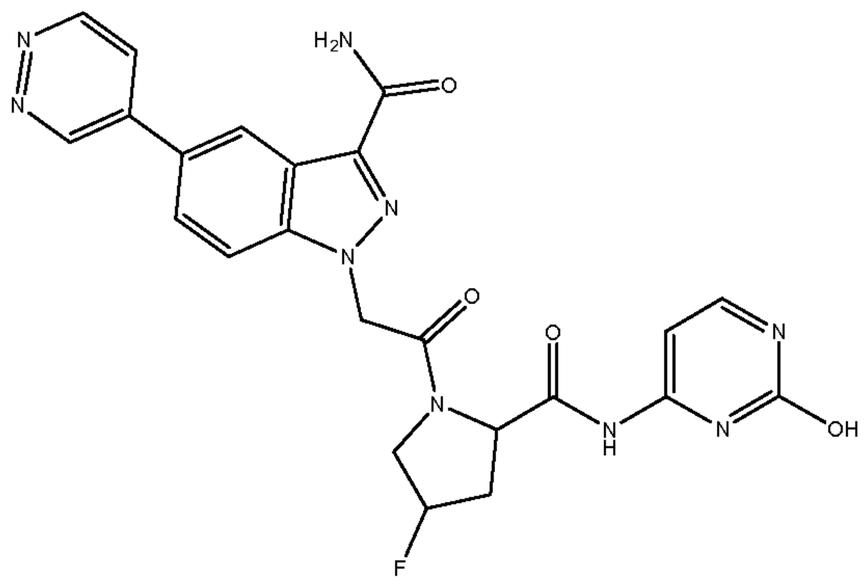


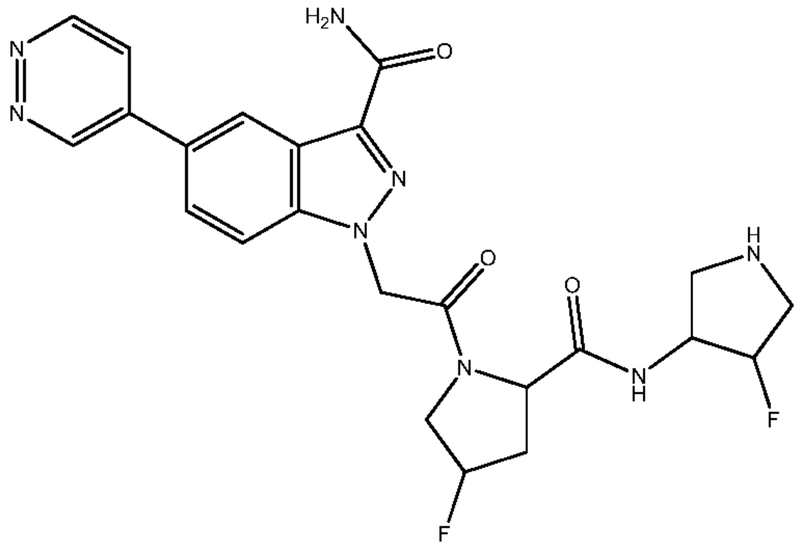


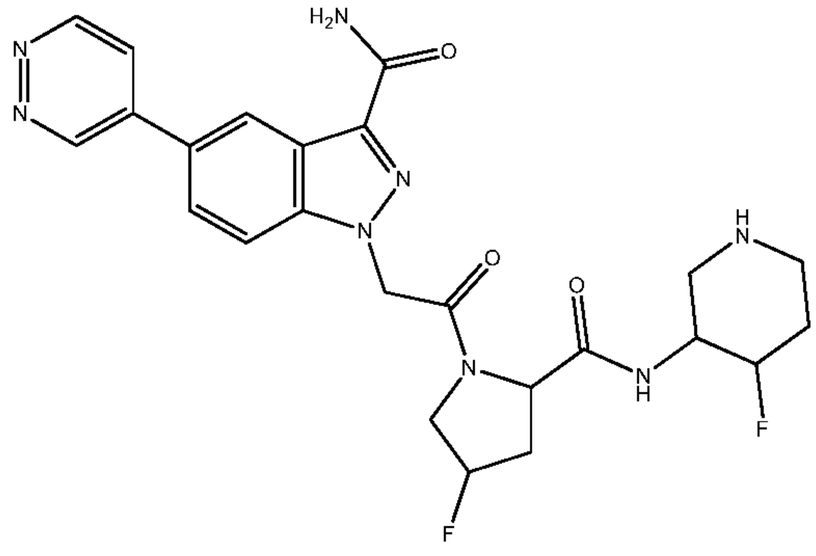


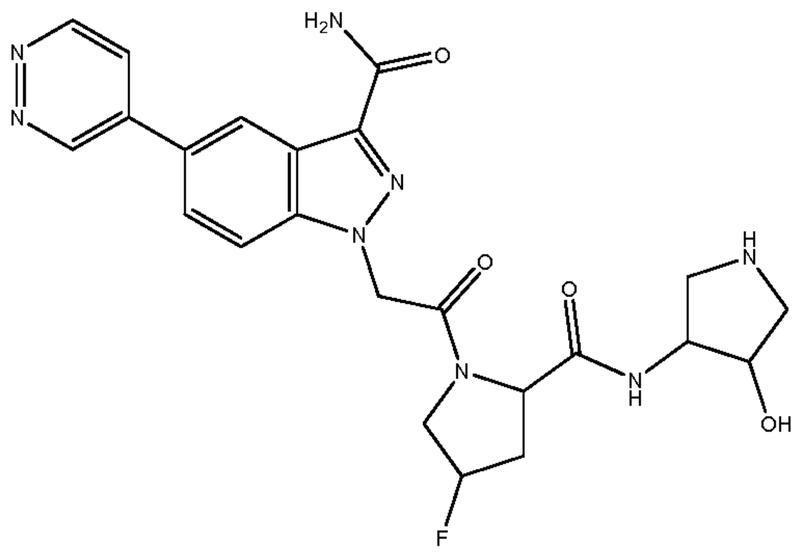


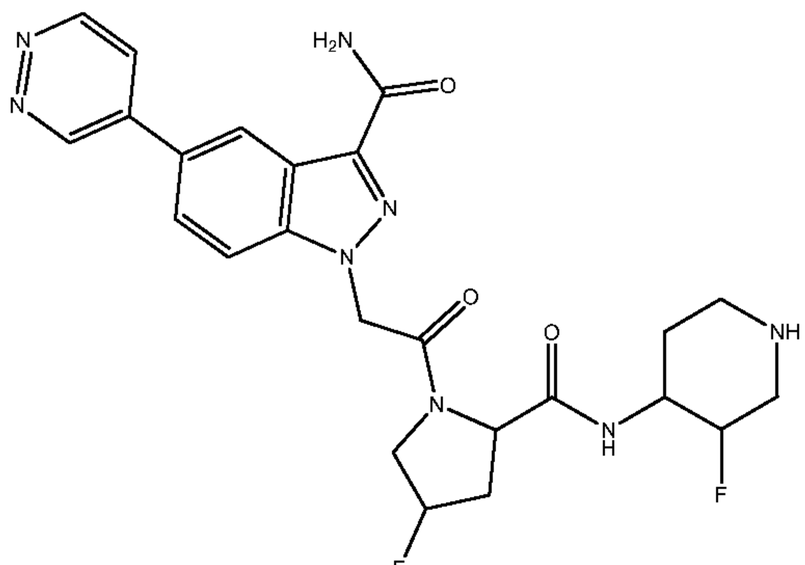


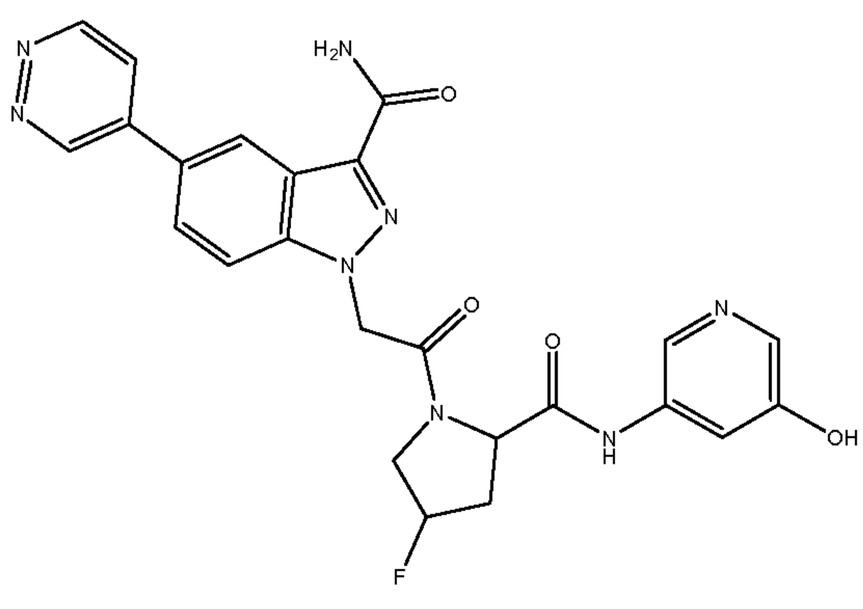


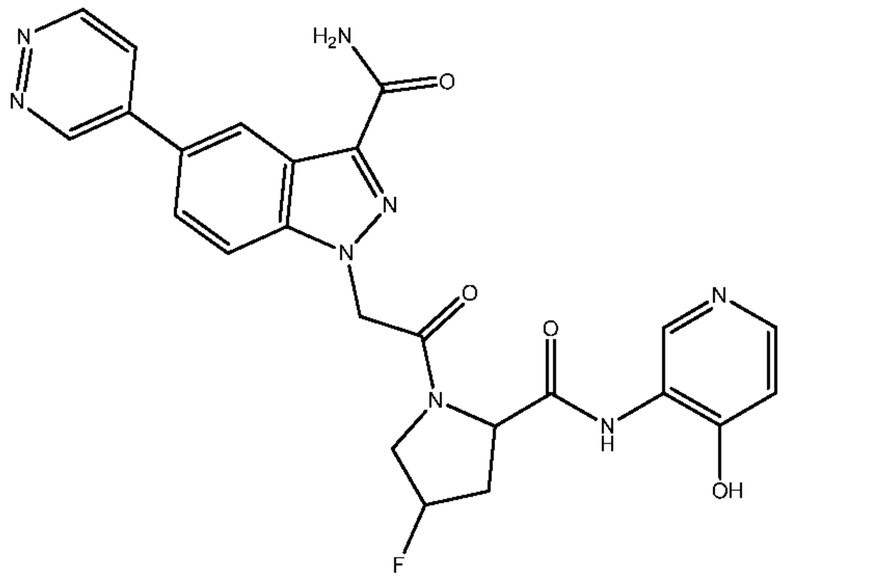


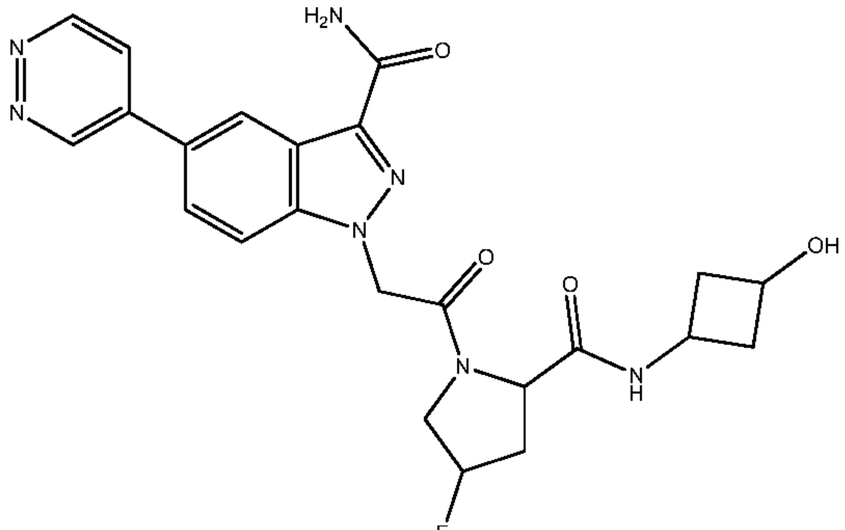


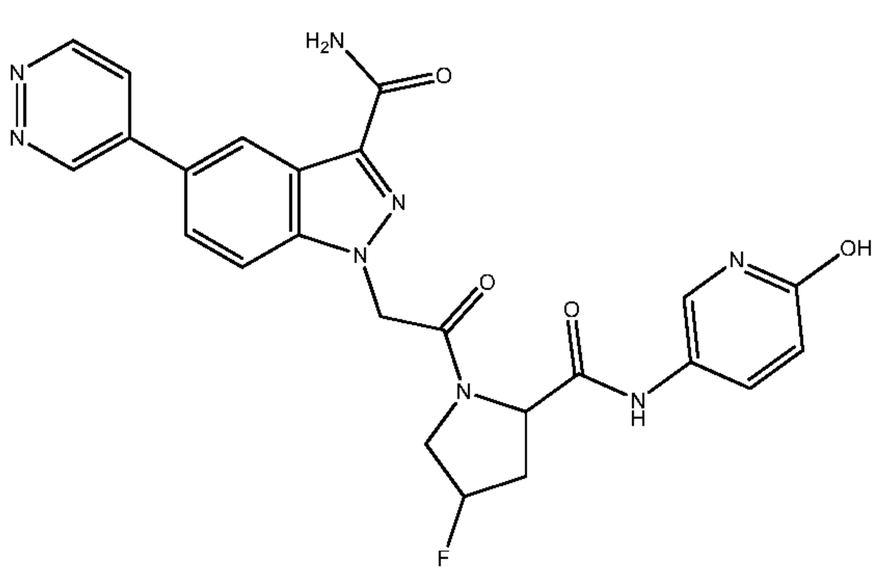


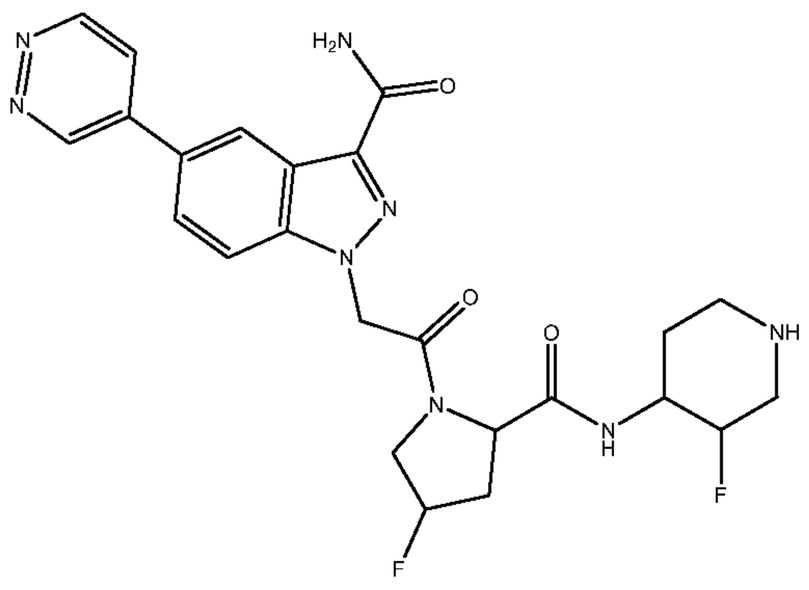


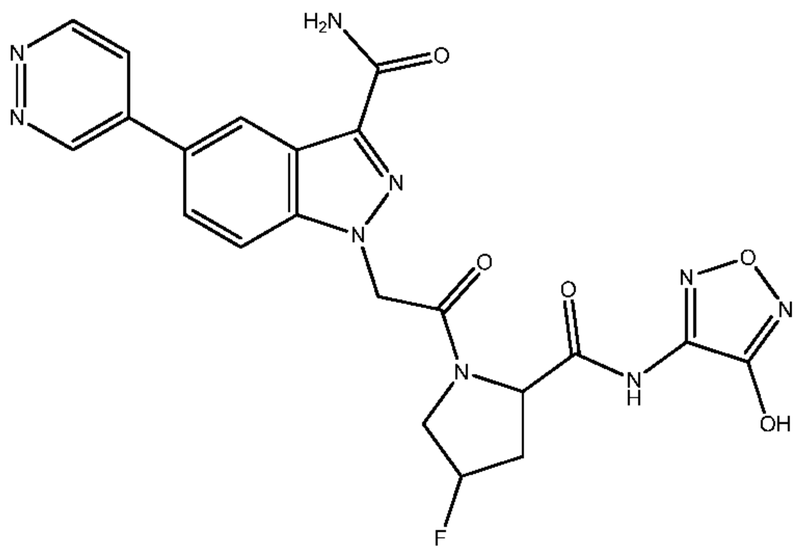


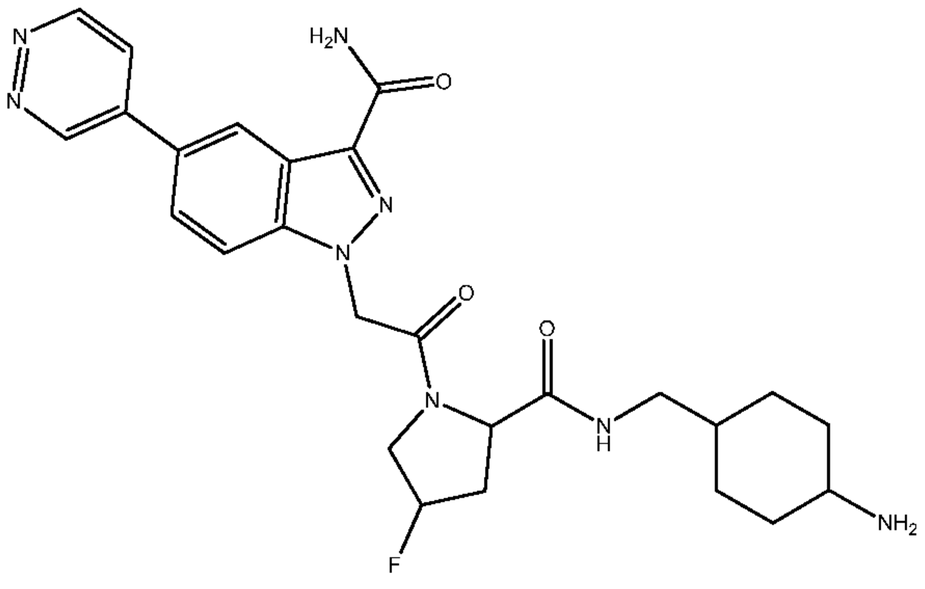


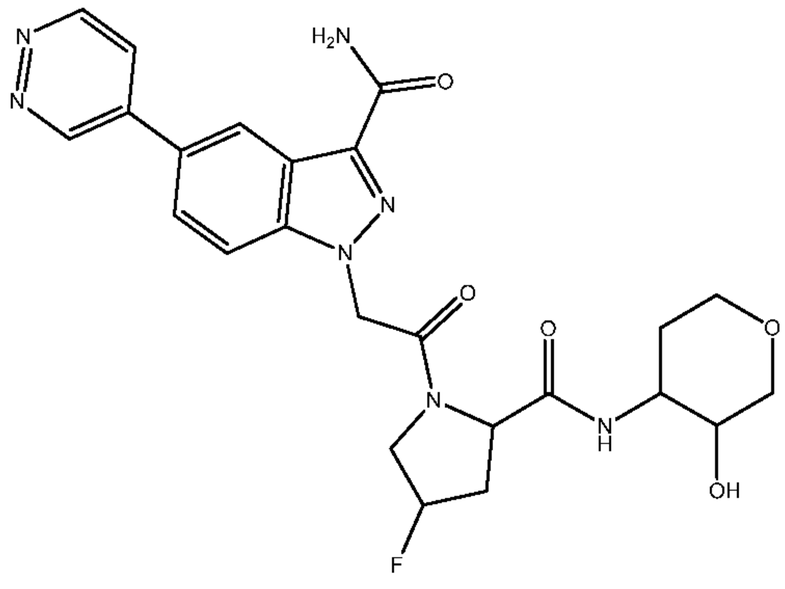


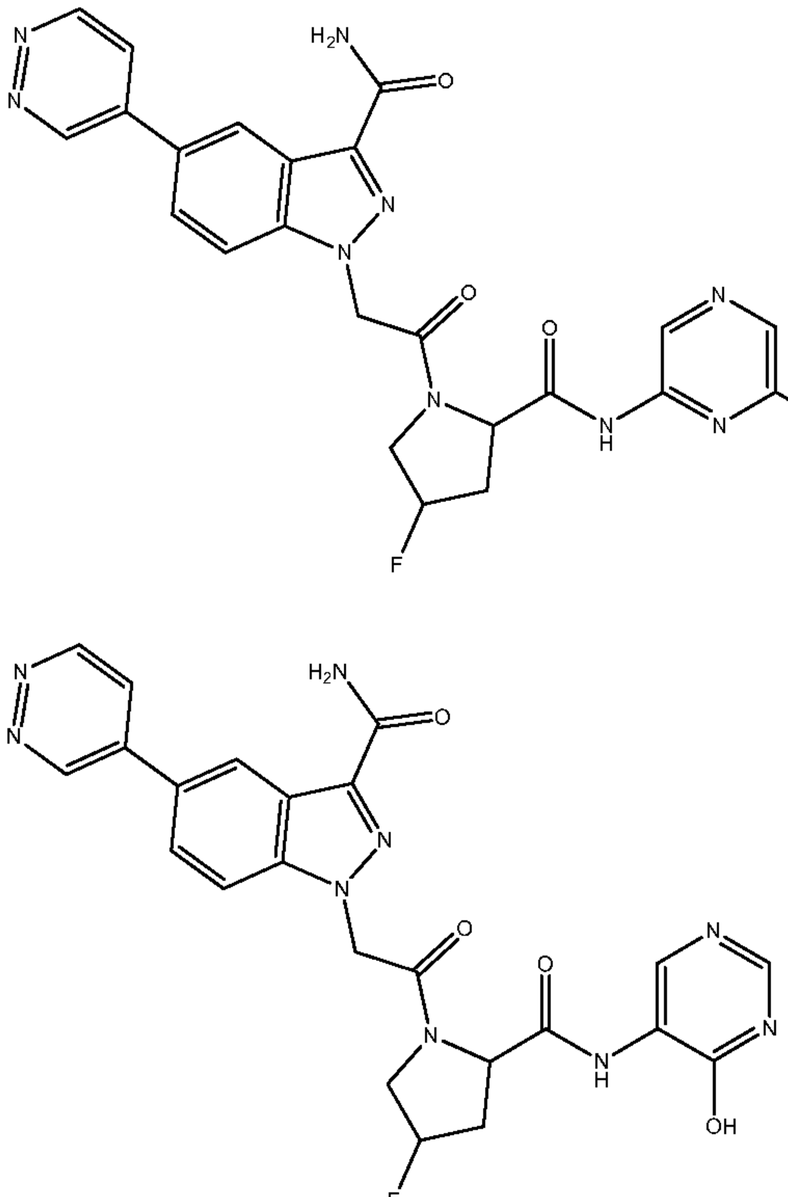


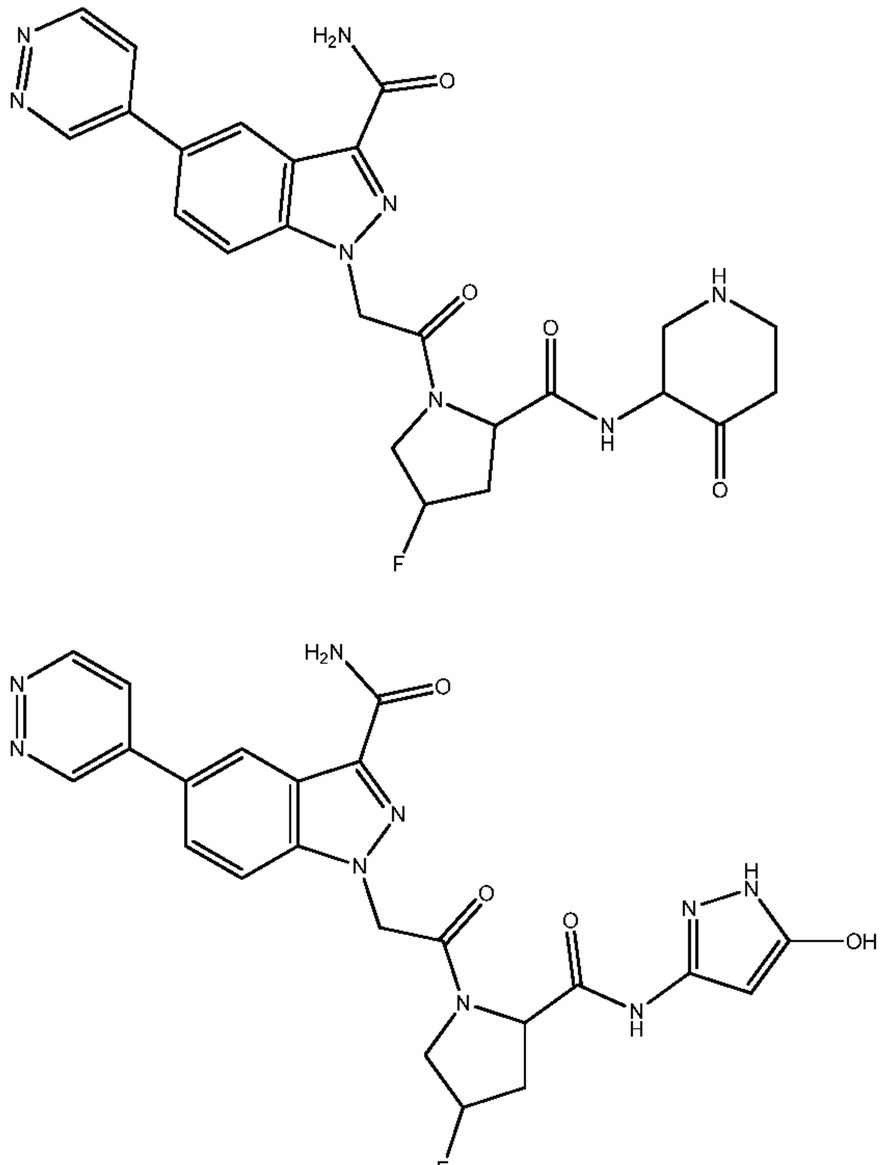


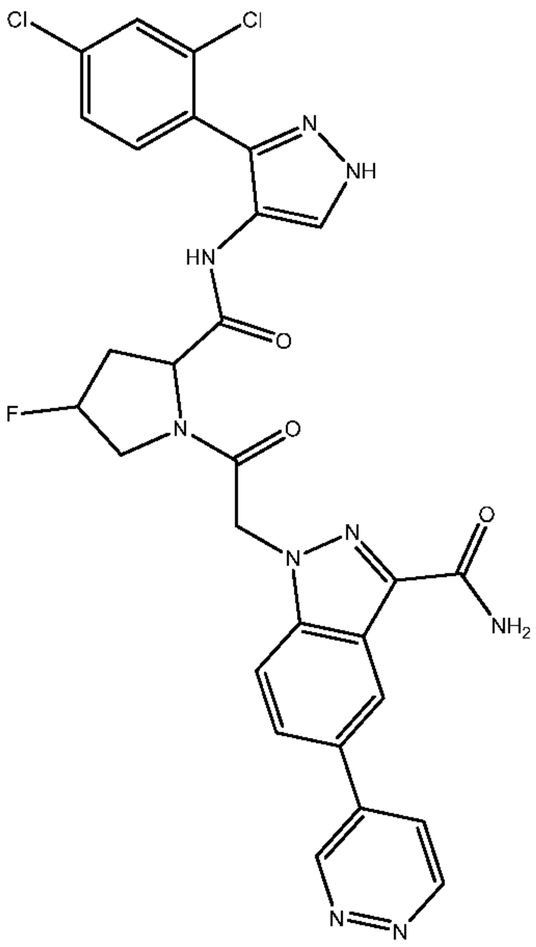


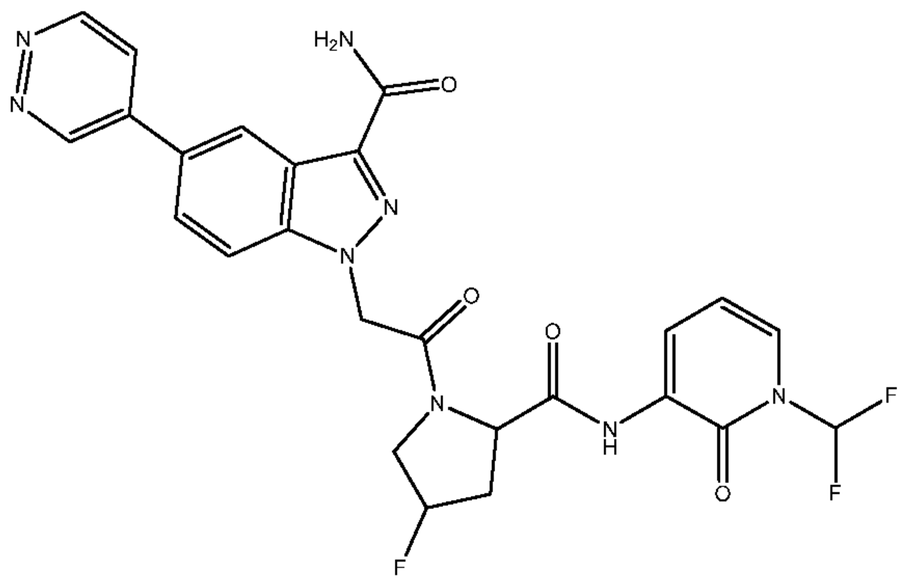


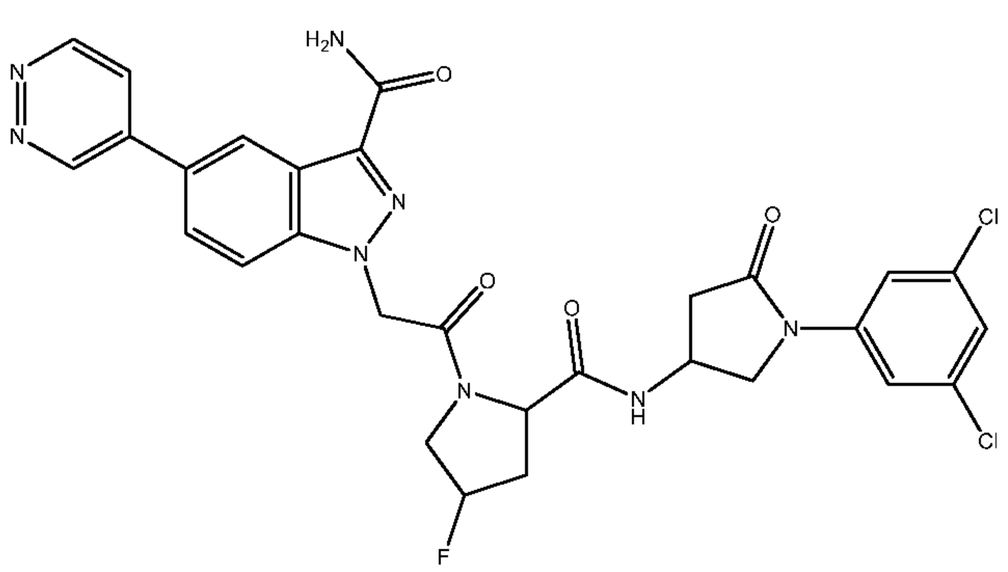


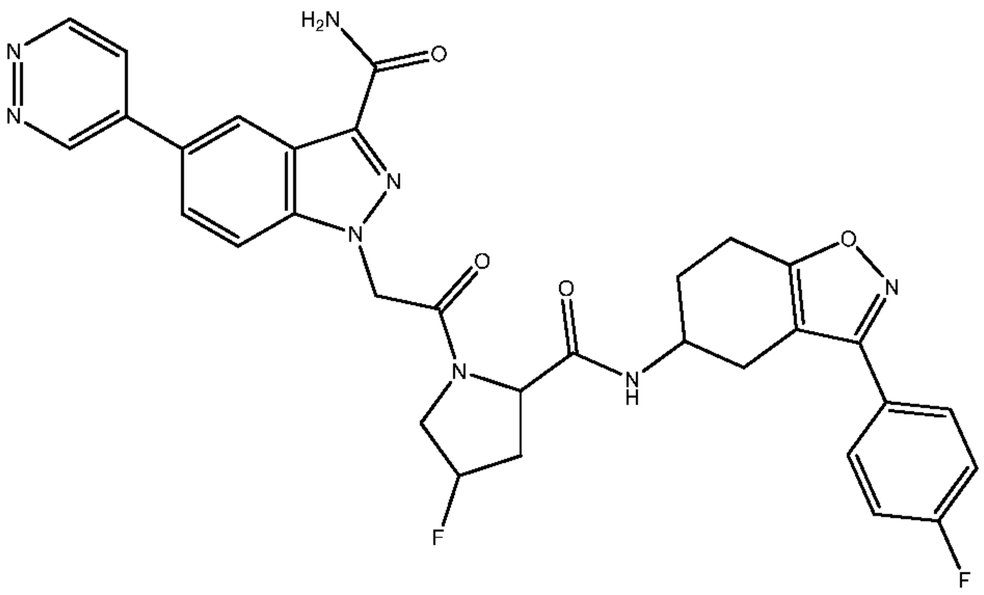


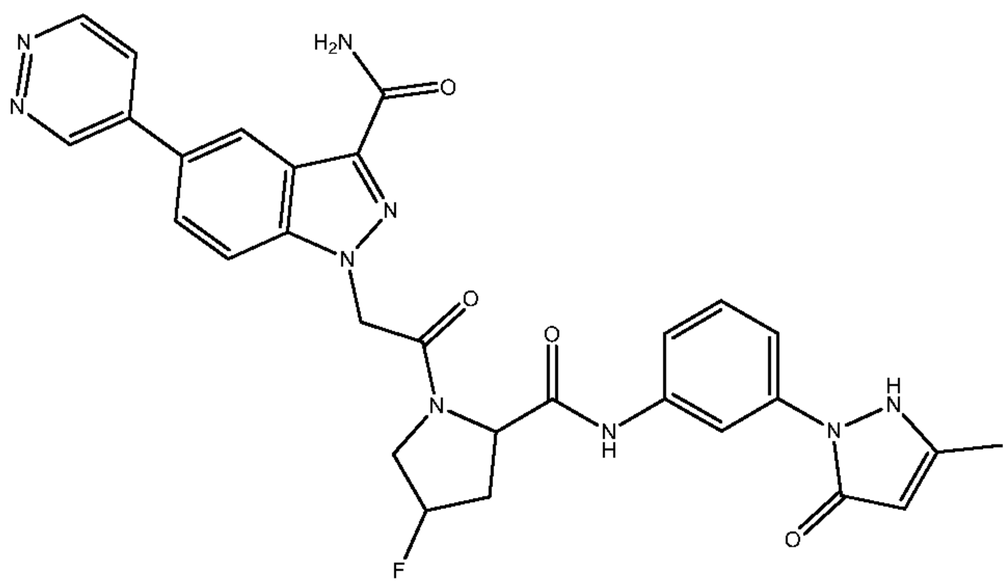


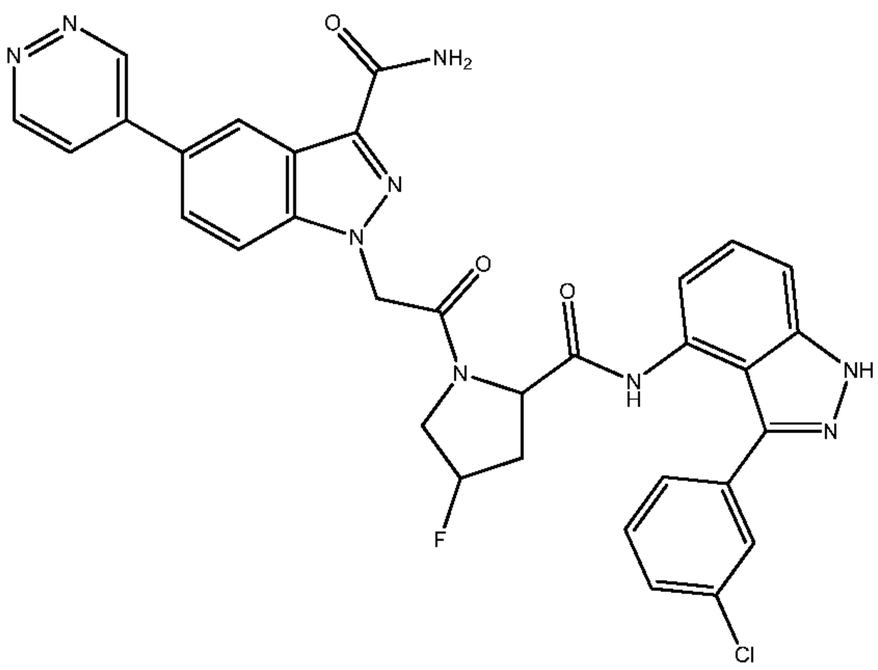


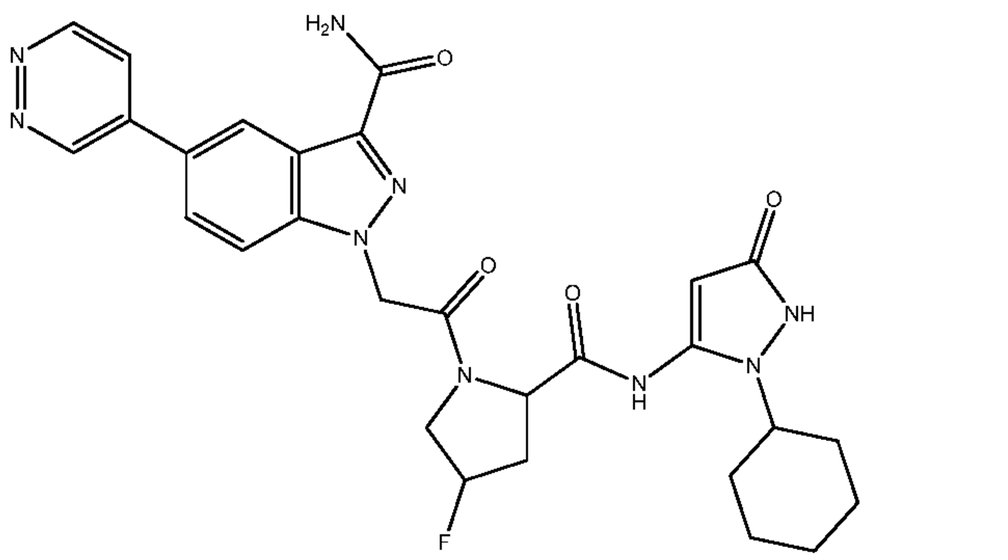


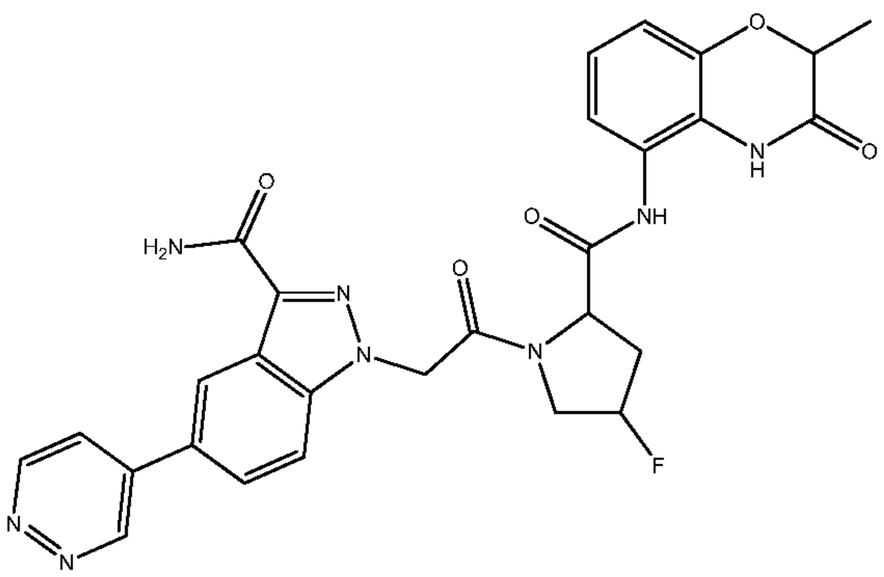


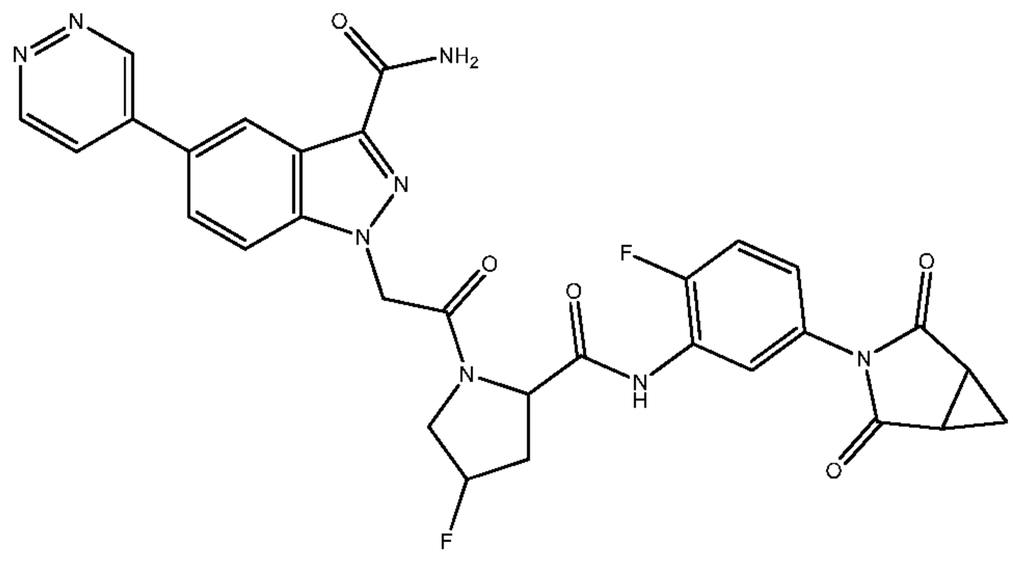


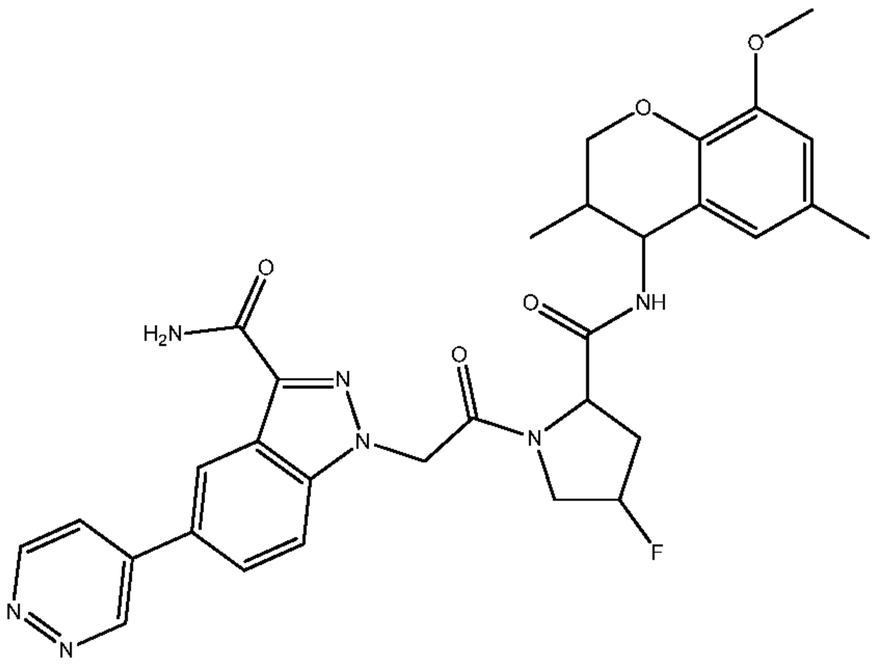


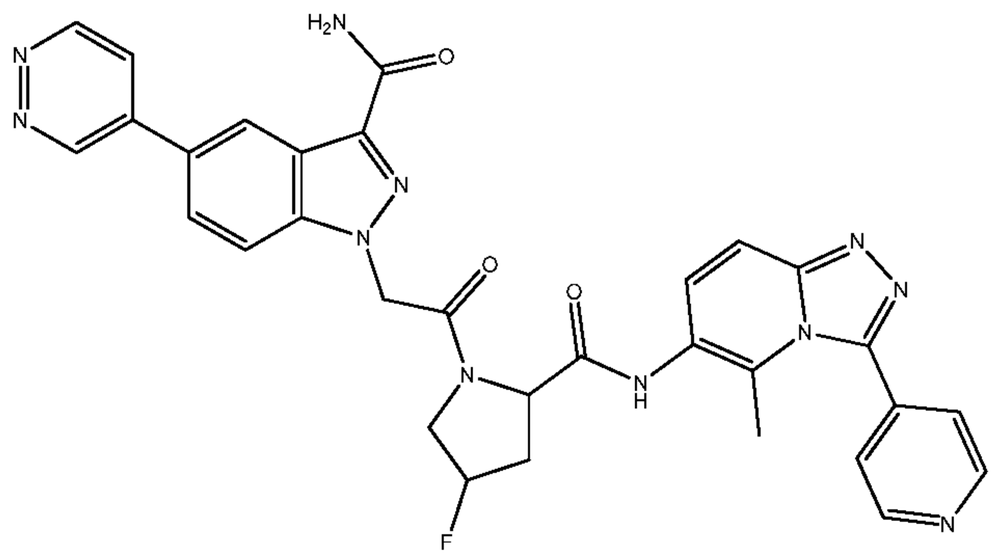


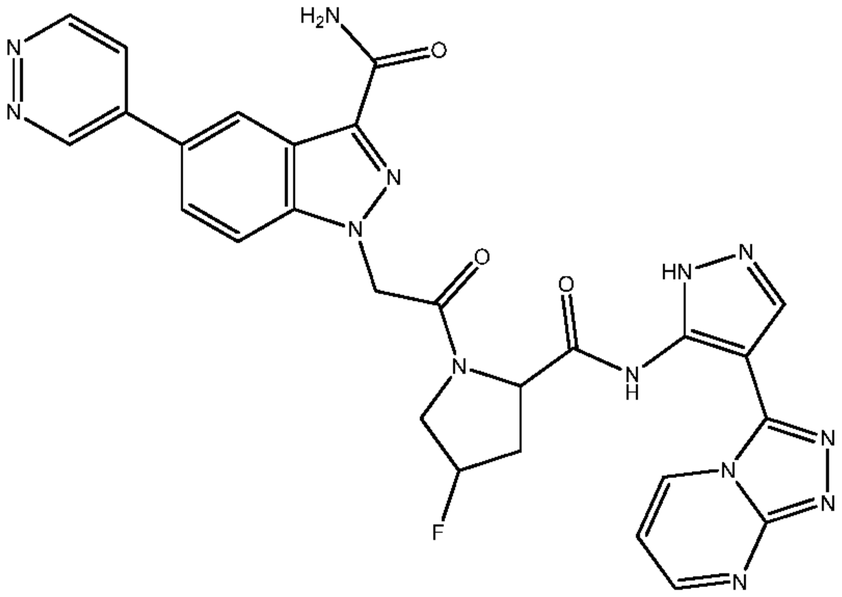


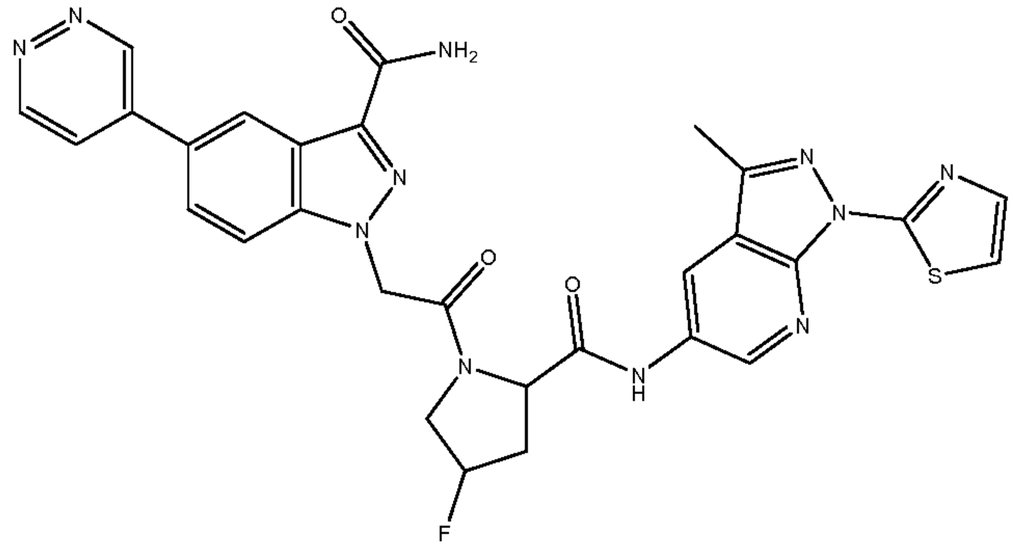


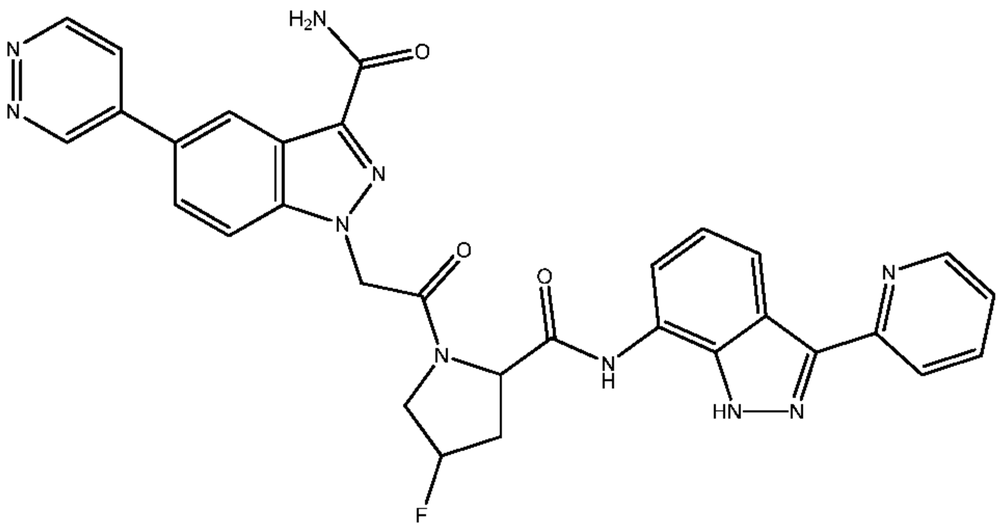


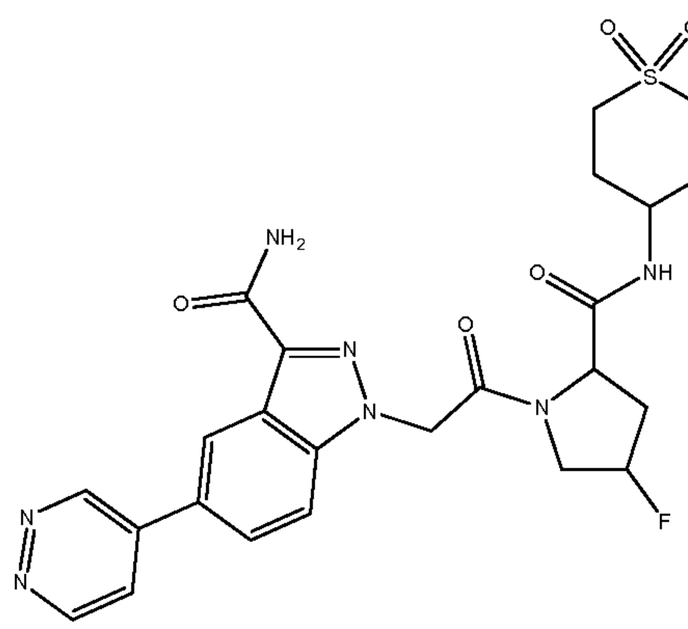


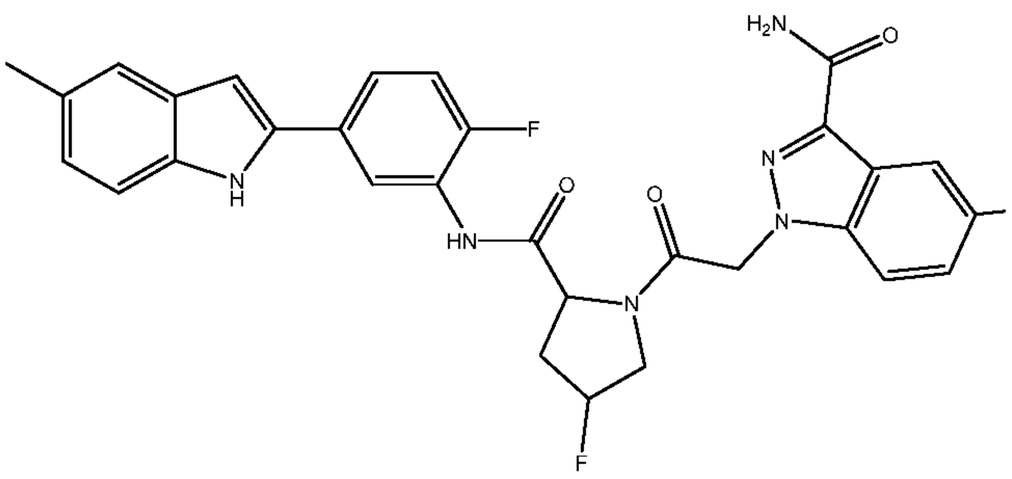


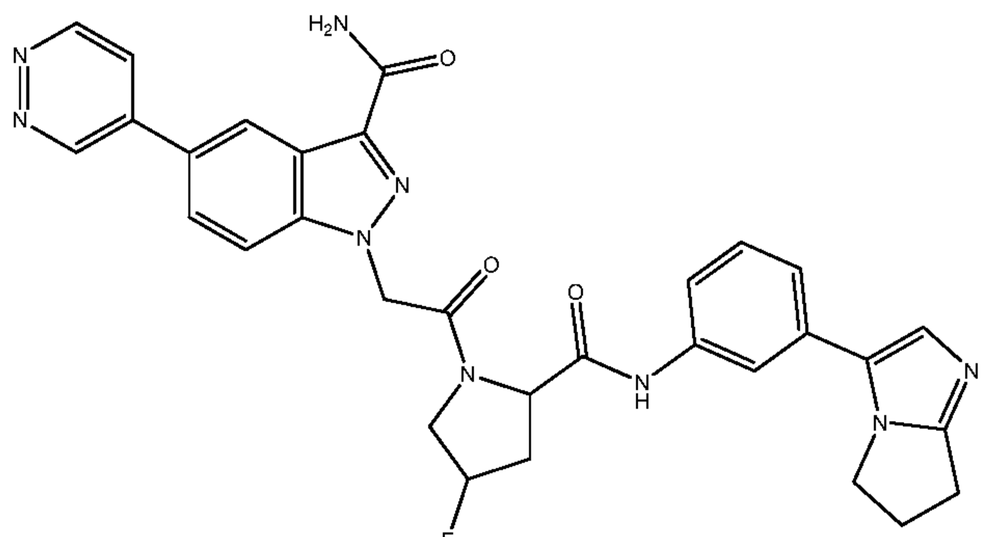


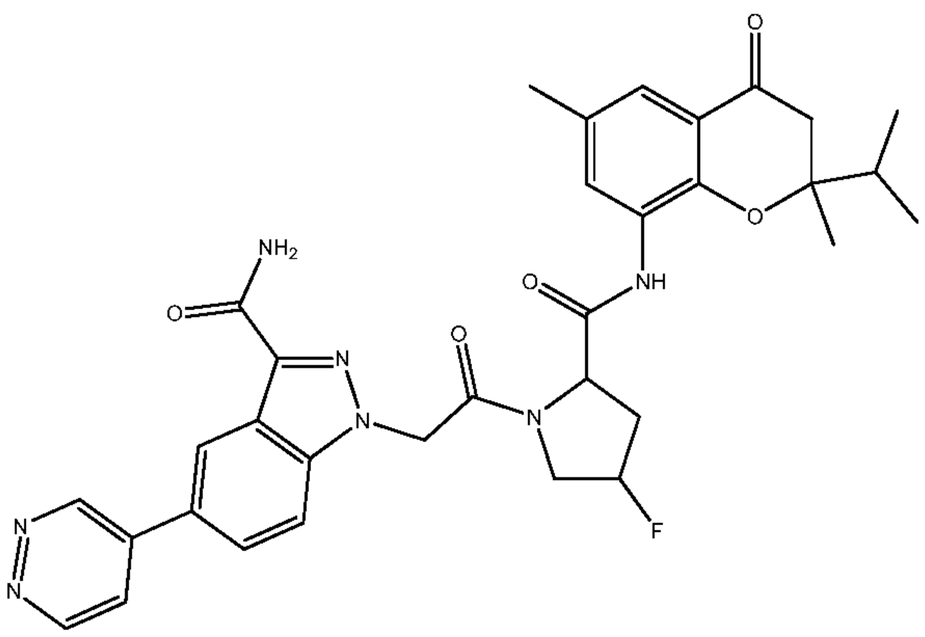


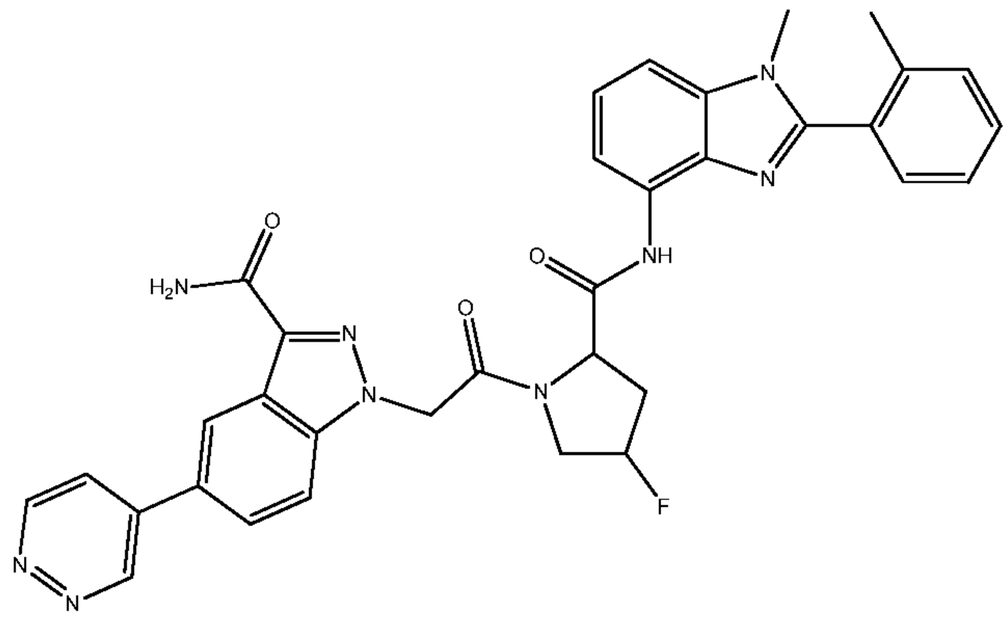


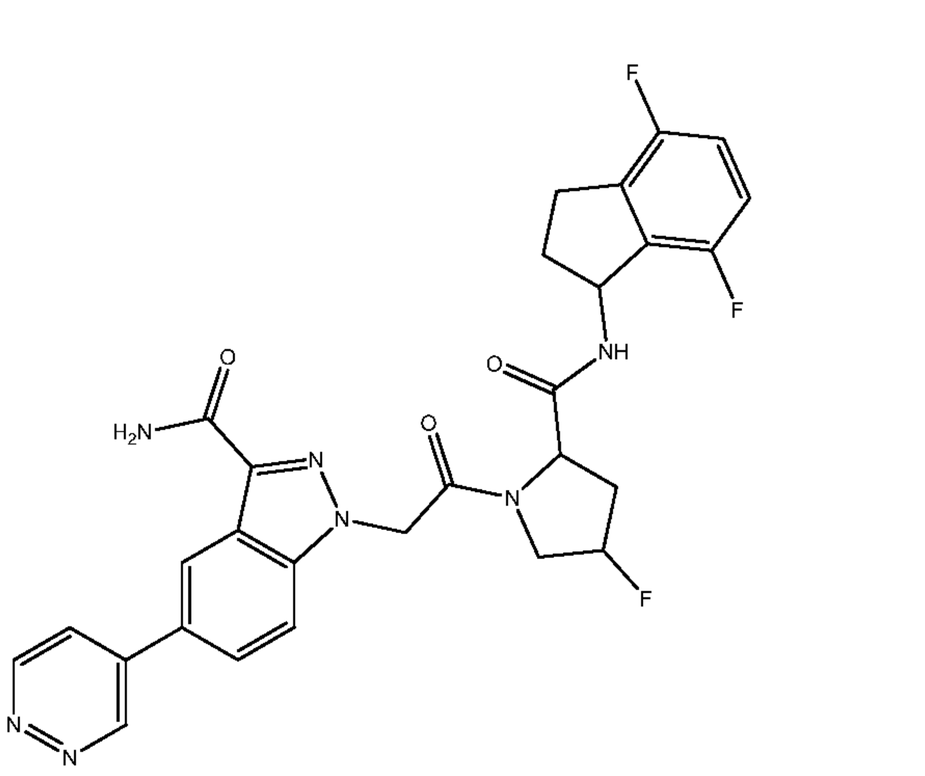


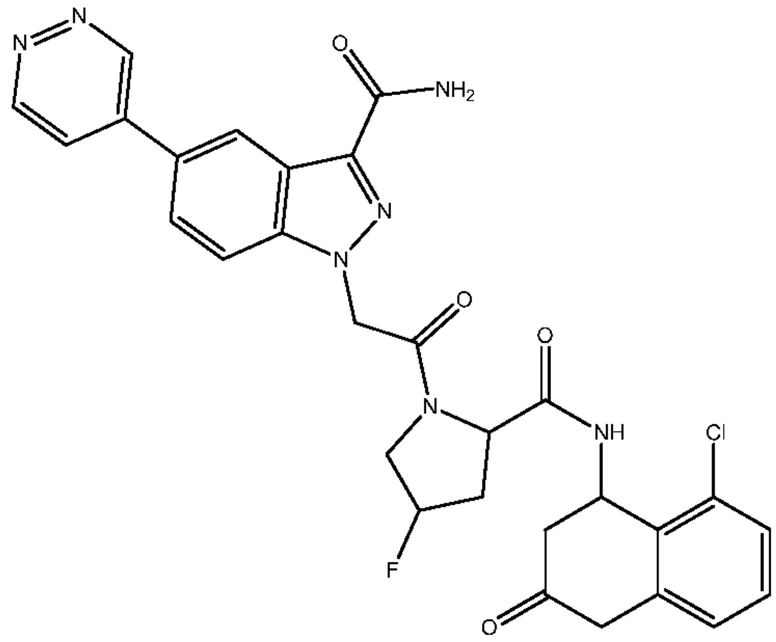


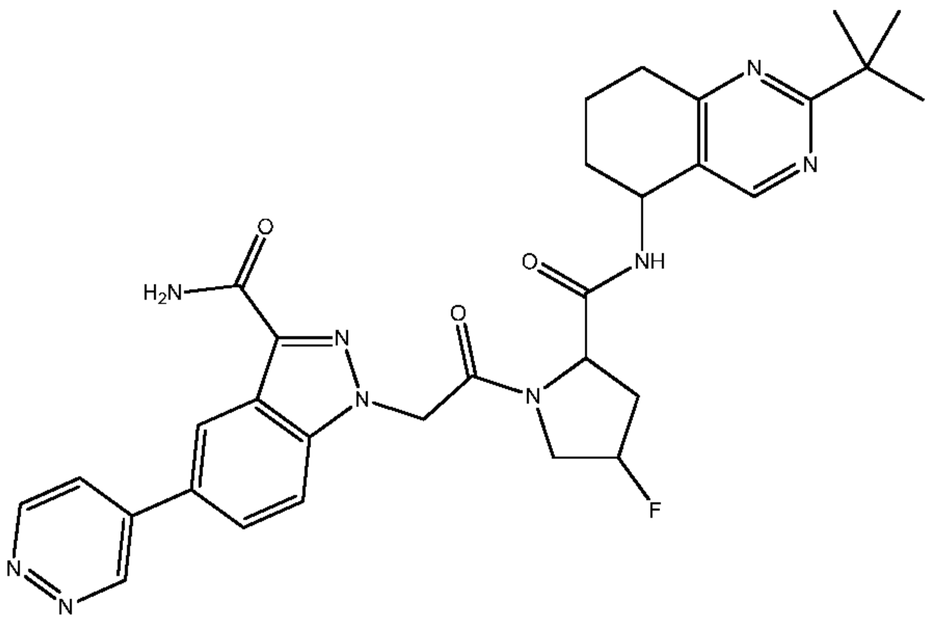


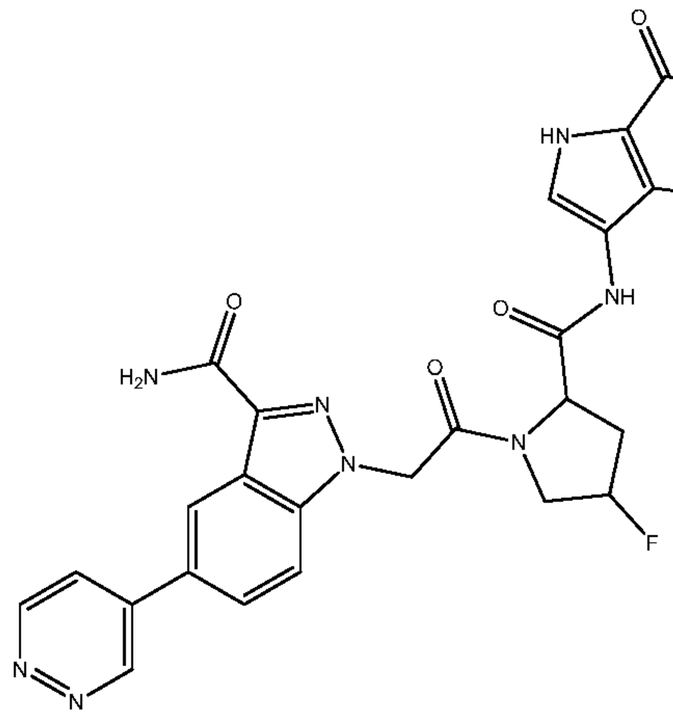


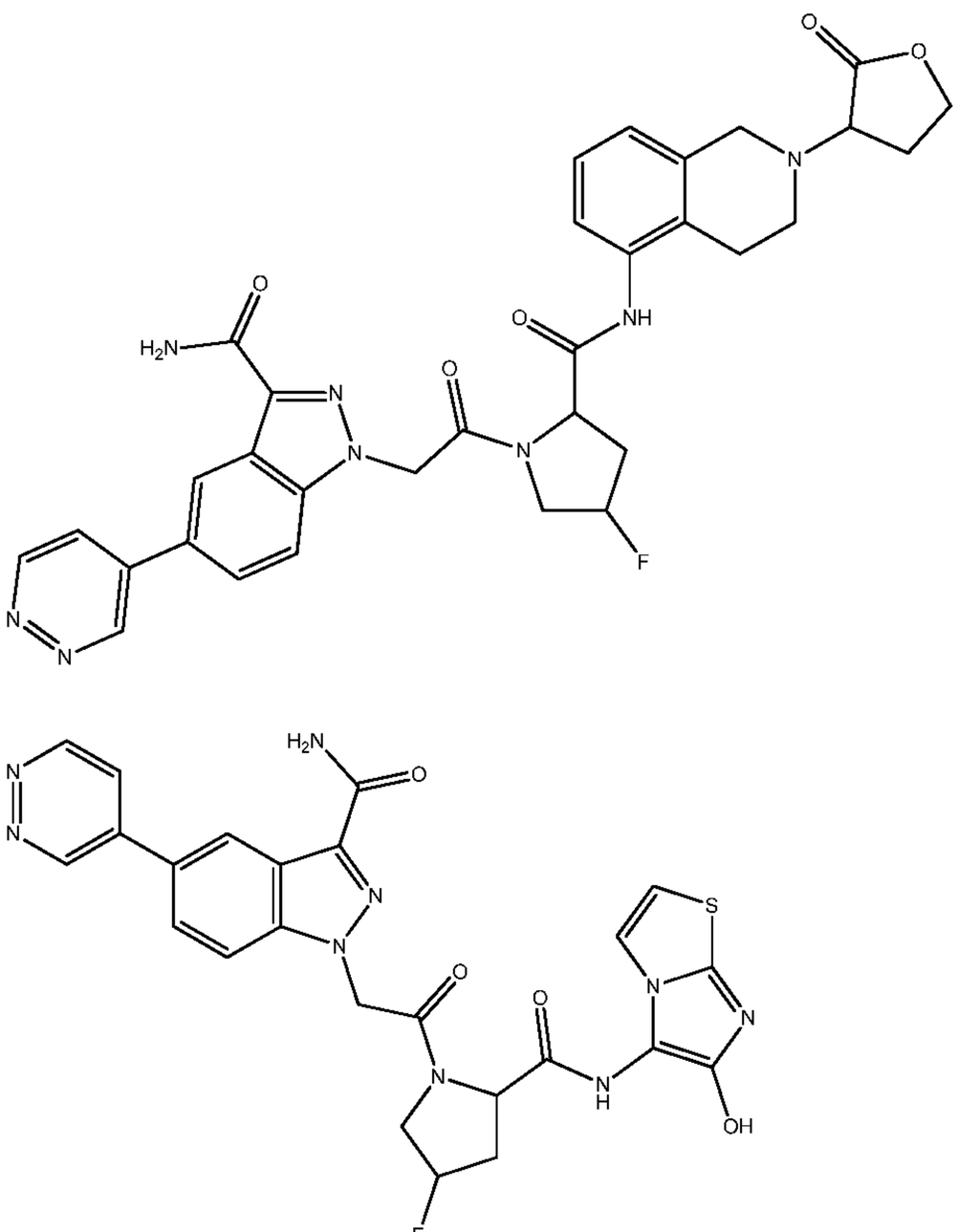


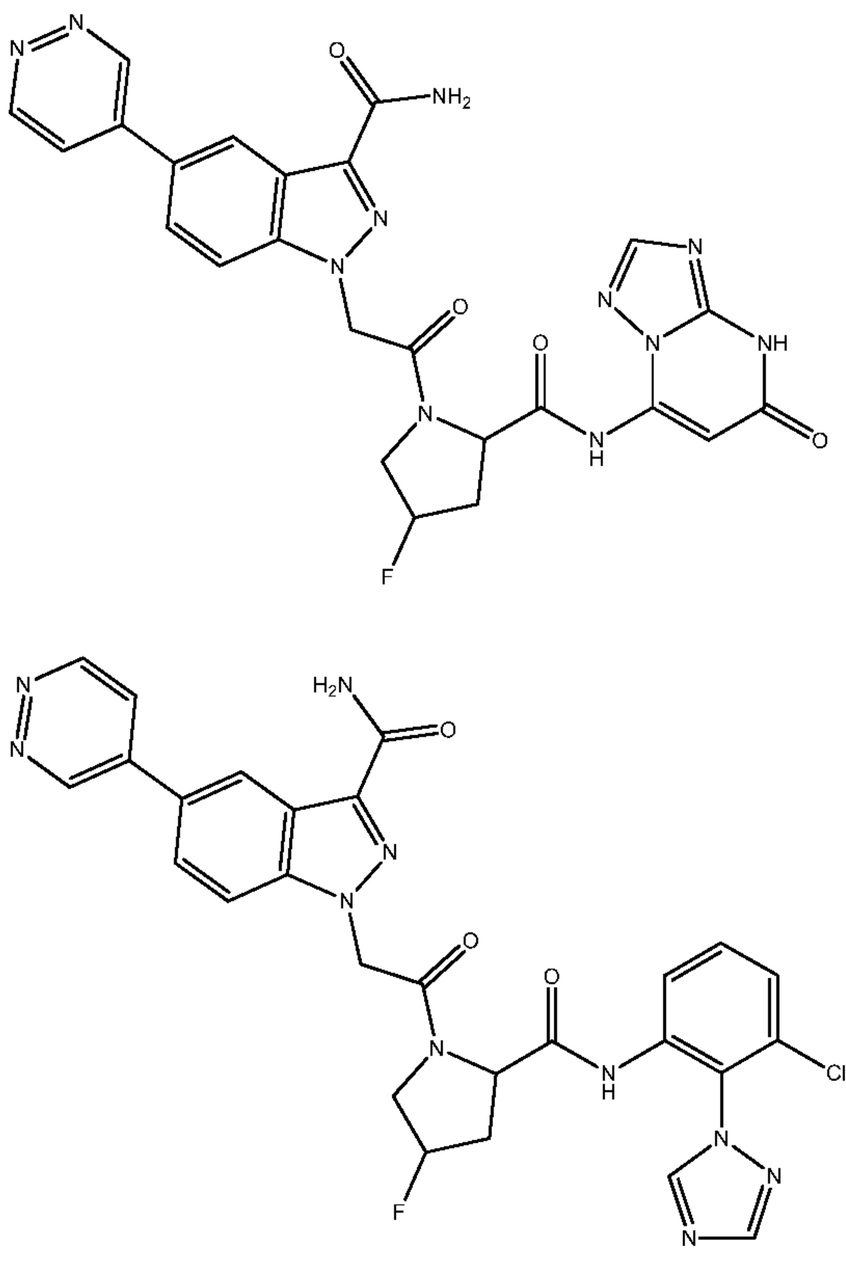


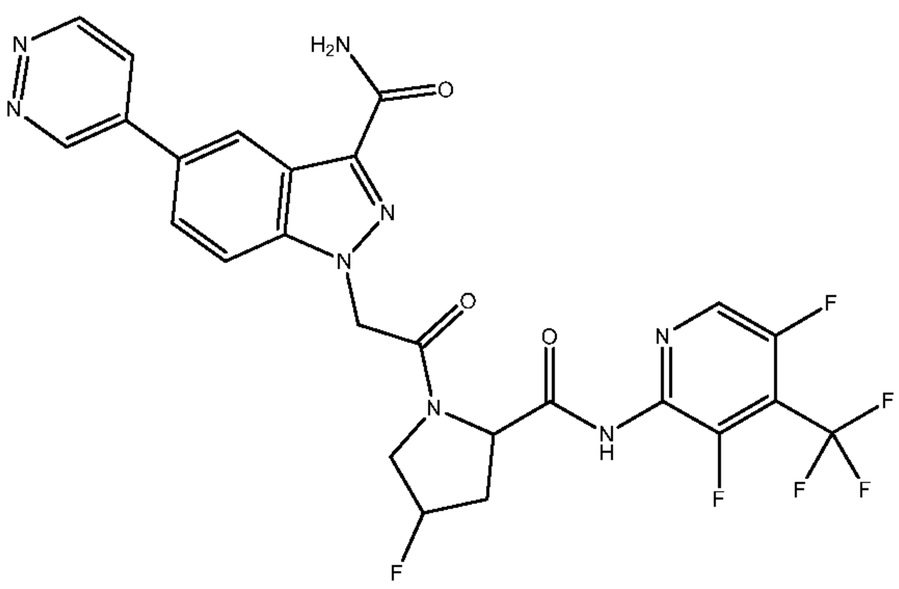


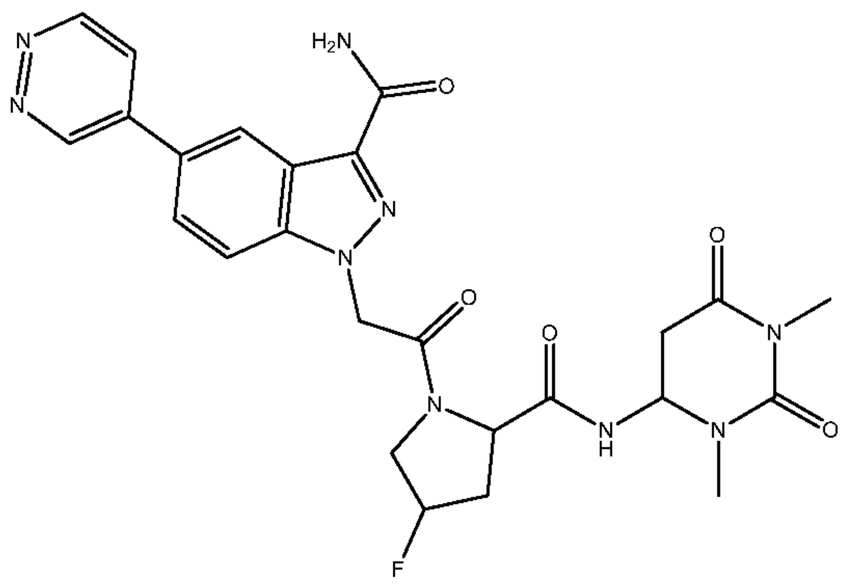


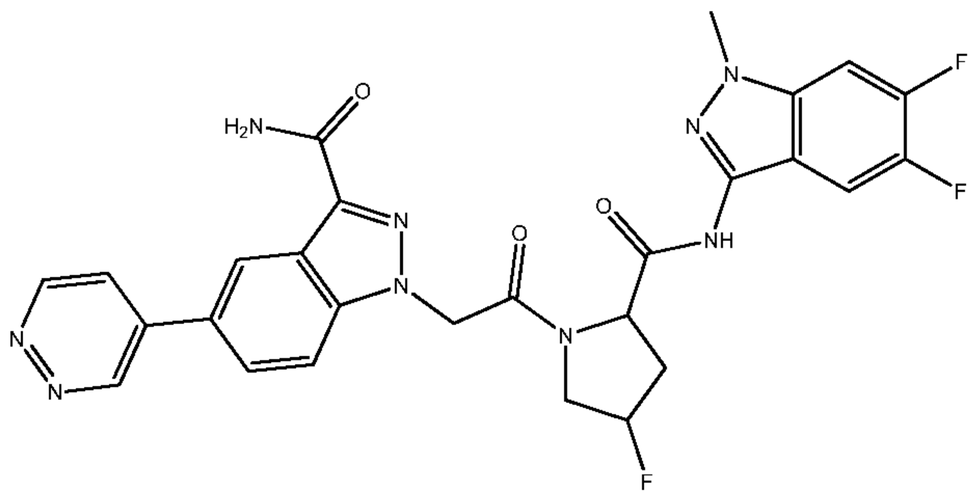


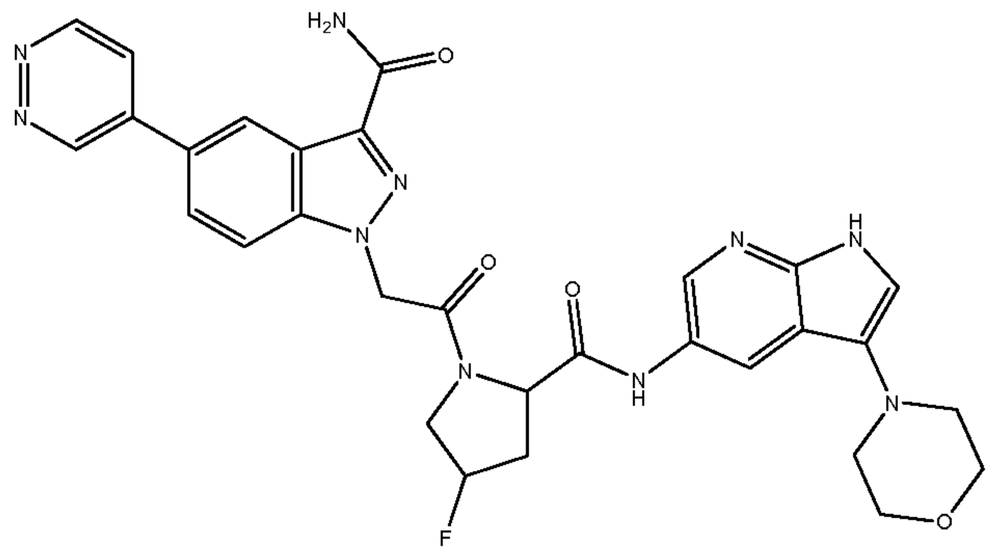


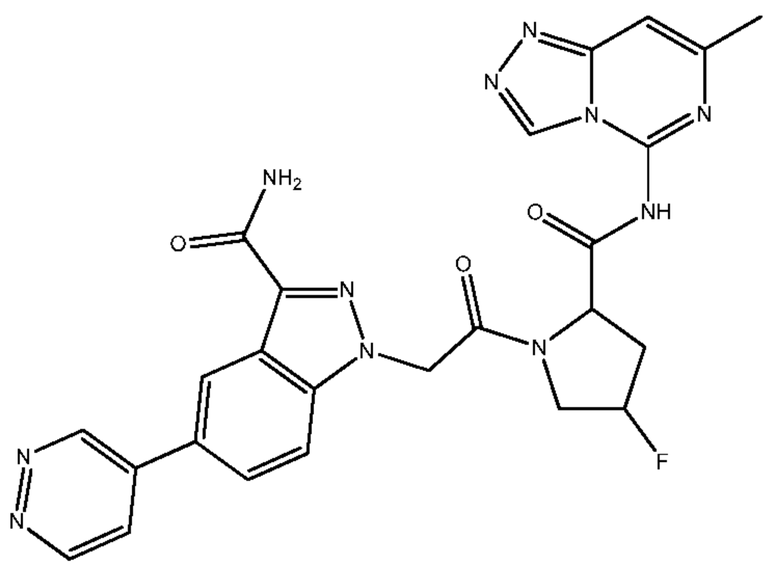


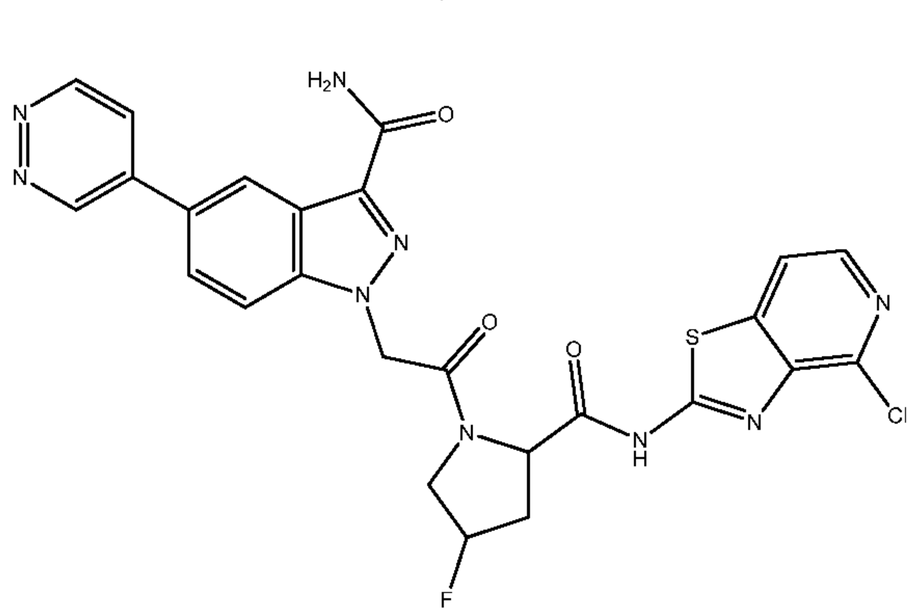


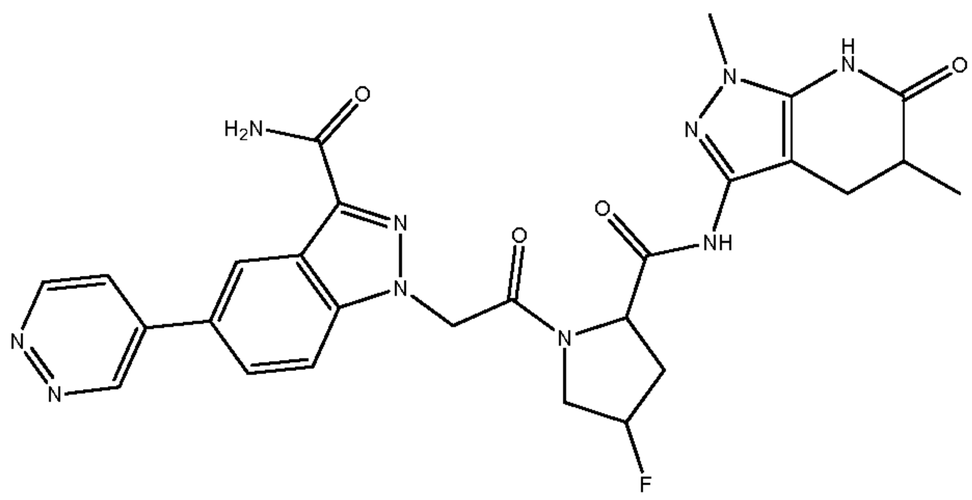


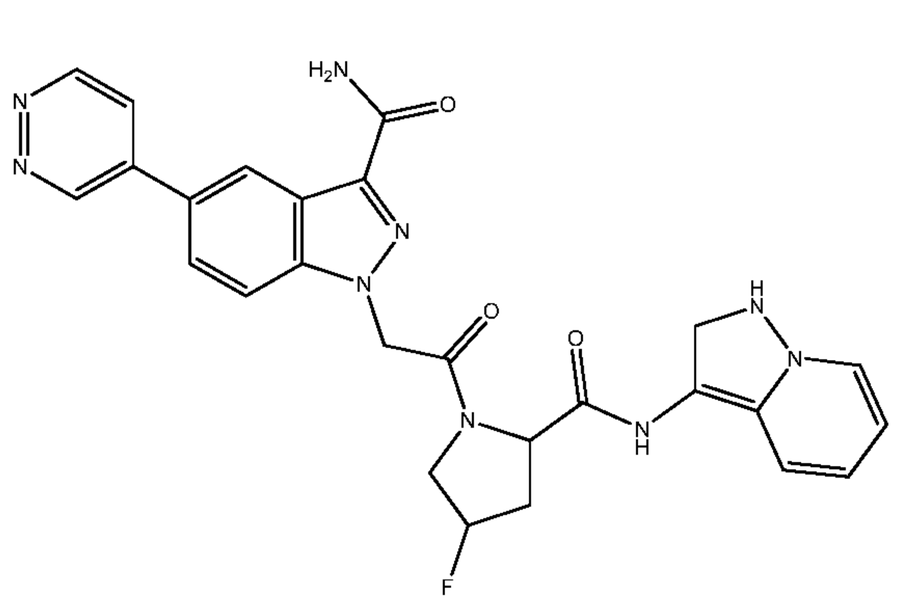


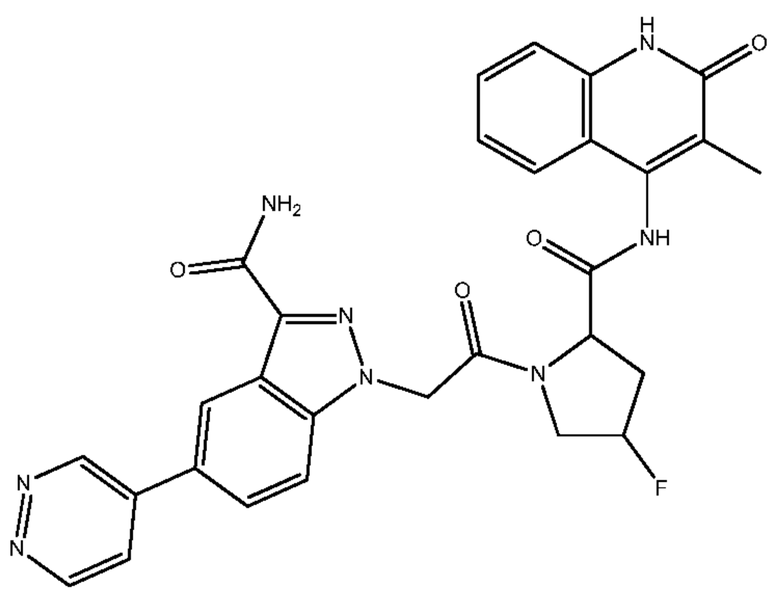


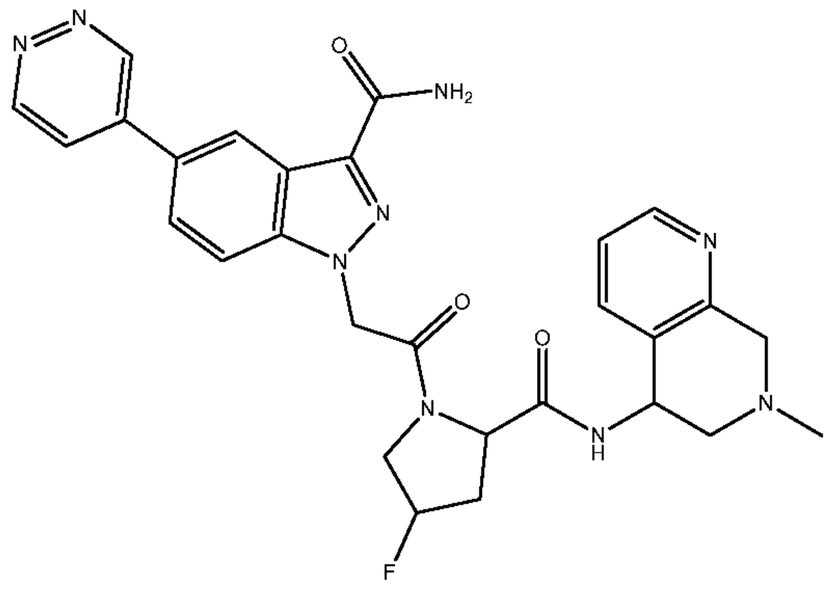


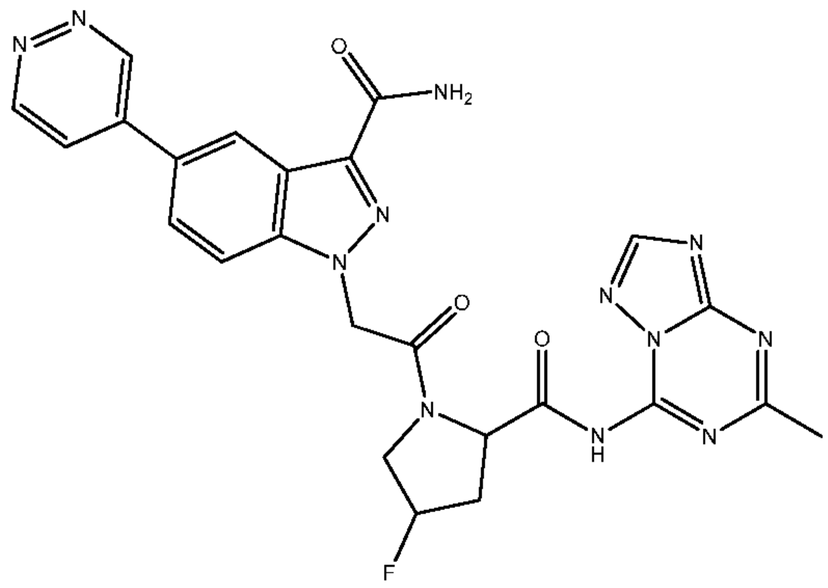


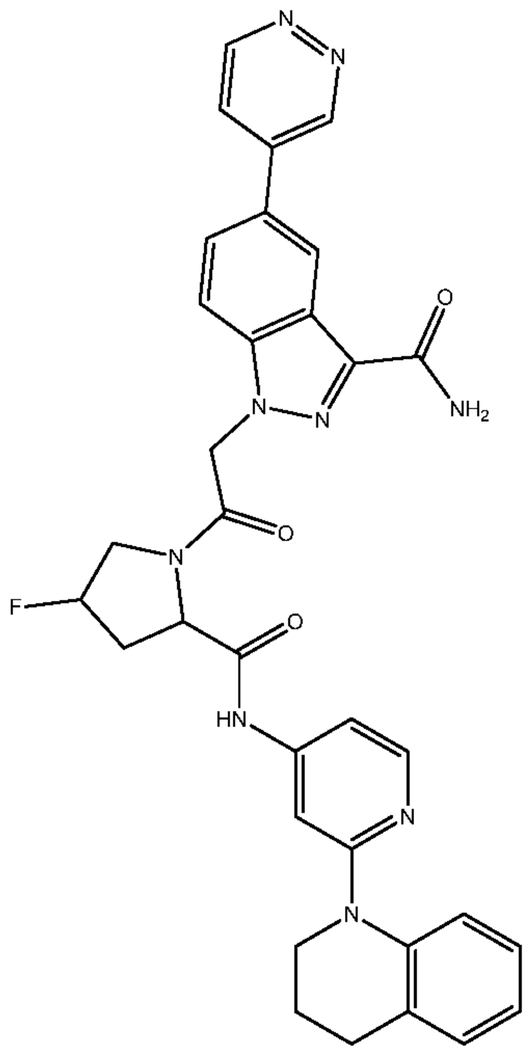


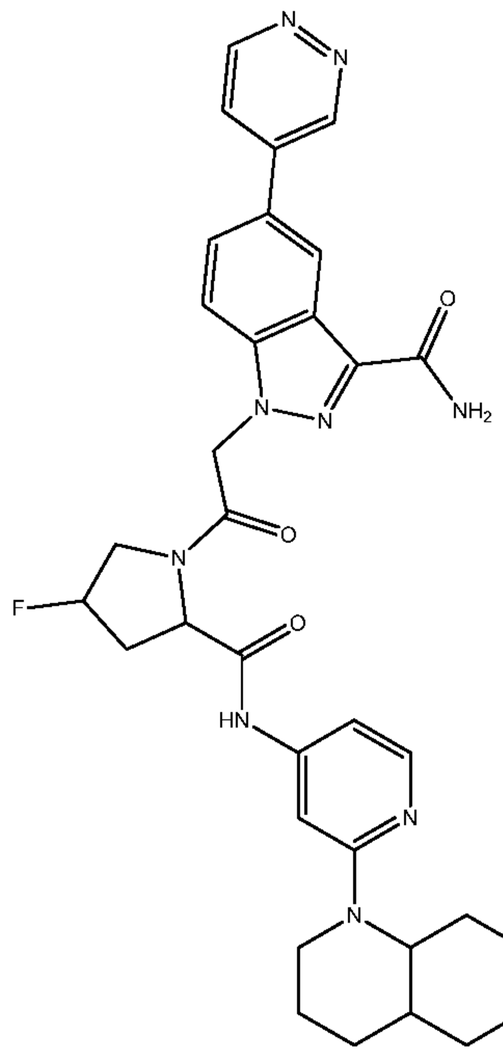


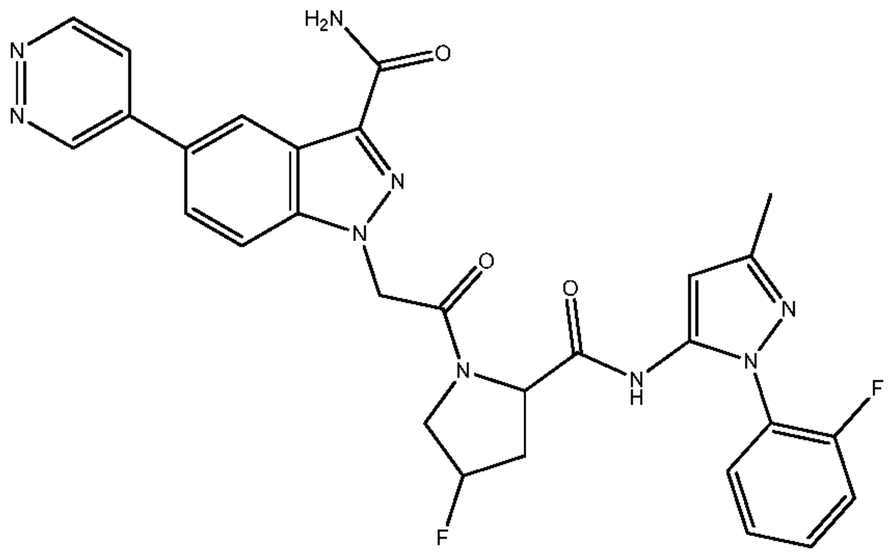


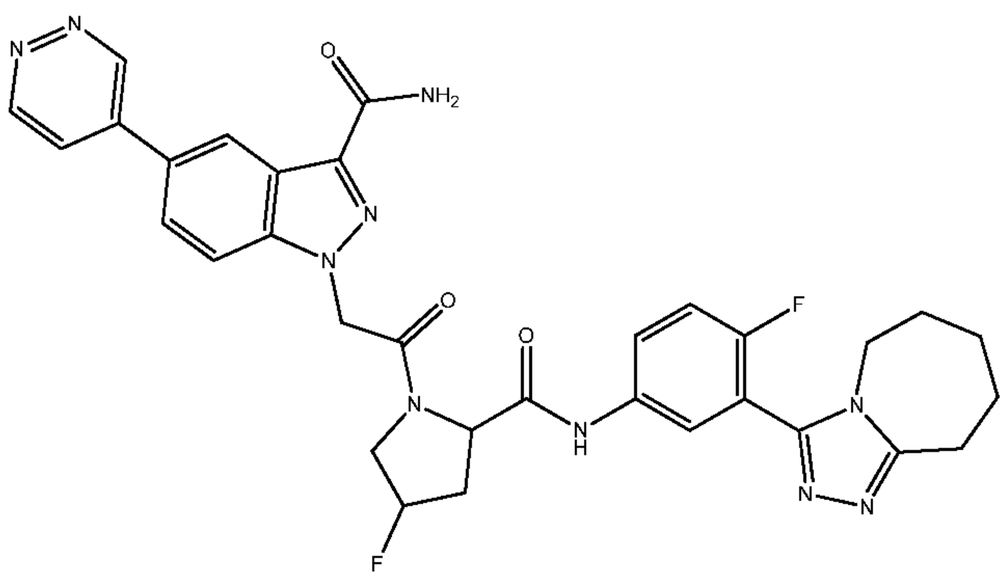


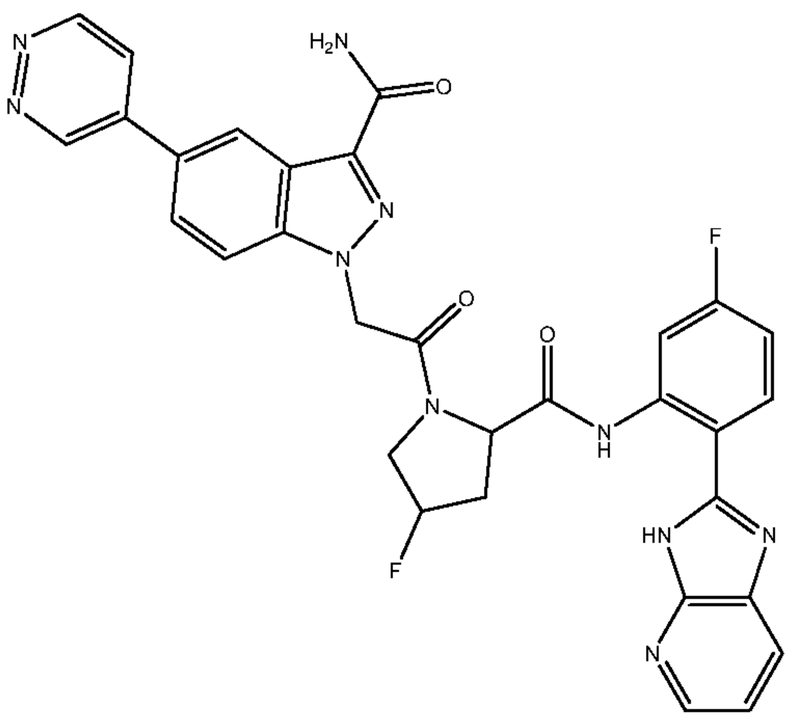


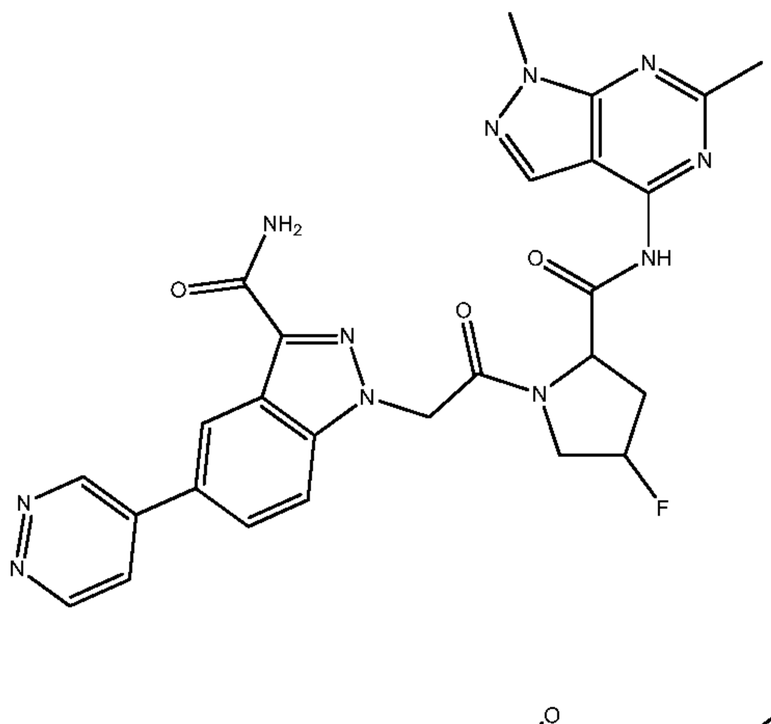


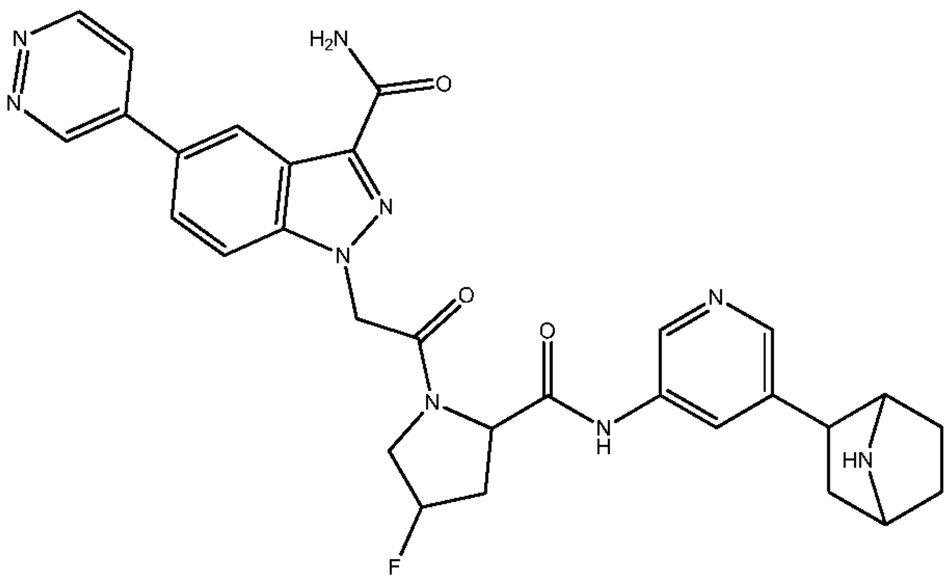


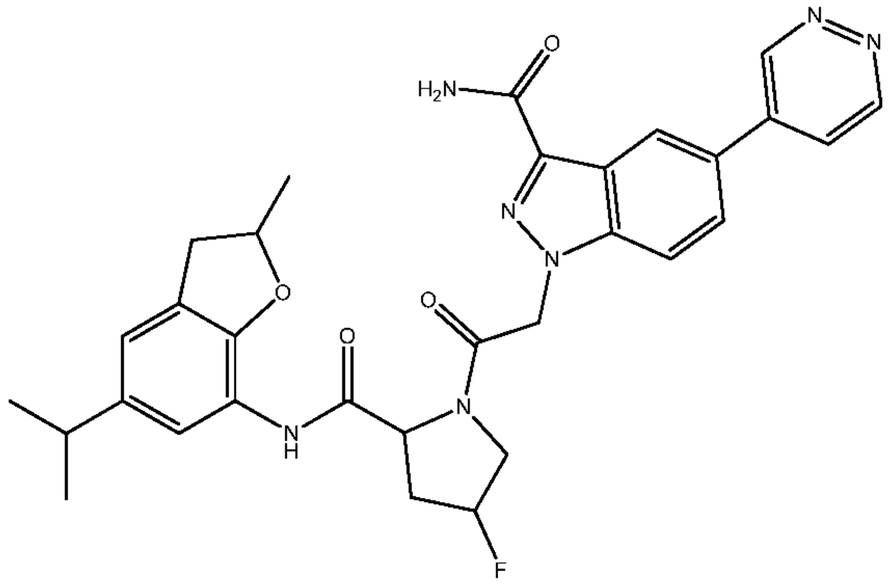


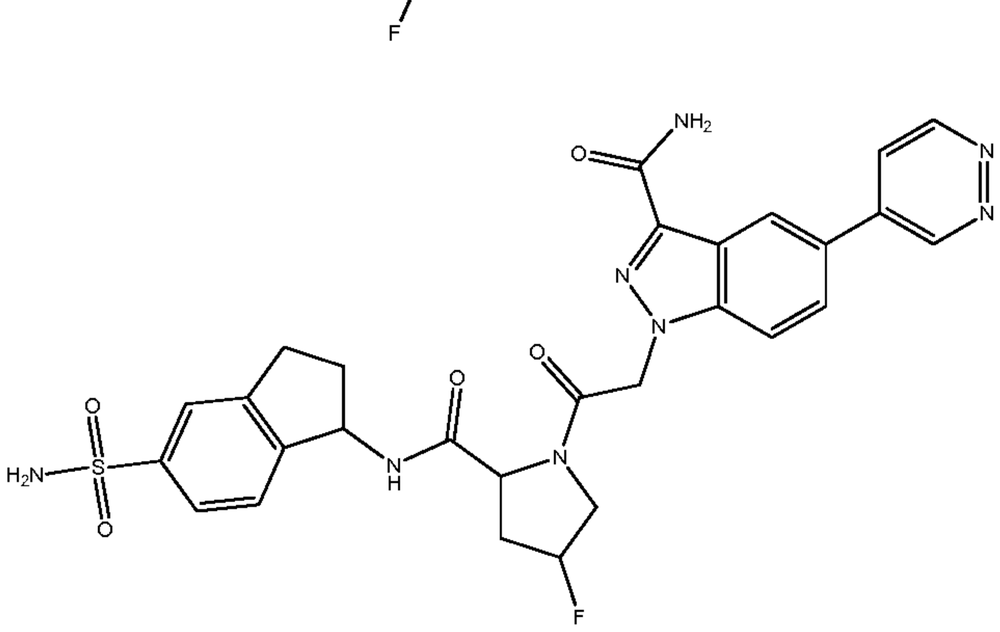


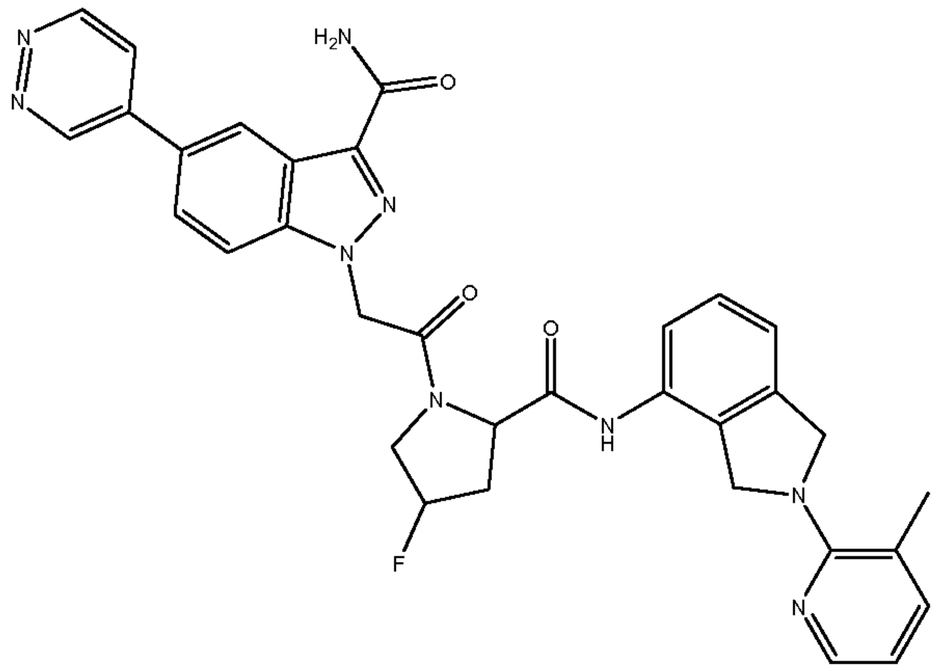


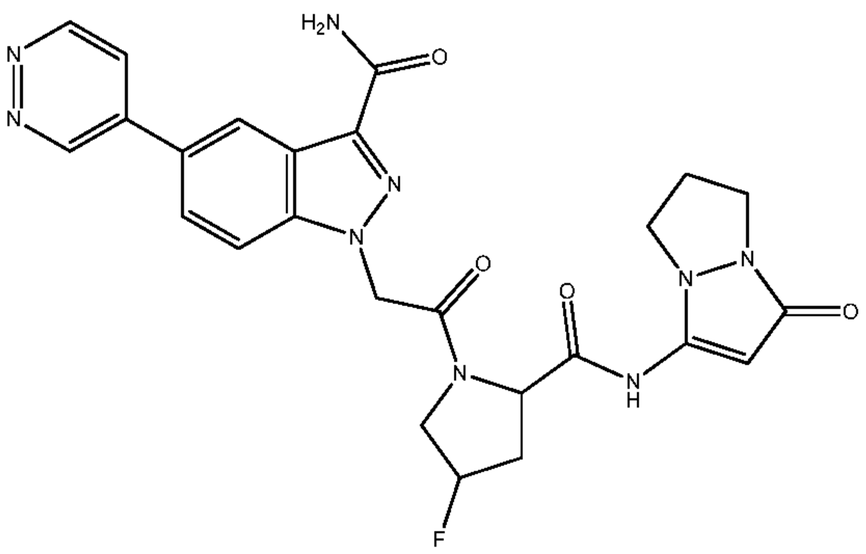


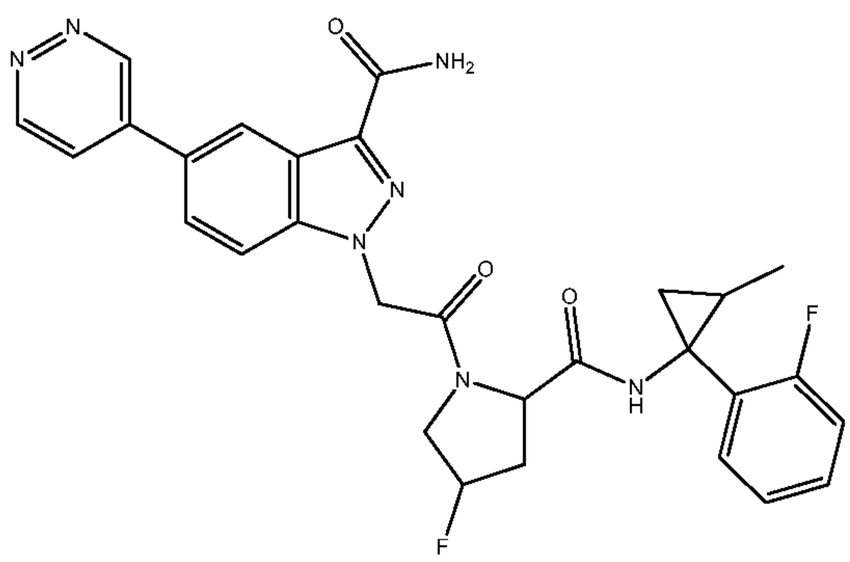


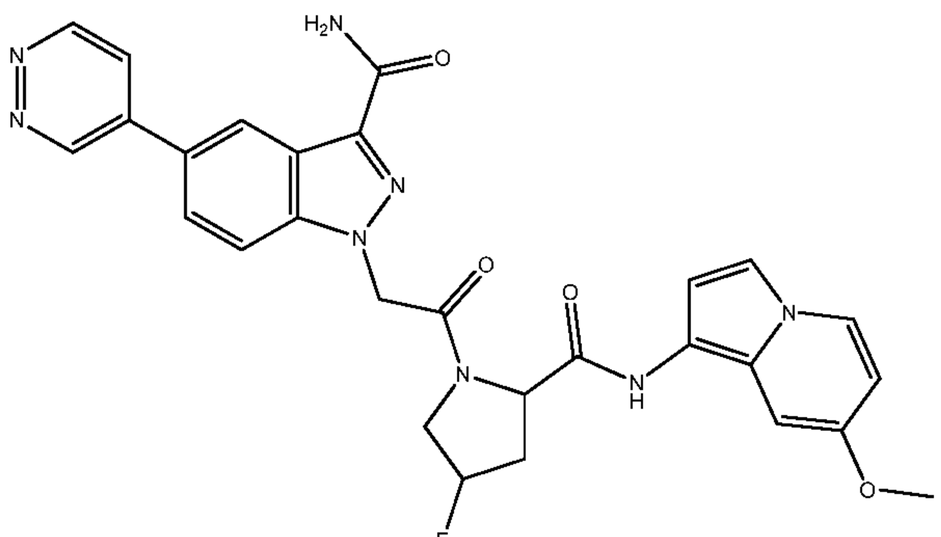


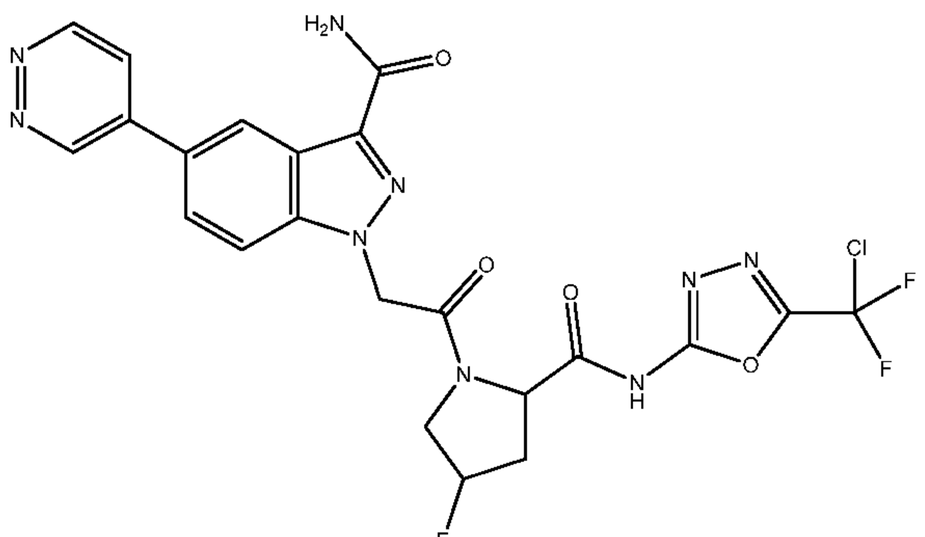


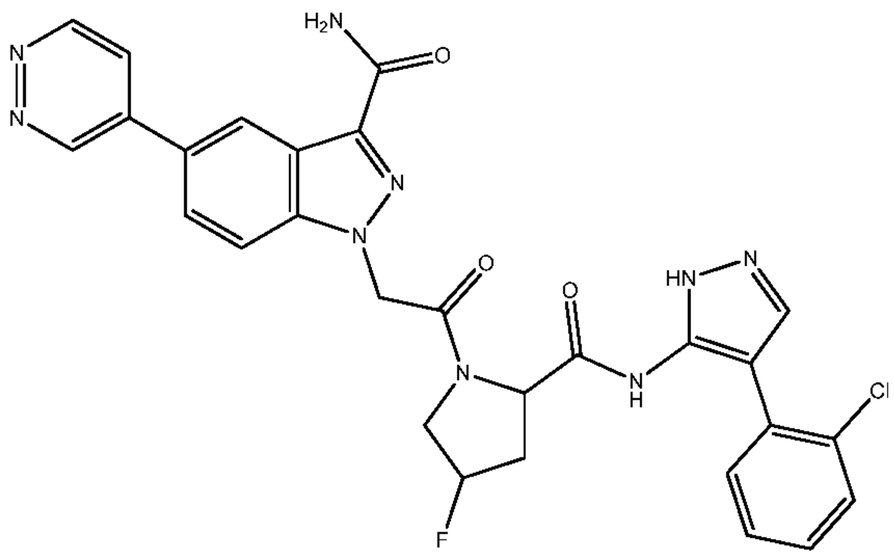


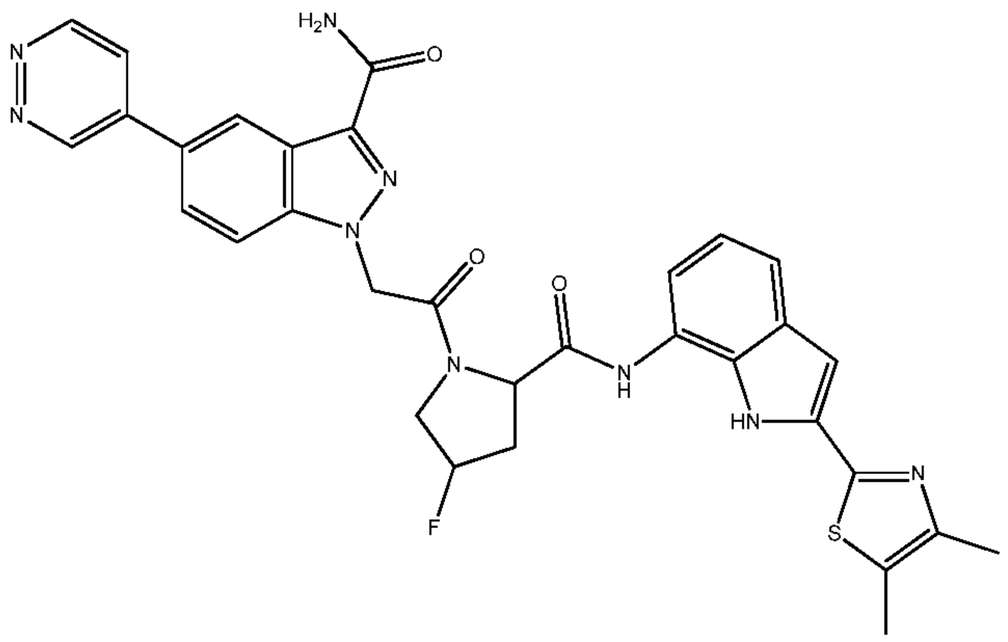


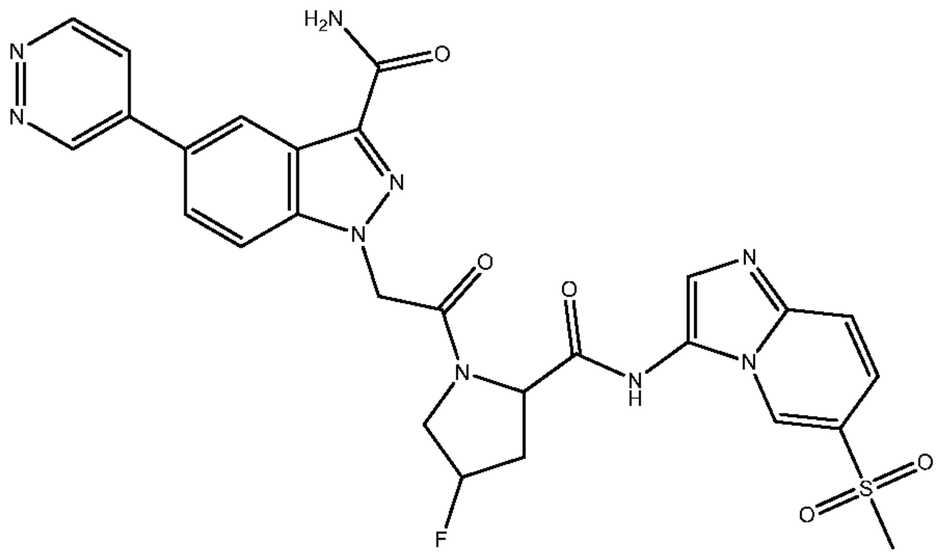


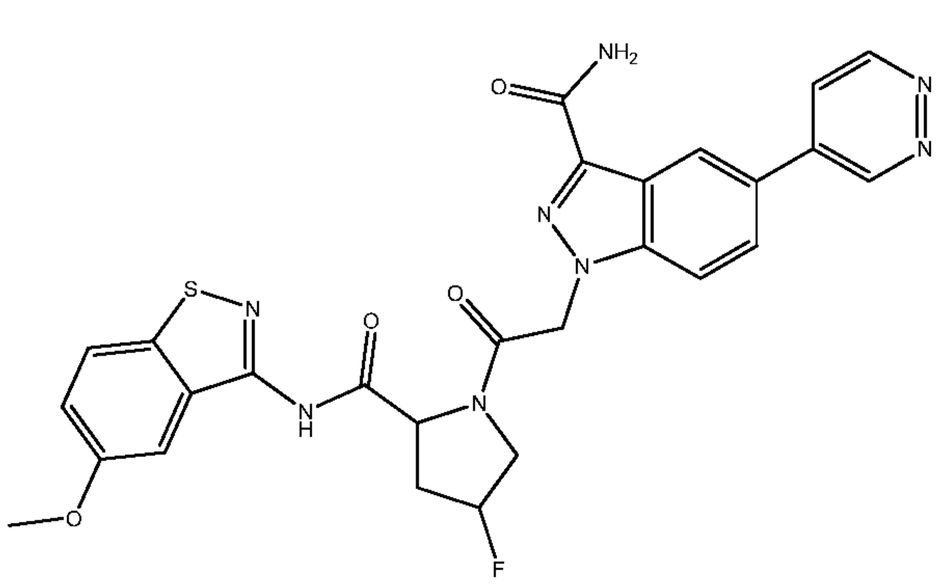


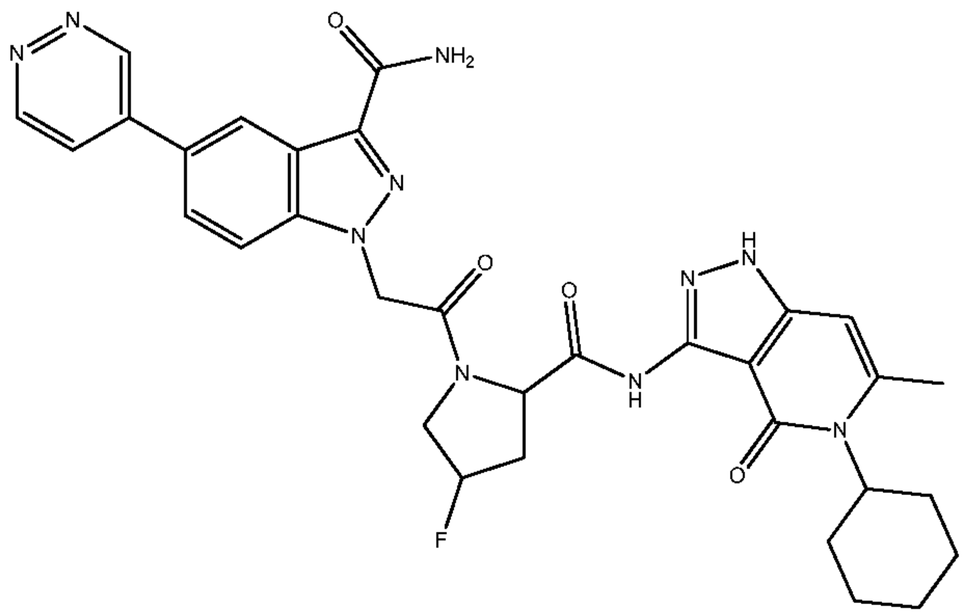


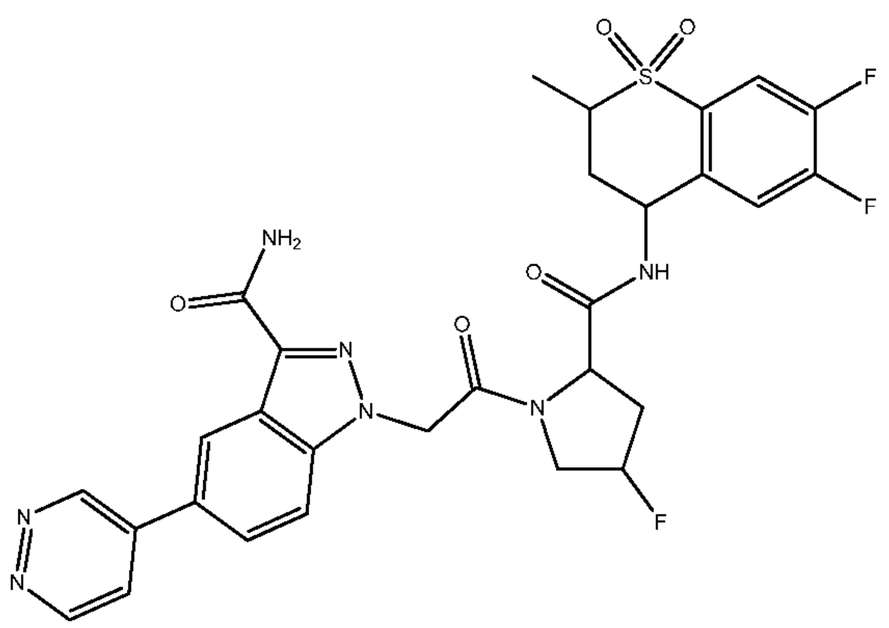


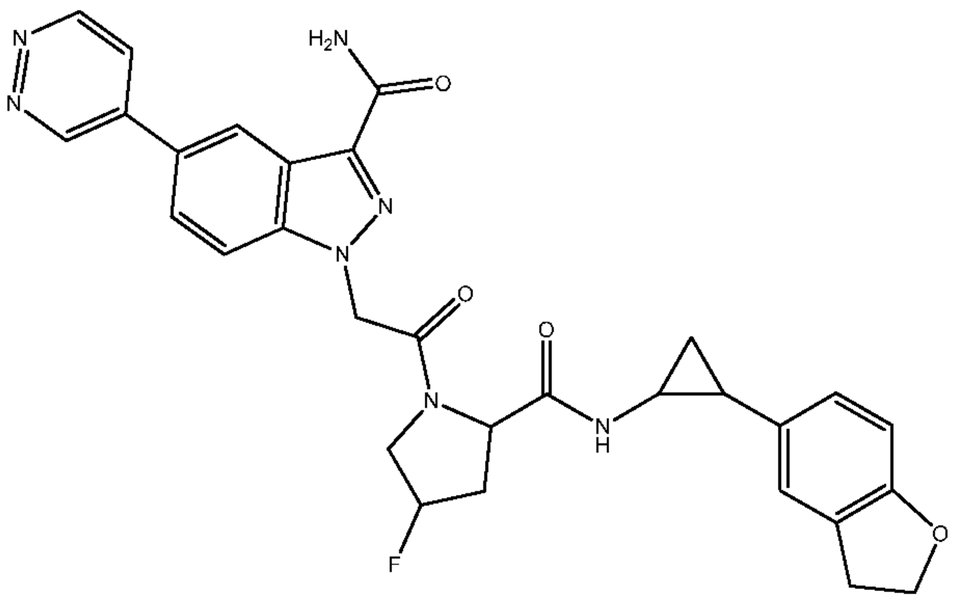


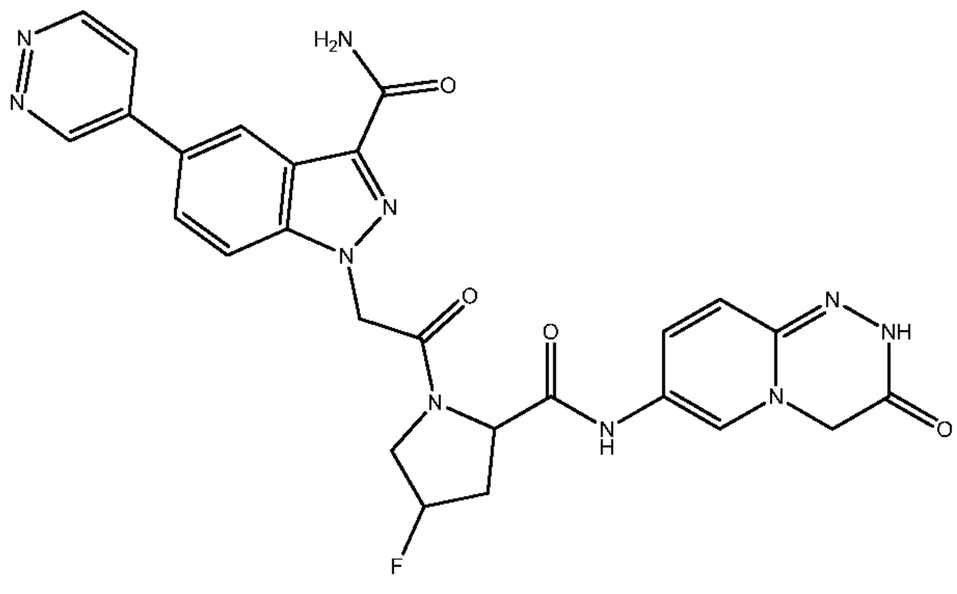


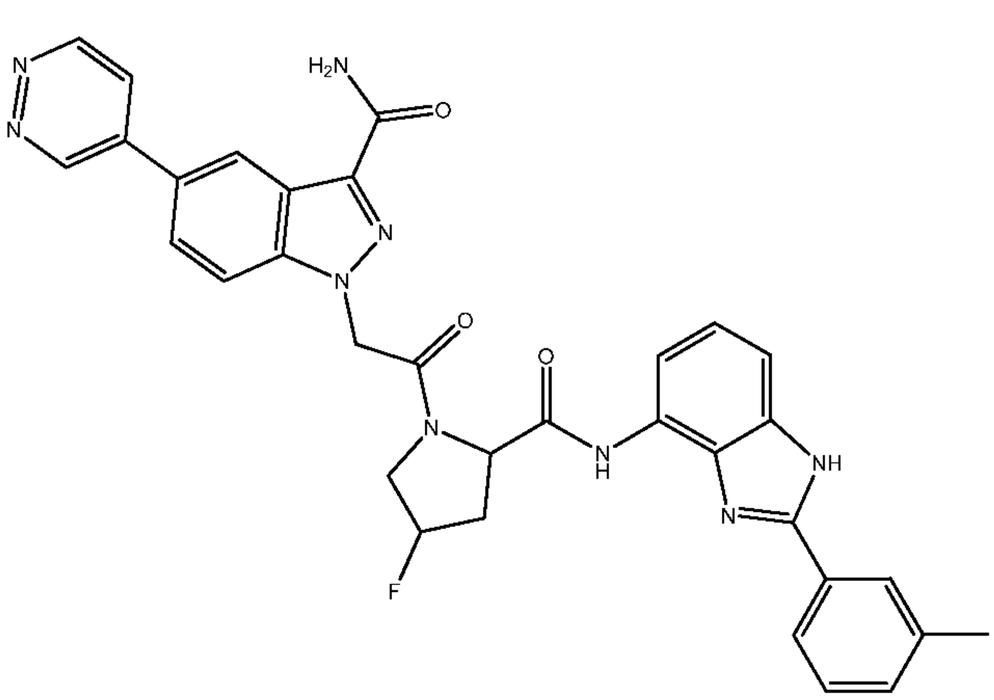


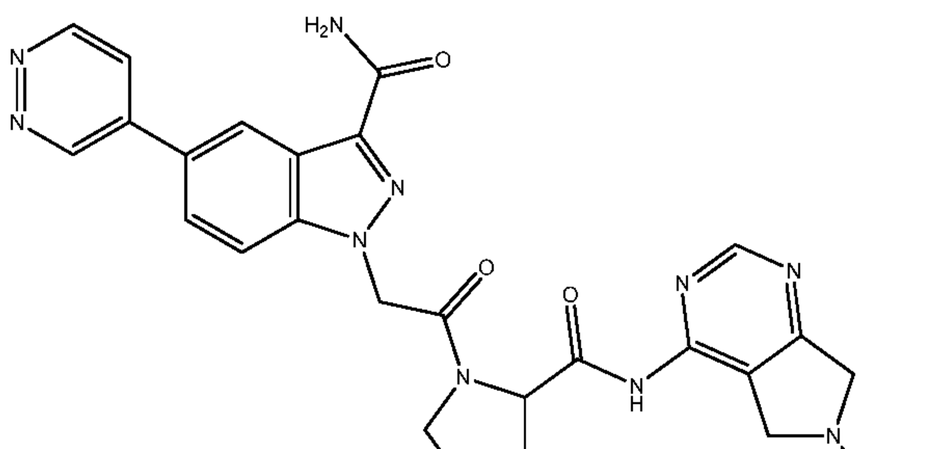


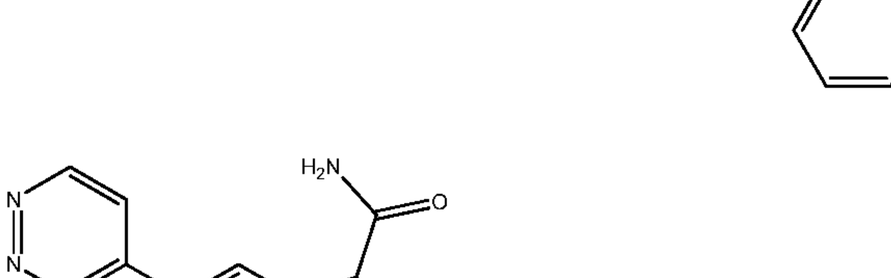


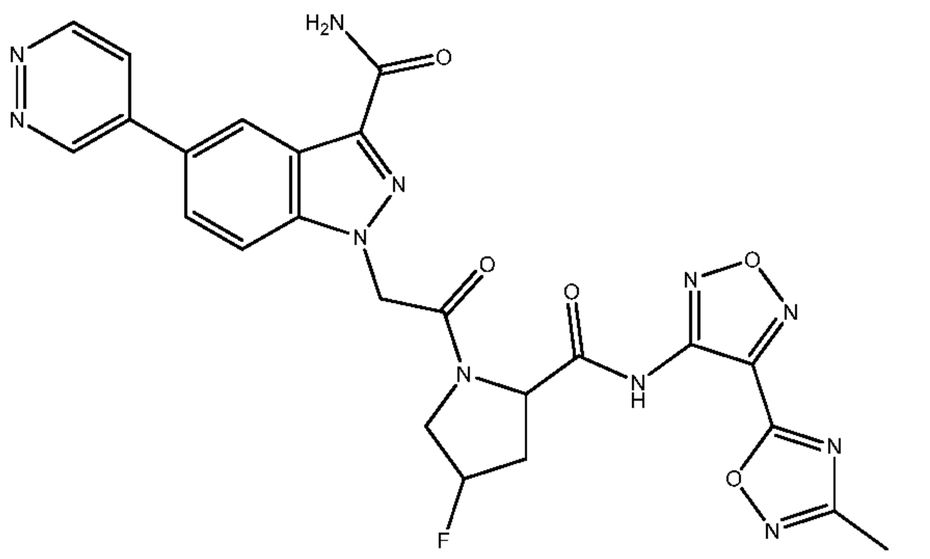


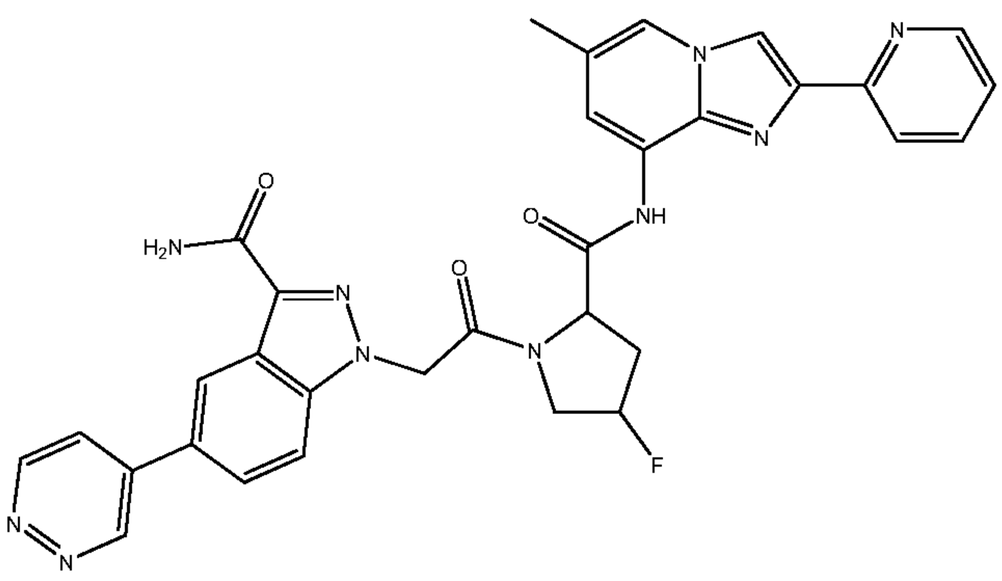


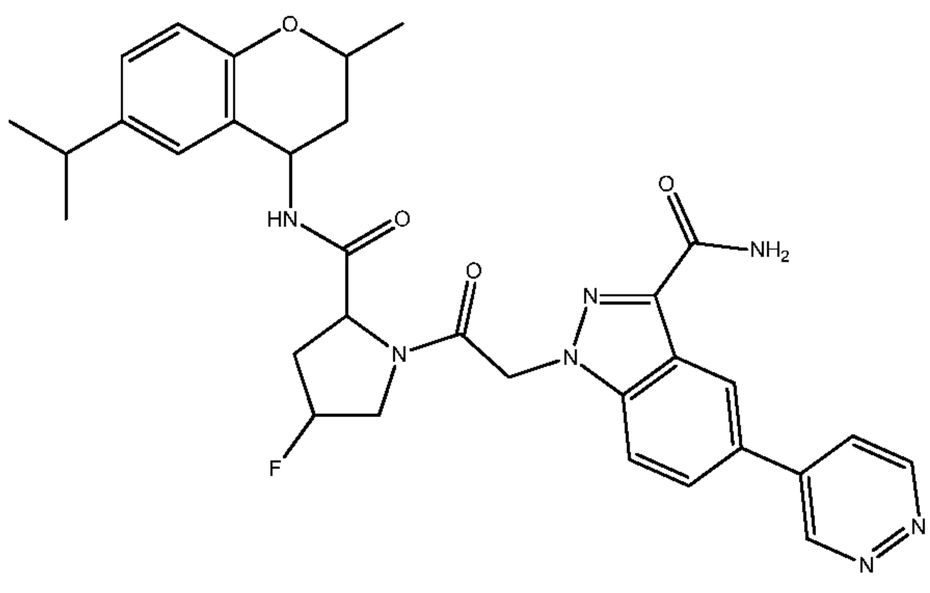


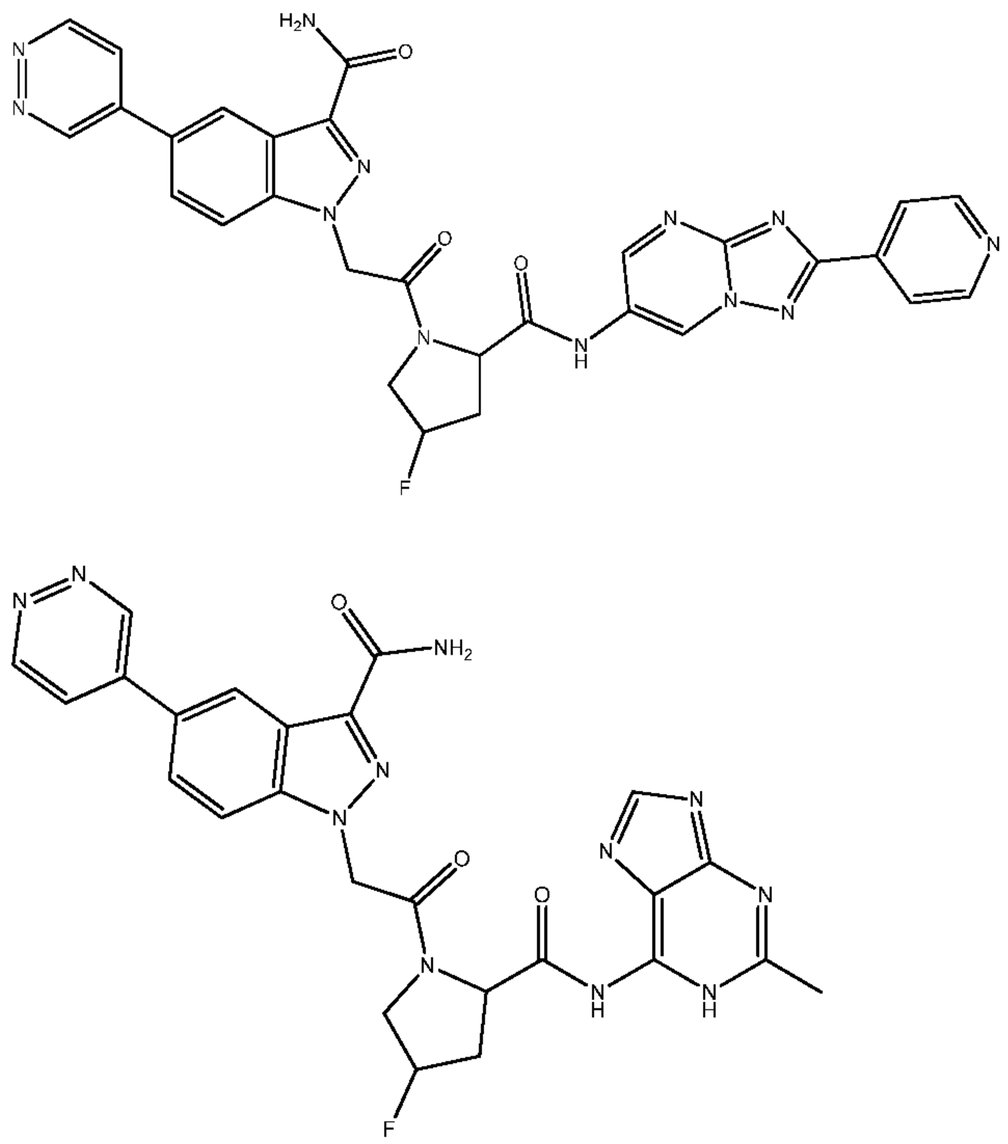


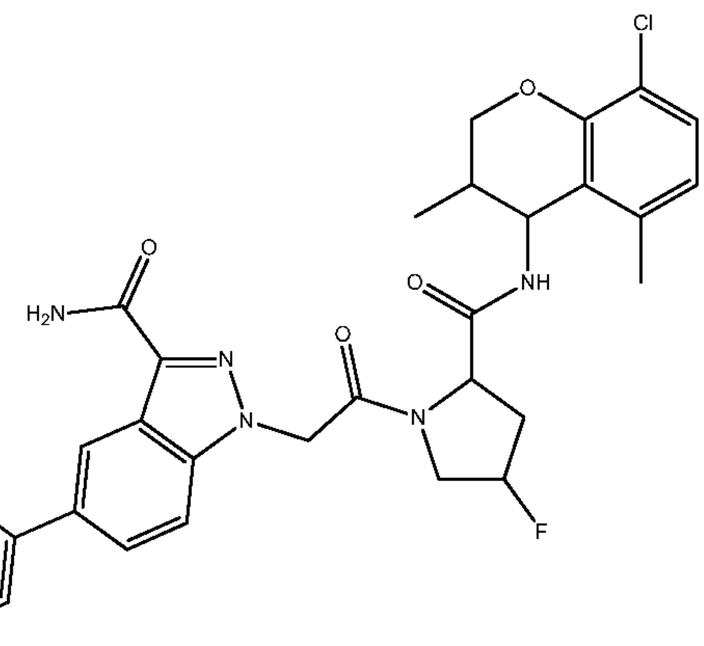


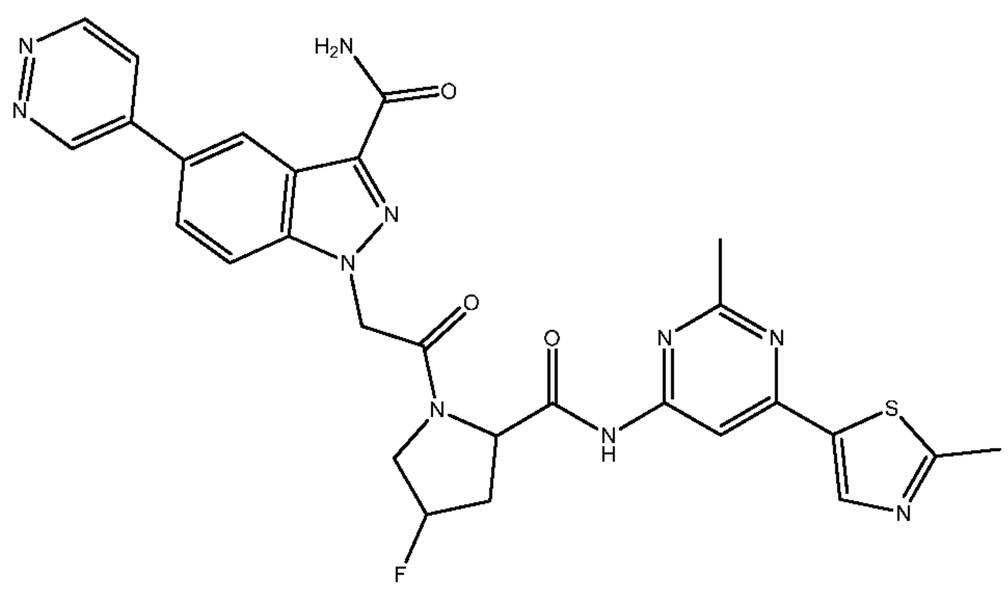


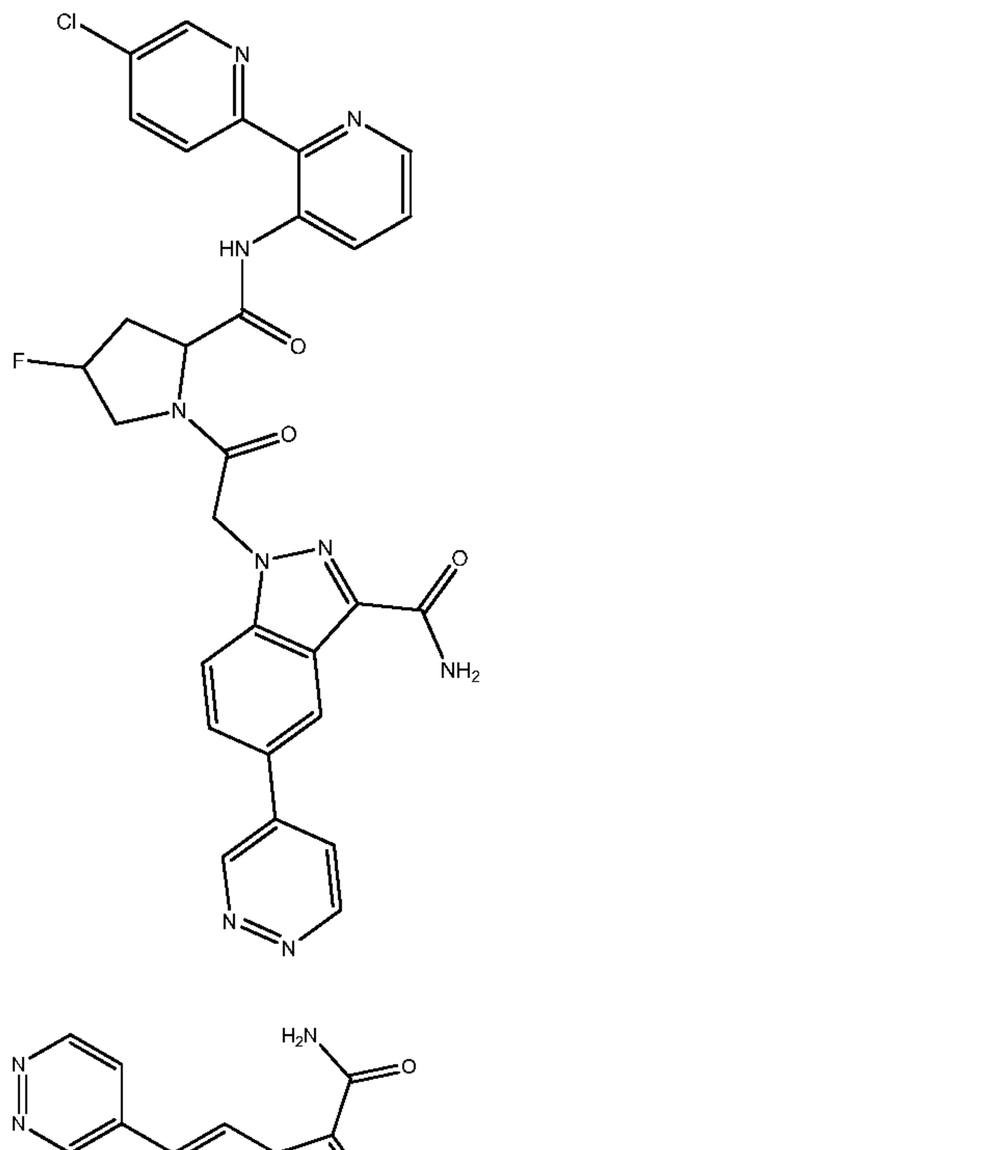


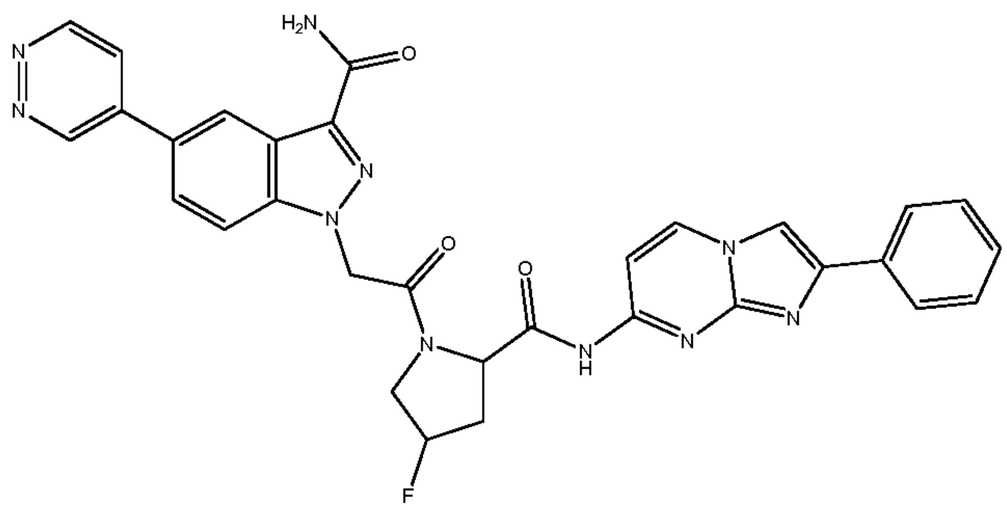


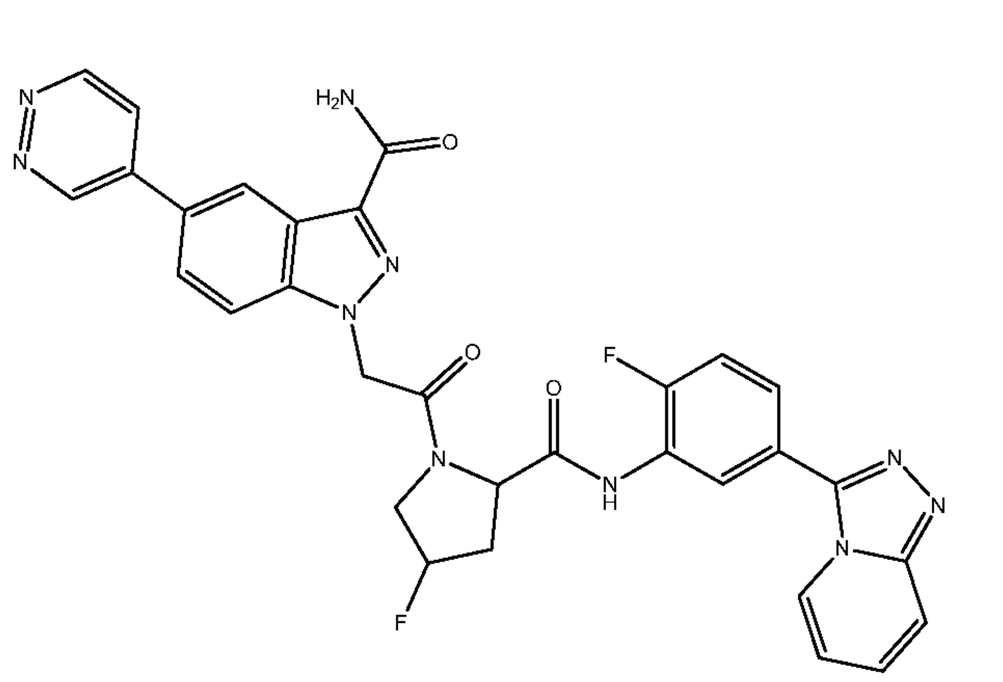


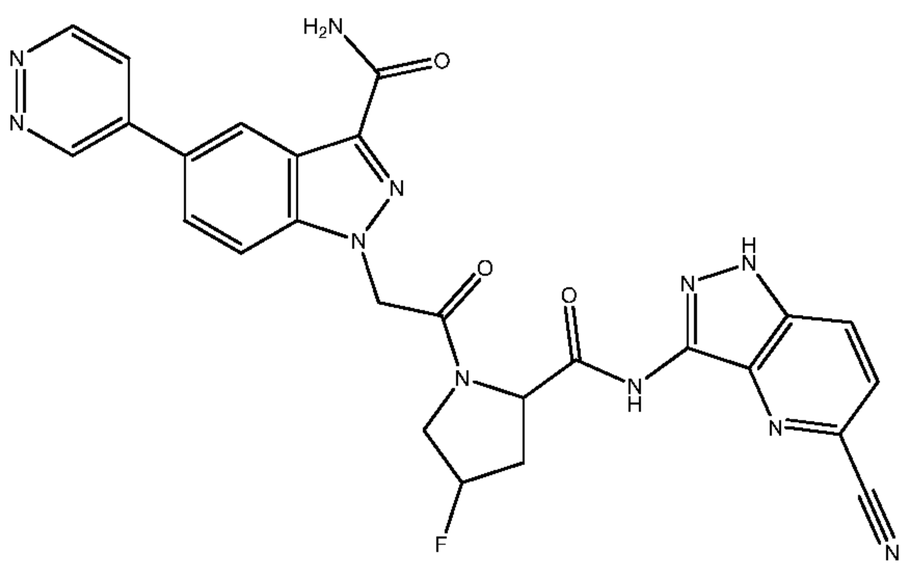


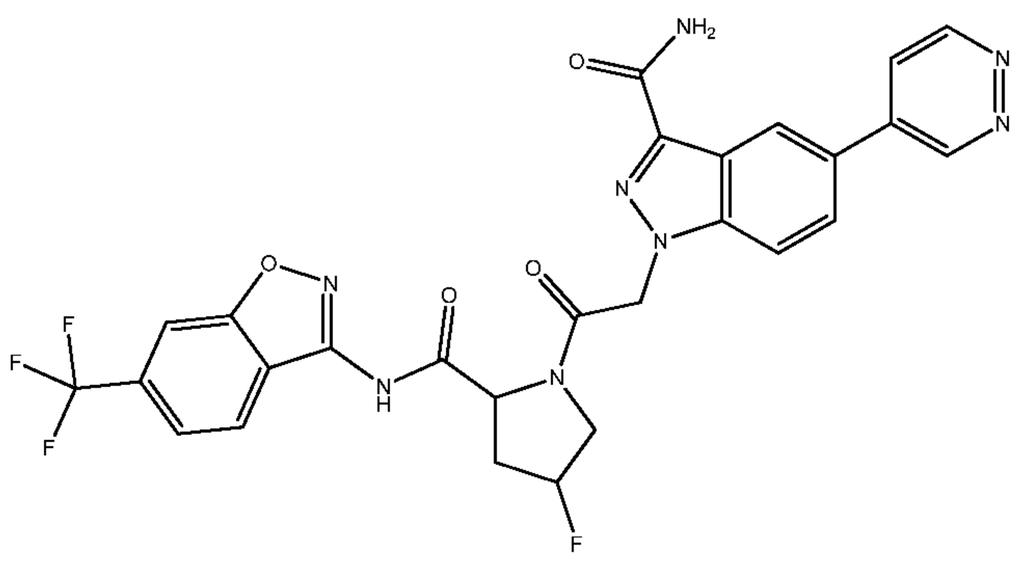


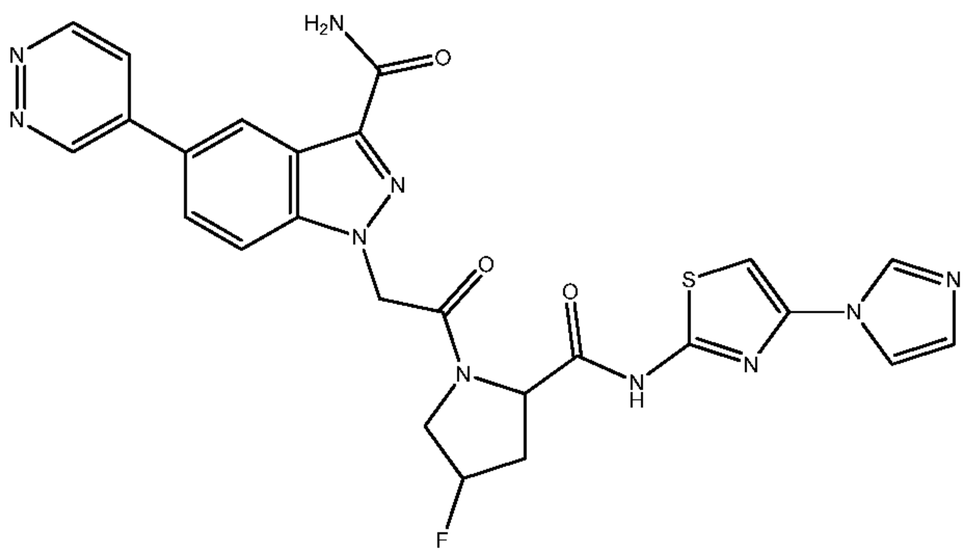


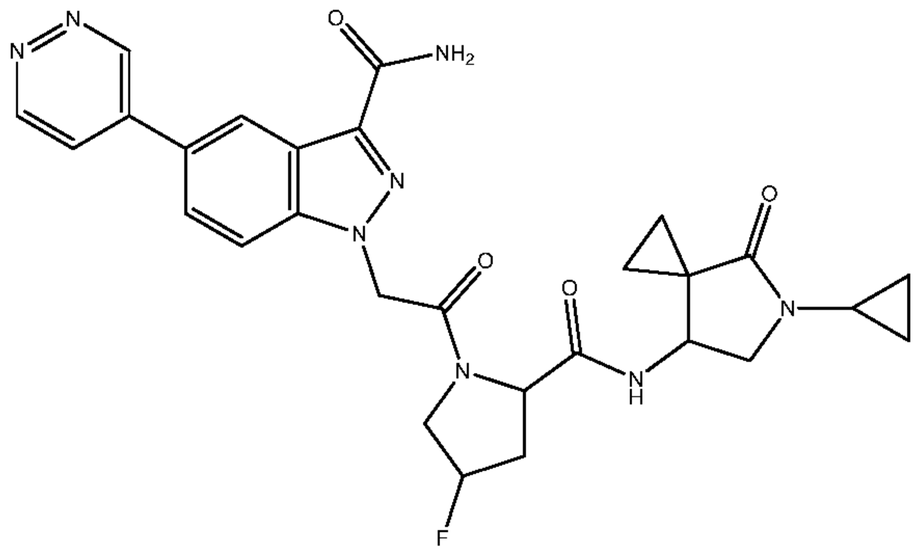


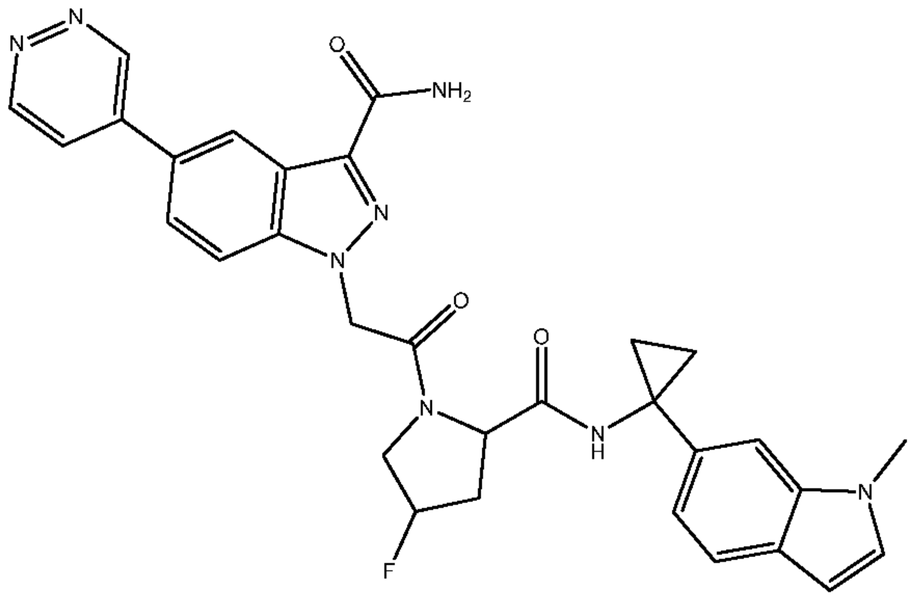


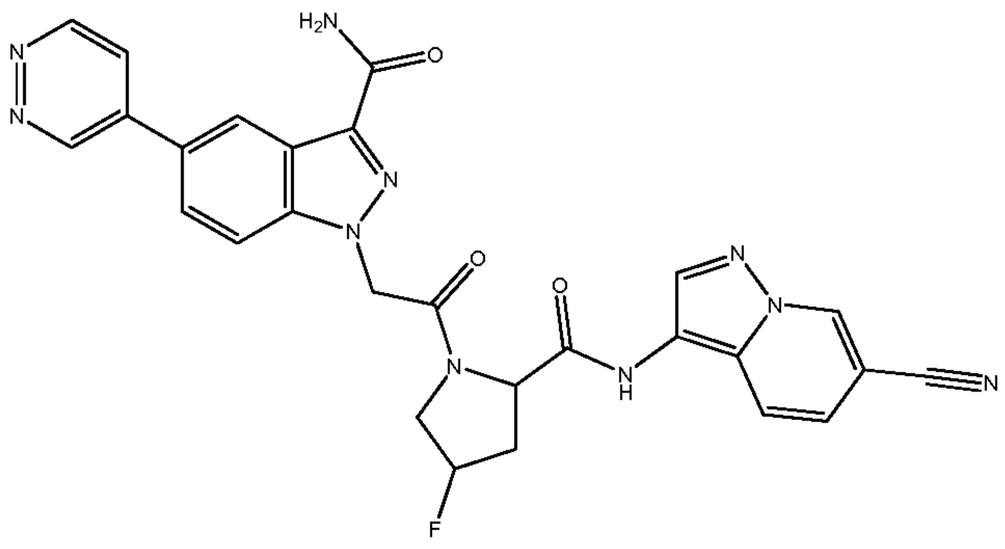


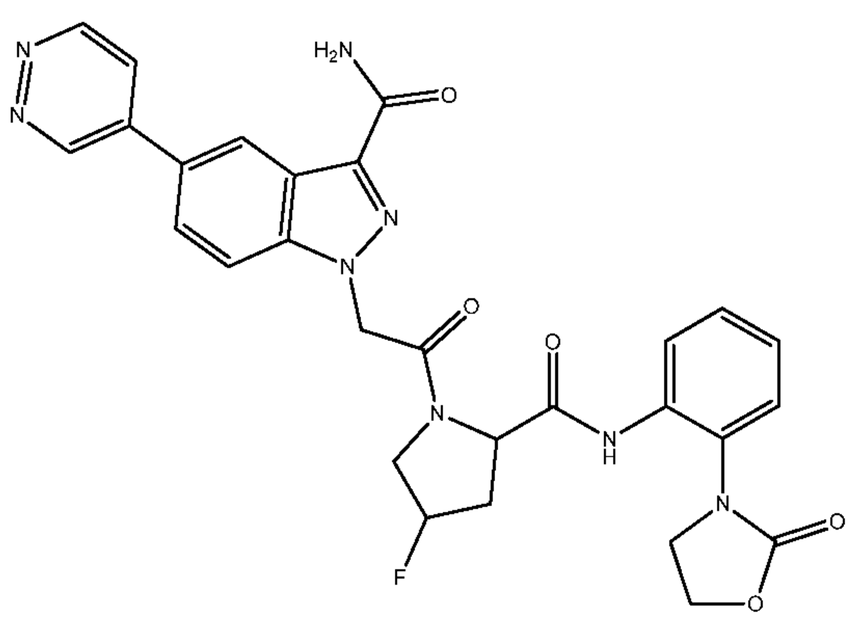


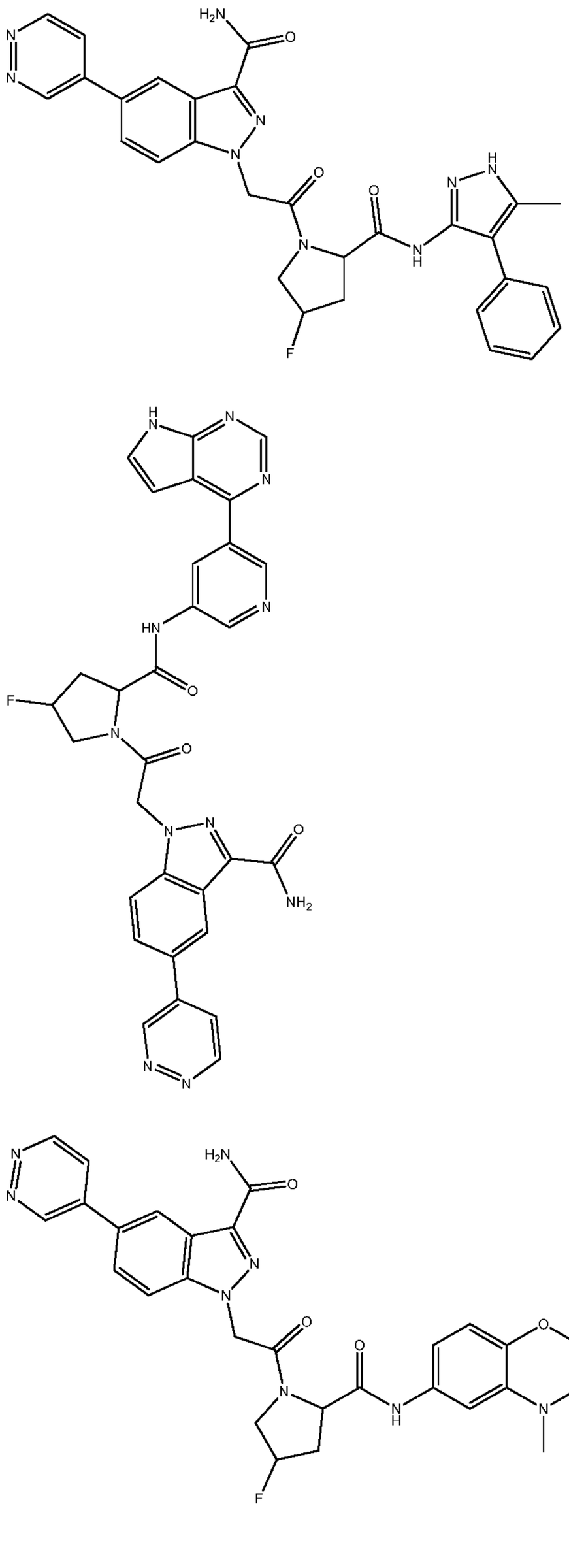


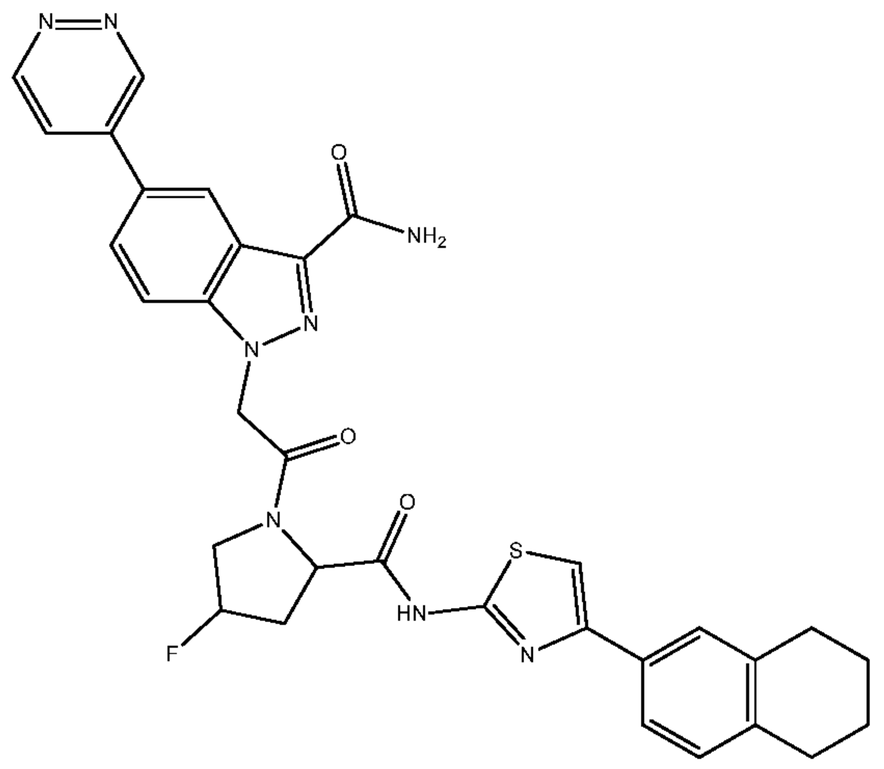


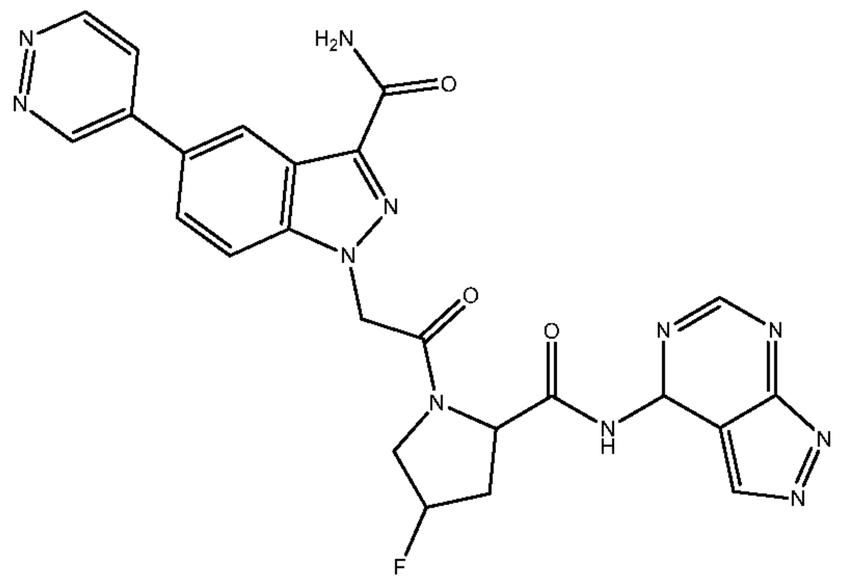


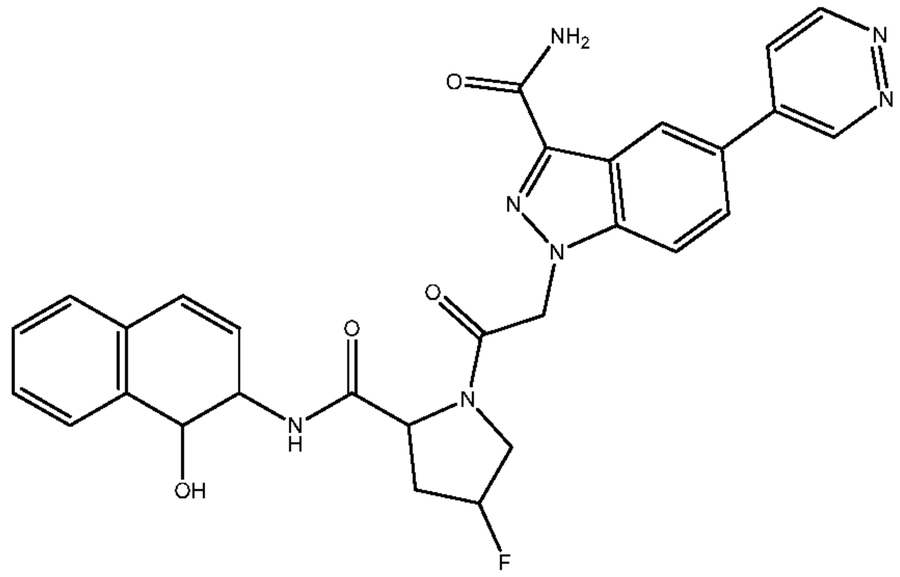


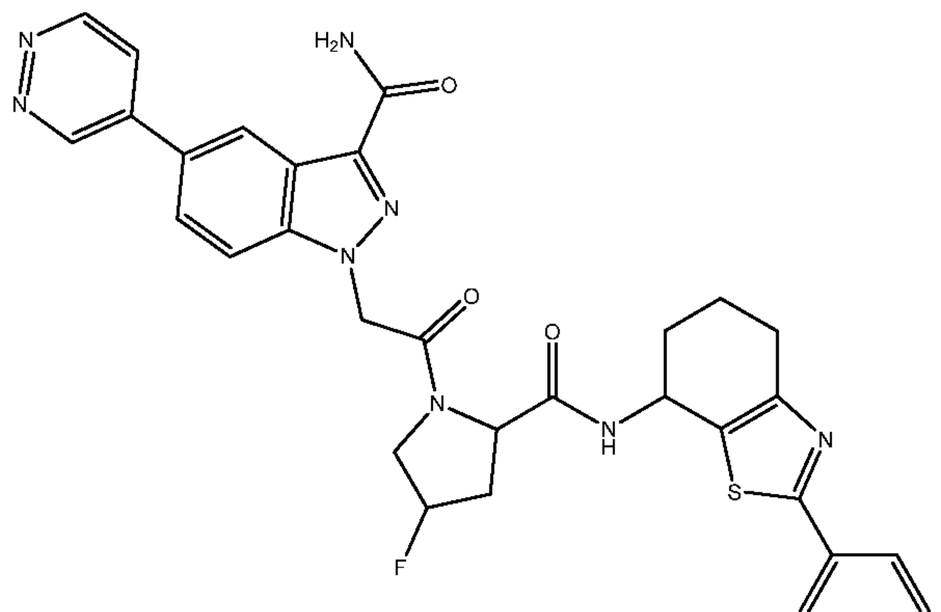


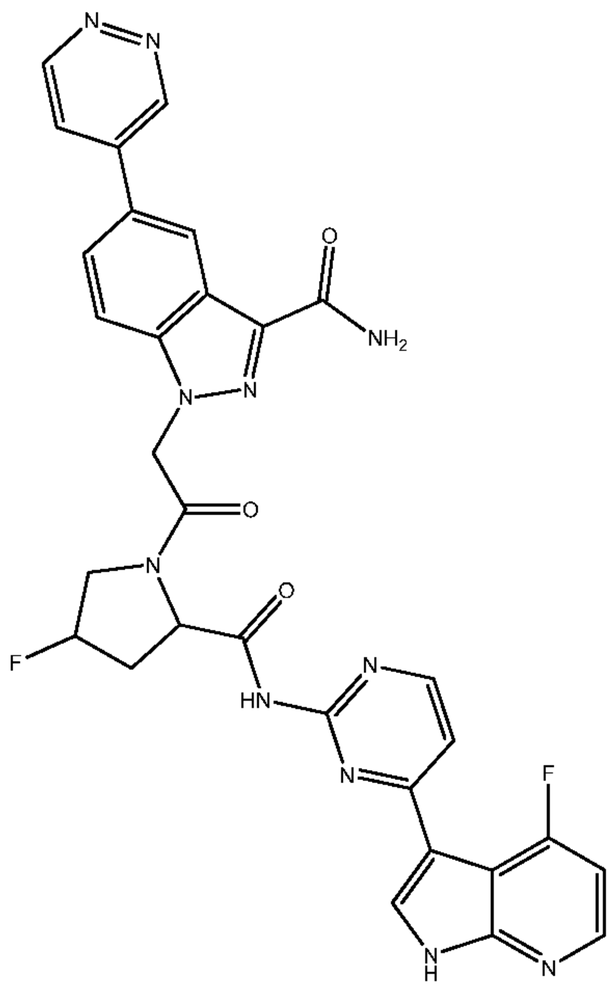


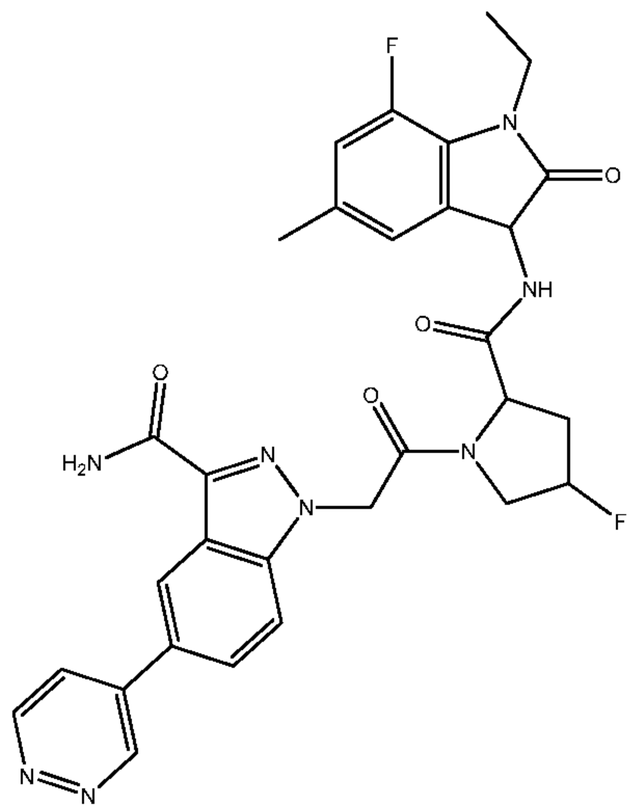


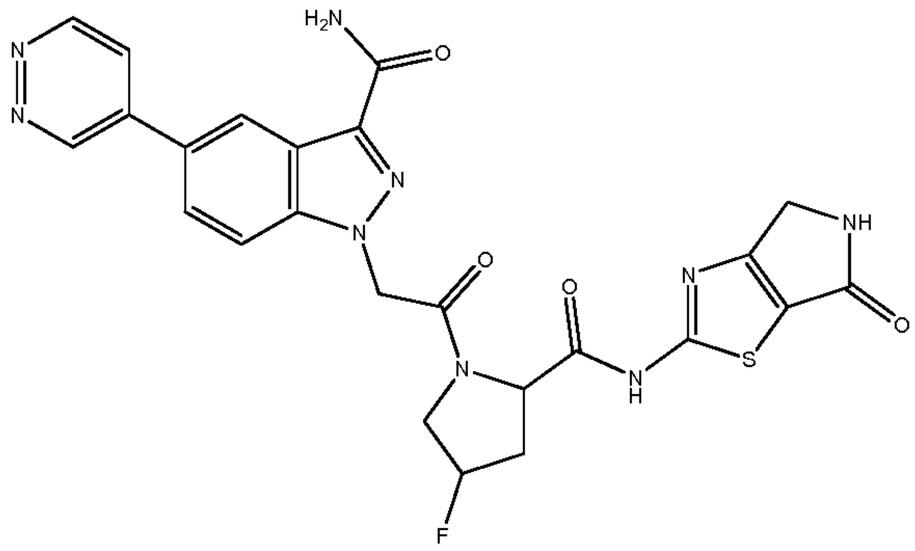


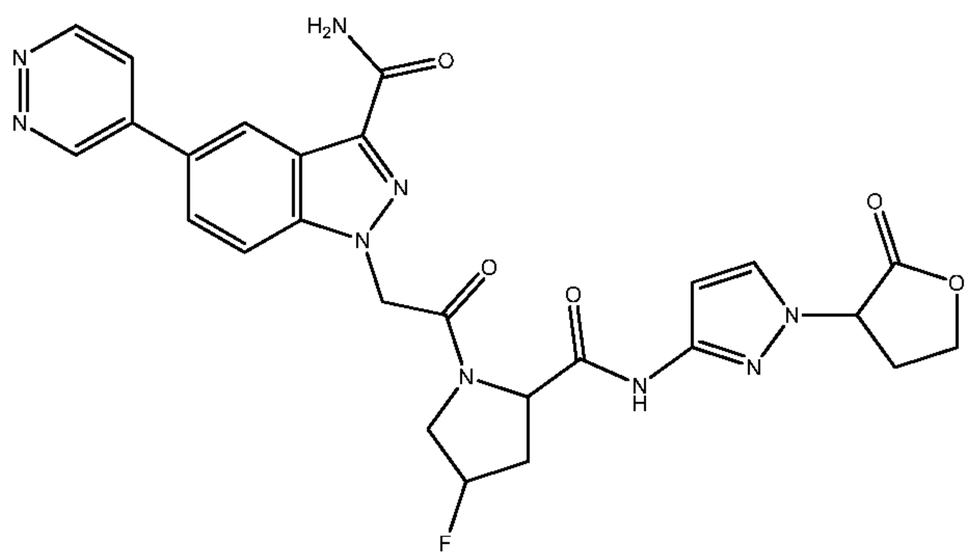


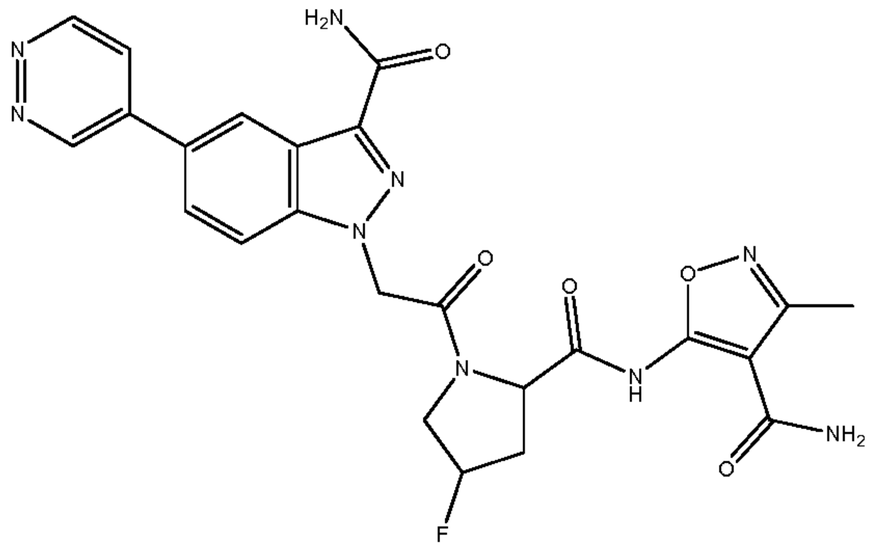


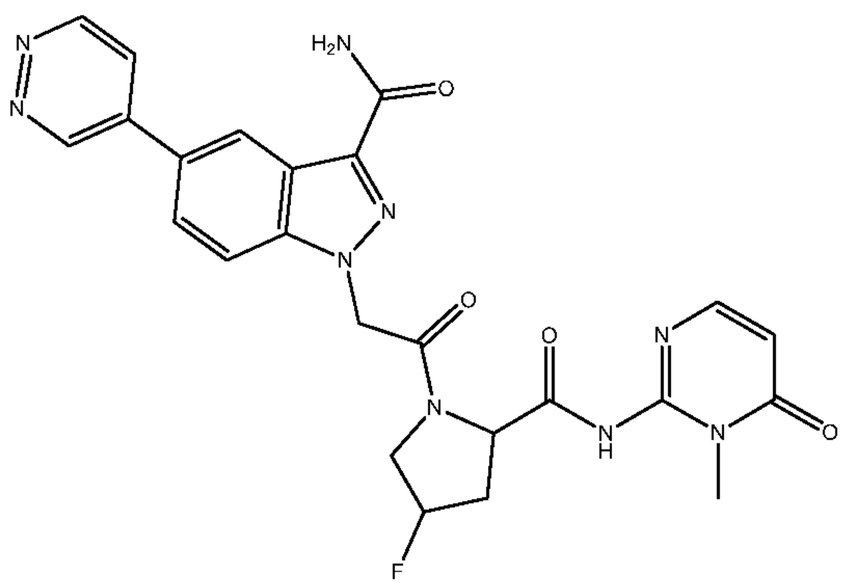


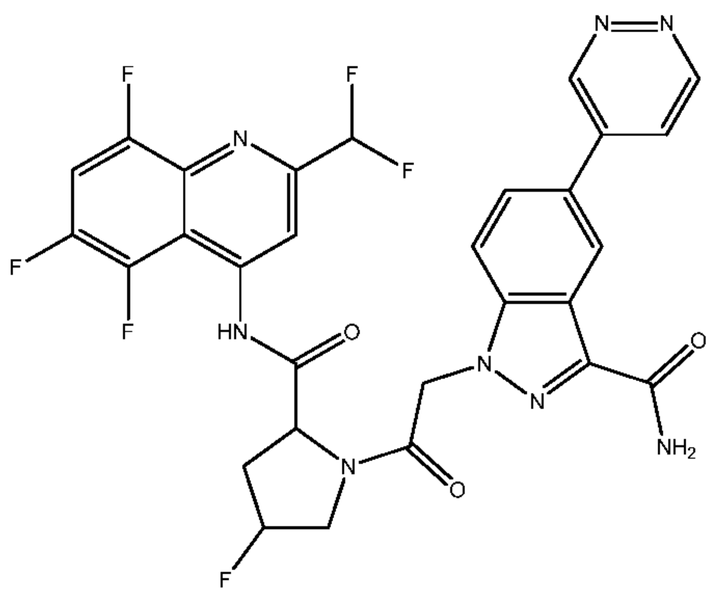


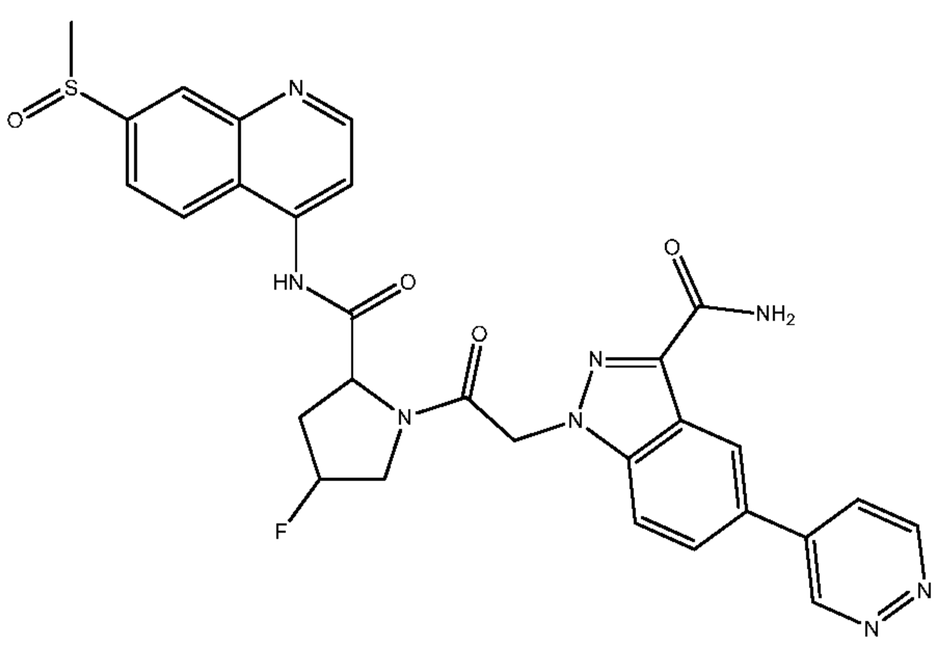


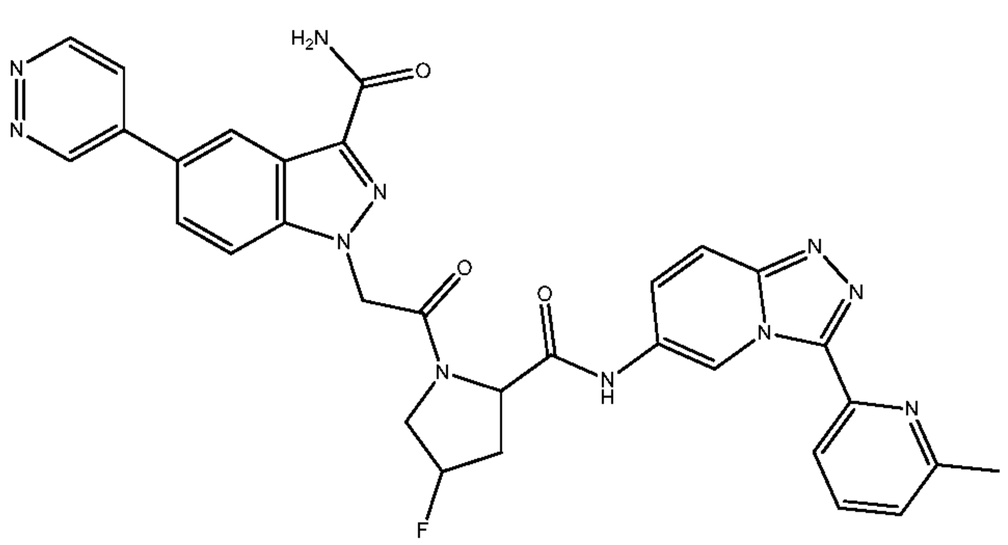


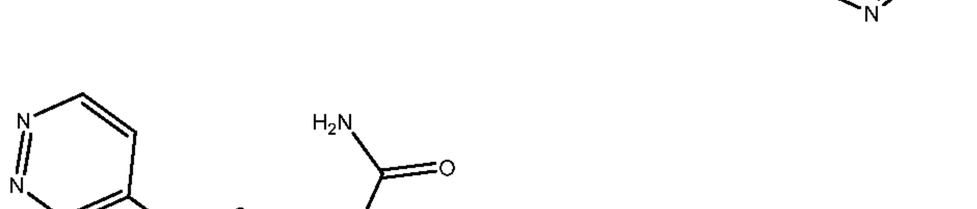


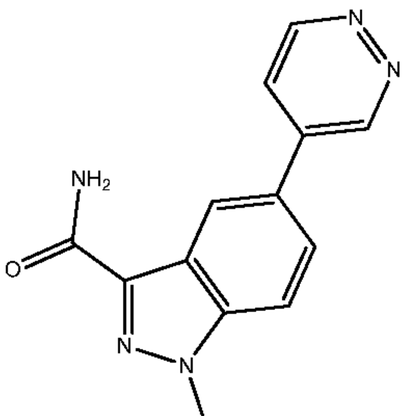


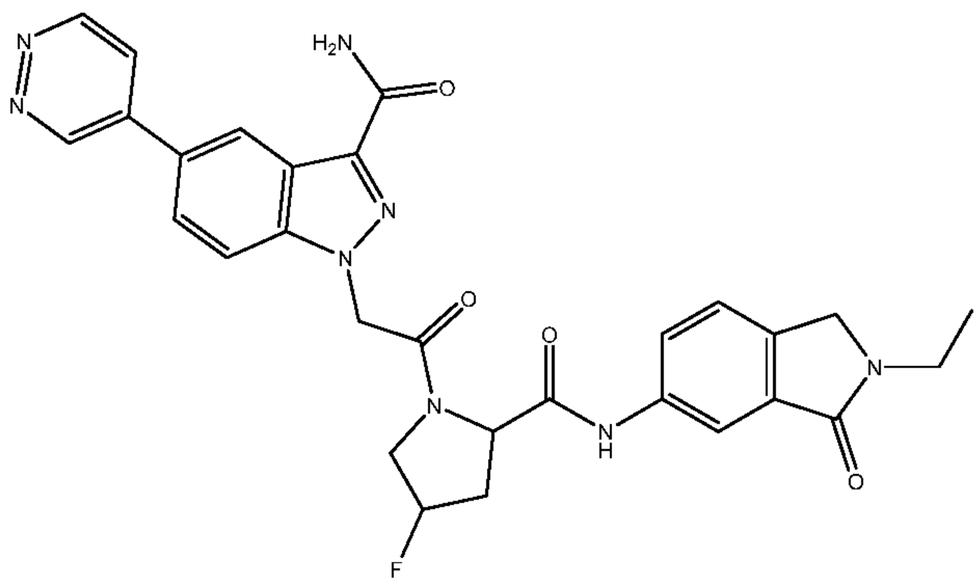


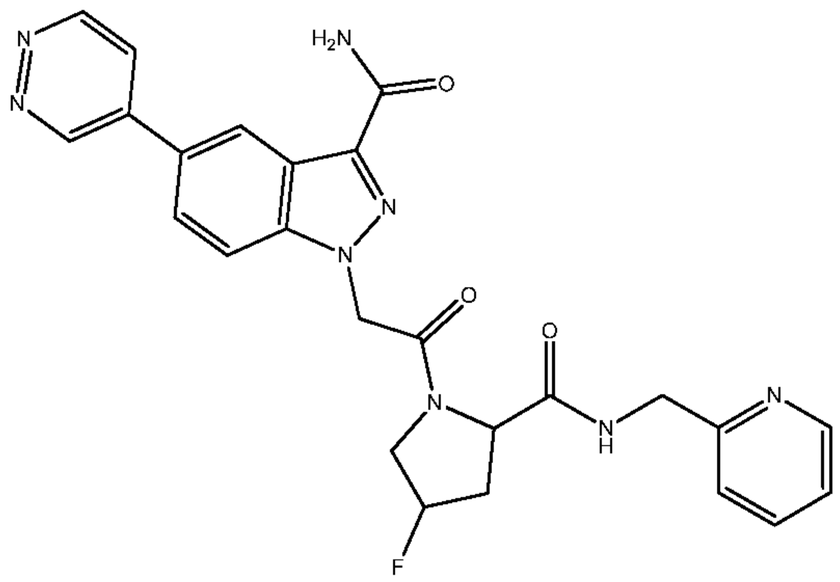


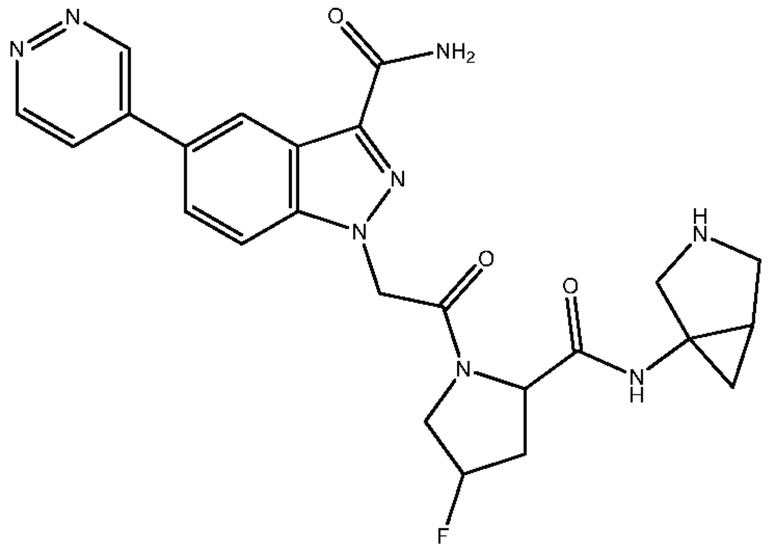


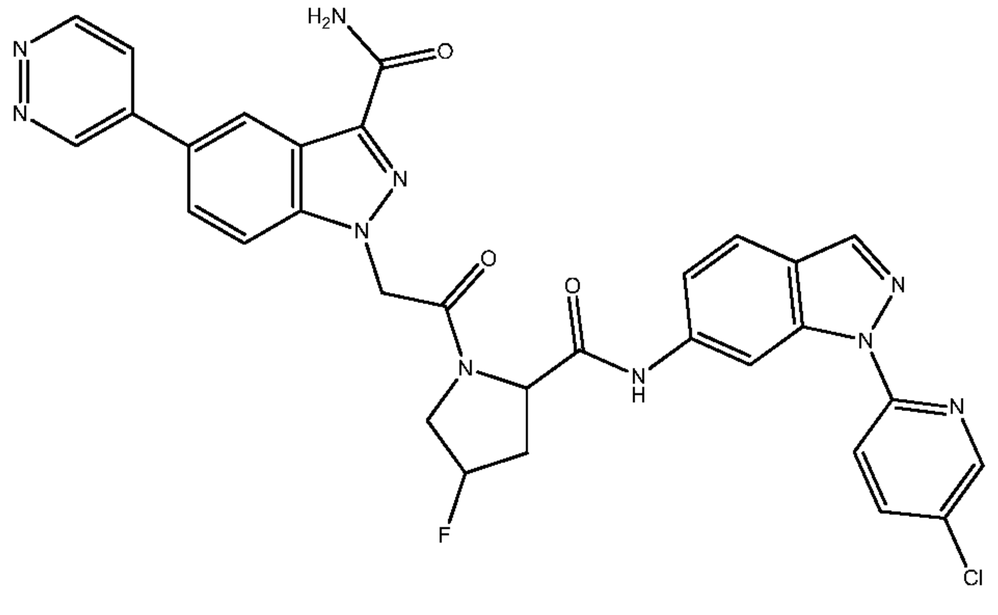


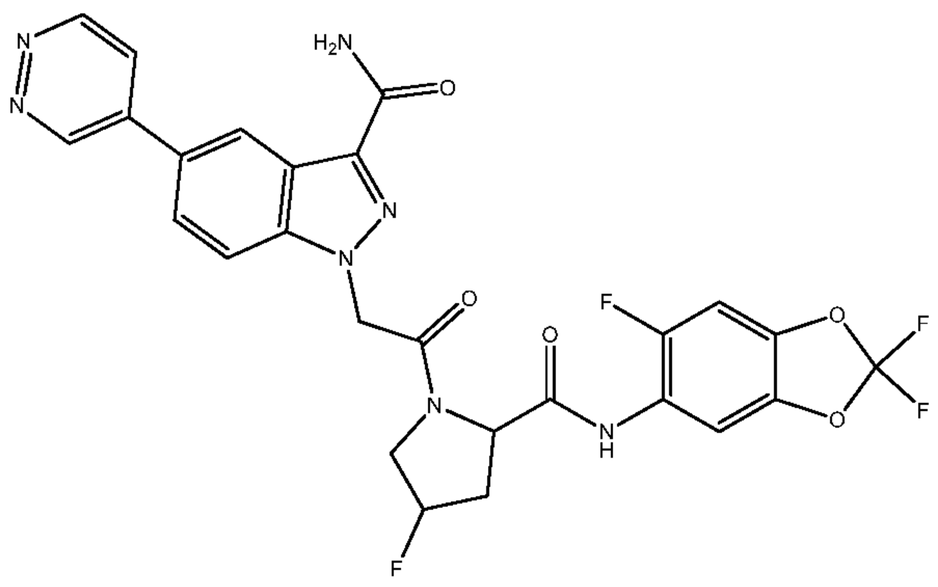


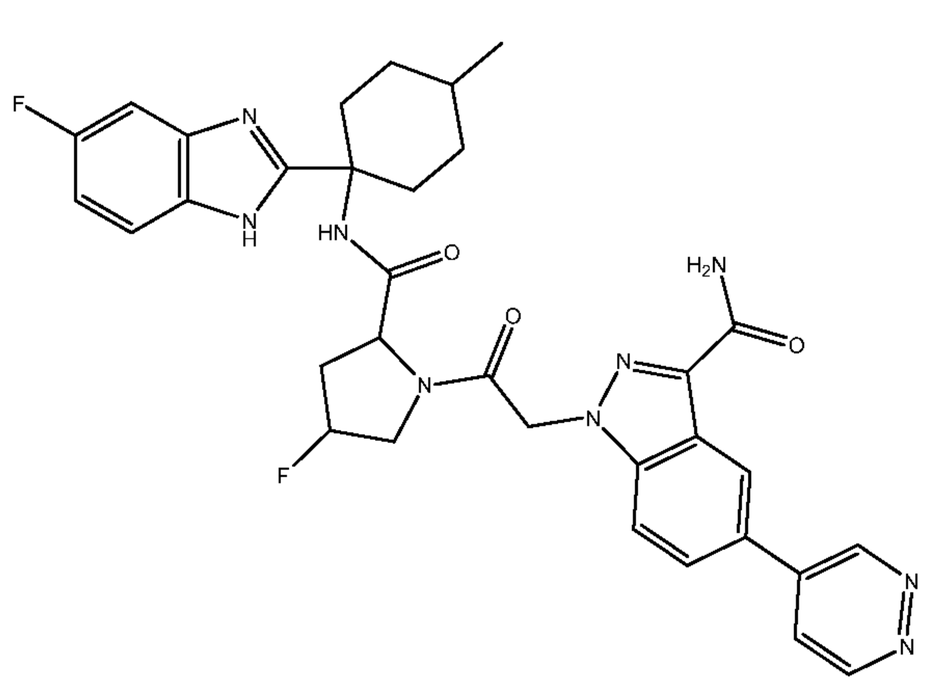


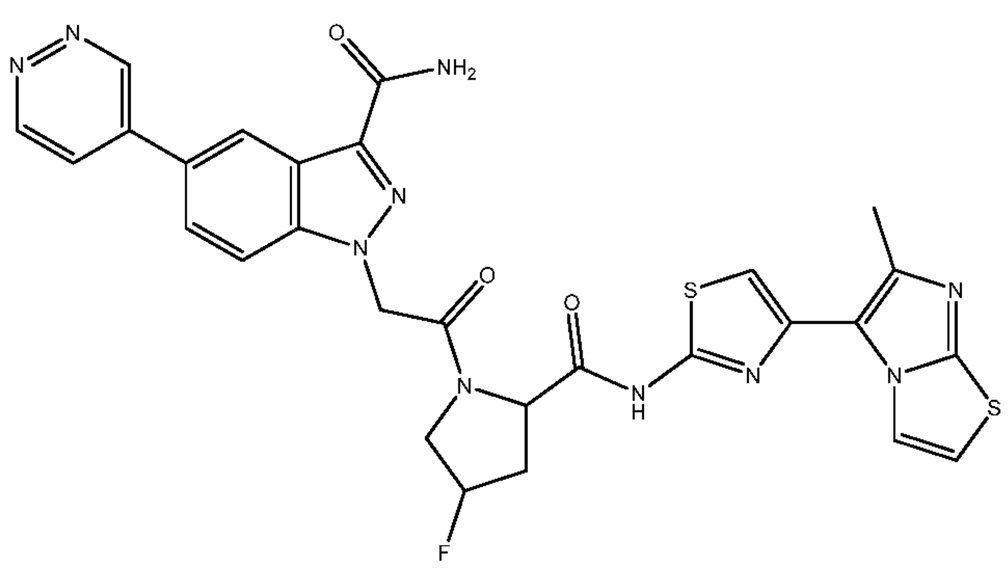


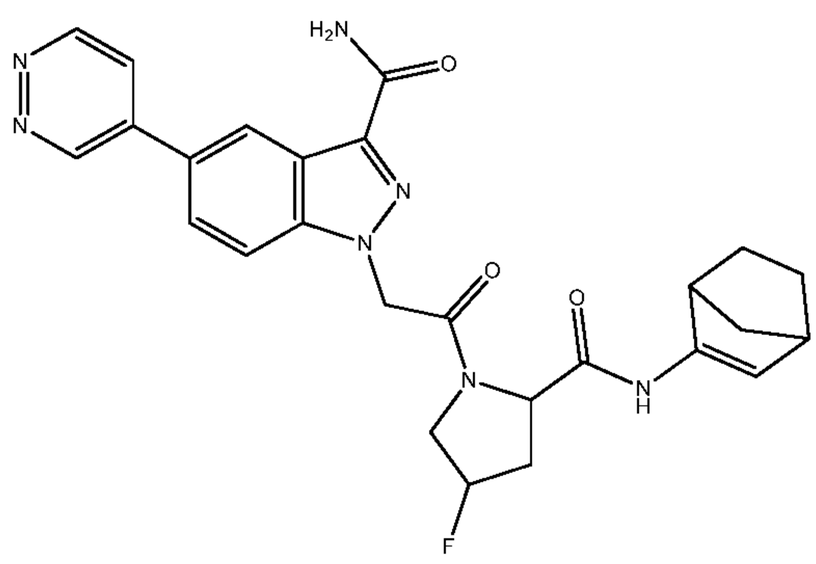


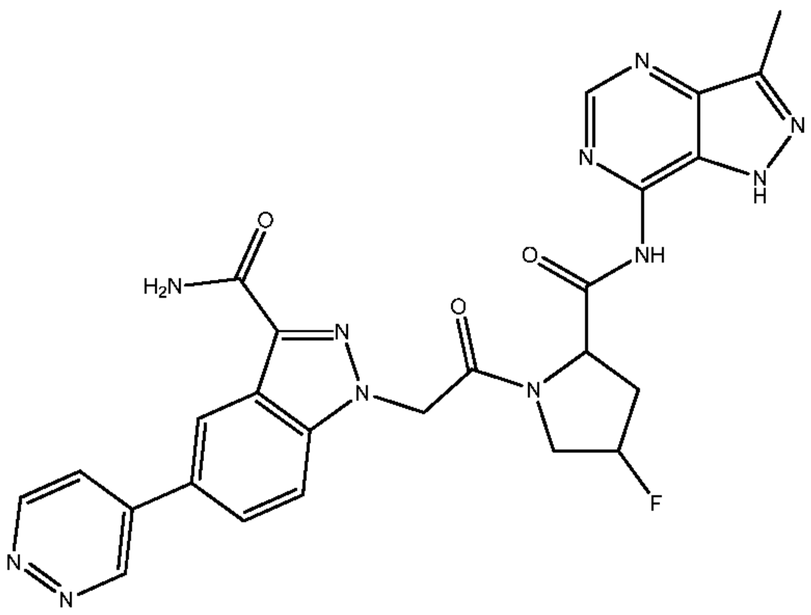


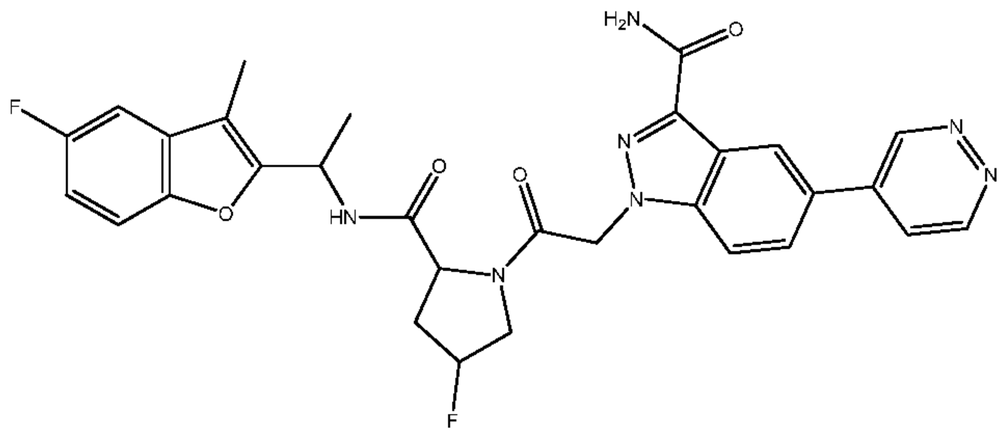


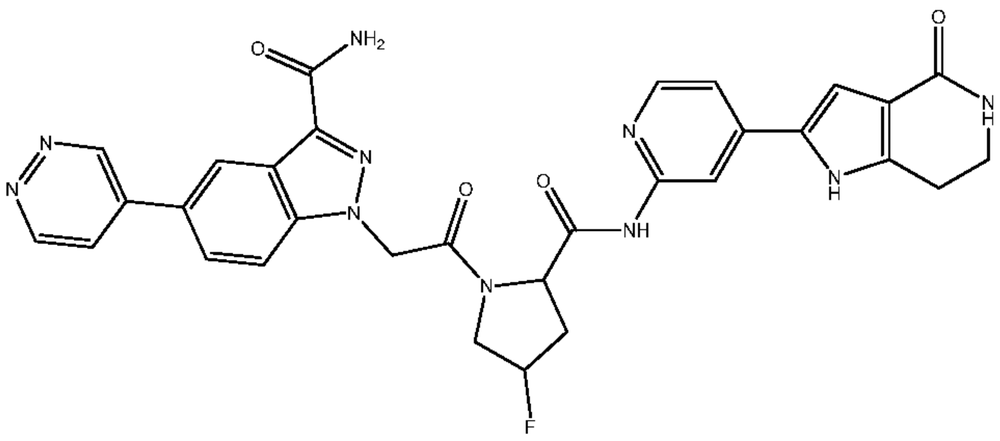


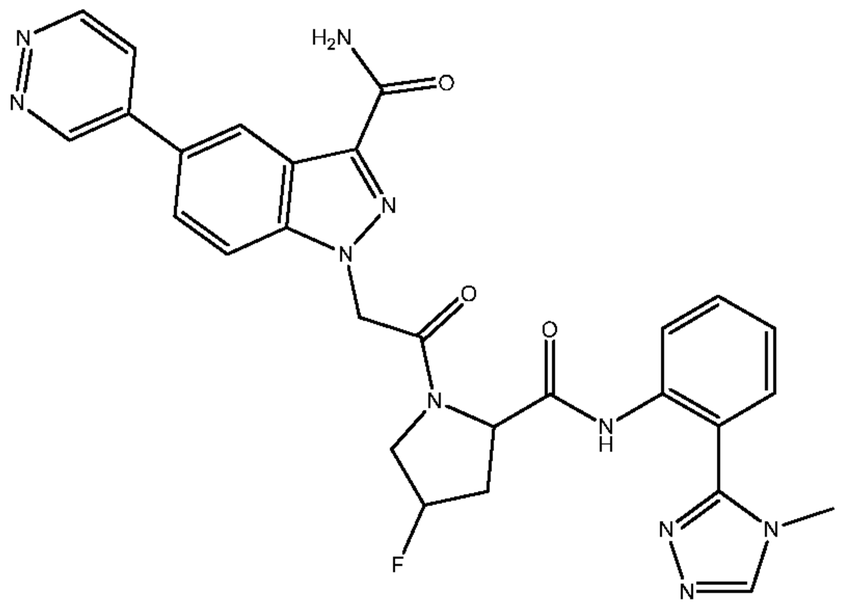


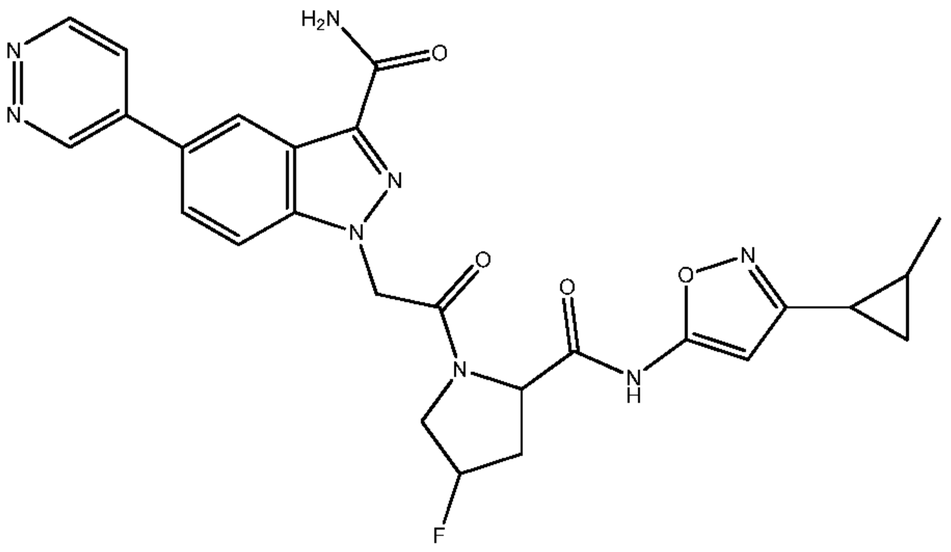


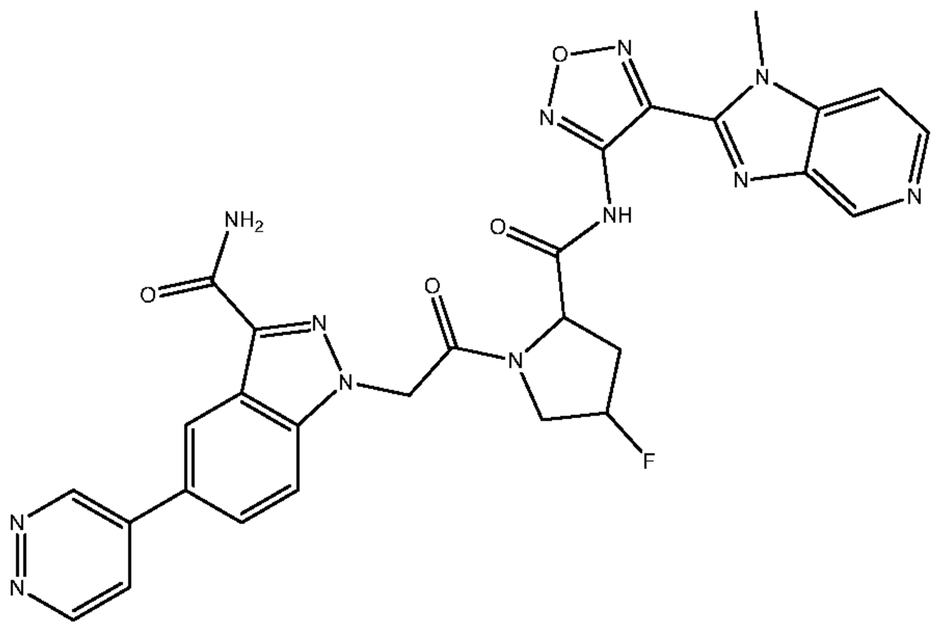


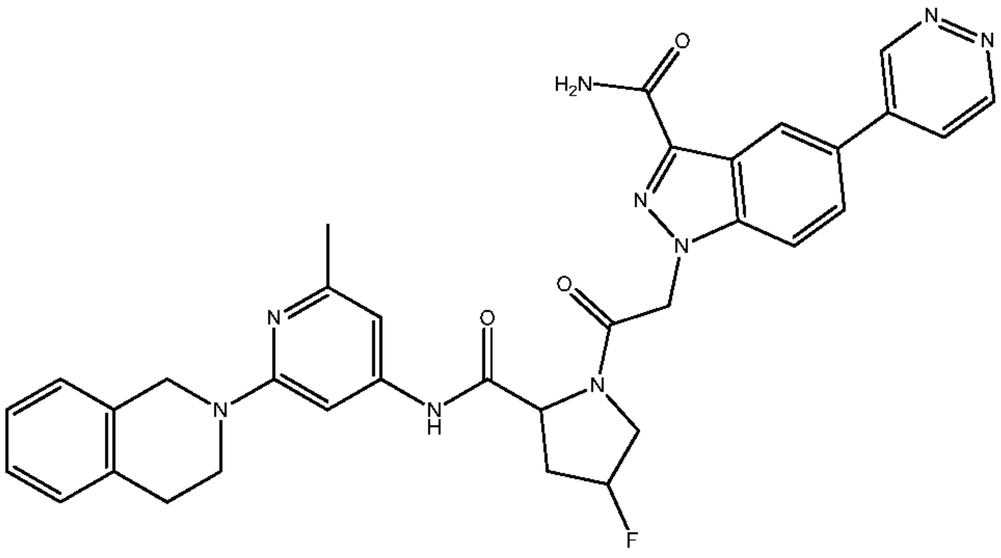


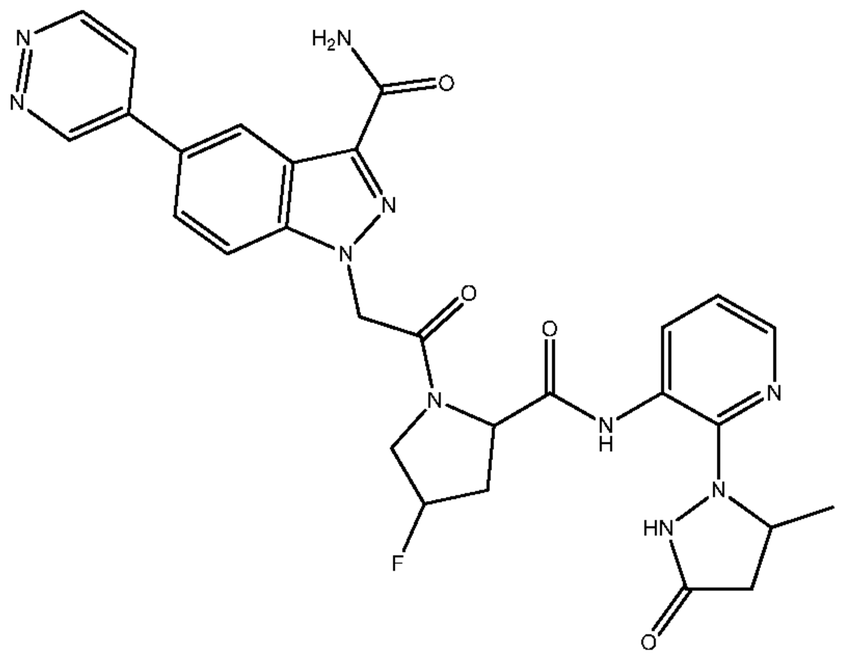


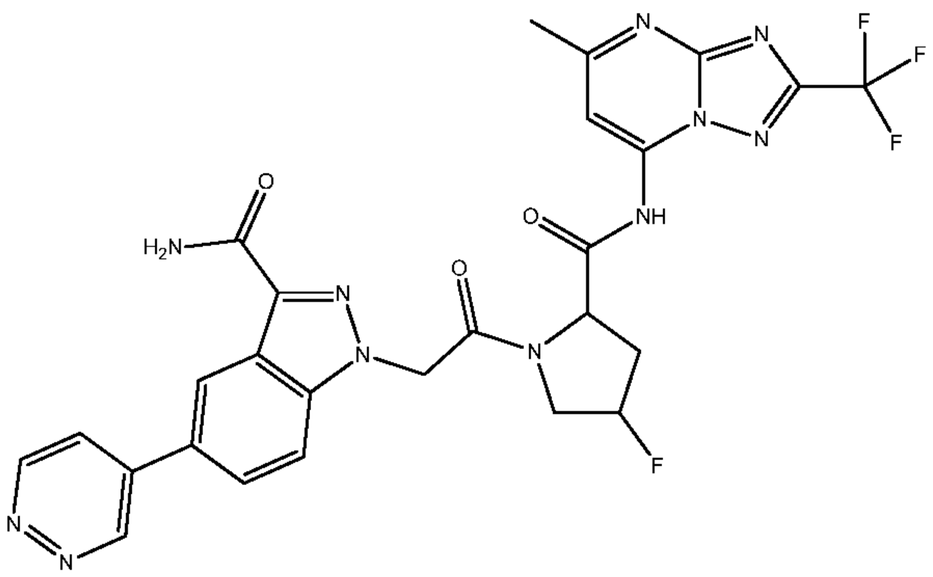


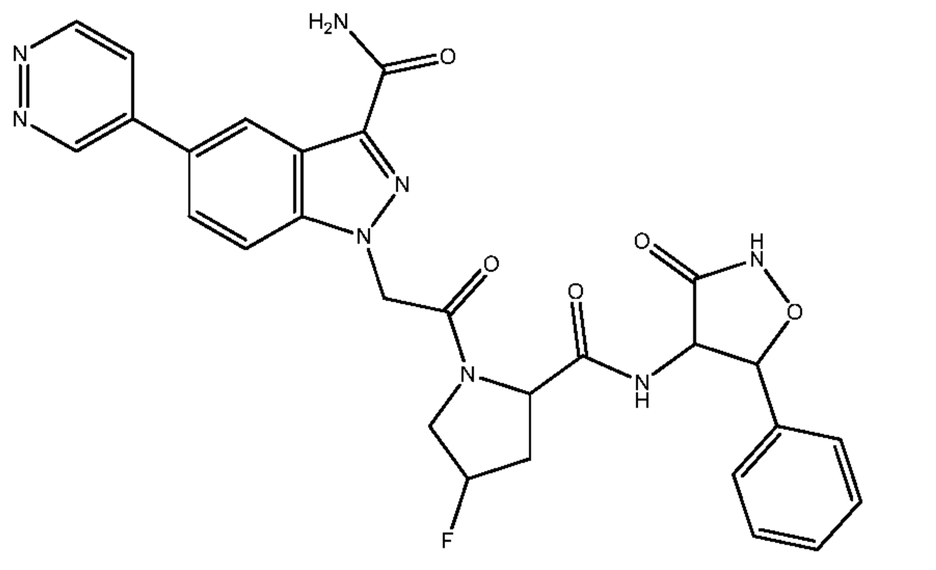


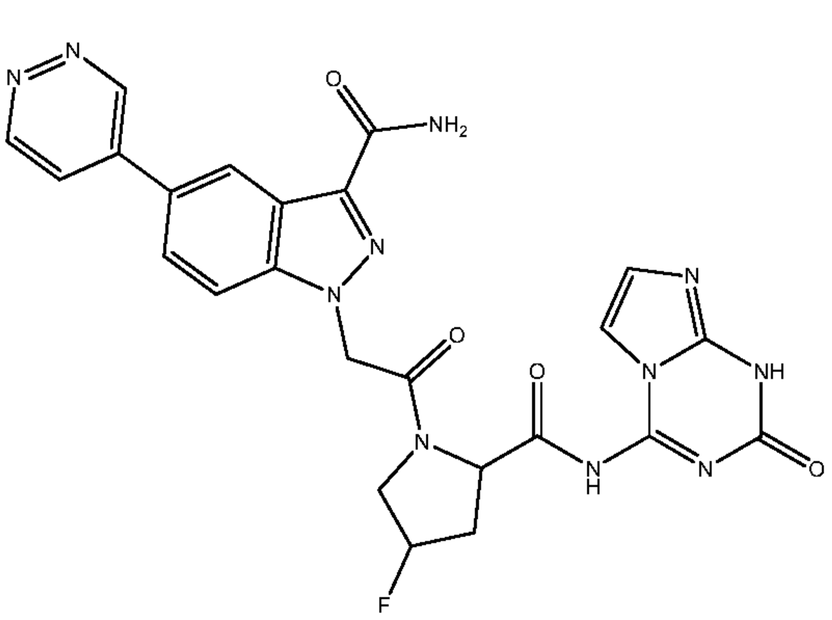


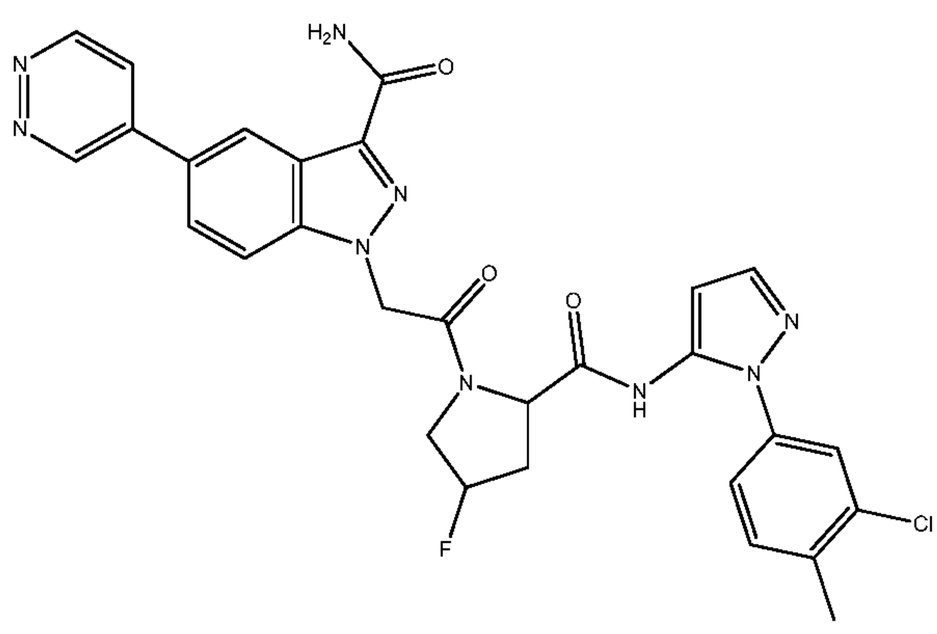


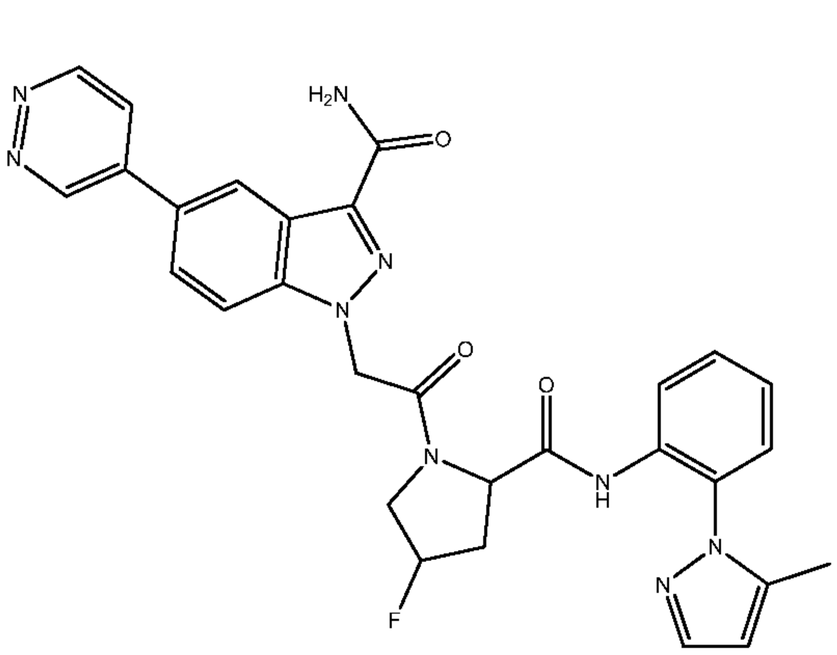


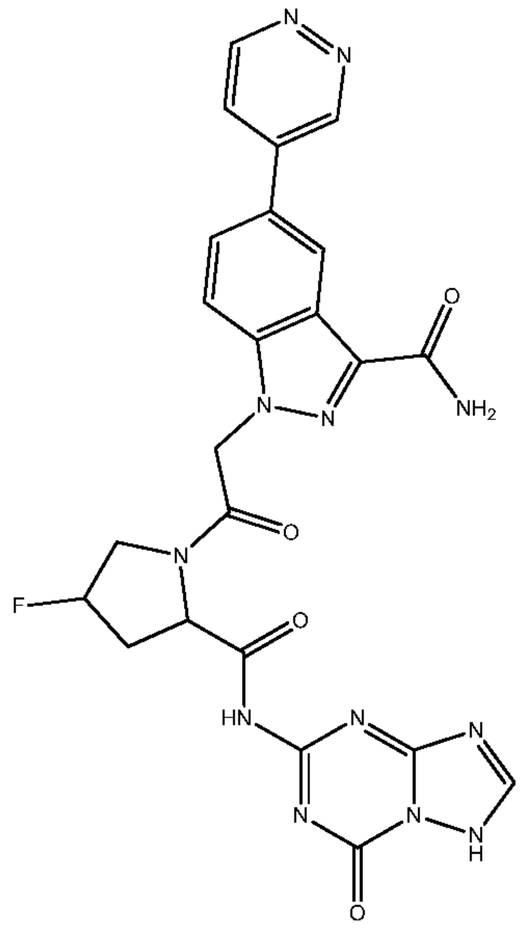


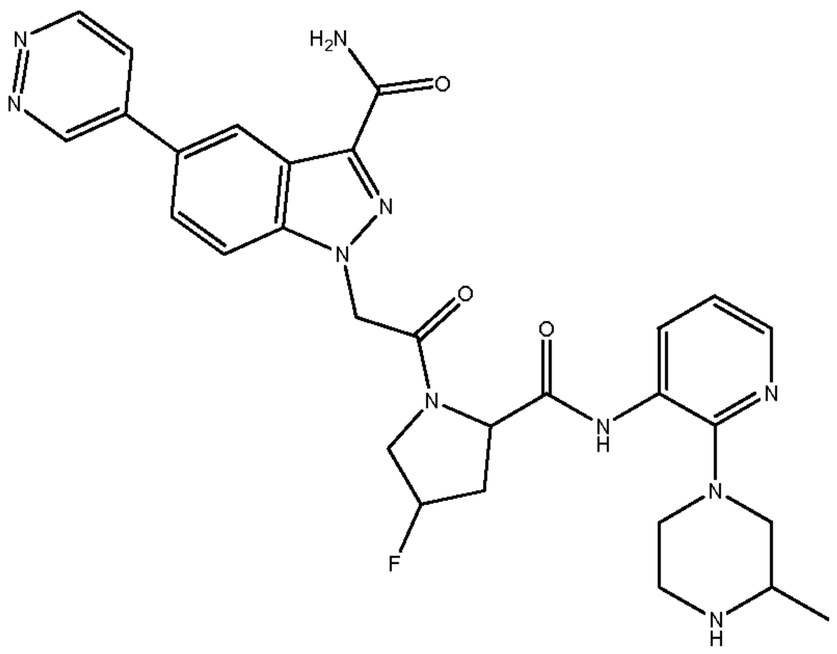


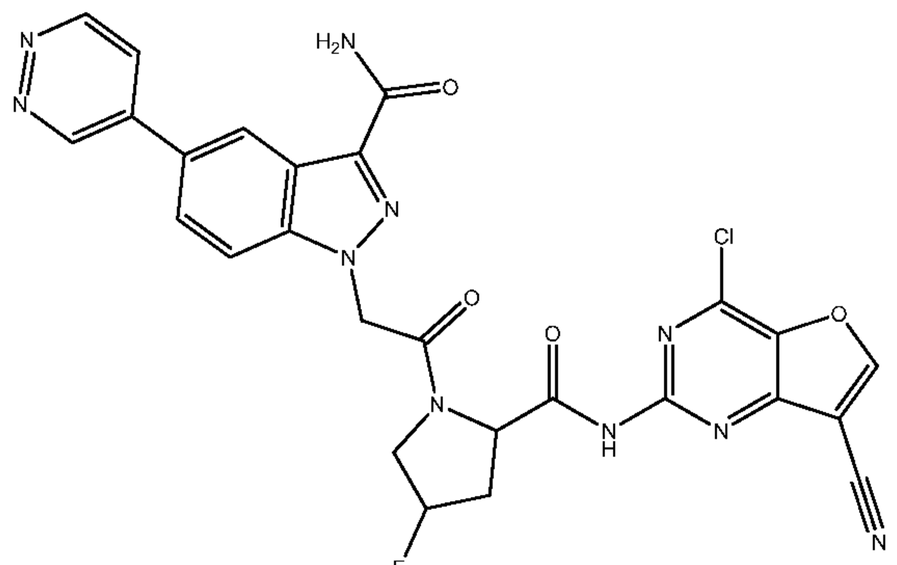


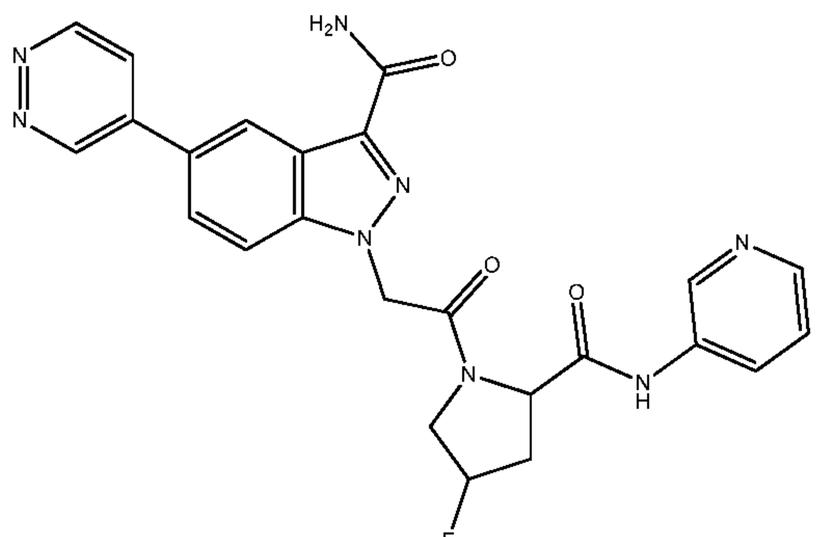


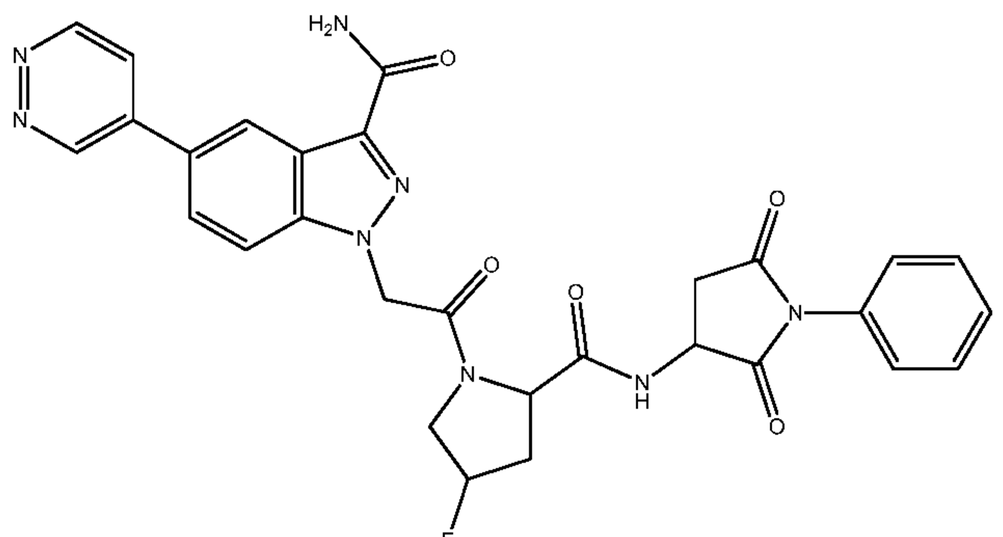


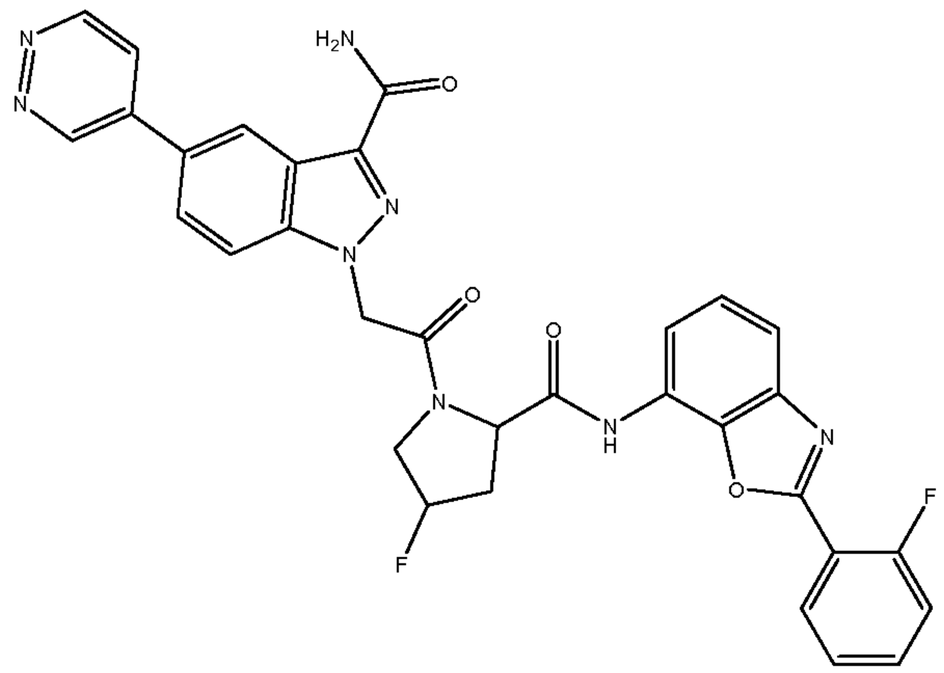


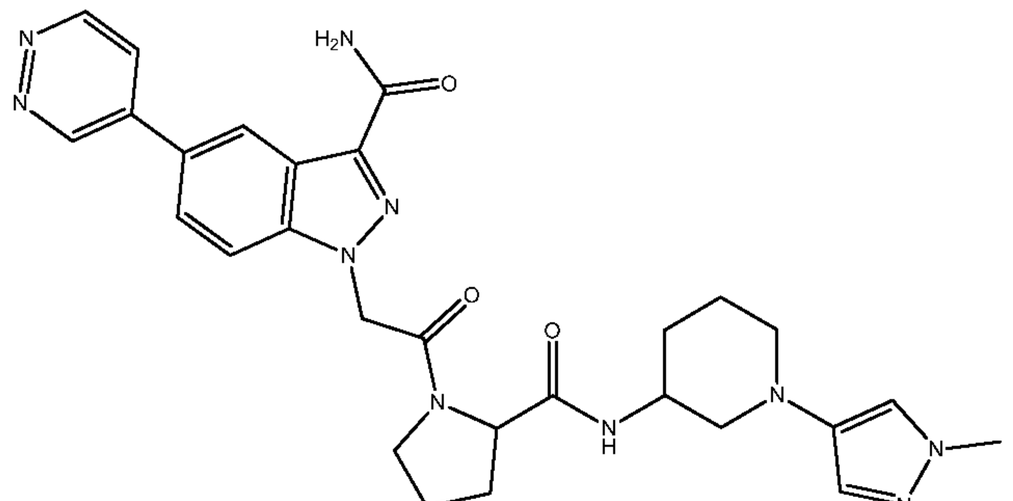


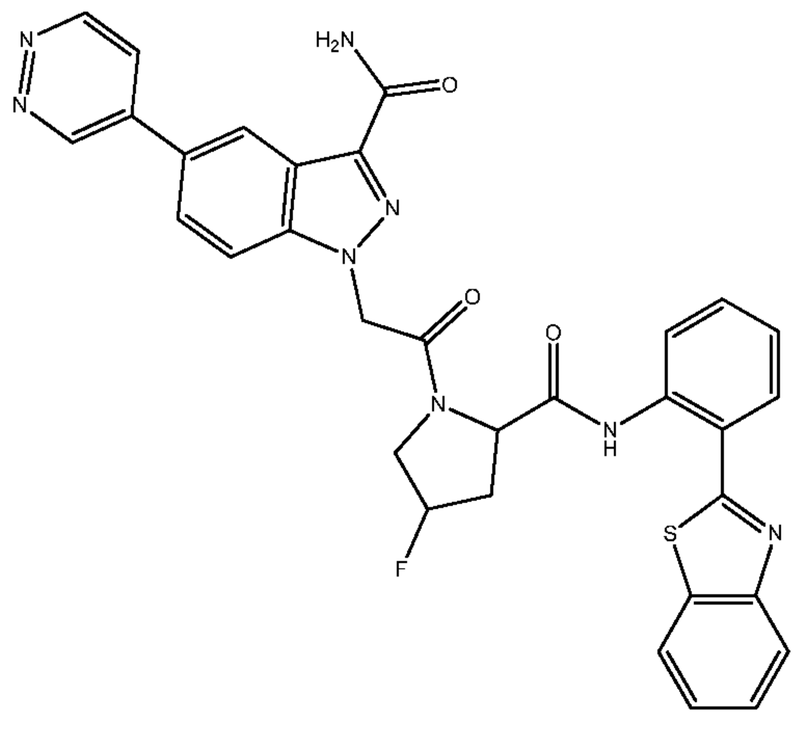


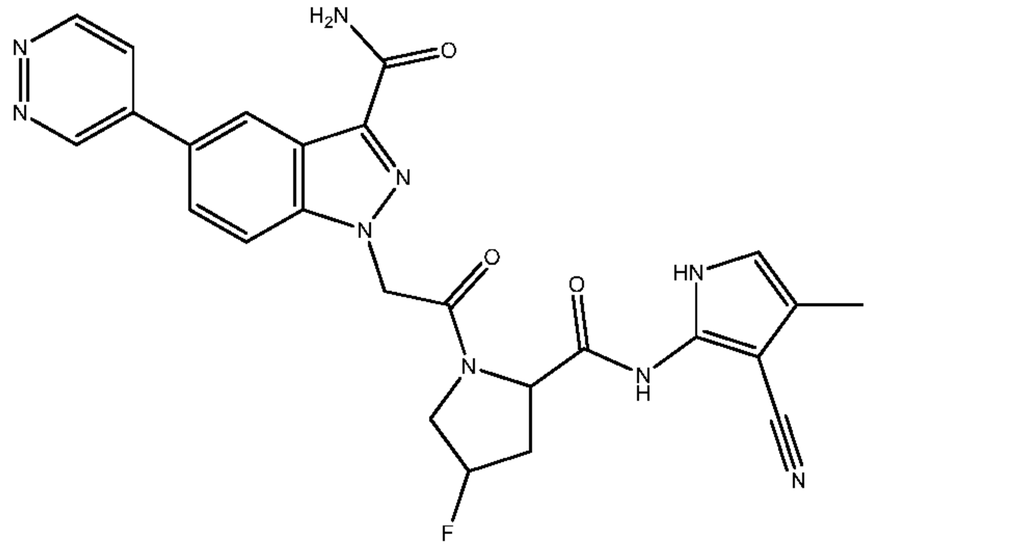


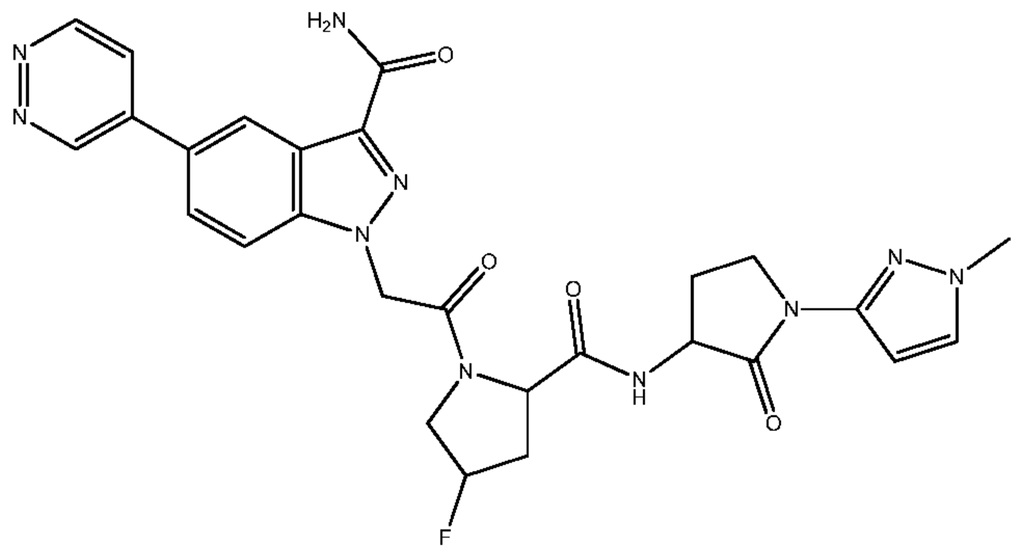


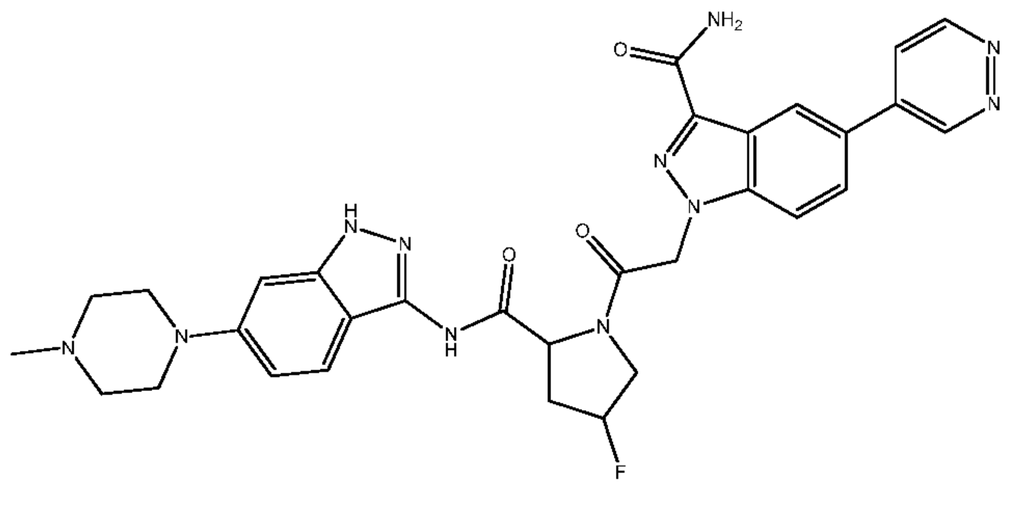


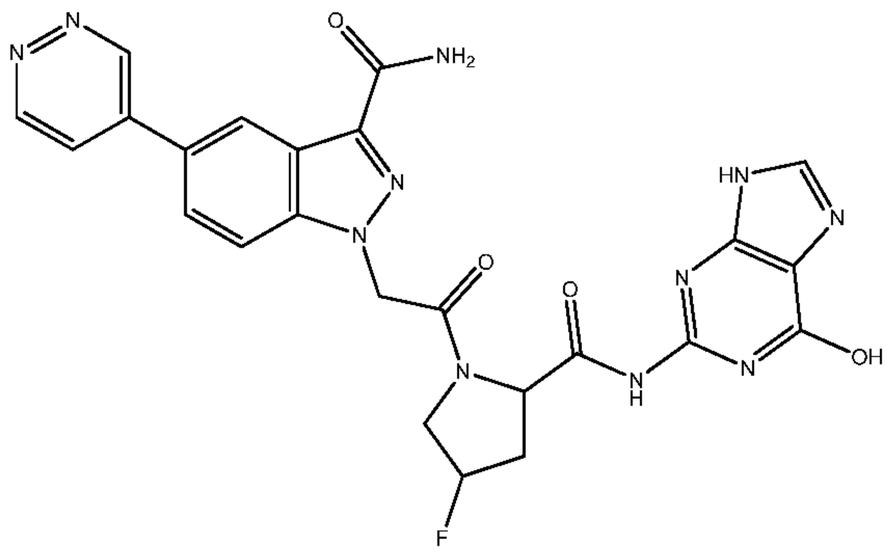


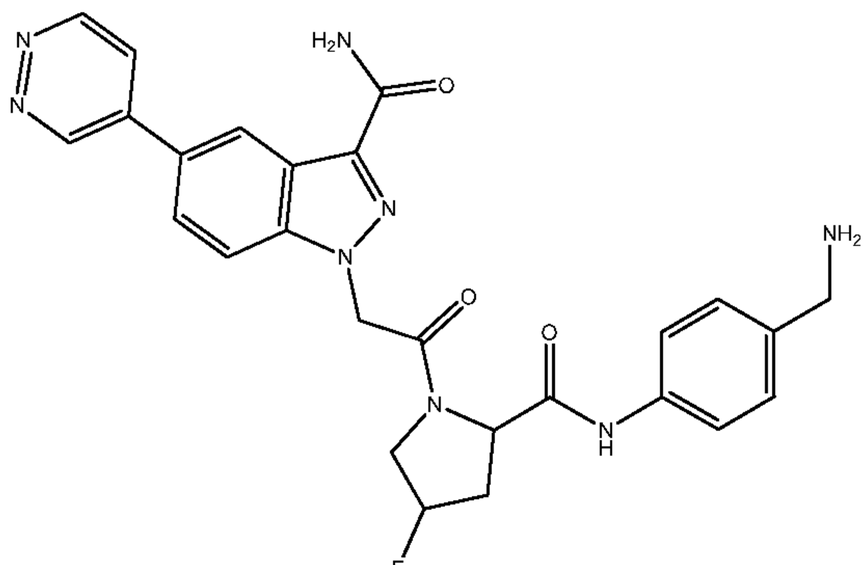


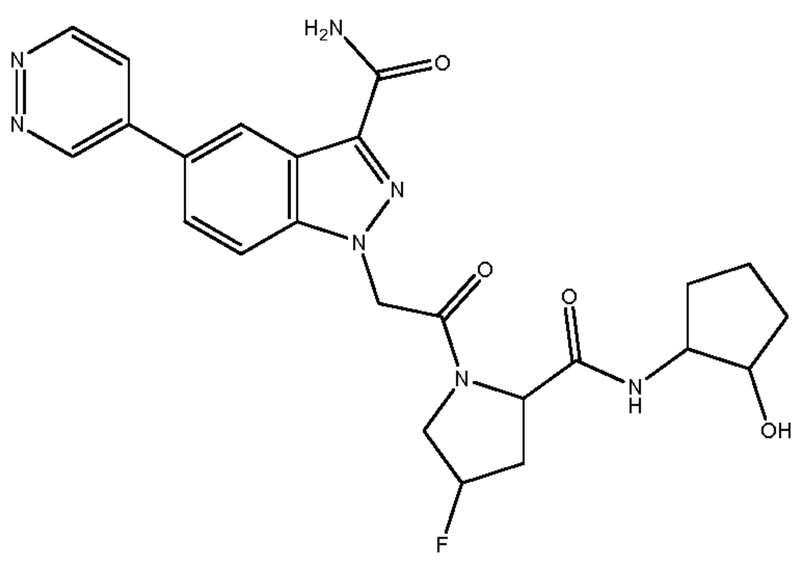


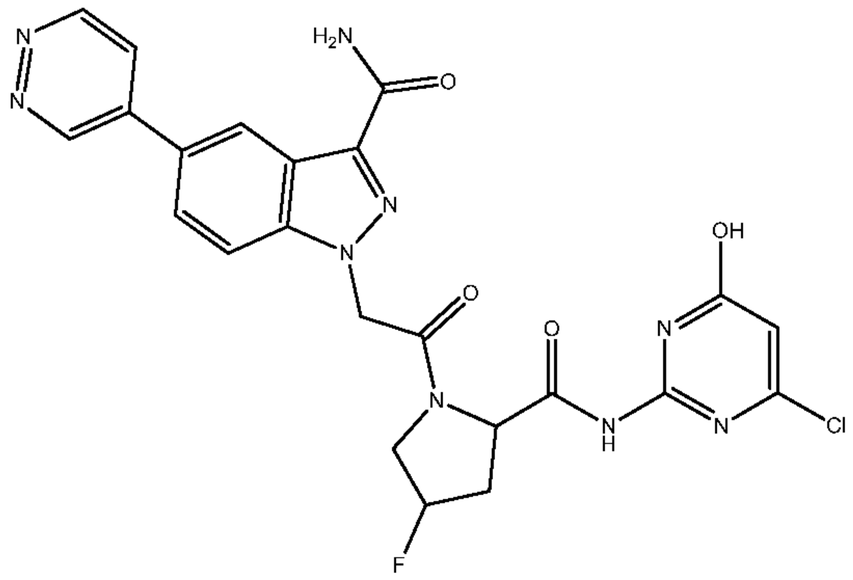


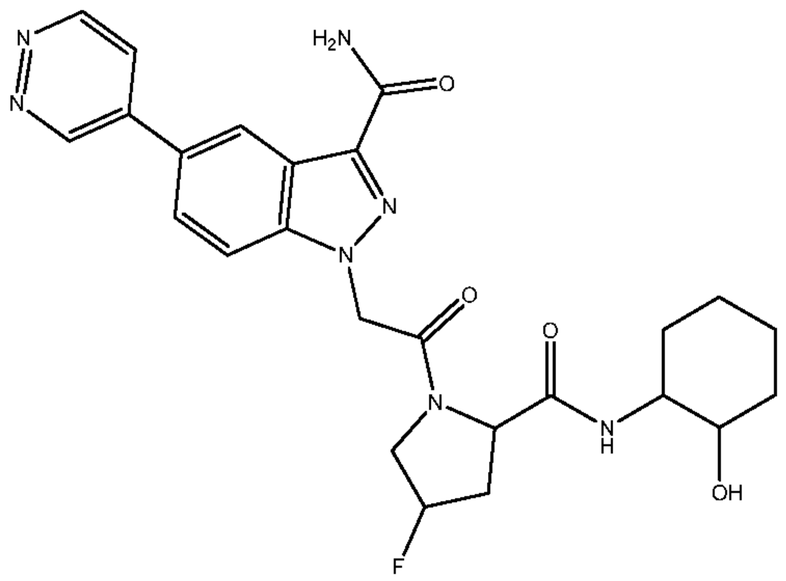


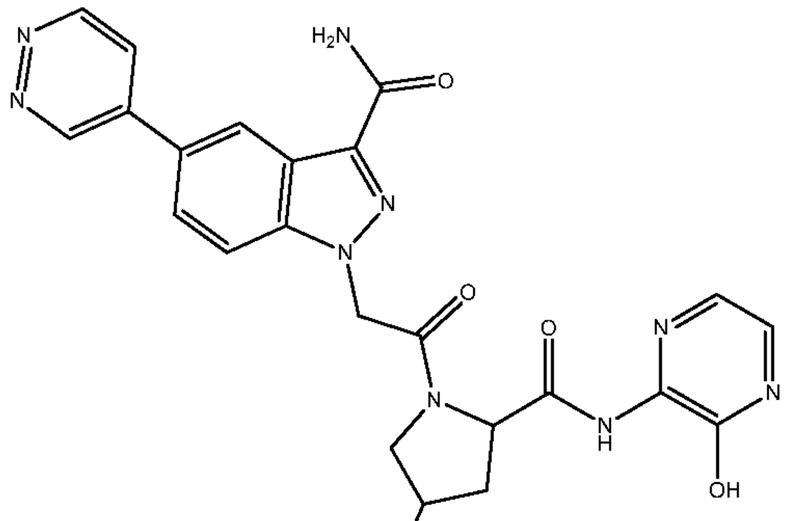


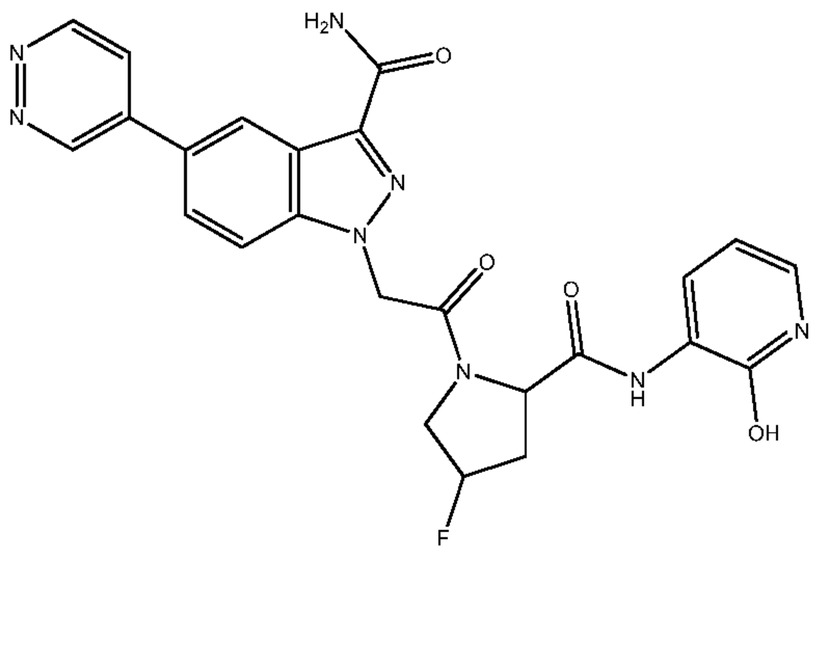


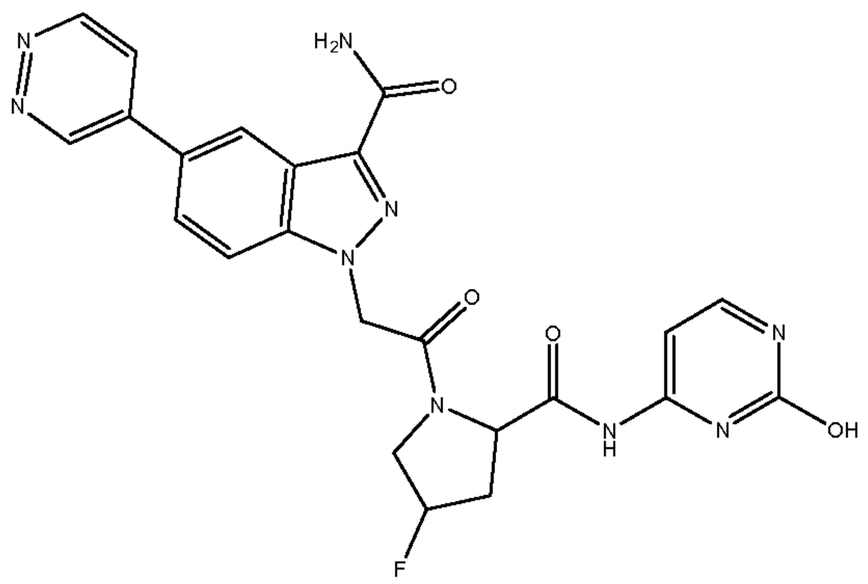


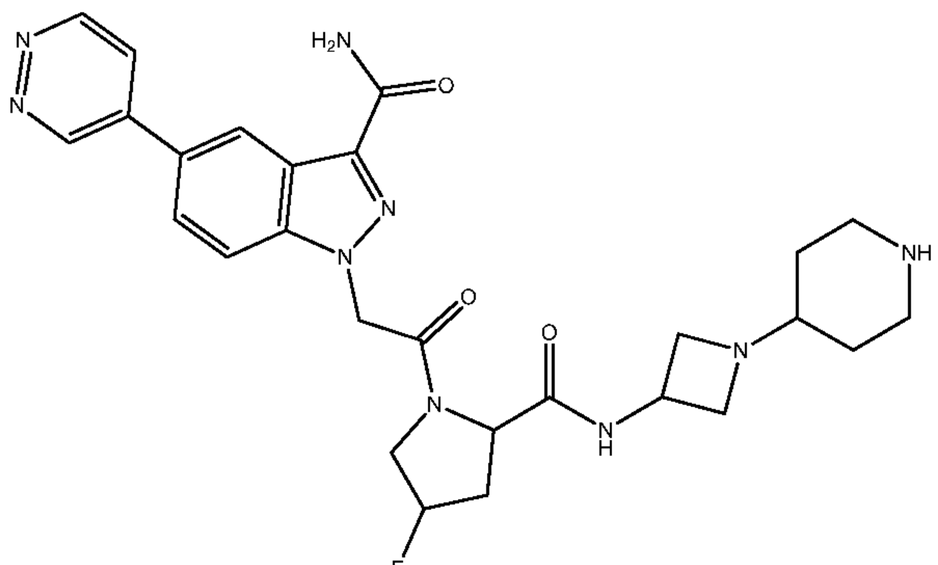


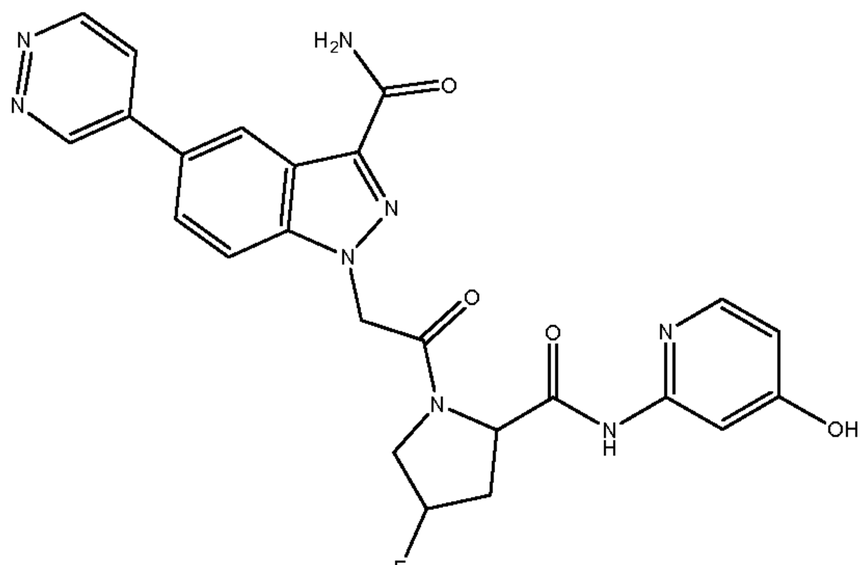


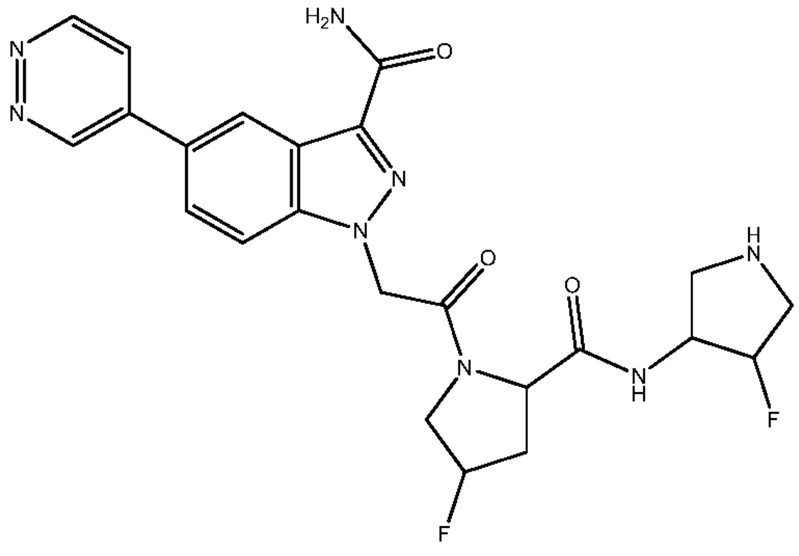


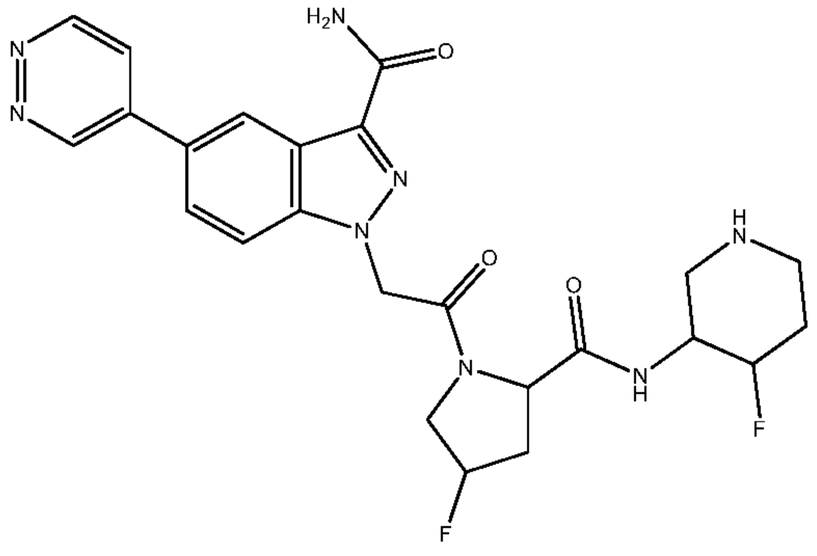


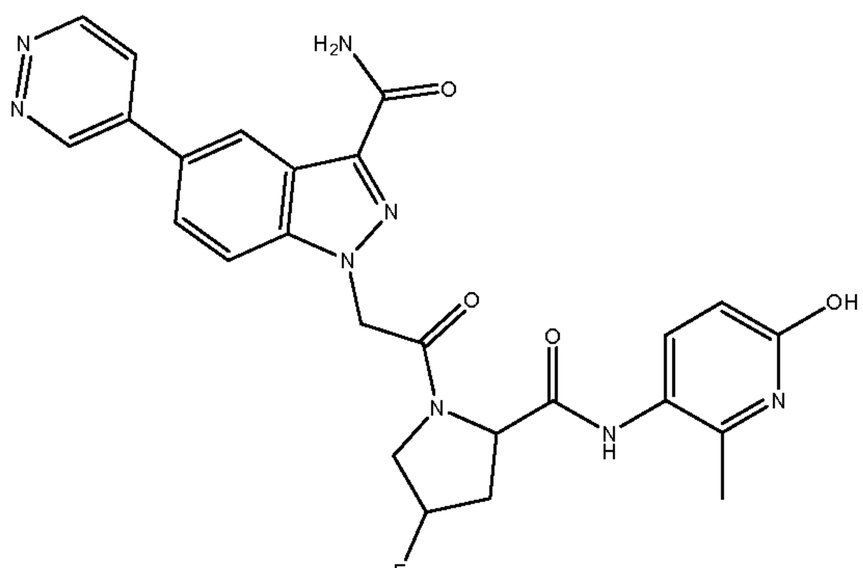


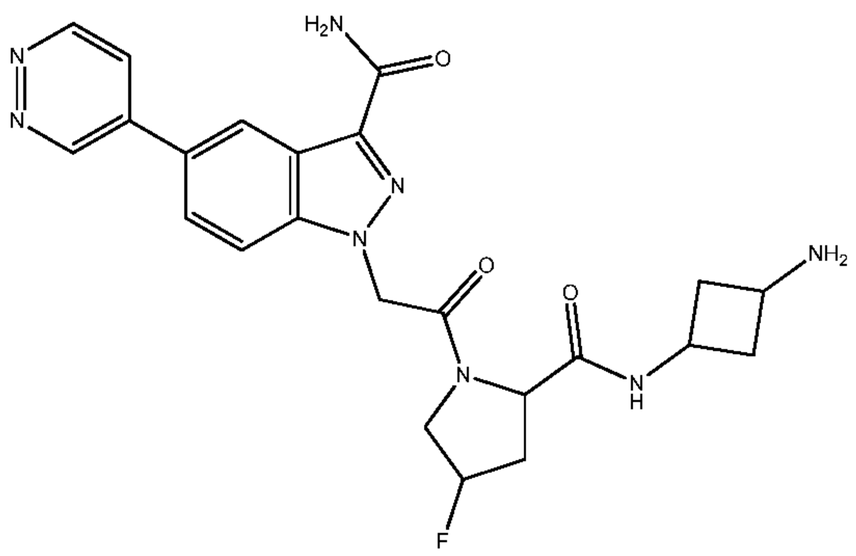


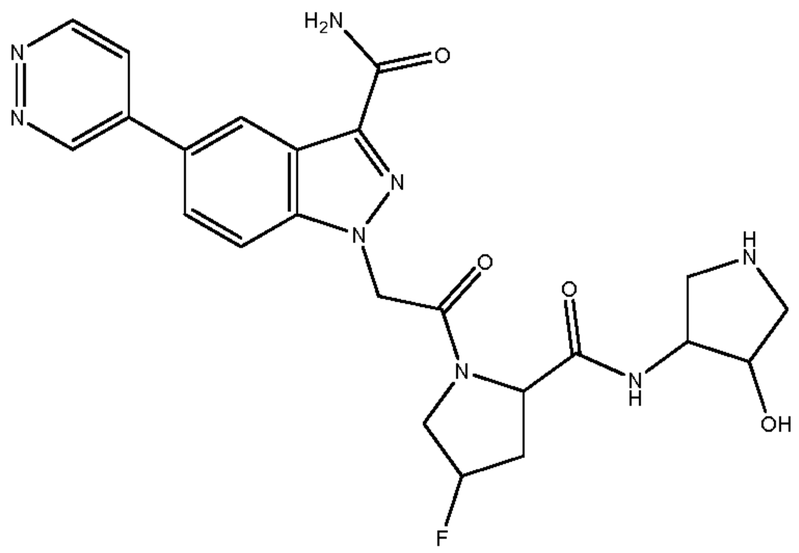


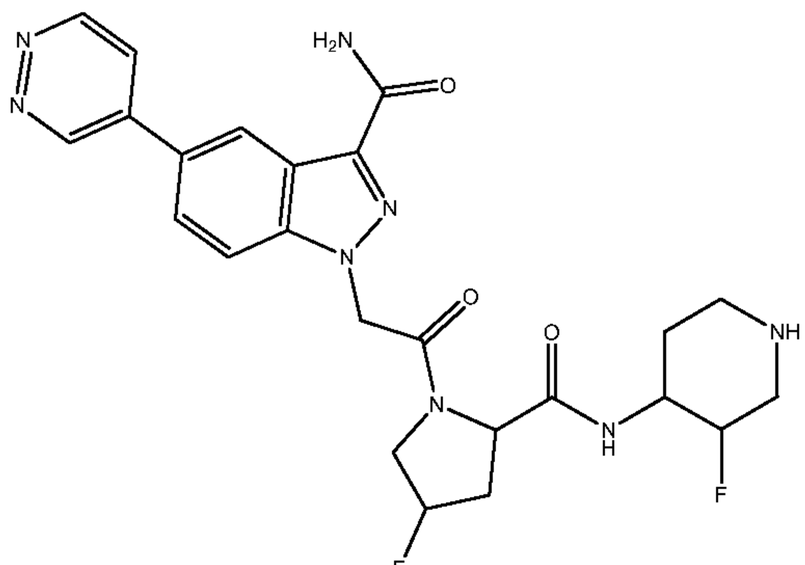


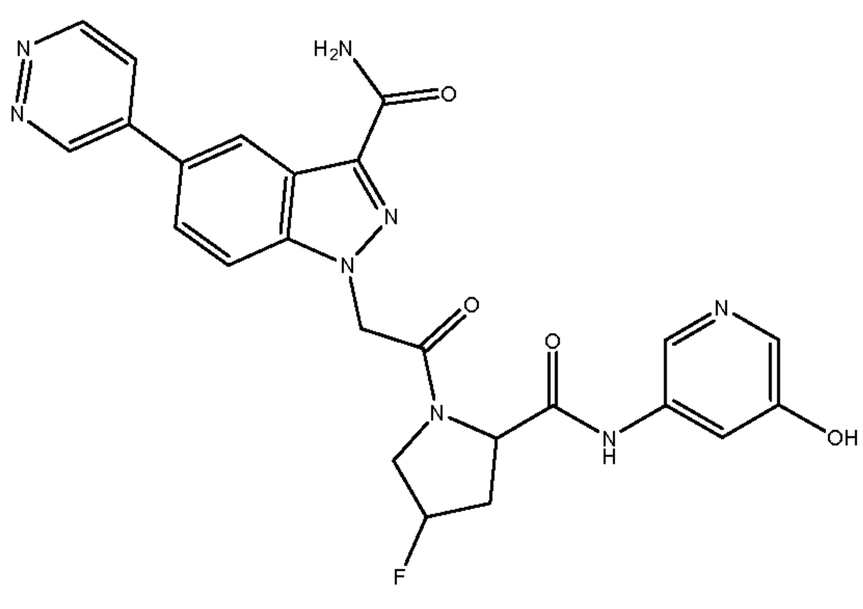


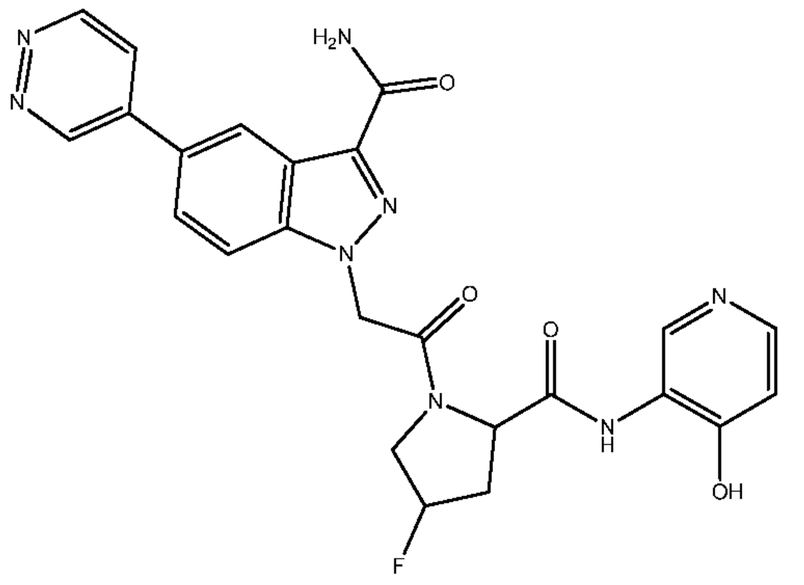


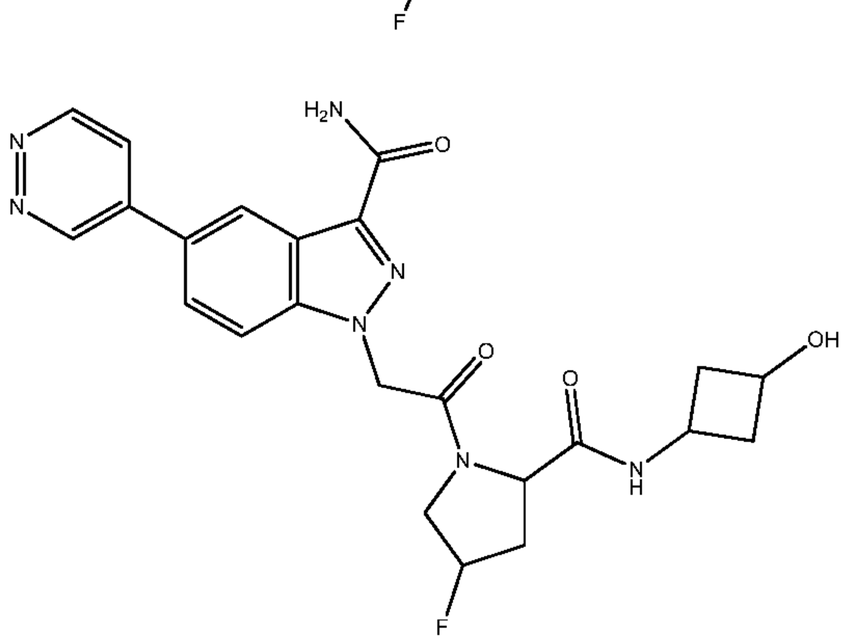


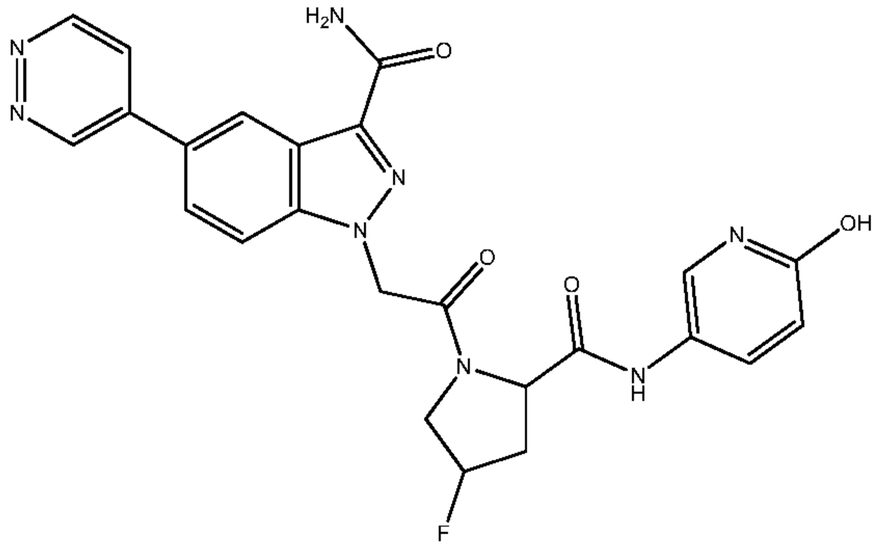


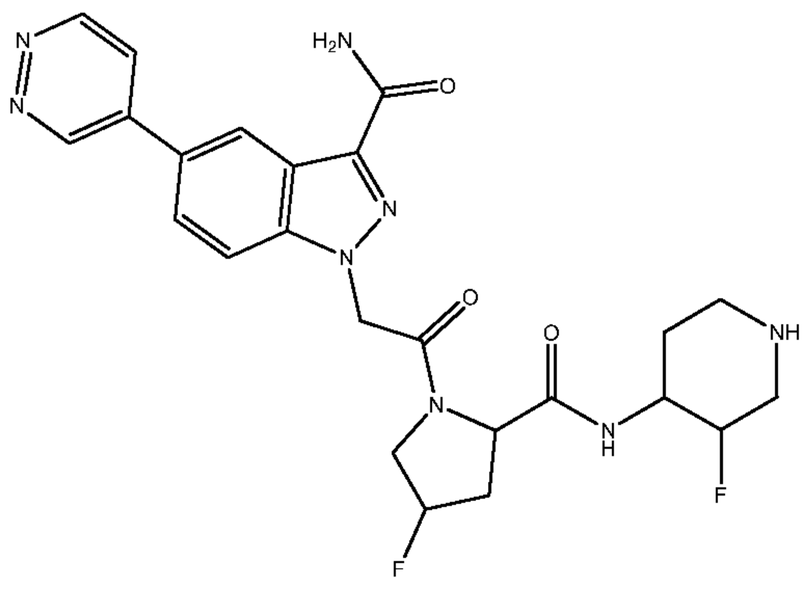


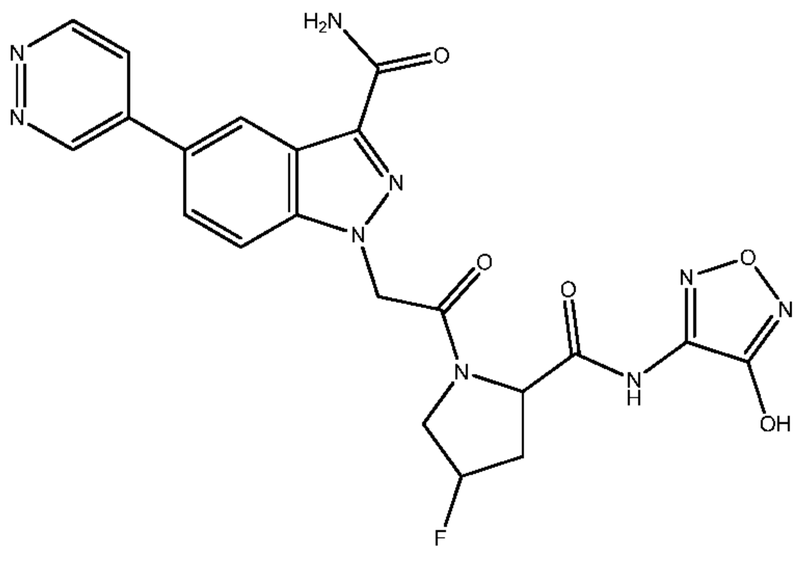


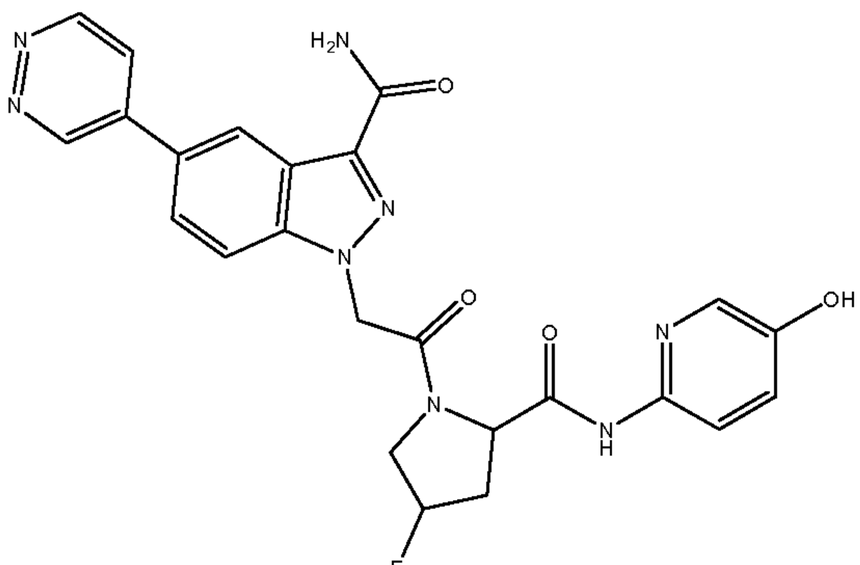


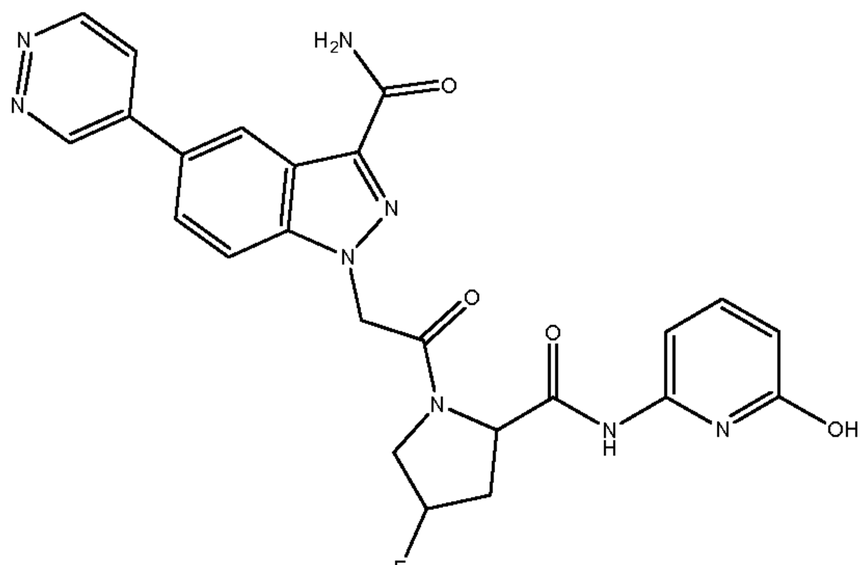


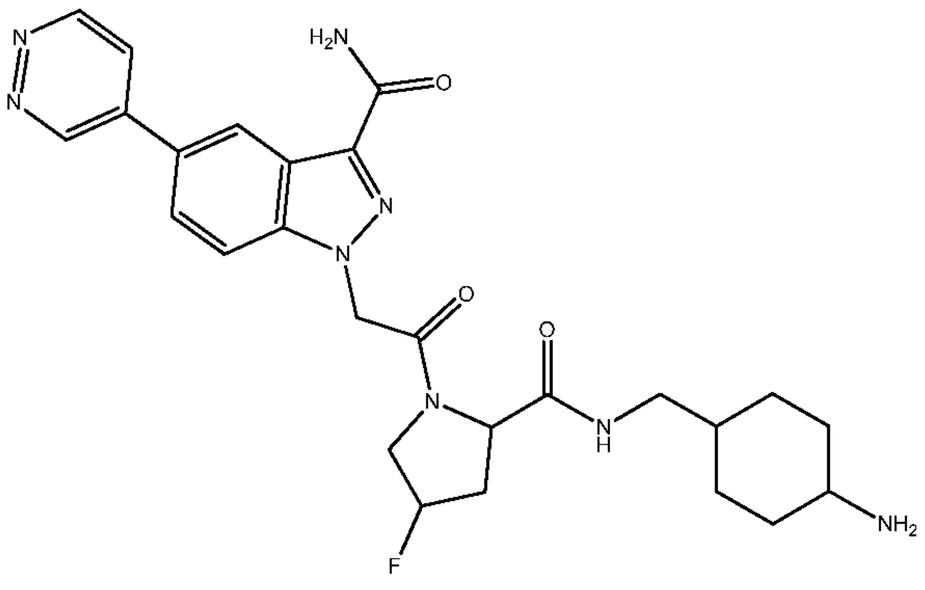


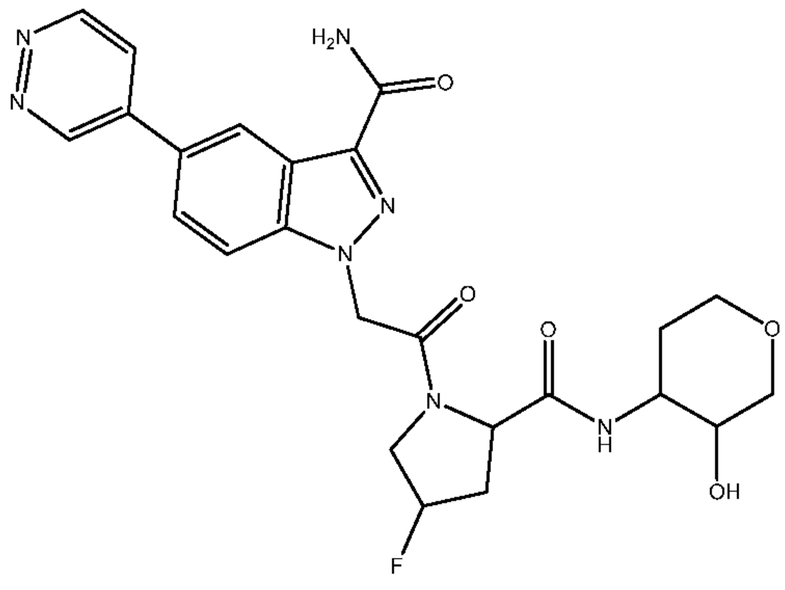


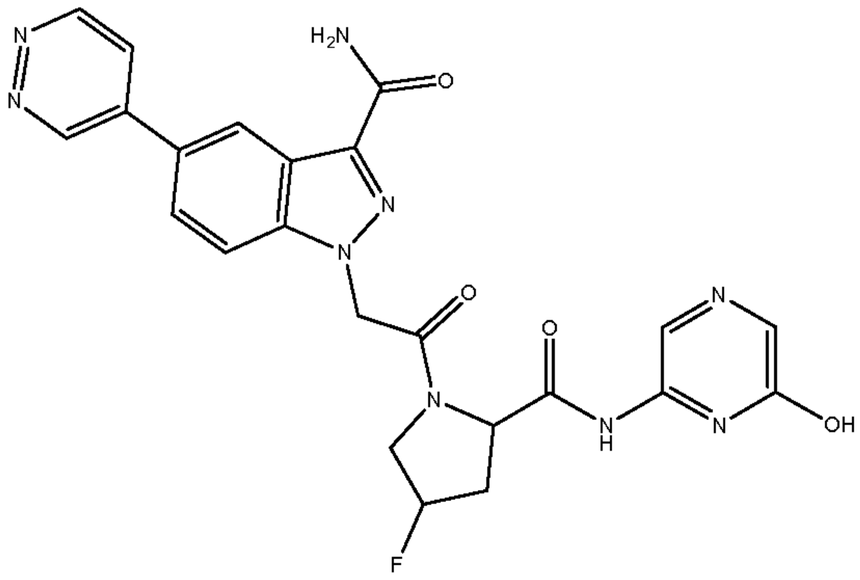


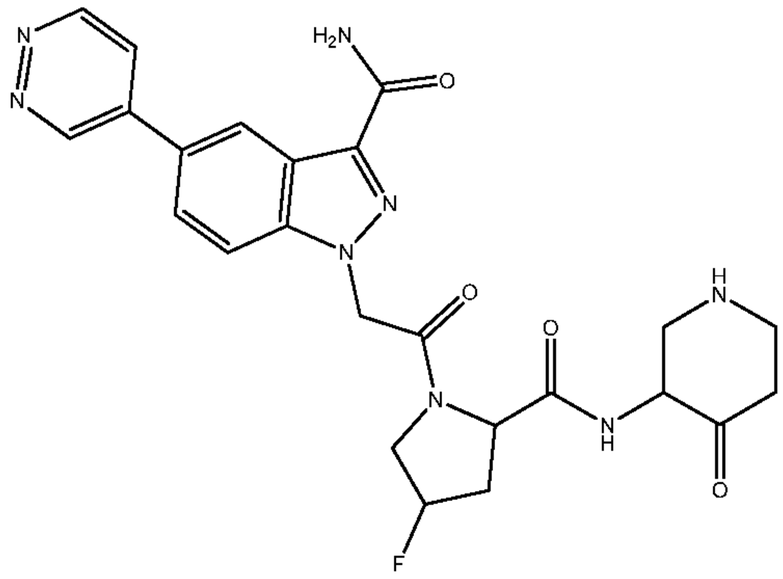


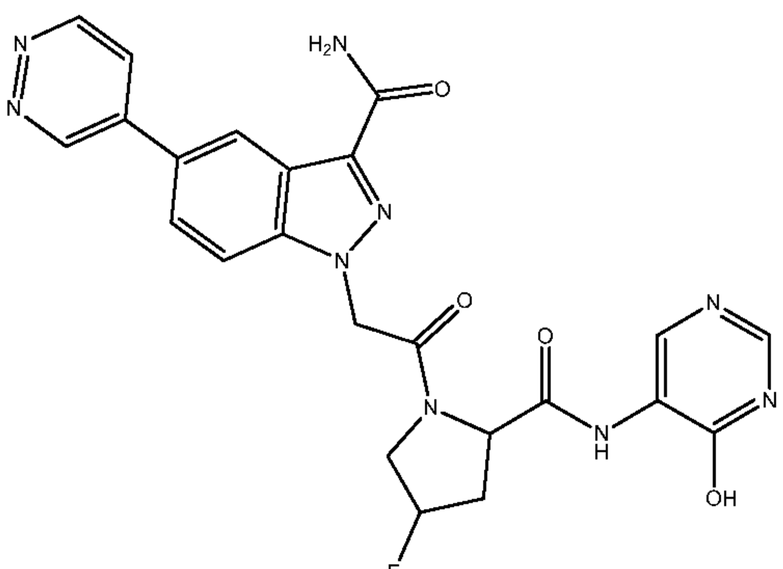


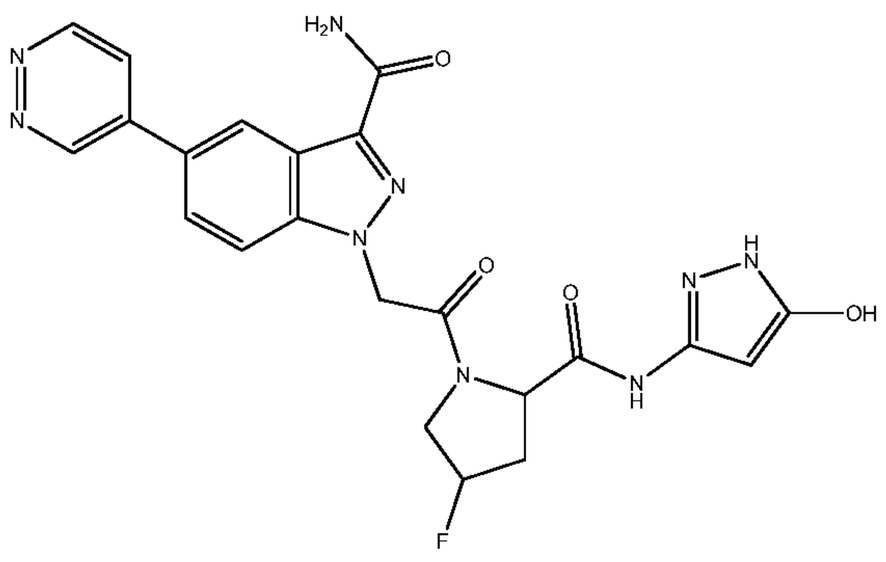










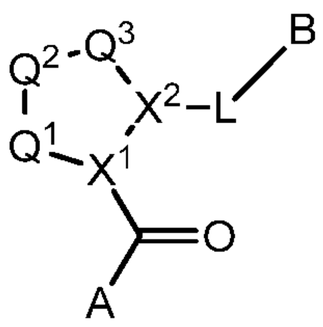


[0411] This specification has been described with reference to embodiments of the invention. However, one of ordinary skill in the art appreciates that various modifications and changes can be made without departing from the scope of the invention as set forth in the claims below. Accordingly, the specification 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.

Part B. INCORPORATION OF TEXT OF PRIORTY DOCUMENTS

[0412] For the purpose of assuring full right of priority to the previously filed priority applications, the text of the provisional U.S. Application 62/046,783, filed September 5, 2014, is hereby incorporated by reference and relevant portions are provided below. Where terms are overlapping, the term as used in a claim is considered to refer to the the terms as provided in Part A above unless otherwise indicated or clear from the text of the claim, however, all disclosure is considered part of the invention for all disclosed purposes.

[0413] The disclosure provides compounds of Formula I



(I)

and the pharmaceutically acceptable salts thereof. Within Formula I the variables, e.g, A, B, L, X^1, X^2, Q^1, Q^2, and Q^3 carry the following values.

[0414] Q^1 is $N(R^1)$ or $C(R^1R^{1'})$.

[0415] Q^2 is $C(R^2R^{2'})$, $C(R^2R^{2'})$-$C(R^2R^{2'})$, or $C(R^2R^{2'})O$.

[0416] Q^3 is $N(R^3)$, S, or $C(R^3R^{3'})$.

[0417] (a) X^1 and X^2 are independently N or CH, or (b) X^1 and X^2 together are C=C.

[0418] R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently chosen at each occurence from (c) and (d):

[0419] (c) hydrogen, halogen, hydroxyl, nitro, cyano, amino, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkynyl, C_2-C_6alkanoyl, C_1-C_6thioalkyl, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, -C_0-C_4alkylNR^9R^{10}, $-C(O)OR^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-OC(O)NR^9R^{10}$, $-NR^9C(O)OR^{10}$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, where R^9 and R^{10} are

independently chosen at each occurrence from hydrogen, C_1-C_6alkyl, and (C_3-C_7cycloalkyl)C_0-C_4alkyl;

[0420] (d) -C_0-C_4alkyl(C_3-C_7cycloalkyl) and -O-C_0-C_4alkyl(C_3-C_7cycloalkyl).

[0421] Additionally any one of the following rings (e), (f), (g), (h), (i), or (j) may be present:

[0422] (e)R^1 and $R^{1'}$ or R^3 and $R^{3'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently chosen from N, O, or S;

[0423] (f) R^2 and $R^{2'}$ may be taken together to form a 3- to 6-membered carbocyclic spiro ring,

[0424] (g) R^2 and $R^{2'}$may be taken together to form a 3- to 6-membered heterocyclic spiro ring,

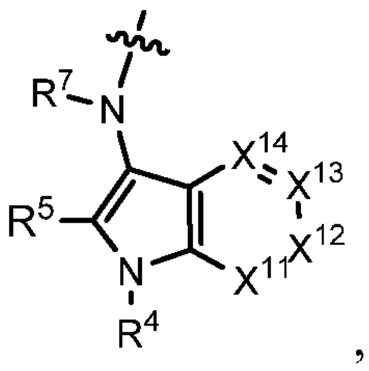
[0425] each of which spiro rings (e), (f), and (g) is unsubstituted or substituted with one or more halogen or methyl substituents;

[0426] (h) R^1 and R^2 may be taken together to form a 3-membered carbocyclic ring;

[0427] (i) R^1 and R^2 may be taken together to form a 4- to 6-membered carbocyclic ring or a 4- to 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently chosen from N, O, and S.

[0428] (j) R^2 and R^3, if bound to adjacent carbon atoms, may be taken together to form a 3- to 6-membered carbocyclic ring or a 3- to 6-membered heterocyclic ring; each of which ring (g), (h), and (i) may be unsubstituted or substituted with 1 or more substituents independently chosen from halogen, hydroxyl, cyano, -COOH, C_1-C_4alkyl, C_2-C_4alkenyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, hydroxyC_1-C_4alkyl, (mono- and di-C_1-C_4alkylamino)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0429] A is a heterocyclic group chosen from (k) and (l) where (k) is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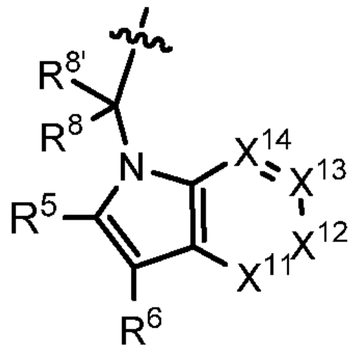
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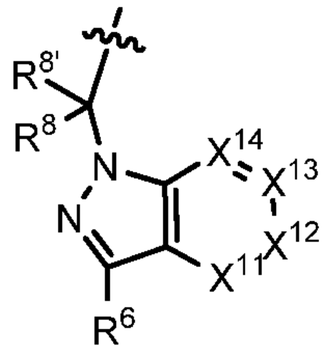
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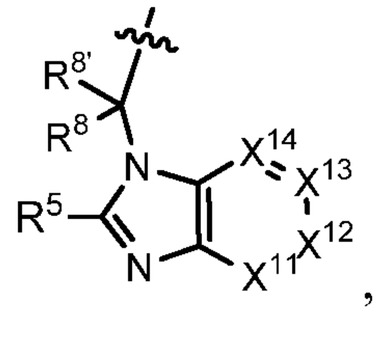
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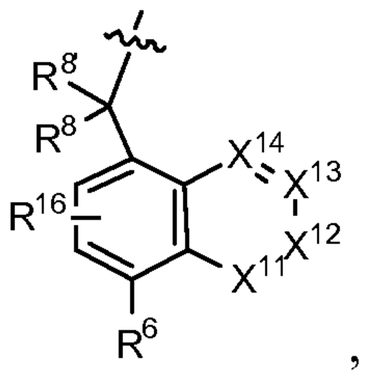
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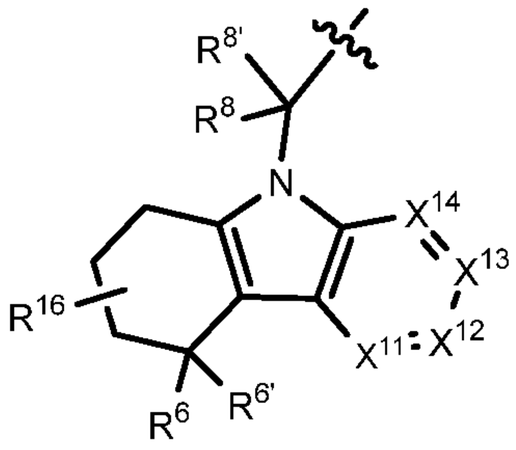
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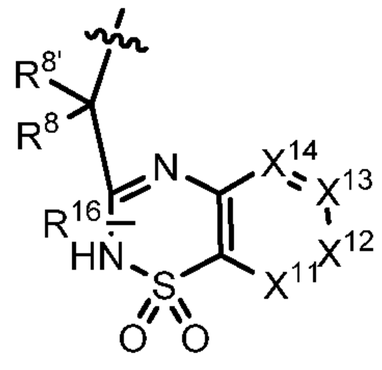
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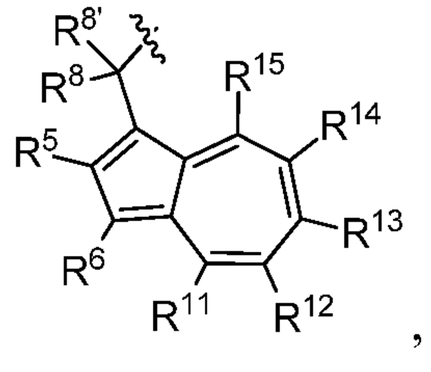
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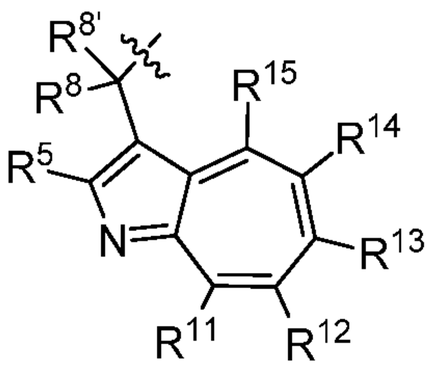
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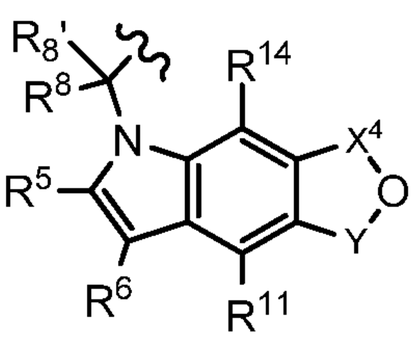
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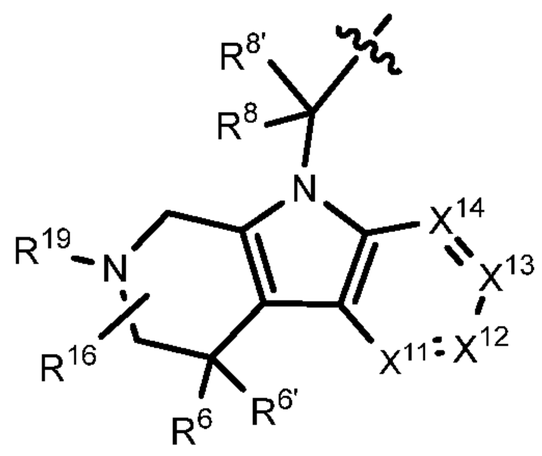
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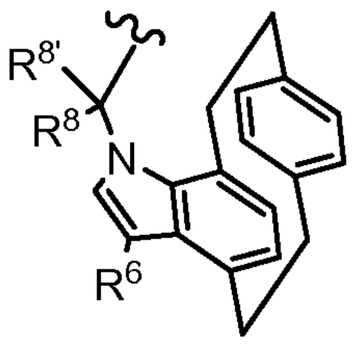
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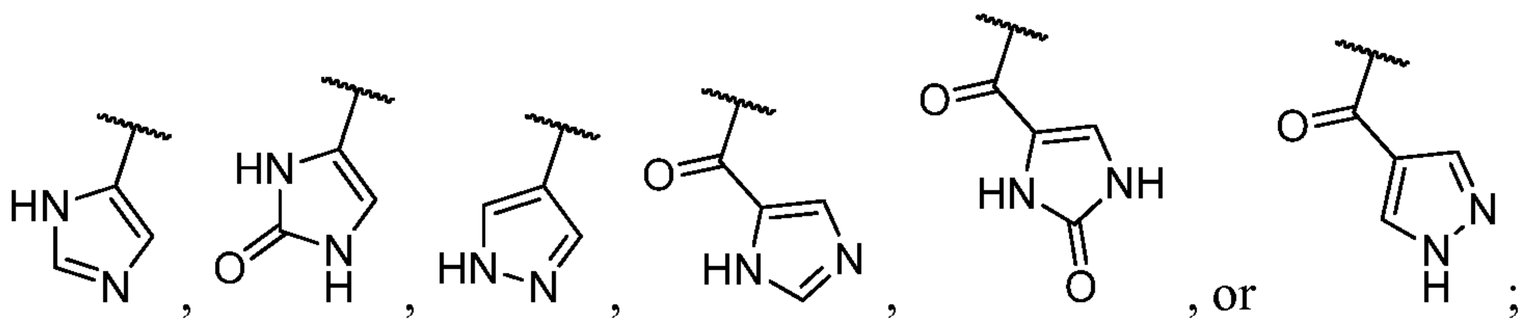
[0430] X^4 is B(OH) and Y is CHR^9; or X^4 is CHR^9 and Y is B(OH).

[0431] R^4 is (m) or (n):

[0432] (m) -CHO, -$CONH_2$, or C_2-C_6alkanoyl;

[0433] (n) hydrogen, -SO_2NH_2, -$C(CH_2)F$, -$CH(CF_3)NH_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_2alkyl(C_3-C_7cycloalkyl),



each of which R^4 other than hydrogen, -CHO, and –$CONH_2$, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_2alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0434] R^5 and R^6 are independently chosen from (o) and (p):

[0435] (o) –CHO, -$C(O)NH_2$, -$C(O)NH(CH_3)$, or C_2-C_6alkanoyl;

[0436] (p) hydrogen, hydroxyl, halogen, cyano, nitro, -COOH, -SO_2NH_2, vinyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C(O)C_0-C_4alkyl(C_3-C_7cycloalkyl), -P(O)(OR^9)$_2$, -OC(O)R^9, -C(O)OR^9, -C(O)N($CH_2CH_2R^9$)(R^{10}), -NR^9C(O)R^{10}, phenyl, or 5- to 6-membered heteroaryl.

[0437] Each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, imino, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_4alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0438] $R^{6'}$ is hydrogen, halogen, hydroxyl, C_1-C_4alkyl, or C_1-C_4alkoxy; or R^6 and $R^{6'}$may be taken together to form an oxo, vinyl, or imino group.

[0439] R^7 is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl.

[0440] R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, C_1-C_6alkoxy, and (C_1-C_4alkylamino)C_0-C_2alkyl, or R^8 and $R^{8'}$ are taken together to form an oxo group.

[0441] R^{16} is 0 or 1 or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0442] R^{19} is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -SO_2C_1-C_6alkyl, (mono- and di-C_1-C_6alkylamino)C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), each of which R^{19} other than hydrogen is substituted with 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, -COOH, and –C(O)OC_1-C_4alkyl.

[0443] X^{11} is N or CR^{11}.

[0444] X^{12} is N or CR^{12}.

[0445] X^{13} is N or CR^{13}.

[0446] X^{14} is N or CR^{14}.

[0447] X^{15} is N or CR^{15}.

[0448] No more than 2 of X^{11}, X^{12}, X^{13}, X^{14}, and X^{15} are N.

[0449] R^{11}, R^{14}, and R^{15} are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -O(PO)(OR^9)$_2$, -(PO)(OR^9)$_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkoxy(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0450] R^{12} and R^{13} are independently chosen from (q), (r), and (s):

[0451] (q) hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy,

[0452] (r) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_2-C_6alkenyloxy, -C(O)OR^9, C_1-C_6thioalkyl, -C_0-C_4alkylNR^9R^{10}, -C(O)NR^9R^{10}, -$SO_2R^9R^{10}$, -$SO_2NR^9R^{10}$, -OC(O)R^9, and -C(NR^9)NR^9R^{10}, each of which (r) is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and each of which (r) is also optionally substituted with one substituent chosen from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl)(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0453] (s) -C_2-C_6alkynyl, -C_2-C_6alkynylR^{23}, C_2-C_6alkanoyl, -JC_3-C_7cycloalkyl, -$B(OH)_2$, -JC(O)NR^9R^{23},-$JOSO_2OR^{21}$, -C(O)$(CH_2)_{1-4}$S(O)R^{21}, -O$(CH_2)_{1-4}$S(O)$NR^{21}NR^{22}$, -JOP(O)(OR^{21})(OR^{22}), -JP(O)(OR^{21})(OR^{22}), -JOP(O)(OR^{21})R^{22}, -JP(O)(OR^{21})R^{22}, -JOP(O)$R^{21}R^{22}$, -JP(O)$R^{21}R^{22}$, -JSP(O)(OR^{21})(OR^{22}), -JSP(O)(OR^{21})(R^{22}), -JSP(O)(R^{21})(R^{22}), -JNR^9P(O)(NHR^{21})(NHR^{22}), -JNR^9P(O)(OR^{21})(NHR^{22}), -JNR^9P(O)(OR^{21})(OR^{22}), -JC(S)R^{21}, -J$NR^{21}SO_2R^{22}$, -JNR^9S(O)$NR^{10}R^{22}$, -J$NR^9SO_2NR^{10}R^{22}$, -J$SO_2NR^9COR^{22}$, -O$(CH_2)_{1-4}SO_2NR^{21}R^{22}$, -J$SO_2NR^9CONR^{21}R^{22}$, -J$NR^{21}SO_2R^{22}$, -JC(O)$NR^{21}SO_2R^{22}$, -JC($NH_2$)$NR^{22}$, -JC($NH_2$)N$S(O)_2R^{22}$, -JOC(O)$NR^{21}R^{22}$, -JOC(O)$NR^{24}R^{25}$, -J$NR^9$C(O)$OR^{10}$, -J$NR^9$C(O)$OR^{23}$, -J$NR^{21}$OC(O)$R^{22}$, -$(CH_2)_{1-4}$C(O)$NR^{21}R^{22}$, -JC(O)$R^{24}R^{25}$, -J$NR^9$C(O)$R^{21}$, -JC(O)$R^{21}$, -J$NR^9$C(O)$NR^9R^{10}$, -J$NR^9$C(O)$NR^{10}R^{23}$, -J$NR^9$C(O)$NR^{24}R^{25}$, -C$CR^{21}$, -$(CH_2)_{1-4}$OC(O)$R^{21}$, -JC(O)O$R^{23}$, -$C_2$-$C_4$alkyl$R^{23}$, -$C_2$-$C_4$alkenyl$R^{23}$, -$C_2$-$C_4$alkynyl$R^{23}$, and –Jparacyclophane.

[0454] J is independently chosen at each occurrence from a covalent bond, C_1-C_4alkylene, -OC_1-C_4alkylene, C_2-C_4alkenylene, and C_2-C_4alkynylene.

[0455] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, -C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3

heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S.

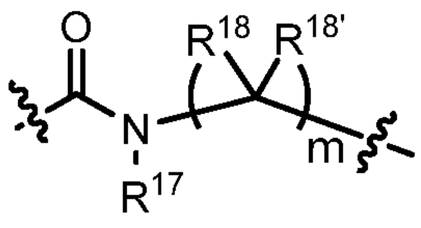
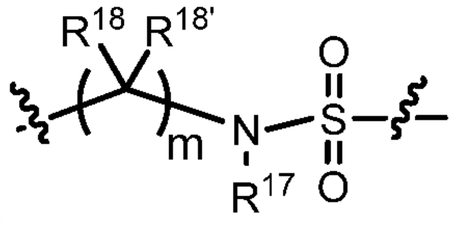
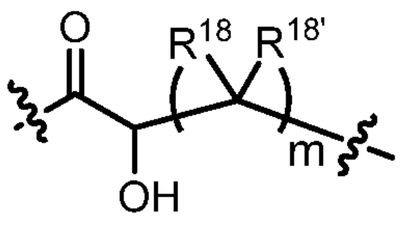
[0456] R^{23} is independently chosen at each occurrence from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S.

[0457] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyl group, or a 6- to 10- membered bicyclic heterocyclic group having fused, spiro, or bridged rings.

[0458] Each of which (s) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

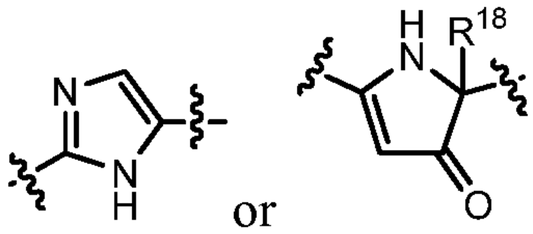
[0459] L is either (t), (u), or (v):

[0460] (t) is a group of the formula


, 
, or 
where R^{17} is hydrogen or C_1-C_6alkyl and R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, and methyl; and m is 0, 1, 2, or 3; and

[0461] (u) is a bond,

[0462] (v) or a group of the formula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[0463] B is a monocyclic or bicyclic carbocyclic or carbocyclic-oxy group or 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, or B is a C_2-C_6alkenyl or C_2-C_6alkynyl group.

[0464] Each of which B is unsubstituted or substituted with one or more substituents independently chosen from (w) and (x) and 0 or 1 substituents chosen from (y) and (z):

[0465] (w) halogen, hydroxyl, -COOH, cyano, C_1-C_6alkyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkylNR^{9}R^{10}, -SO$_2$R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0466] (x) nitro, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6thioalkyl, -JC_3-C_7cycloalkyl, -B(OH)$_2$, -JC(O)NR^{9}R^{23},-JOSO$_2$OR^{21}, -C(O)(CH$_2$)$_{1-4}$S(O)R^{21}, -O(CH$_2$)$_{1-4}$S(O)NR^{21}R^{22}, -JOP(O)(OR^{21})(OR^{22}), -JP(O)(OR^{21})(OR^{22}), -JOP(O)(OR^{21})R^{22}, -JP(O)(OR^{21})R^{22}, -JOP(O)R^{21}R^{22}, -JP(O)R^{21}R^{22}, -JSP(O)(OR^{21})(OR^{22}), -JSP(O)(OR^{21})(R^{22}), -JSP(O)(R^{21})(R^{22}), -JNR^{9}P(O)(NHR^{21})(NHR^{22}), -JNR^{9}P(O)(OR^{21})(NHR^{22}), -JNR^{9}P(O)(OR^{21})(OR^{22}), -JC(S)R^{21}, -JNR^{21}SO$_2$R^{22}, -JNR^{9}S(O)NR^{10}R^{22}, -JNR^{9}SO$_2$NR^{10}R^{22}, -JSO$_2$NR^{9}COR^{22}, -JSO$_2$NR^{9}CONR^{21}R^{22}, -JNR^{21}SO$_2$R^{22}, -JC(O)NR^{21}SO$_2$R^{22}, -JC(NH$_2$)NR^{22}, -JC(NH$_2$)NS(O)$_2$R^{22}, -JOC(O)NR^{21}R^{22}, -JNR^{21}C(O)OR^{22}, -JNR^{21}OC(O)R^{22}, -(CH$_2$)$_{1-4}$C(O)NR^{21}R^{22}, -JC(O)R^{24}R^{25}, -JNR^{9}C(O)R^{21}, -JC(O)R^{21}, -JNR^{9}C(O)NR^{10}R^{22}, -CCR^{21}, -(CH$_2$)$_{1-4}$OC(O)R^{21}, and -JC(O)OR^{23}; each of which (x) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -CONH$_2$, -P(O)(OH)$_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0467] (y) naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl containing 1 or 2 heteroatoms chosen from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and containing 4- to 7-ring atoms in each ring; each of which (y) is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO$_2$R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

[0468] (z) tetrazolyl, (phenyl)C_0-C_2alkyl, (phenyl)C_1-C_2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently chosen from N, O, B, and S, each of which (z) is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-

C_7cycloalkyl), $-SO_2R^9$, $-OSi(CH_3)_2C(CH_3)_3$, $–Si(CH_3)_2C(CH_3)_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0469] Either X^2 is nitrogen or at least one of (d), (e), (g), (i), (l), (n), (p), (s), (v), (x), and (y) is present.Pharmaceutical composition comprising a compound or salt of Formula I together with a pharmaceutically acceptable carrier are also disclosed.

[0470] Methods of treating or preventing disorders mediated by complement cascade Factor D, such as age-related macular degeneration and retinal degeneration, comprising administering a therapeutically effective amount of a compound or salt of Formula I to a patient in need of such treatment are also disclosed.

TERMINOLOGY OF PRIORITY DOCUMENT

[0471] 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. Unless clearly contraindicated by the context each compound name includes the free acid or free base form of the compound as well as all pharmaceutically acceptable salts of the compound.

[0472] The term “Formula I” encompasses all compounds that satisfy Formula I, including any enantiomers, racemates and stereoisomers, as well as all pharmaceutically acceptable salts of such compounds. “Formula I” includes all subgeneric groups of Formula I, such as Formula IA and Formula IB and also includes pharmaceutically acceptable salts of a compound of Formula I, unless clearly contraindicated by the context in which this phrase is used.

[0473] The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The open-ended transitional phrase “comprising” encompasses the intermediate transitional phrase “consisting essentially of” and the close-ended phrase “consisting of.” Claims reciting one of these three transitional phrases, or with an alternate transitional phrase such as “containing” or “including” can be written with any other transitional phrase unless clearly precluded by the context or art. 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 any and all 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. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. 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.

[0474] Compounds of Formula I include all compounds of Formula I having isotopic substitutions at any position. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C. While the compounds of Formula I require a moderate or high level of deuteration (substitution of a hydrogen with deuterium) at identified positions, Formula I includes embodiments in which other positions are isotopically enriched.

[0475] An "active agent" means a compound (including a compound disclosed herein), element, or mixture that when administered to a patient, alone or in combination with another compound, element, or mixture, confers, directly or indirectly, a physiological effect on the patient. The indirect physiological effect may occur via a metabolite or other indirect mechanism.

[0476] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-(C=O)NH_2$ is attached through carbon of the keto (C=O) group.

[0477] "Alkyl" is a branched or straight chain saturated aliphatic hydrocarbon group, having the specified number of carbon atoms, generally from 1 to about 12 carbon atoms. The term C_1-C_6alkyl as used herein indicates an alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms. Other embodiments include alkyl groups having from 1 to 8 carbon atoms, 1 to 4 carbon atoms or 1 or 2 carbon atoms, e.g. C_1-C_8alkyl, C_1-C_4alkyl, and C_1-C_2alkyl. When C_0-C_n alkyl is used herein in conjunction with another group, for example, (C_3-C_7cycloalkyl)C_0-C_4 alkyl, or –C_0-C_4alkyl(C_3-C_7cycloalkyl), the indicated group, in this case cycloalkyl, is either directly

bound by a single covalent bond (C_0alkyl), or attached by an alkyl chain having the specified number of carbon atoms, in this case 1, 2, 3, or 4 carbon atoms. Alkyls can also be attached via other groups such as heteroatoms as in –O-C_0-C_4alkyl(C_3-C_7cycloalkyl). Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, 3-methylbutyl, t-butyl, n-pentyl, and sec-pentyl.

[0478] "Alkenyl" is a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds that may occur at any stable point along the chain, having the specified number of carbon atoms. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

[0479] "Alkynyl" is a branched or straight chain aliphatic hydrocarbon group having one or more double carbon-carbon triple bonds that may occur at any stable point along the chain, having the specified number of carbon atoms.

[0480] "Alkylene"is a bivalent saturated hydrocarbon. Alkylenes include groups having 1 to 8 carbon atoms, 1 to 6 carbon atoms, or the indicated number of carbon atoms, for example C_1-C_4alkylene.

[0481] "Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenylenes include groups having 2 to 8 carbon atoms, 2 to 6 carbon atoms, or the indicated number of carbon atoms, for example C_2-C_4alkenylene.

[0482] "Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynylenes include groups having 2 to 8 carbon atoms, 2 to 6 carbon atoms, or the indicated number of carbon atoms, for example C_2-C_4alkenylene.

[0483] "Alkoxy" is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by 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- methylpentoxy. Similarly an "Alkylthio" or a "thioalkyl" group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by a sulfur bridge (-S-).

[0484] "Alkenyloxy" is an alkenyl group as defined above with the indicated number of carbon atoms covalently bound to the group it substitutes by an oxygen bridge (-O-).

[0485] "Alkanoyl" is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group is substitutes through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, that is C_2alkanoyl is a CH_3(C=O)- group.

[0486] "Alkylester" is an alkyl group as defined herein covalently bound to the group it substitutes by 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.

[0487] "Carbocyclic group" is a saturated, unsaturated, or partially unsaturated (e.g. 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.
"Carbocyclic ring" is a saturated, unsaturated, or partially unsaturated (e.g. aromatic) ring containing all carbon ring atoms. A carbocyclic ring typically contains 1 ring of 3 to 7 carbon atoms or a "carbocyclic group" may contain 1 carbocyclic ring or 2 fused carbocyclic rings each containing 3 to 7 carbon atoms. Examples of carbocyclic rings include phenyl, cyclohexenyl, cyclohexyl, and cyclopropyl rings.

[0488] "Carbocyclic-oxy group"is a monocyclic carbocyclic ring or a mono- or bi-cyclic carbocyclic group as defined above attached to the group it substitutes via an oxygen, -O-, linker.

[0489] "Cycloalkyl" is a saturated hydrocarbon ring group, having the specified number of carbon atoms. Monocyclic cycloalkyl groups typically have from 3 to about 8 carbon ring atoms or from 3 to 7 (3, 4, 5, 6, or 7) carbon ring atoms. Cycloalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents may have a cycloalkyl group, which is attached as a spiro group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0490] "Haloalkyl" indicates both branched and straight-chain alkyl groups having the specified number of carbon atoms, 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.

[0491] "Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

[0492] "Hydroxyalkyl"is an alkyl group as previously described, substituted with at least one hydroxyl subsitutuent.

[0493] “Aminoalkyl” is an alkyl group as previously described, substituted with at least one amino subsitutuent. “Halo” or “halogen” indicates any of fluoro, chloro, bromo, and iodo.

[0494] "Aryl" indicates aromatic groups containing only carbon in the aromatic ring or rings. Typical aryl groups contain 1 to 3 separate, fused, or pendant rings and from 6 to about 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 5 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, and S, to form, for example, a 3,4-methylenedioxy-phenyl group. Aryl groups include, for example, phenyl, naphthyl, including 1- naphthyl and 2-naphthyl, and bi-phenyl.

[0495] A “Heterocyclic ring” is a saturated, unsaturated, or partially unsaturated (e.g. aromatic) ring containing 1 to 4 ring heteroatoms independently chosen from N, O, and S, or if indicated, N, O, S, and B, with remaining ring atoms being carbon. A” heterocyclic group” may contain 1 heterocyclic ring 1 ring of 3 to 7 ring atoms or 2 fused rings each containing 3 to 7 ring atoms with at least one ring being a heterocyclic ring.

[0496] “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.

[0497] “Heteroaryl” indicates a stable monocyclic aromatic ring having the indicated number of ring atoms which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 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 O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl,

pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl. "Heteroaryloxy" is a heteroaryl group as described bound to the group it substituted via an oxygen bridge.

[0498] "Heterocycloalkyl" is a saturated ring group, having 1, 2, 3, or 4 heteroatoms independently chosen from N, S, and O, with remaining ring atoms being carbon. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

[0499] The term "mono- and/ or di-alkylamino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are independently chosen alkyl groups, as defined herein, having the indicated number of carbon atoms. 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.

[0500] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When the substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. When an oxo group substitutes aromatic moieties, the corresponding partially unsaturated ring replaces the aromatic ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent. Unless otherwise specified substituents are named into the core structure. For example, it is to be understood that when aminoalkyl is listed as a possible substituent the point of attachment of this substituent to the core structure is in the alkyl portion.

[0501] Suitable groups that may be present on a "substituted" or "optionally substituted" position include, but are not limited to, e.g., halogen; cyano; hydroxyl; nitro; azido; alkanoyl (such as a C_2-C_6 alkanoyl group); carboxamide; alkyl groups (including cycloalkyl groups) having 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms; alkenyl and alkynyl groups

including groups having one or more unsaturated linkages and from 2 to about 8, or 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 8, or from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those having one or more thioether linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those having one or more sulfinyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those having one or more sulfonyl linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms; aminoalkyl groups including groups having one or more N atoms and from 1 to about 8, or from 1 to about 6 carbon atoms; aryl having 6 or more carbons and one or more rings, (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted aromatic); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy having 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyloxy being an exemplary arylalkoxy group; or a saturated, unsaturated, or aromatic heterocyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such heterocyclic groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen and amino. In certain embodiments "optionally substituted" includes one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, -CHO, -COOH, $-CONH_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_1-C_6alkoxy, C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0502] A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, creams, ointments, suppositories, inhalable forms, transdermal forms, and the like.

[0503] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt of Formula I, and at least one other substance, such as a carrier. Pharmaceutical compositions optional contain one or more additional active agents. When specified, pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs. "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 a disorder, such as hepatitis C.

[0504] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds 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, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

[0505] Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. 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).

[0506] 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.

[0507] 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 undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

[0508] A "patient" is a human or non-human animal in need of medical treatment. Medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In some embodiments the patient is a human patient.

[0509] "Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

[0510] "Providing a compound of Formula I with at least one additional active agent" means the compound of Formula I 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 separated by some amount of time that is within the time in which both the compound of Formula I and the at least one additional active agent are within the blood stream of a patient. In certain embodiments the compound of Formula I 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 of Formula I 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 or topical contact.

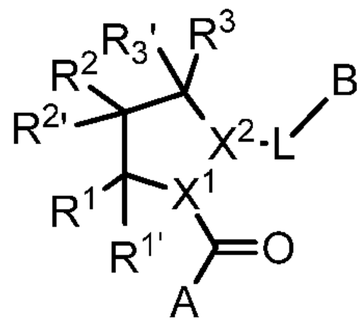
[0511] "Treatment," as used herein includes providing a compound of Formula I, either as the only active agent or together with at least one additional active agent sufficient to: (a) prevent a disease or a symptom of a disease from occurring in a patient who may be predisposed to the disease but has not yet been diagnosed as having it (e.g. including diseases that may be associated with or caused by a primary disease (as in macular degeneration that can result in the context of factor D activation); (b) inhibiting the disease, i.e. arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. "Treating" and "treatment" also means providing a therapeutically effective amount of a compound of Formula I, as the only active agent or together with at least one additional active agent to a patient having or susceptible to a condition mediated by complement factor D.

[0512] A "therapeutically effective amount" of a pharmaceutical composition/ combination of this invention means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of a macular degeneration. A therapeutically effective amount is also an amount sufficient to prevent a significant increase or significantly reduce the detectable level of complement Factor D in the patient's blood, serum, or tissues.

CHEMICAL DESCRIPTION

[0513] In addition to compounds of Formula I shown in the SUMMARY section the disclosure also include compounds in which the variables, e.g., A, B, L, R^1-$R^{3'}$, and L carry the following definitions. The disclosure includes all combinations of these definitions so long as a stable compound results.

[0514] For example the disclosure includes compounds and salts of Fomula II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XX, XXI, and XXII which are with in the scope of Formula I. The variables shown in Formula II-XXIV carry the definitions set forth in the SUMMARY section for Formula I or any of the defintions set forth in this disclosure.



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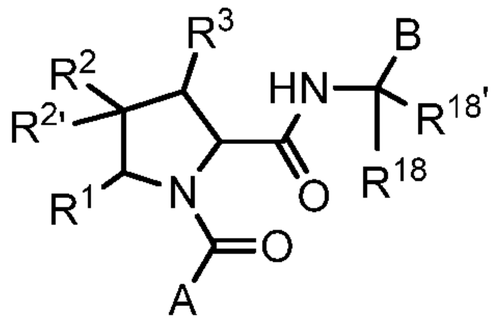

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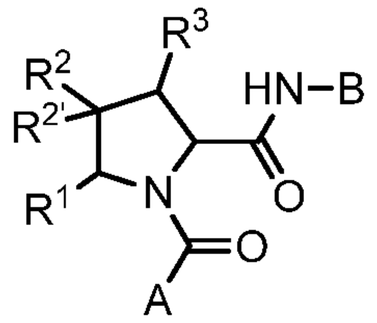

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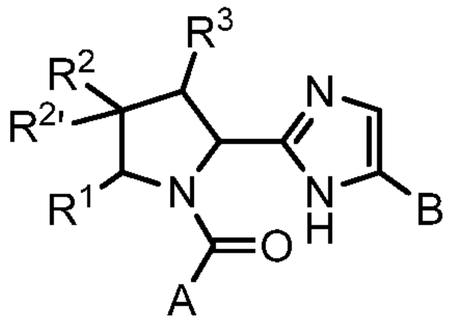

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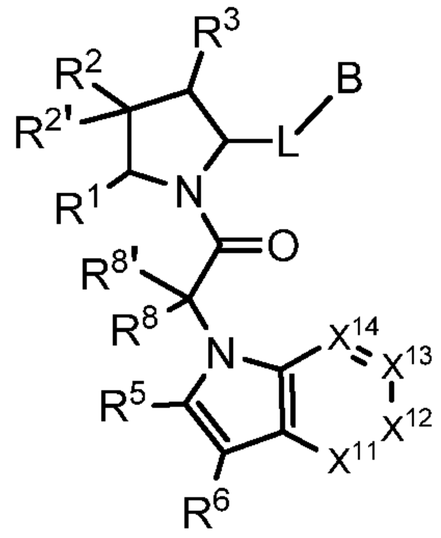
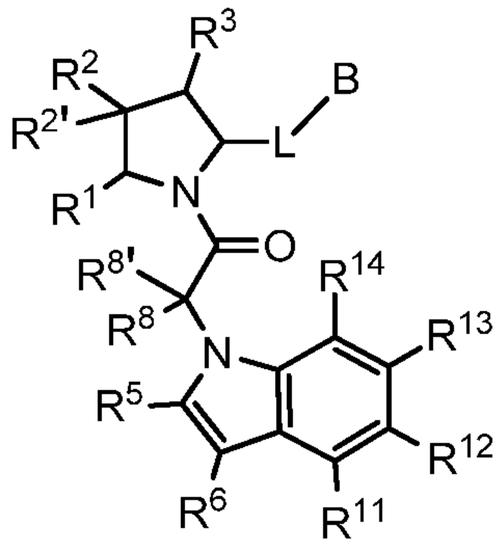


Formula VI



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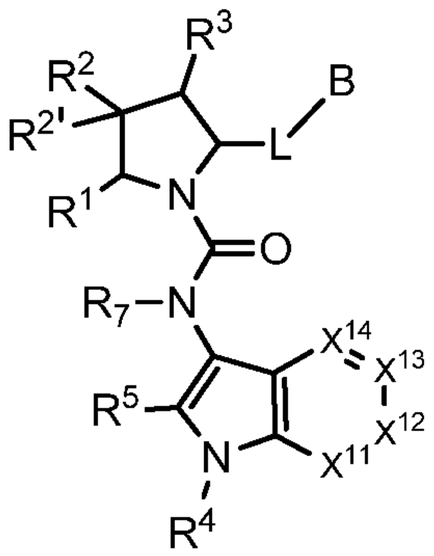

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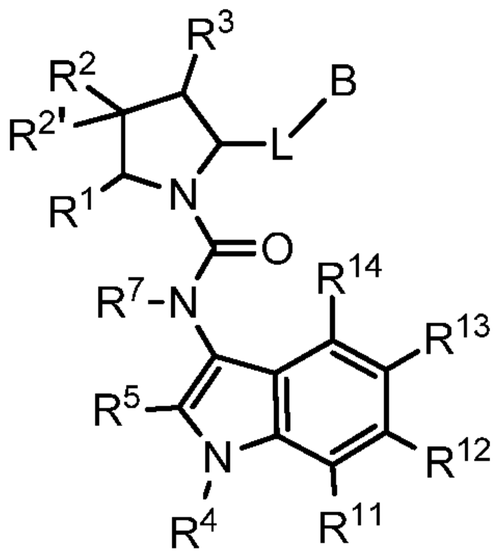

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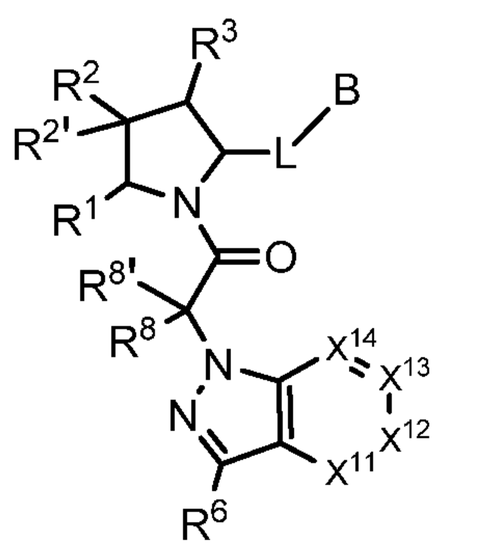

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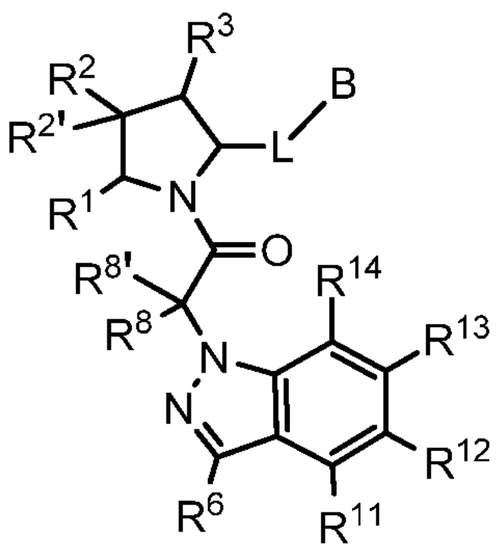

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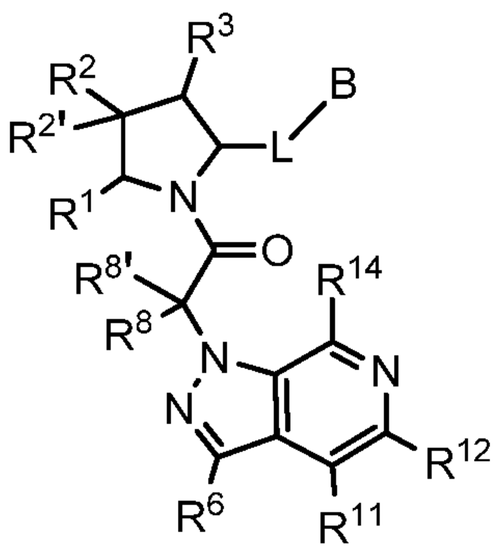

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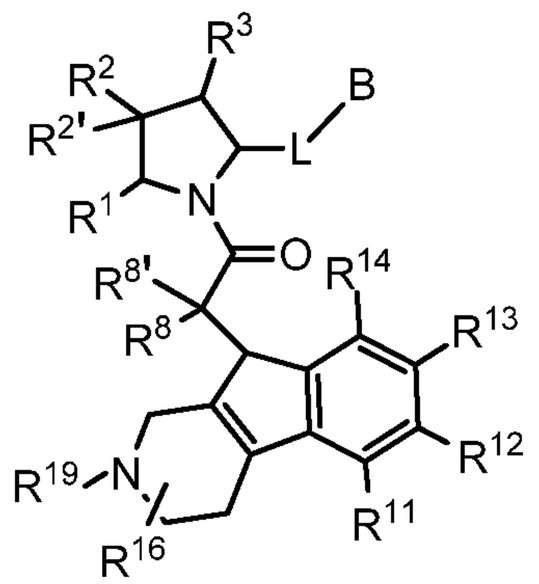

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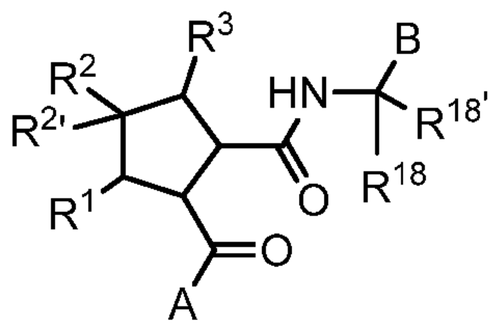

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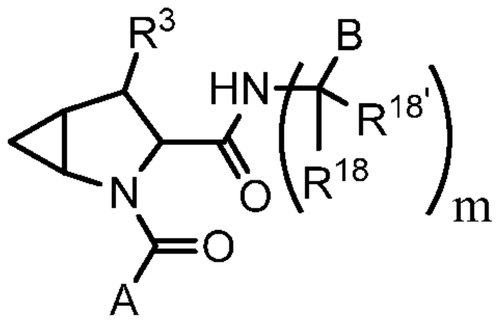

m is 0 or 1.

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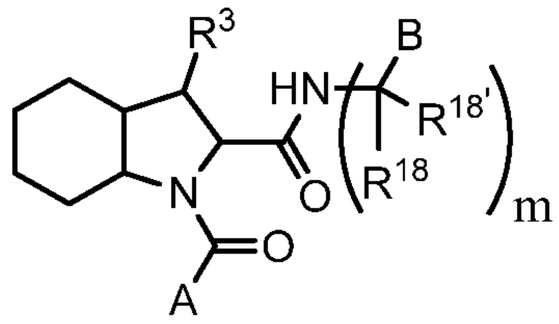

m is 0 or 1.

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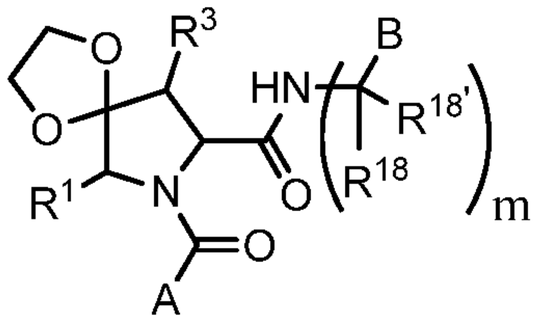

m is 0 or 1.

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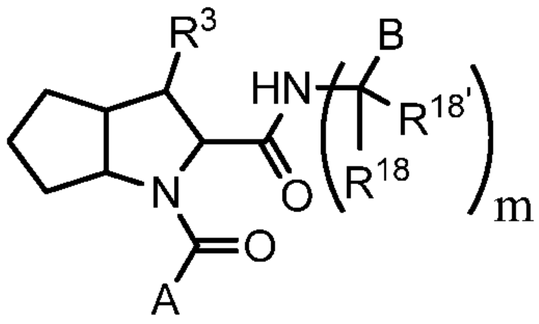

m is 0 or 1.

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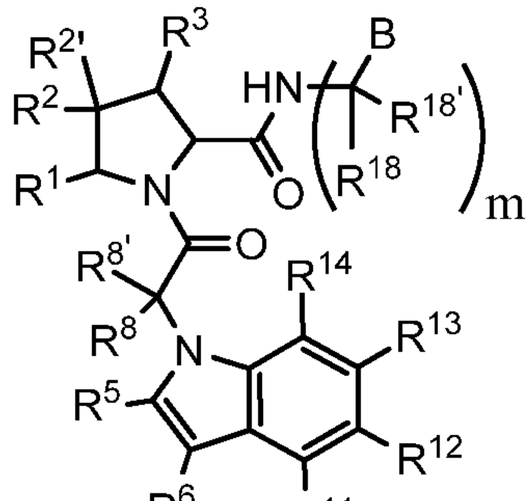

m is 0 or 1.

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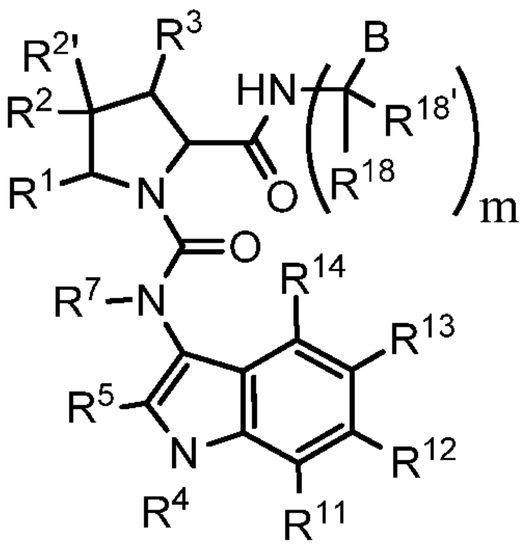
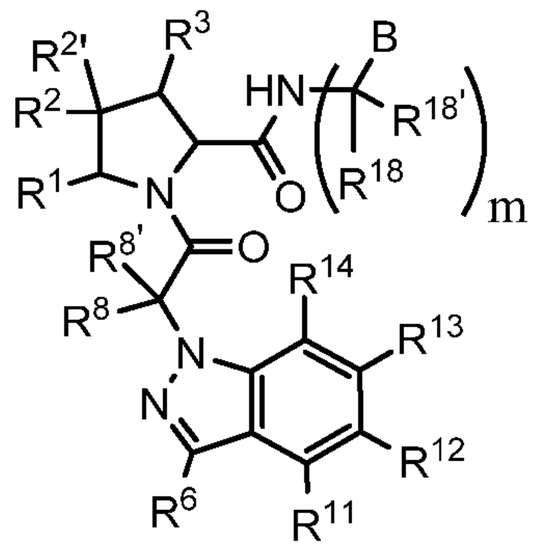


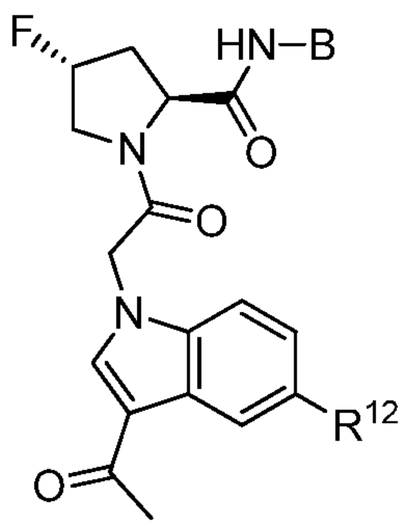
m is 0 or 1.

Formula XX

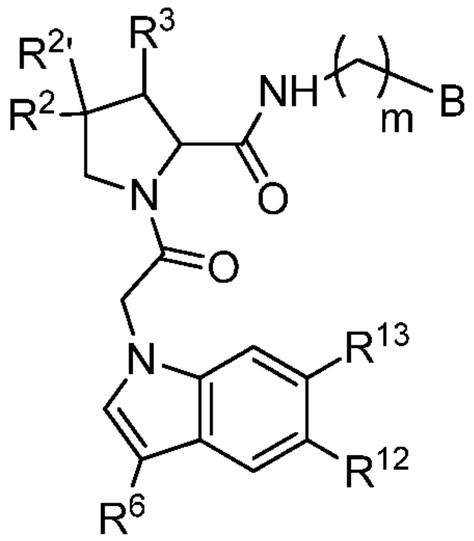


m is 0 or 1.

Formula XXI



Formula XXIII



Formula XXIV

[0515] Additionally, the disclosure includes compounds and salts of Formula I and any of its subformulae (II-XXIV) in which at least one of the following conditions is met.

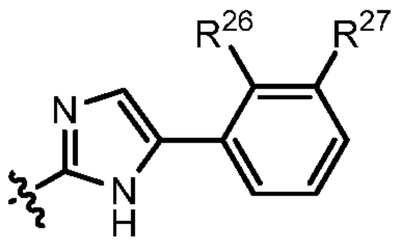
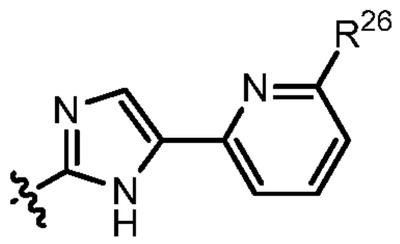
[0516] R^1, $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro.

[0517] R^1, $R^{1'}$, $R^{2'}$, and $R^{3'}$, if present, are all hydrogen; and R^2 is fluoro and R^3 is -C_0-C_4alkyl(C_3-C_7cycloalkyl) or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl.

[0518] R^1 and R^2 are taken together to form a 3- to 6-membered cycloalkyl group, and $R^{1'}$, $R^{2'}$, R^3, and $R^{3'}$, where present, are all hydrogen.

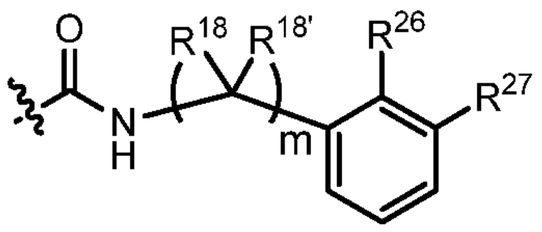
[0519] R^1, $R^{1'}$, R^3, and $R^{3'}$, if present, are all hydrogen, and R^2 and $R^{2'}$ are taken together to form a 5- or 6-membered heterocycloalkyl group having 1 or 2 oxygen atoms.

[0520] –L-B- is

 or  , where

R^{26} and R^{27} are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkoxy(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, C_1-C_2haloalkoxy, and C_1-C_2haloalkylthio.

[0521] (f) –L-B- is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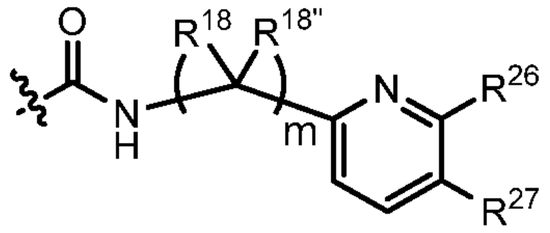
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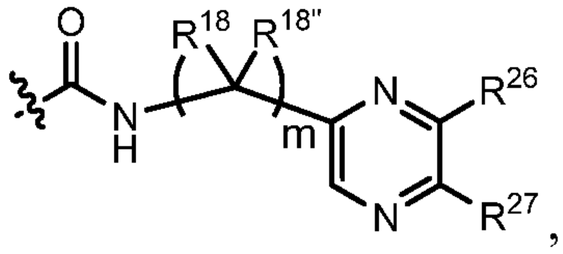
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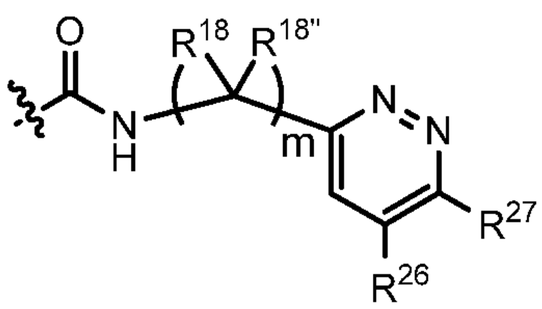
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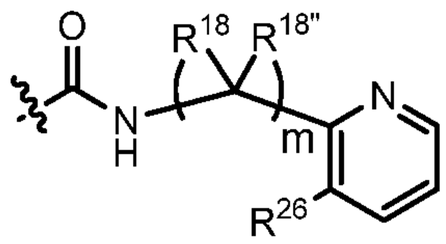
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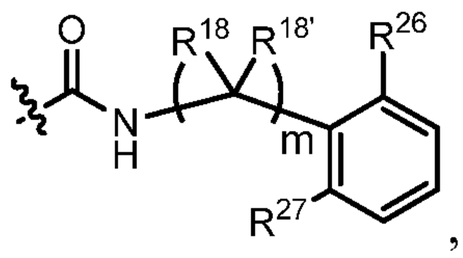
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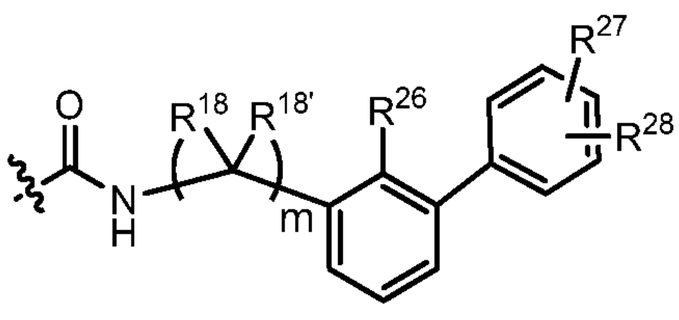
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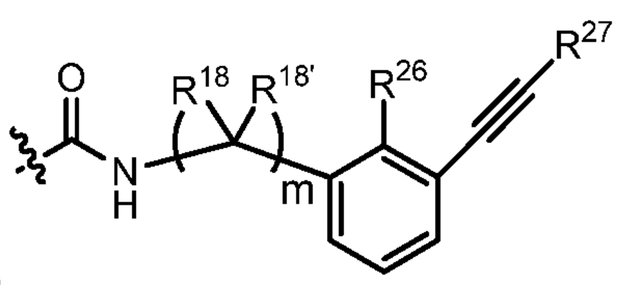
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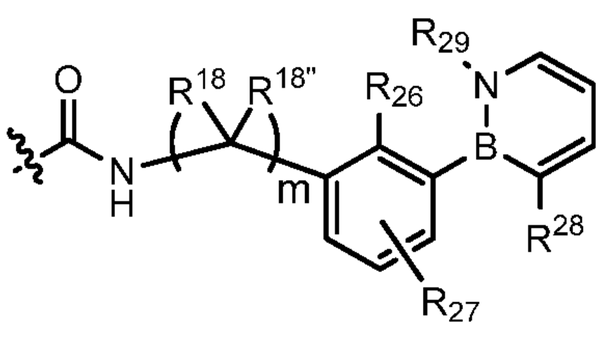
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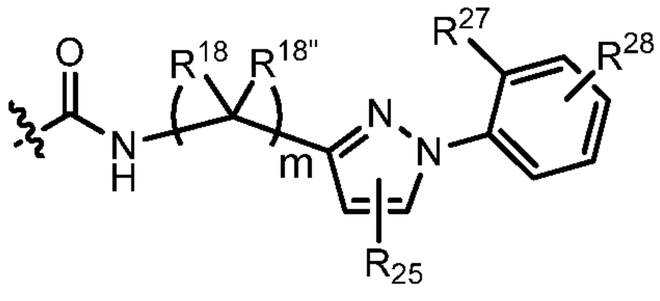

; wherein

[0522] R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, and methyl; and m is 0 or 1; and

[0523] R^{26}, R^{27}, and R^{28} are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, and -C_0-C_4alkoxy(C_3-C_7cycloalkyl); each of which R^{26}, R^{27}, and R^{28} other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, C_1-C_2alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

[0524] R^{29} is hydrogen, C_1-C_2alkyl, C_1C_2haloalkyl or $–Si(CH_3)_2C(CH_3)_3$.

[0525] (g) R8 and R8’ are independently hydrogen or methyl.

[0526] (h) R8 and R8’ are hydrogen.

[0527] (i) R7 is hydrogen or methyl.

[0528] (j) R7 is hydrogen.

[0529] (k) One of R^{12} and R^{13} is chosen from hydrogen, halogen, hydroxyl, amino, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -OC_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0530] (l) R^1, $R^{1'}$, R^2, and $R^{3'}$are all hydrogen;

[0531] R^2 is fluoro and R^3 is hydrogen, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl);

[0532] R^5 is hydrogen, halogen, or C_1-C_2alkyl;

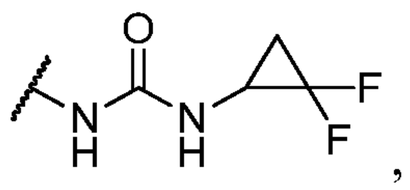
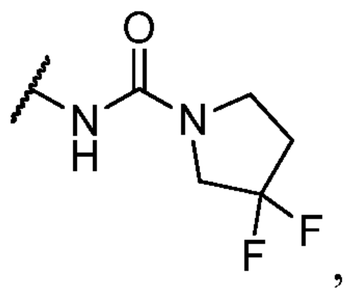
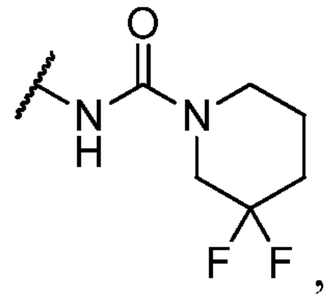
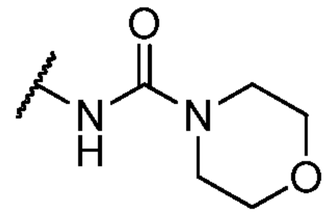
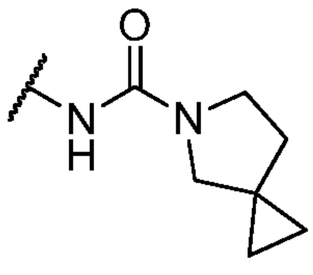
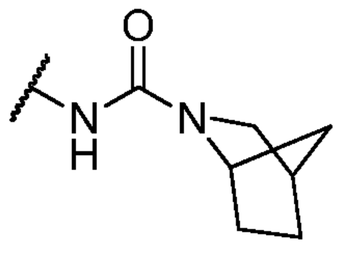
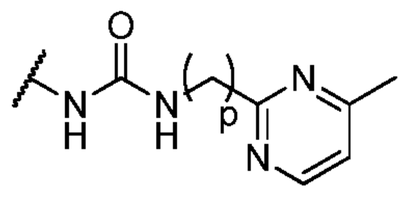
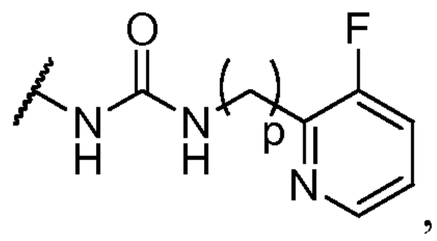
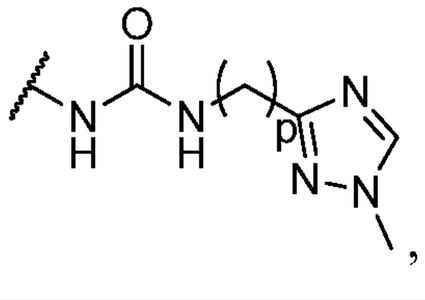
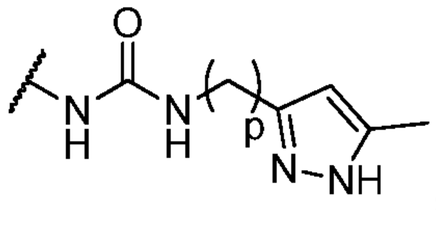
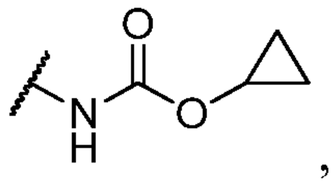
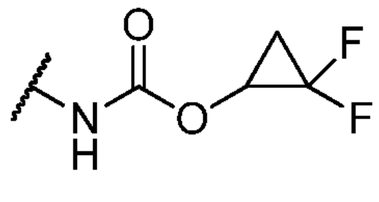
[0533] R^{11}, R^{13} R^{14}, and R^{15}, if present, are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, amino, C_1-C_4alkyl, C_1-C_4alkoxy, - C_0-C_2alkyl(mono- and di-C_1-C_2alkylamino), trifluoromethyl, and trifluoromethoxy;

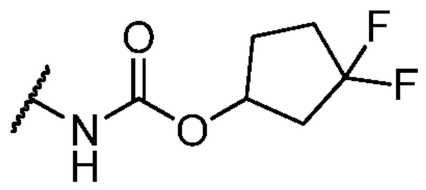
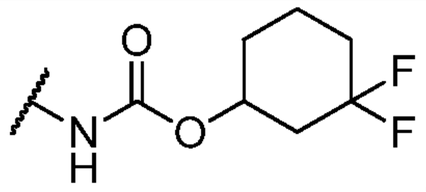
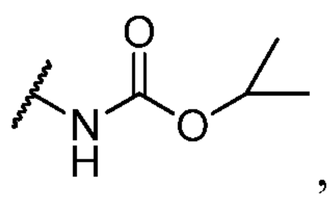
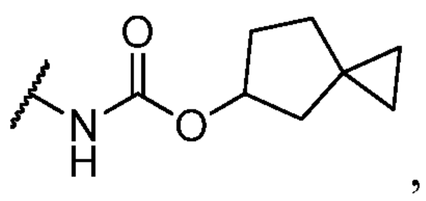
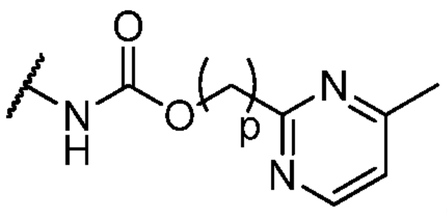
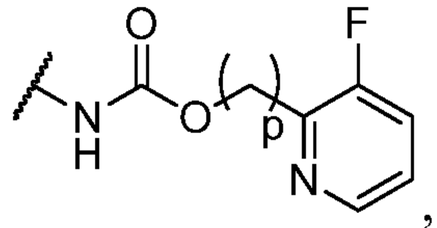
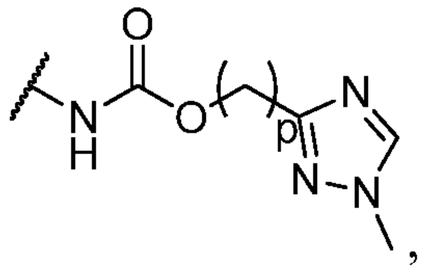
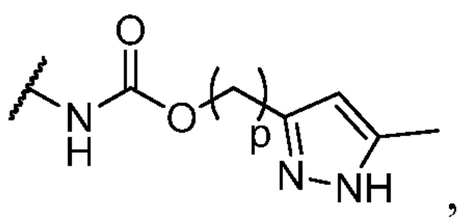
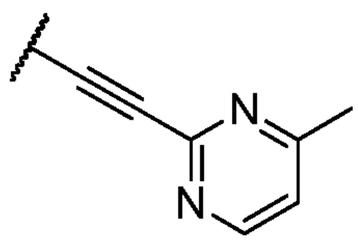
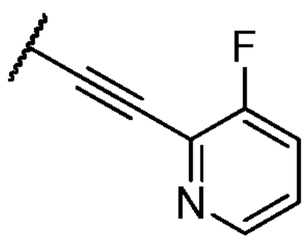
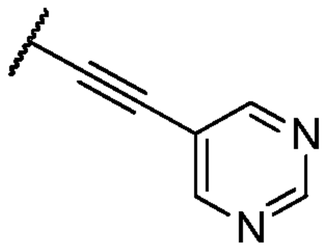
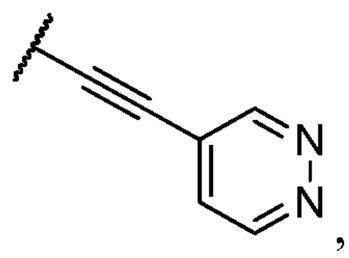
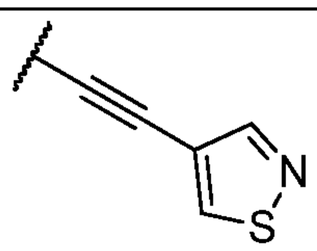
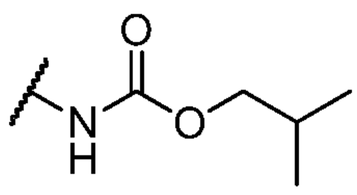
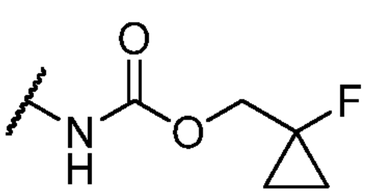
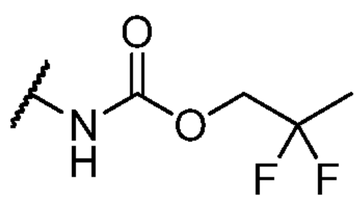
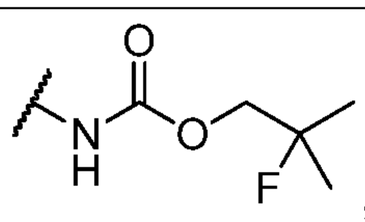
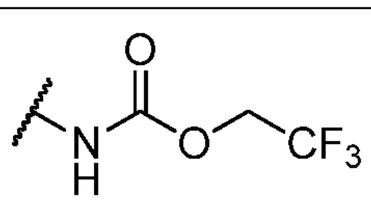
[0534] X^{12} is CR^{12}; and

[0535] R^{12} is -J$NR^9C(O)OR^{10}$, -J$NR^9C(O)OR^{23}$, -J$OC(O)NR^{21}R^{22}$, -J$OC(O)NR^{24}R^{25}$, -J$NR^9C(O)NR^{10}R^{23}$, or -J$NR^9C(O)NR^{24}R^{25}$.

[0536] (m) J is a bond.

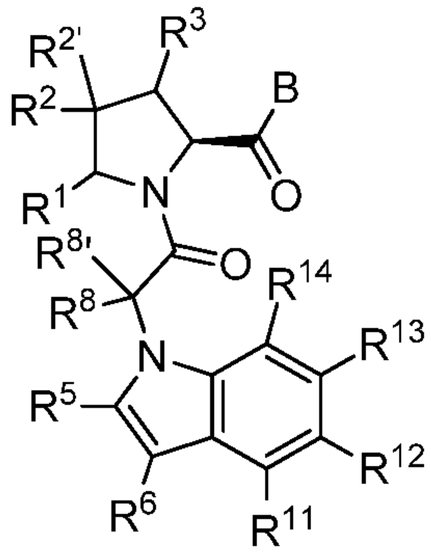
[0537] (n) One of R^{12} and R^{13} is selected from

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 , and	 .		

where p is 0, 1, 2, 3, or 4.

[0538] (o)The disclosure includes compounds and salts for Formula VII



(VII), wherein:

[0539] R^1, R^2, $R^{2'}$, and R^3 are independently chosen from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, -C_0-C_2alkylNR^9R^{10}, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -O-C_0-C_4alkyl(C_3-C_7cycloalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0540] R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, and methyl;

[0541] R^5 is hydrogen, hydroxyl, cyano, -COOH, C_1-C_6alkyl, C_1-C_6alkoxy, C_2-C_6alkanoyl -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C(O)C_0-C_4alkyl(C_3-C_7cycloalkyl, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy;

[0542] R^6 is –C(O)CH_3, -C(O)NH_2, -C(O)CF_3, -C(O)(cyclopropyl), or -ethyl(cyanoimino); and

[0543] R^{11} and R^{14} are independently chosen from hydrogen, halogen, hydroxyl, amino, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -OC_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0544] (p) B is selected from

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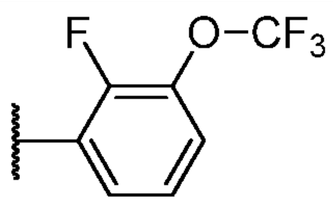
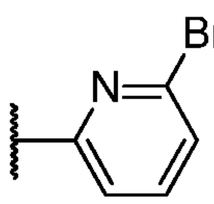
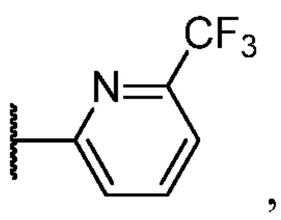
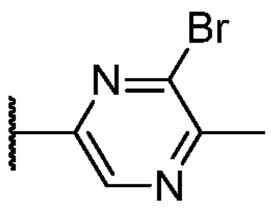
<td>  ,</td>
<td>  ,</td>
<td>  ,</td>
<td>  ,</td>
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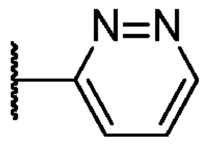
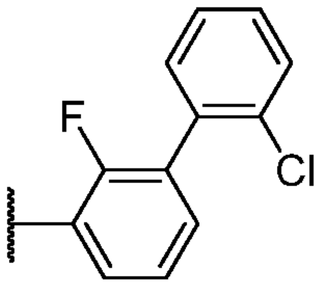
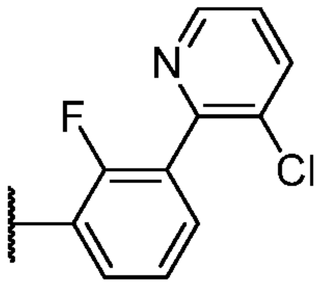
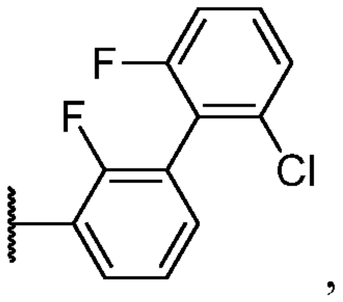
<td>  ,</td>
<td>  ,</td>
<td>  ,</td>
<td>  ,</td>
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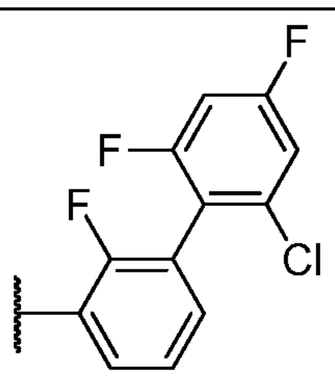
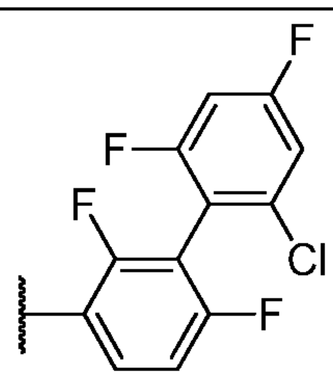
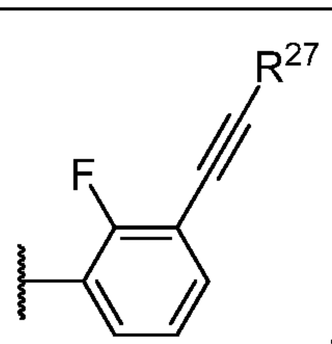
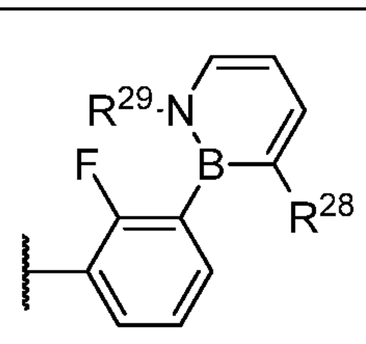
<td>  </td>
<td>  </td>
<td>  , and</td>
<td>  .</td>
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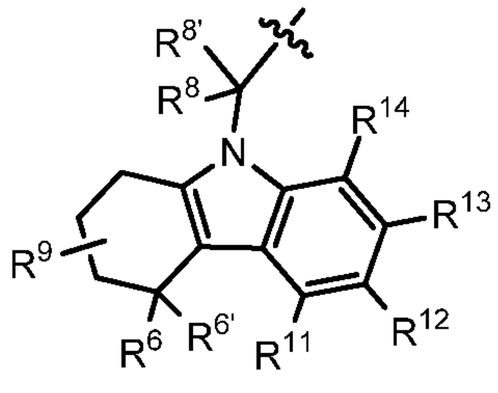
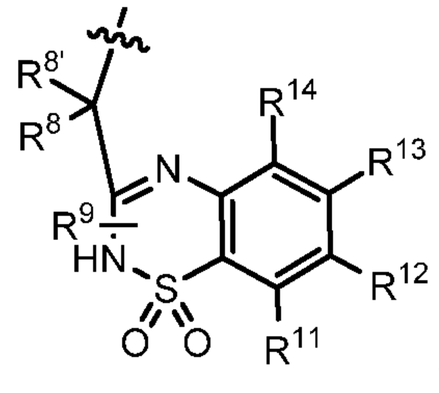
where R^{27} is hydrogen, methyl, or trifluoromethyl; R^{28} is hydrogen or halogen; and R^{29} is hydrogen, methyl, trifluoromethyl, or –Si(CH_3)$_2$C(CH_3)$_3$.

[0545] (q) B is phenyl, pyridyl, or indanyl each of which is unsubstituted or substituted with one or more substituents independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, -C_0-C_4alkoxy(C_3-C_7cycloalkyl), (phenyl)C_0-C_2alkyl, (pyridyl)C_0-C_2alkyl; each of which substituents other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, C_1-C_2alkyl, C_1-C_2alkoxy, –OSi(CH_3)$_2$C(CH_3)$_3$, –Si(CH_3)$_2$C(CH_3)$_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0546] (r) B is phenyl or pyridyl substituted with 1, 2, or 3 substituents chosen from chloro, bromo, hydroxyl, -SCF_3, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, and trifluoromethoxy.

[0547] (s) A is a group of the formula



or 

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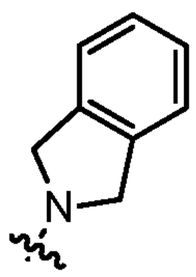
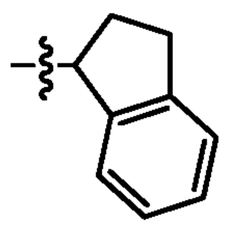
[0548] (t) –L-B is a bond and indanyl group of the formula



or 

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[0549] This disclosure further includes embodiments in which m is 0 or 1;

[0550] R^2 is halogen, $R^{2'}$ is hydrogen or halogen, and R^3 is hydrogen, halogen, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or -O-C_0-C_4alkyl(C_3-C_7cycloalkyl;

[0551] R^6 is –C(O)C_1-C_4alkyl, -C(O)NH_2, -C(O)CF_3, -C(O)(C_3-C_7cycloalkyl), or -ethyl(cyanoimino);

[0552] one of R^{12} and R^{13} is selected from hydrogen, halogen, C_1-C_4alkyl, C_1-C_4alkoxy, trifluoromethyl, and trifluoromethoxy;he other of R^{12} and R^{13} a is chosen from (s),

[0553] where (s) is C_2-C_6alkynyl, -C_2-C_6alkynylR^{23}, C_2-C_6alkanoyl, -JC_3-C_7cycloalkyl, -$B(OH)_2$, -JC(O)NR^9R^{23}, -JOSO_2OR^{21}, -C(O)$(CH_2)_{1-4}S(O)R^{21}$, -O$(CH_2)_{1-4}S(O)NR^{21}NR^{22}$, -JOP(O)$(OR^{21})(OR^{22})$, -JP(O)$(OR^{21})(OR^{22})$, -JOP(O)$(OR^{21})R^{22}$, -JP(O)$(OR^{21})R^{22}$, -JOP(O)$R^{21}R^{22}$, -JP(O)$R^{21}R^{22}$, -JSP(O)$(OR^{21})(OR^{22})$, -JSP(O)$(OR^{21})(R^{22})$, -JSP(O)$(R^{21})(R^{22})$, -J$NR^9$P(O)$(NHR^{21})(NHR^{22})$, -J$NR^9$P(O)$(OR^{21})(NHR^{22})$, -J$NR^9$P(O)$(OR^{21})(OR^{22})$, -JC(S)$R^{21}$, -J$NR^{21}SO_2R^{22}$, -J$NR^9$S(O)$NR^{10}R^{22}$, J$NR^9SO_2NR^{10}R^{22}$, -J$SO_2NR^9COR^{22}$, -O$(CH_2)_{1-4}SO_2NR^{21}R^{22}$, -J$SO_2NR^9CONR^{21}R^{22}$, -J$NR^{21}SO_2R^{22}$, -JC(O)$NR^{21}SO_2R^{22}$, -JC$(NH_2)$NCN, -JC$(NH_2)NR^{22}$, -JC$(NH_2)NS(O)_2R^{22}$, -JOC(O)$NR^{21}R^{22}$, -JOC(O)$NR^{24}R^{25}$, -J$NR^9$C(O)$OR^{10}$, -J$NR^9$C(O)$OR^{23}$, -J$NR^{21}$OC(O)$R^{22}$, -$(CH_2)_{1-4}$C(O)$NR^{21}R^{22}$, -J$NR^9$C(O)$R^{21}$, -JC(O)$R^{21}$, -J$NR^9$C(O)$NR^9R^{10}$, -J$NR^9$C(O)$NR^{10}R^{23}$, -J$NR^9$C(O)$NR^{24}R^{25}$, -C$CR^{21}$, -$(CH_2)_{1-4}$OC(O)$R^{21}$, -JC(O)$OR^{23}$, -$C_2$-$C_4$alkyl$R^{23}$, and –Jparacyclophane; where J is independently chosen at each occurrence and is a covalent bond, C_1-C_4alkylene, C_2-C_4alkenylene, or C_2-C_4alkynylene;

[0554] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl,

(phenyl)C_0-C_4alkyl, -C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S;

[0555] R^{23} is independently chosen at each occurrence from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S;

[0556] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a 4- to 7-membered monocyclic heterocycloalkyl group, or a 6- to 10- membered bicyclic heterocycloalkyl group having fused, spiro, or bridged rings; each of which (s) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0557] (r) This disclosure includes compounds and salts in which one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; and the other of

[0558] R^{12} and R^{13} is independently is chosen from (s), where (s) is C_2-C_6alkynyl, -C_2-C_6alkynylR^{23}, C_2-C_6alkanoyl, -JC_3-C_7cycloalkyl, -$JC(O)NR^9R^{23}$,-$C(O)(CH_2)_{1\text{-}4}S(O)R^{21}$, -$JP(O)(OR^{21})(OR^{22})$, -$JOP(O)(OR^{21})R^{22}$, -$JP(O)(OR^{21})R^{22}$, -$JOP(O)R^{21}R^{22}$, -$JP(O)R^{21}R^{22}$, -$JNR^{21}SO_2R^{22}$, -$JNR^{21}SO_2R^{22}$, -$JC(O)NR^{21}SO_2R^{22}$, -$JC(NH_2)NCN$, -$JC(NH_2)NR^{22}$, -$JC(NH_2)NS(O)_2R^{22}$, -$JOC(O)NR^{21}R^{22}$, -$JOC(O)NR^{24}R^{25}$, -$JNR^9C(O)OR^{10}$, -$JNR^9C(O)OR^{23}$, -$JNR^{21}OC(O)R^{22}$, -$JC(O)R^{21}$, -$JNR^9C(O)NR^9R^{10}$, -$JNR^9C(O)NR^{10}R^{23}$, -$JNR^9C(O)NR^{24}R^{25}$, and –Jparacyclophane; where J is independently chosen at each occurrence and is a covalent bond, C_1-C_4alkylene, C_2-C_4alkenylene, or C_2-C_4alkynylene;

[0559] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl,

-C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl,

(pyrrolidinyl)C_0-C_4alkyl, ((morpholinyl)C_0-C_4alkyl, (thiomorpholinyl)C_0-C_4alkyl, (piperidinyl)C_0-C_4alkyl, (piperazinyl)C_0-C_4alkyl, (tetrahydrofuranyl)C_0-C_4alkyl, pyrazolyl)C_0-C_4alkyl, (thiazolyl)C_0-C_4alkyl, (triazolyl)C_0-C_4alkyl, (tetrazolyl)C_0-C_4alkyl, (imidazolyl)C_0-C_4alkyl, (oxazolyl)C_0-C_4alkyl, (furanyl)C_0-C_4alkyl, (pyridinyl)C_0-C_4alkyl, (pyrimidinyl)C_0-C_4alkyl, (pyrazinyl)C_0-C_4alkyl, (pyridizinyl)C_0-C_4alkyl, and (tetrahydropyridinyl)C_0-C_4alkyl;

[0560] R^{23} is independently chosen at each occurrence from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl,(pyrrolidinyl)C_0-C_4alkyl, (morpholinyl)C_0-C_4alkyl, (thiomorpholinyl)C_0-C_4alkyl, (piperidinyl)C_0-C_4alkyl, (piperazinyl)C_0-C_4alkyl, (tetrahydrofuranyl)C_0-C_4alkyl, (pyrazolyl)C_0-C_4alkyl, (thiazolyl)C_0-C_4alkyl, (triazolyl)C_0-C_4alkyl, (tetrazolyl)C_0-C_4alkyl, (imidazolyl)C_0-C_4alkyl, (oxazolyl)C_0-C_4alkyl, (furanyl)C_0-C_4alkyl, (pyridinyl)C_0-C_4alkyl, (pyrimidinyl)C_0-C_4alkyl, (pyrazinyl)C_0-C_4alkyl, (pyridizinyl)C_0-C_4alkyl, and (tetrahydropyridinyl)C_0-C_4alkyl;

[0561] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperazinyl, piperidinyl, or morpholinyl group, each of which is optionally bridged with a methylene or ethylene group or spiro to a C_3-C_5cycloalkyl group;

[0562] each of which (s) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0563] This disclosure includes compounds and salts in which one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; and the other of R^{12} and R^{13} is chosen from (s), where (s) is -$JP(O)(OR^{21})(OR^{22})$, -$JOP(O)(OR^{21})R^{22}$, -$JP(O)(OR^{21})R^{22}$, -$JOP(O)R^{21}R^{22}$, or -$JP(O)R^{21}R^{22}$;

[0564] where J is independently chosen at each occurrence and is a covalent bond, C_1-C_4alkylene, C_2-C_4alkenylene, or C_2-C_4alkynylene;

[0565] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, and -C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl;

[0566] each of which (s) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, $-B(OH)_2$, $-Si(CH_3)_3$, -COOH, $-CONH_2$, $-P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, $-C_0$-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0567] This disclosure includes compounds and salts in which one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; and the other of R^{12} and R^{13} is $-C_2$-C_6alkynylR^{23}; where

[0568] R^{23} is from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl,(pyrrolidinyl)C_0-C_4alkyl, (morpholinyl)C_0-C_4alkyl, (thiomorpholinyl)C_0-C_4alkyl, (piperidinyl)C_0-C_4alkyl, (piperazinyl)C_0-C_4alkyl, (tetrahydrofuranyl)C_0-C_4alkyl, (pyrazolyl)C_0-C_4alkyl, (thiazolyl)C_0-C_4alkyl, (triazolyl)C_0-C_4alkyl, (tetrazolyl)C_0-C_4alkyl, (imidazolyl)C_0-C_4alkyl, (oxazolyl)C_0-C_4alkyl, (furanyl)C_0-C_4alkyl, (pyridinyl)C_0-C_4alkyl, (pyrimidinyl)C_0-C_4alkyl, (pyrazinyl)C_0-C_4alkyl, (pyridizinyl)C_0-C_4alkyl, and (tetrahydropyridinyl)C_0-C_4alkyl; which may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, $-B(OH)_2$, $-Si(CH_3)_3$, -COOH, $-CONH_2$, $-P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, $-C_0$-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

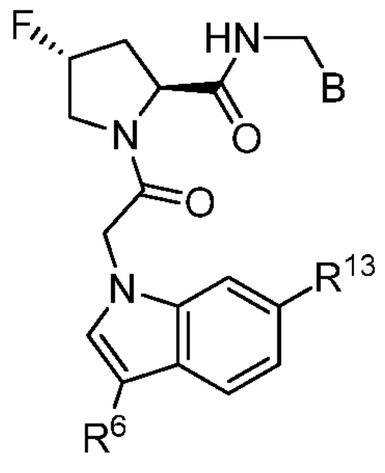
[0569] This disclosure includes compounds and salts in which one of R^{12} and R^{13} is hydrogen, hydroxyl, halogen, methyl, or methoxy; the other of R^{12} and R^{13} is chosen from (s) where (s) is chosen from $-JNR^9C(O)OR^{10}$, $-JNR^9C(O)OR^{23}$, $-JOC(O)NR^{21}R^{22}$, $JOC(O)NR^{24}R^{25}$, $JNR^9C(O)NR^{10}R^{23}$, and $-JNR^9C(O)NR^{24}R^{25}$;

[0570] R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, $-C_1$-C_4alkylOC(O)OC_1-C_6alkyl, $-C_1$-C_4alkylOC(O)C_1-C_6alkyl, $-C_1$-C_4alkylC(O)OC_1-C_6alkyl, (pyrrolidinyl)C_0-C_4alkyl, ((morpholinyl)C_0-C_4alkyl, (thiomorpholinyl)C_0-C_4alkyl, (piperidinyl)C_0-C_4alkyl, (piperazinyl)C_0-C_4alkyl, (tetrahydrofuranyl)C_0-C_4alkyl, pyrazolyl)C_0-C_4alkyl, (thiazolyl)C_0-C_4alkyl, (triazolyl)C_0-C_4alkyl, (tetrazolyl)C_0-C_4alkyl, (imidazolyl)C_0-C_4alkyl, (oxazolyl)C_0-C_4alkyl, (furanyl)C_0-C_4alkyl, (pyridinyl)C_0-C_4alkyl, (pyrimidinyl)C_0-C_4alkyl, (pyrazinyl)C_0-C_4alkyl, (pyridizinyl)C_0-C_4alkyl, and (tetrahydropyridinyl)C_0-C_4alkyl;

[0571] R^{23} is independently chosen at each occurrence from (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl,(pyrrolidinyl)C_0-C_4alkyl, (morpholinyl)C_0-C_4alkyl, (thiomorpholinyl)C_0-C_4alkyl, (piperidinyl)C_0-C_4alkyl, (piperazinyl)C_0-C_4alkyl, (tetrahydrofuranyl)C_0-C_4alkyl, (pyrazolyl)C_0-C_4alkyl, (thiazolyl)C_0-C_4alkyl, (triazolyl)C_0-C_4alkyl, (tetrazolyl)C_0-C_4alkyl, (imidazolyl)C_0-C_4alkyl, (oxazolyl)C_0-C_4alkyl, (furanyl)C_0-C_4alkyl, (pyridinyl)C_0-C_4alkyl, (pyrimidinyl)C_0-C_4alkyl, (pyrazinyl)C_0-C_4alkyl, (pyridizinyl)C_0-C_4alkyl, and (tetrahydropyridinyl)C_0-C_4alkyl;

[0572] R^{24} and R^{25} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperazinyl, piperidinyl, or morpholinyl group, each of which is optionally bridged with a methylene or ethylene group or spiro to a C_3-C_5cycloalkyl group; each of which (s) may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo, -$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

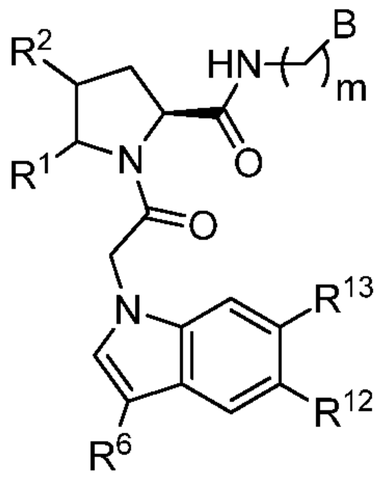
[0573] This disclosure includes compounds and salts of Formula IA:



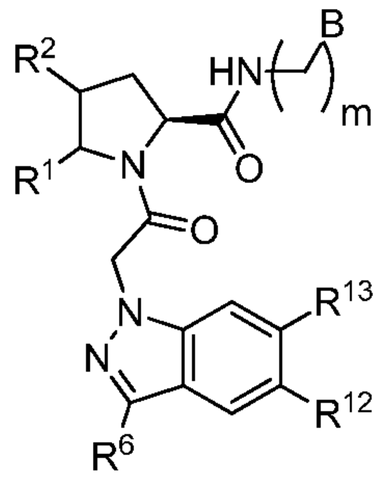
(IA) where

B may carry any of the definitions set forth herein for this variable. In certain embodiments B is a 2-fluoro-3-chlorophenyl or a 2-fluoro-3-trifluoromethoxy-phenyl. Examples of such compounds include the compounds shown in Table 1. In any of the compounds shown in Table 1 the 2-fluoro-3-chloro-phenyl group may be replaced by a 2-fluoro-3-trifluoromethoxy-phenyl.

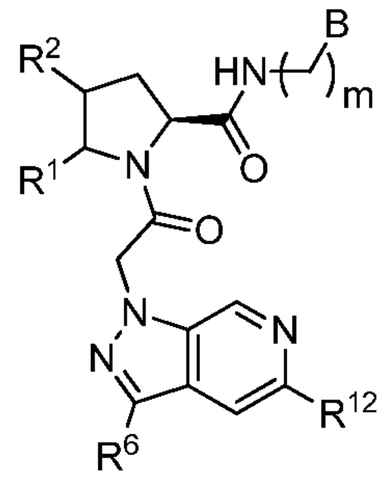
[0574] This disclosure includes compounds and salts of Formula IB, IC, and ID.



IB



IC



ID.

[0575] In Formula IB, IC, and ID the variables may include any of the definitions set forth herein that results in a stable compound. In certain embodiments tohe following conditions apply for Formula IB, IC, and ID.

[0576] R^1 is hydrogen and R^2 is fluoro.

[0577] R^1 and R^2 are joined to form a 3 membered ring.

[0578] m is 0.

[0579] B is pyridyl, optionally substituted with halogen, C_1-C_2alkoxy, and trifluoromethyl.

[0580] B is phenyl, substituted with 1, 2, or 3 substituents independently selected from halogen, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, and optionally substituted phenyl.

[0581] R^{13} is hydrogen and R^{12} is $-NHC(O)NR^{24}R^{25}$.

[0582] R^{13} is hydrogen and R^{12} is $-CCR^{23}$.

[0583] R^{13} is hydrogen and R^{12} is $-NHC(O)NHR^{23}$.

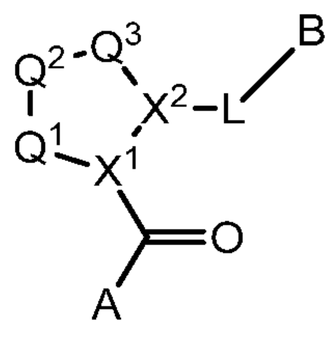
[0584] R^{13} is hydrogen and R^{12} is $-C(O)R^{23}$.

[0585] 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.

CLAIMS

What is claimed is:

1. A compound of Formula I



(I)

and the pharmaceutically acceptable salts thereof, wherein:

Q^1 is $N(R^1)$ or $C(R^1R^{1'})$;

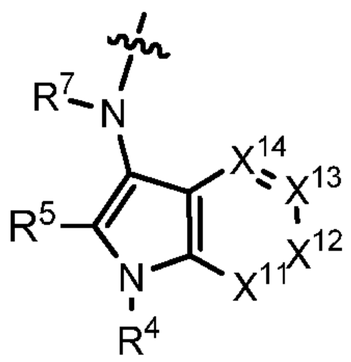
Q^2 is $C(R^2R^{2'})$, $C(R^2R^{2'})$-$C(R^2R^{2'})$, S, O, $N(R^2)$ or $C(R^2R^{2'})O$;

Q^3 is $N(R^3)$, S, or $C(R^3R^{3'})$;

X^1 and X^2 are independently N or CH, or X^1 and X^2 together are C=C;

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, and $R^{3'}$ are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, C_2-C_6alkynyl, C_2-C_6alkanoyl, C_1-C_6thioalkyl, hydroxyC_1-C_6alkyl, aminoC_1-C_6alkyl, -C_0-C_4alkylNR^9R^{10}, $-C(O)OR^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-OC(O)NR^9R^{10}$, $-NR^9C(O)OR^{10}$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, where R^9 and R^{10} are independently chosen at each occurrence from hydrogen, C_1-C_6alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), and -O-C_0-C_4alkyl(C_3-C_7cycloalkyl);

A is a group selected from: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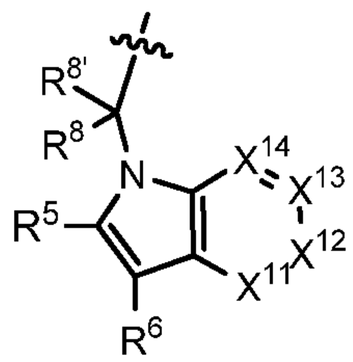
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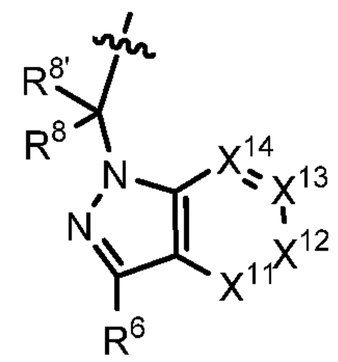
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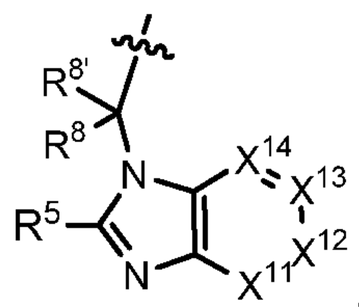
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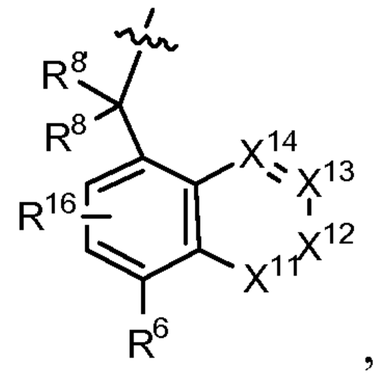
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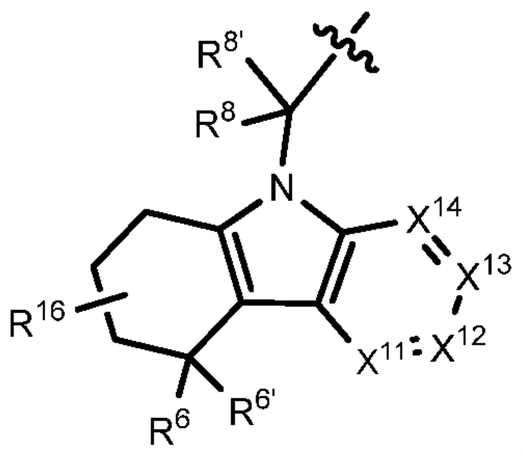
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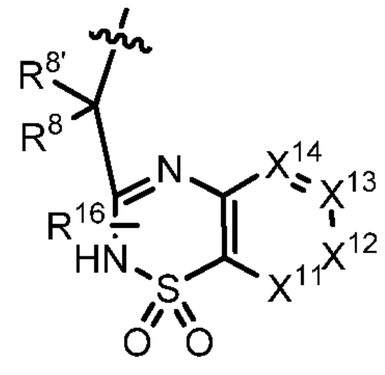
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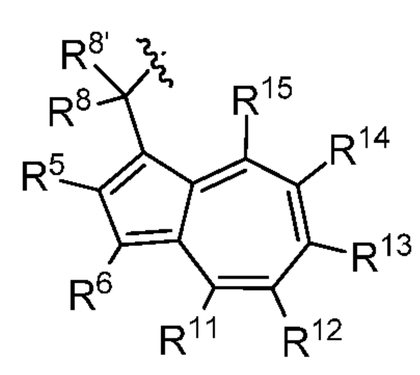
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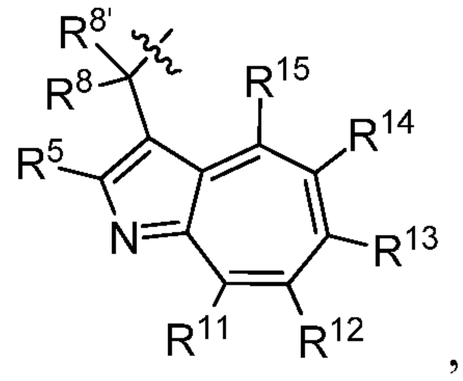
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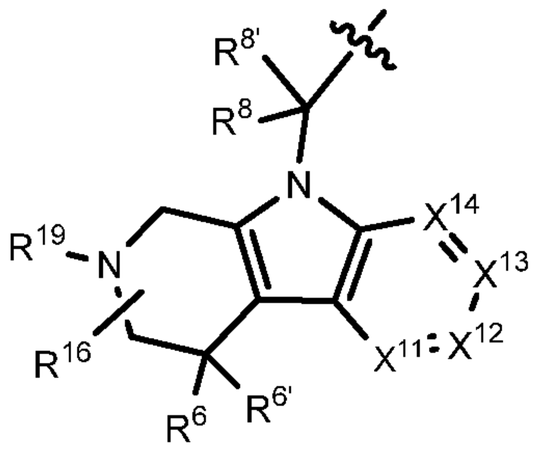
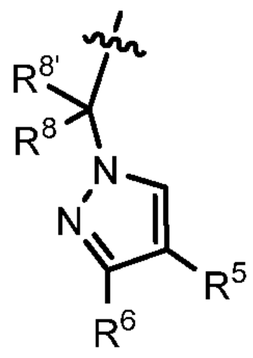
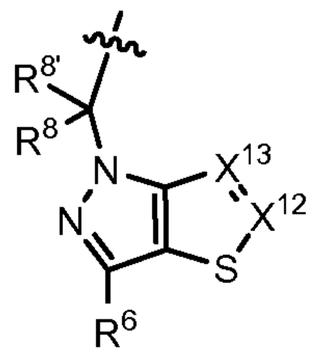
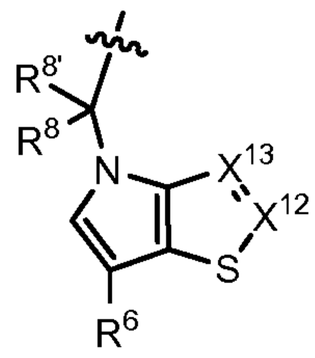
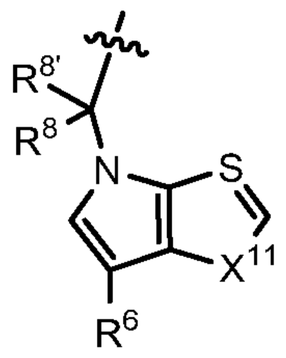
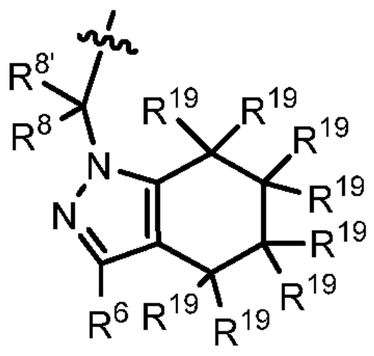
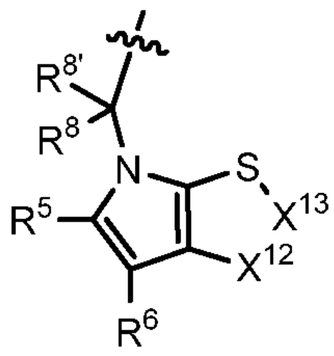
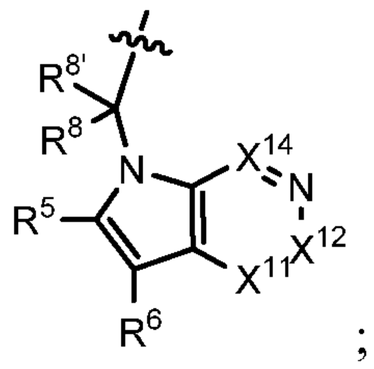









each of which R^4 other than hydrogen, -CHO, and $–CONH_2$, is unsubstituted or substituted with one or more of amino, imino, halogen, hydroxyl, cyano, cyanoimino, C_1-C_2alkyl, C_1-C_2alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

R^5 and R^6 are independently selected from –CHO, -$C(O)NH_2$, -$C(O)NH(CH_3)$, C_2-C_6alkanoyl, hydrogen, hydroxyl, halogen, cyano, nitro, -COOH, -SO_2NH_2, vinyl, C_1-C_6alkyl (including methyl), C_2-C_6alkenyl, C_1-C_6alkoxy, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -$C(O)C_0$-C_4alkyl(C_3-C_7cycloalkyl), -$P(O)(OR^9)_2$, -$OC(O)R^9$, -$C(O)OR^9$, -$C(O)N(CH_2CH_2R^9)(R^{10})$, -$NR^9C(O)R^{10}$, phenyl, or 5- to 6-membered heteroaryl; and wherein each R^5 and R^6 other than hydrogen, hydroxyl, cyano, and –COOH is unsubstituted or optionally substituted;

$R^{6'}$ is hydrogen, halogen, hydroxyl, C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), or C_1-C_4alkoxy; or R^6 and $R^{6'}$ may be taken together to form an oxo, vinyl, or imino group;

R^7 is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl);

R^8 and $R^{8'}$ are independently chosen from hydrogen, halogen, hydroxyl, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, and (C_1-C_4alkylamino)C_0-C_2alkyl; or R^8 and $R^{8'}$ are taken together to form an oxo group; or R^8 and $R^{8'}$ can be taken together with the carbon that they are bonded to form a 3-membered carbocyclic ring;

R^{16} is absent or may include one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-

C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

R^{19} is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, -SO_2C_1-C_6alkyl, (mono- and di-C_1-C_6alkylamino)C_1-C_4alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkyl(C_3-C_7heterocycloalkyl), -C_0-C_4alkyl(aryl), C_0-C_4alkyl(heteroaryl), and wherein R^{19} other than hydrogen is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, -COOH, and –C(O)OC_1-C_4alkyl;

X^{11} is N or CR^{11};

X^{12} is N or CR^{12};

X^{13} is N or CR^{13};

X^{14} is N or CR^{14}, and wherein no more than two of X^{11}, X^{12}, X^{13}, and X^{14} are N;

one of R^{12} and R^{13} is chosen from R^{31} and the other of R^{12} and R^{13} is chosen from R^{32}:

R^{31} is chosen from hydrogen, halogen, hydroxyl, nitro, cyano, amino, -COOH, C_1-C_2haloalkyl, C_1-C_2haloalkoxy, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_2-C_6alkenyloxy, -C(O)OR^9, C_1-C_6thioalkyl, -C_0-C_4alkylNR^9R^{10}, -C(O)NR^9R^{10}, -SO_2R^9, -$SO_2NR^9R^{10}$, -OC(O)R^9, and -C(NR^9)NR^9R^{10}, each of which R^{31} other than hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy is unsubstituted or substituted with one or more substituents independently selected from halogen, hydroxyl, nitro, cyano, amino, -COOH, -$CONH_2$ C_1-C_2haloalkyl, and C_1-C_2haloalkoxy, and each of which R^{31} is also optionally substituted with one substituent chosen from phenyl and 4- to 7-membered heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S; which phenyl or 4- to 7-membered heterocycle is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl)(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

[0001] R^{32} is selected from aryl; saturated or unsaturated heterocycle, wherein the heterocycle is bonded through a carbon atom in the heterocyclic ring to a carbon atom of ring A in the R^{12} or R^{13} position; and heteroaryl, wherein the aryl, heterocycle or heteroaryl ring can be optionally substituted.

R^{11}, R^{14}, and R^{15} are independently chosen at each occurrence from hydrogen, halogen, hydroxyl, nitro, cyano, -O(PO)(OR^9)$_2$, -(PO)(OR^9)$_2$, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_2-

C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, -C_0-C_4alkyl(mono- and di-C_1-C_6alkylamino), -C_0-C_4alkyl(C_3-C_7cycloalkyl), -C_0-C_4alkoxy(C_3-C_7cycloalkyl), C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

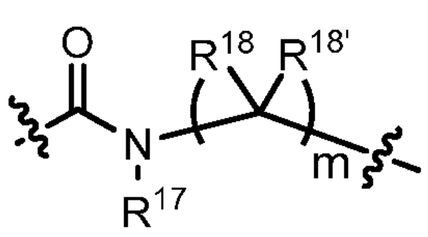
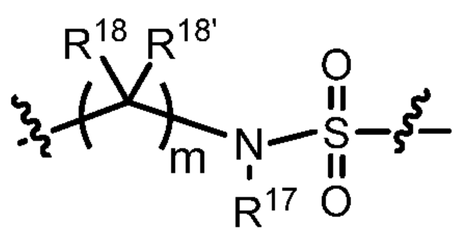
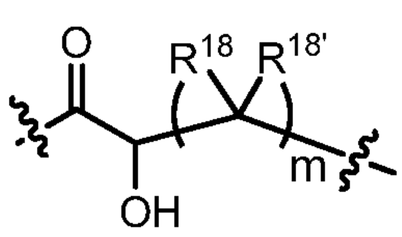
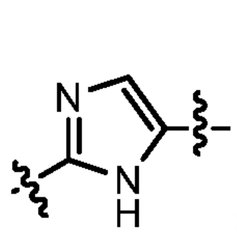
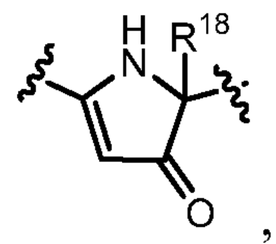
R^{21} and R^{22} are independently chosen at each occurrence from hydrogen, hydroxyl, cyano, amino, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, -C_1-C_4alkylOC(O)OC_1-C_6alkyl, -C_1-C_4alkylOC(O)C_1-C_6alkyl, -C_1-C_4alkylC(O)OC_1-C_6alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{21} and R^{22} can be optionally substituted;

R^{23} is independently chosen at each occurrence from C_1-C_6alkyl, C_1-C_6haloalkyl, (aryl)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and each R^{23} can be optionally substituted;

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

R^{30} is independently chosen at each occurrence from hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, (aryl)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (phenyl)C_0-C_4alkyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S; (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S; COOH, $Si(CH_3)_3$, $COOR^{30a}$, C_2-C_6alkanoyl, -$B(OH)_2$, -$C(O)(CH_2)_{1-4}S(O)R^{21}$, -$P(O)(OR^{21})(OR^{22})$, -$P(O)(OR^{21})R^{22}$, -$P(O)R^{21}R^{22}$, -$NR^9P(O)(NHR^{21})(NHR^{22})$, -$NR^9P(O)(OR^{21})(NHR^{22})$, -$NR^9P(O)(OR^{21})(OR^{22})$, -$C(S)R^{21}$, -$NR^{21}SO_2R^{22}$, -$NR^9S(O)NR^{10}R^{22}$, -$NR^9SO_2NR^{10}R^{22}$, -$SO_2NR^9COR^{22}$, -$SO_2NR^9CONR^{21}R^{22}$, -$NR^{21}SO_2R^{22}$, -$C(O)NR^{21}SO_2R^{22}$, -$C(NH_2)NR^9R^{22}$, -$C(NH_2)NR^9S(O)_2R^{22}$, -$NR^9C(O)OR^{10}$, -$NR^{21}OC(O)R^{22}$, -$(CH_2)_{1-4}C(O)NR^{21}R^{22}$, -$C(O)R^{24}R^{25}$, -$NR^9C(O)R^{21}$, -$C(O)R^{21}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9C(O)NR^{24}R^{25}$, -$(CH_2)_{1-4}OC(O)R^{21}$, each of which R^{30} can be optionally substituted;

R^{30a} is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl-, (aryl)C_0-C_4alkyl-, (3- to 7-membered heterocycloalkyl)C_0-C_4alkyl- having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and (5- or 6- membered unsaturated or aromatic heterocycle)C_0-C_4alkyl having 1, 2, or 3 heteroatoms independently chosen from N, O, and S, each of which R^{30a} can be optionally substituted;

L is a bond or is chosen from the formulas  ,  ,  ,  and  ,

where R^{17} is hydrogen, C_1-C_6alkyl, or -C_0-C_4alkyl(C_3-C_7cycloalkyl), and R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, hydroxymethyl, and methyl; and m is 0, 1, 2, or 3;

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_2-C_6alkenyl; C_2-C_6alkynyl; –(C_0-C_4alkyl)(aryl); –(C_0-C_4alkyl)(heteroaryl); or –(C_0-C_4alkyl)(biphenyl) each of which B is unsubstituted or substituted with one or more substituents independently chosen from R^{33} and R^{34}, and 0 or 1 substituents chosen from R^{35} and R^{36};

R^{33} is independently chosen from halogen, hydroxyl, -COOH, cyano, C_1-C_6alkyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, -C_0-C_4alkylNR^9R^{10}, -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

R^{34} is independently chosen from nitro, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6thioalkyl, -JC_3-C_7cycloalkyl, -$B(OH)_2$, -J$C(O)NR^9R^{23}$,-JOSO_2OR^{21}, -$C(O)(CH_2)_{1\text{-}4}S(O)R^{21}$, -$O(CH_2)_{1\text{-}4}S(O)NR^{21}R^{22}$, -J$OP(O)(OR^{21})(OR^{22})$, -J$P(O)(OR^{21})(OR^{22})$, -J$OP(O)(OR^{21})R^{22}$, -J$P(O)(OR^{21})R^{22}$, -J$OP(O)R^{21}R^{22}$, -J$P(O)R^{21}R^{22}$, -J$SP(O)(OR^{21})(OR^{22})$, -J$SP(O)(OR^{21})(R^{22})$, -J$SP(O)(R^{21})(R^{22})$, -J$NR^9P(O)(NHR^{21})(NHR^{22})$, -J$NR^9P(O)(OR^{21})(NHR^{22})$, -J$NR^9P(O)(OR^{21})(OR^{22})$, -J$C(S)R^{21}$, -J$NR^{21}SO_2R^{22}$, -J$NR^9S(O)NR^{10}R^{22}$, -J$NR^9SO_2NR^{10}R^{22}$, -J$SO_2NR^9COR^{22}$, -J$SO_2NR^9CONR^{21}R^{22}$, -J$NR^{21}SO_2R^{22}$, -J$C(O)NR^{21}SO_2R^{22}$, -J$C(NH_2)NR^{22}$, -J$C(NH_2)NR^9S(O)_2R^{22}$, -J$OC(O)NR^{21}R^{22}$, -J$NR^{21}C(O)OR^{22}$, -J$NR^{21}OC(O)R^{22}$, -$(CH_2)_{1\text{-}4}C(O)NR^{21}R^{22}$, -J$C(O)R^{24}R^{25}$, -J$NR^9C(O)R^{21}$, -J$C(O)R^{21}$, -J$NR^9C(O)NR^{10}R^{22}$, -$CCR^{21}$, -$(CH_2)_{1\text{-}4}OC(O)R^{21}$, and -J$C(O)OR^{23}$; each of which R^{34} may be unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, amino, oxo,

-$B(OH)_2$, -$Si(CH_3)_3$, -COOH, -$CONH_2$, -$P(O)(OH)_2$, C_1-C_6alkyl, -C_0-C_4alkyl(C_3-C_7cycloalkyl), C_1-C_6alkoxy, -C_0-C_2alkyl(mono- and di-C_1-C_4alkylamino), C_1-C_6alkylester, C_1-C_4alkylamino, C_1-C_4hydroxylalkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

R^{35} is independently chosen from naphthyl, naphthyloxy, indanyl, (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl containing 1 or 2 heteroatoms chosen from N, O, and S, and bicyclic heterocycle containing 1, 2, or 3 heteroatoms independently chosen from N, O, and S, and containing 4- to 7- ring atoms in each ring; each of which R^{35} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

R^{36} is independently chosen from tetrazolyl, (phenyl)C_0-C_2alkyl, (phenyl)C_1-C_2alkoxy, phenoxy, and 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms independently chosen from N, O, B, and S, each of which R^{36} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, C_1-C_6alkylester, -C_0-C_4alkyl(C_3-C_7cycloalkyl), -SO_2R^9, -$OSi(CH_3)_2C(CH_3)_3$, –$Si(CH_3)_2C(CH_3)_3$, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy; and

J is independently selected at each occurrence from a covalent bond, C_1-C_4alkylene, -OC_1-C_4alkylene, C_2-C_4alkenylene, and C_2-C_4alkynylene.

2. A pharmaceutical composition comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

3. A method for the treatment of a disorder mediated by the complement pathway, comprising administering an effective amount to a host in need thereof of a compound of claim 1, optionally in a pharmaceutically acceptable carrier.

4. The method of claim 3, wherein the host is a human.

5. The method of claim 3, wherein the complement mediated pathway is age-related macular degeneration (AMD).

6. The method of claim 3, wherein the complement mediated pathway is retinal degeneration.

7. The method of claim 3, wherein the complement mediated pathway is an ophthalmic disease.

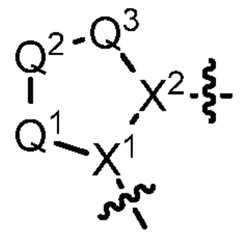
8. The method of claim 3, wherein the complement mediated pathway is paroxysymal nocturnal hemoglobinuria (PNH).

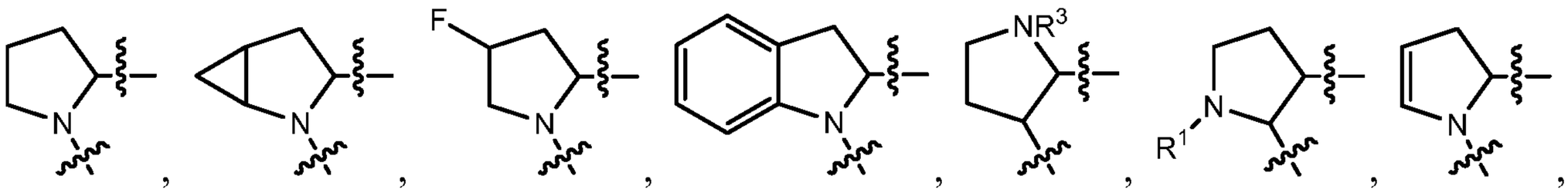
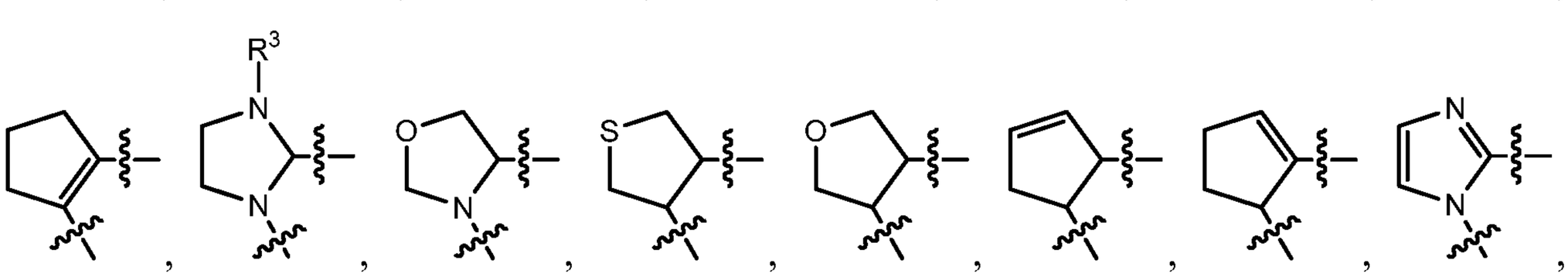
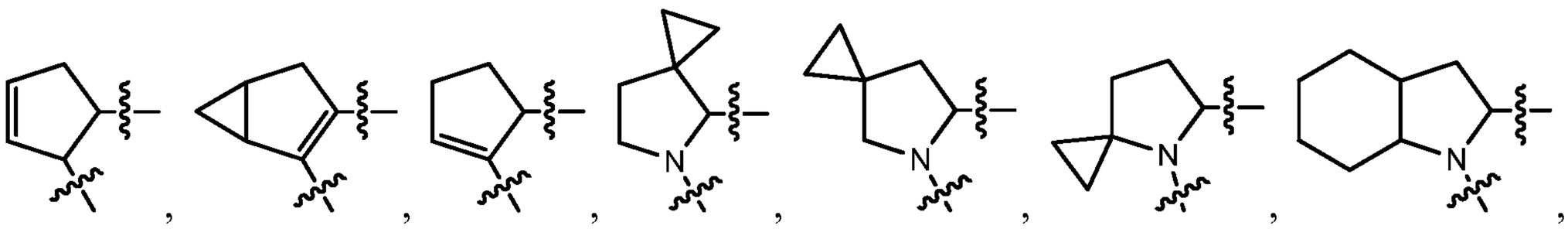
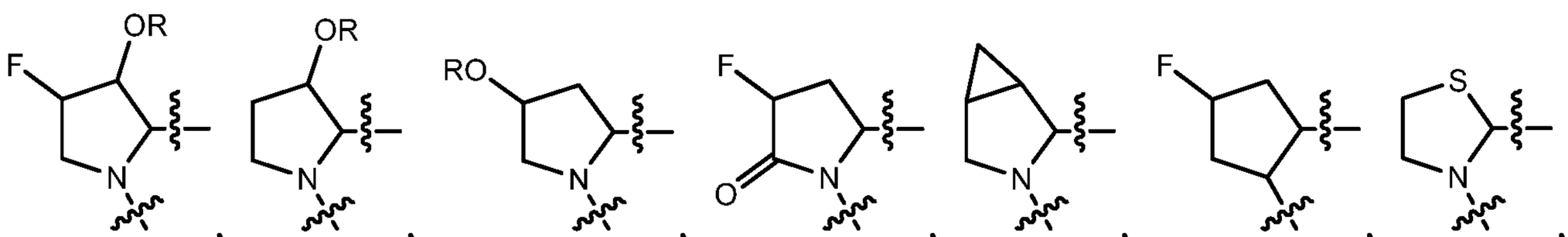
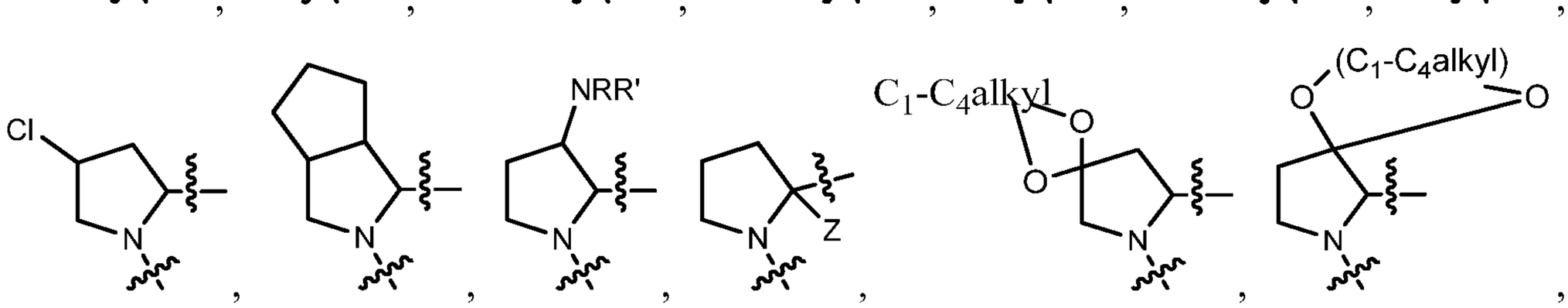
9. The method of claim 3, wherein the complement mediated pathway is multiple sclerosis.

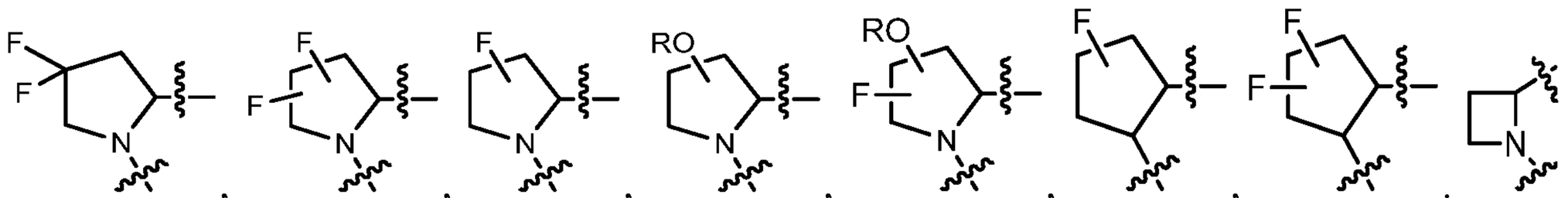
10. The method of claim 3, wherein the complement mediated pathway is arthritis.

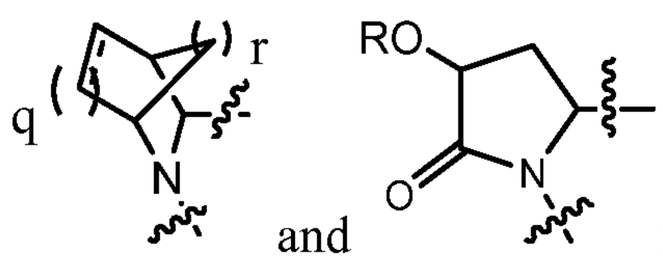
11. The method of claim 3, wherein the complement mediated pathway is rheumatoid arthritis.

12. The method of claim 3, wherein the complement mediated pathway is a respiratory disease or a cardiovascular disease.

13. The compound of claim 1, wherein the  ring is selected from:





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

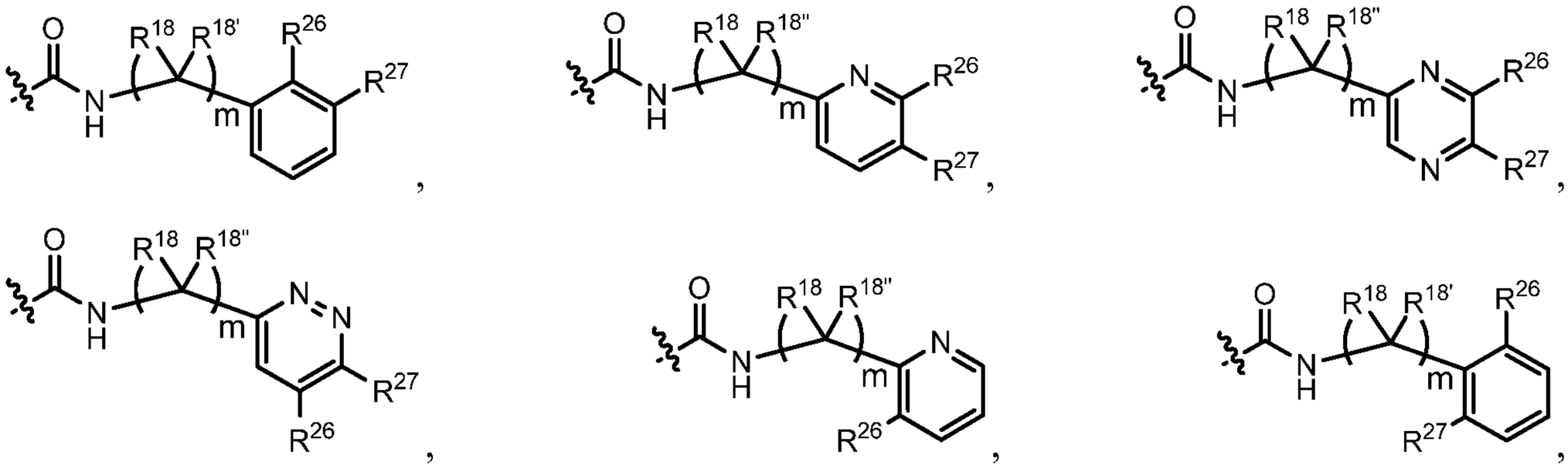
R and R' are independently chosen from H and optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; and,

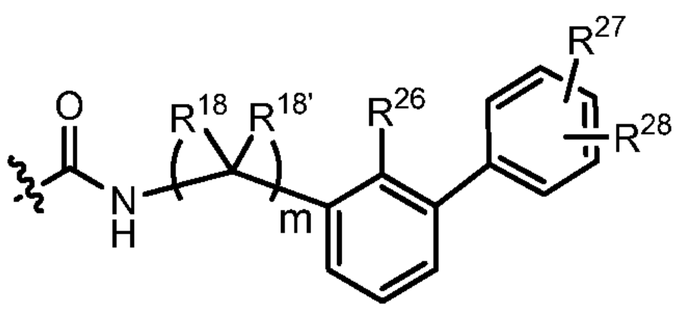
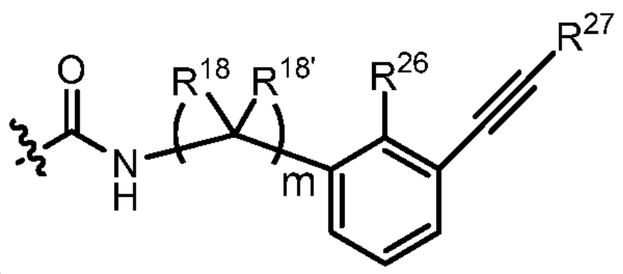
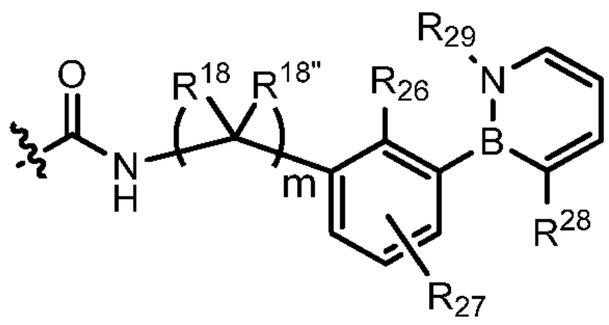
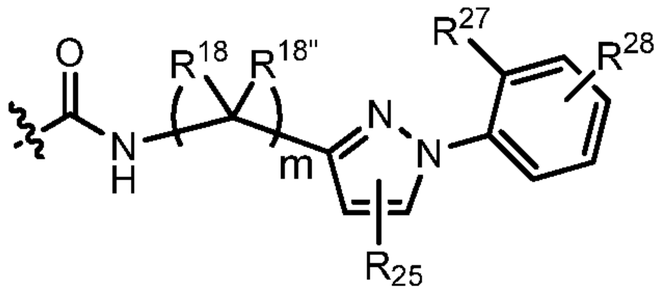
Z is F, Cl, NH_2, CH_3, CH_2D, or CD_3.

14. The compound of claim 1, wherein R^1 and $R^{1'}$ or R^3 and $R^{3'}$ can together form an optionally substituted 3- to 6-membered carbocyclic spiro ring or a 3- to 6-membered heterocyclic spiro ring containing 1 or 2 heteroatoms independently chosen from N, O, or S.

15. The compound of claim 1, wherein R^2 and $R^{2'}$ can together to form an optionally substituted 3- to 6-membered carbocyclic spiro ring; or R^2 and $R^{2'}$ are taken together to form a 3- to 6-membered heterocyclic spiro ring.

16. The compound of claim 1, wherein –L-B- is selected from:




, 
, 
, or 
;

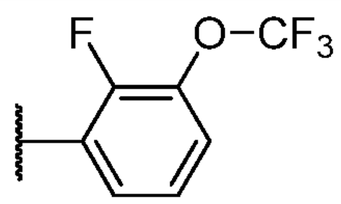
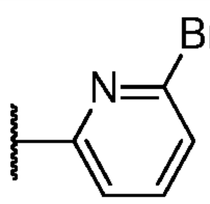
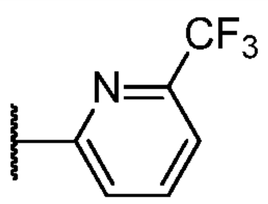
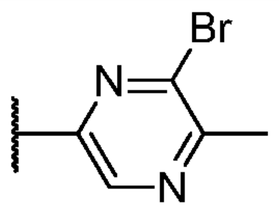
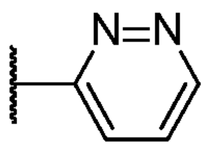
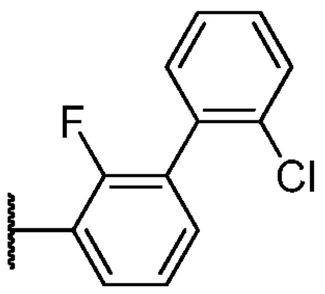
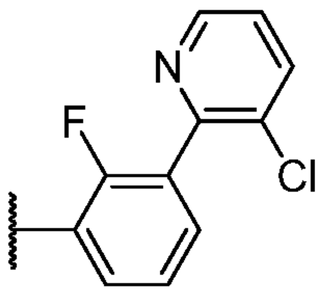
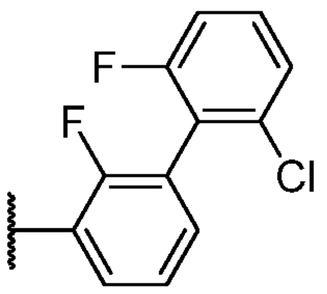
wherein

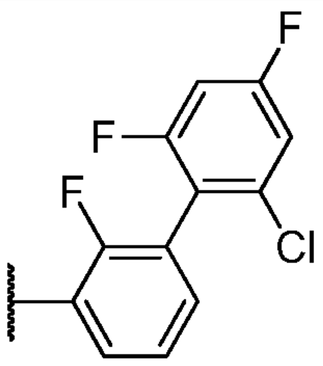
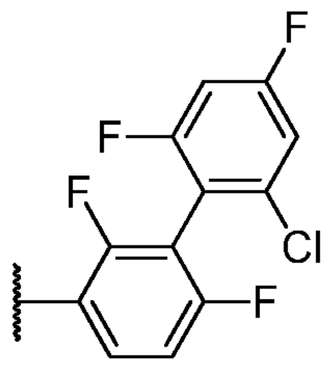
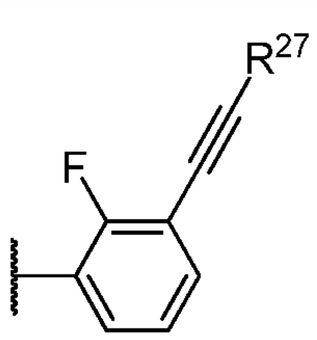
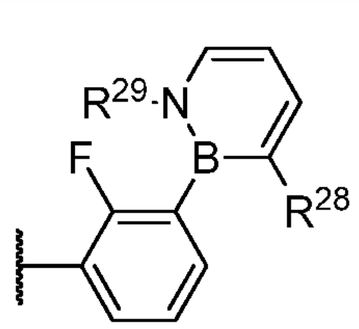
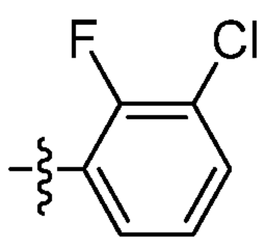
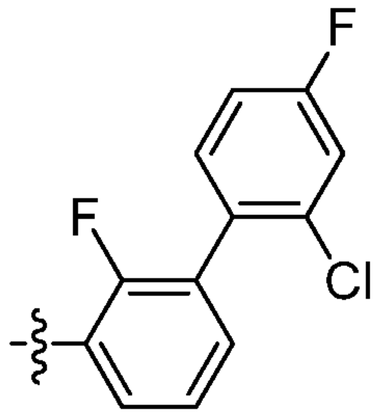
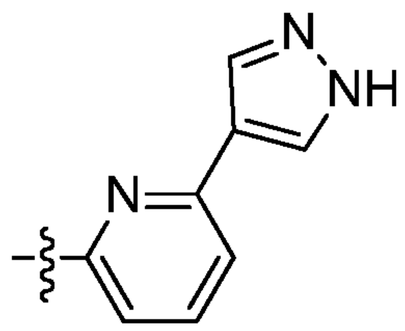
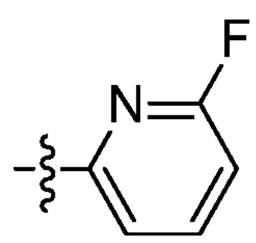
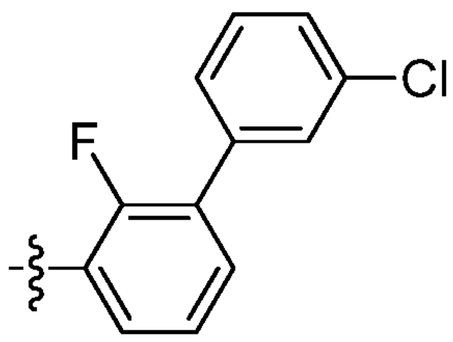
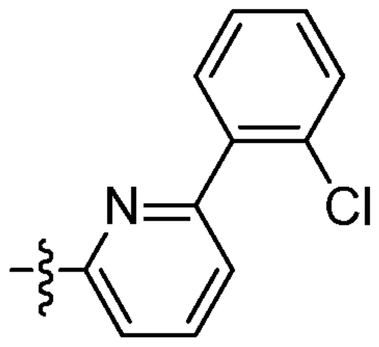
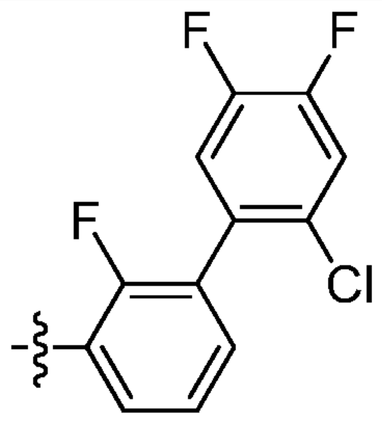
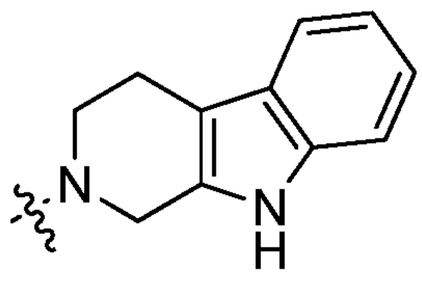
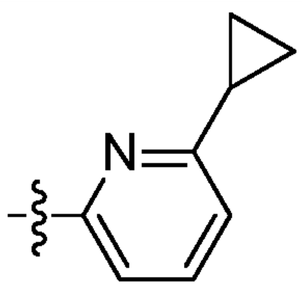
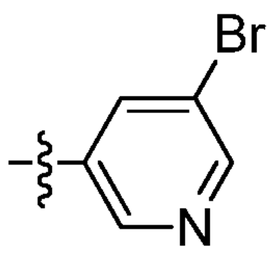
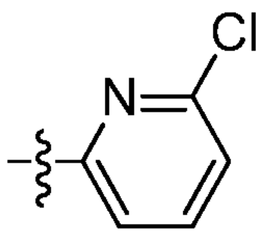
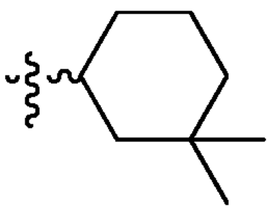
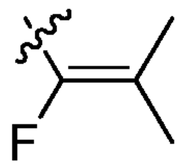
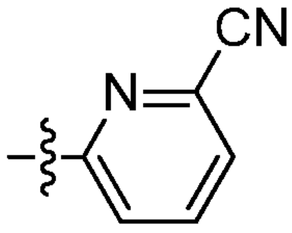
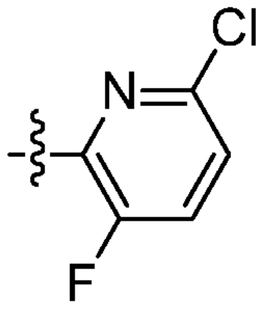
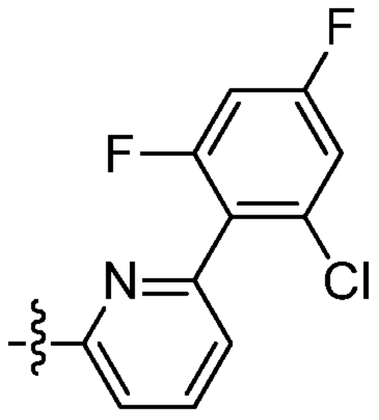
R^{18} and $R^{18'}$ are independently chosen from hydrogen, halogen, hydroxymethyl, and methyl;

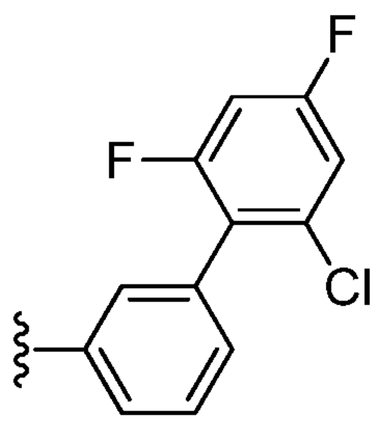
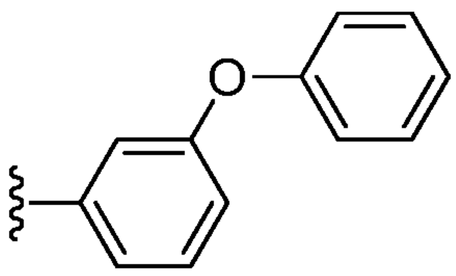
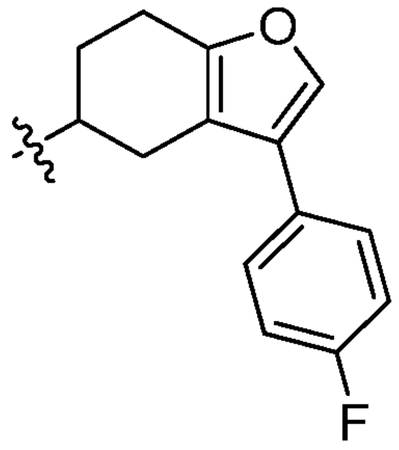
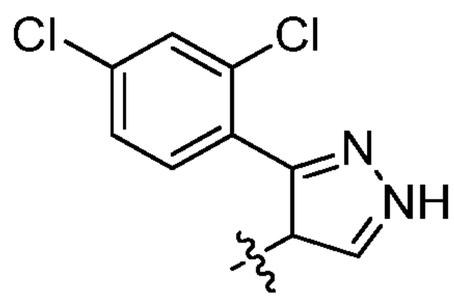
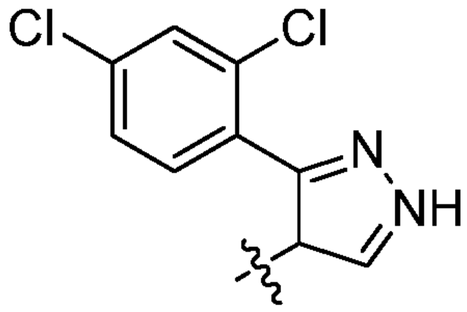
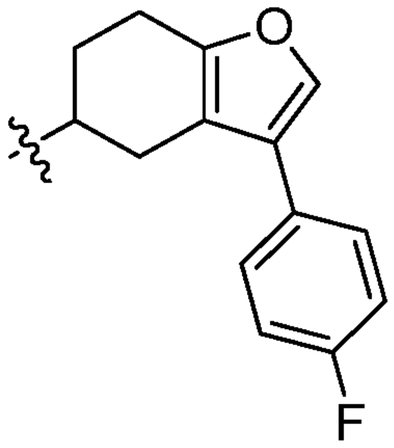
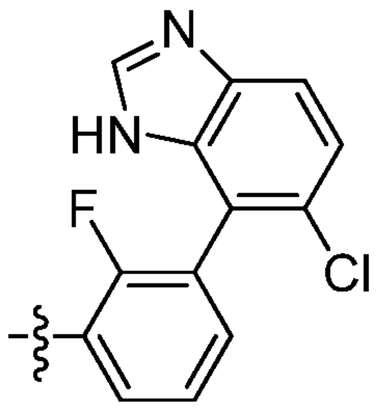
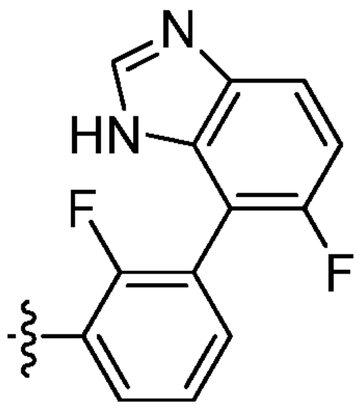
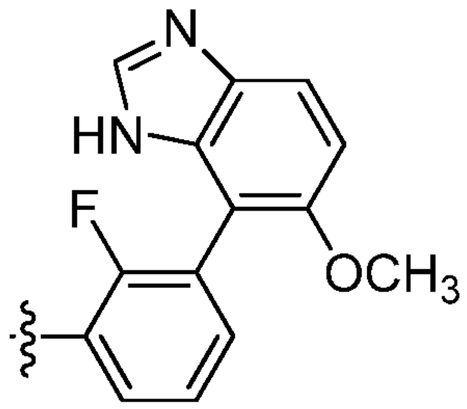
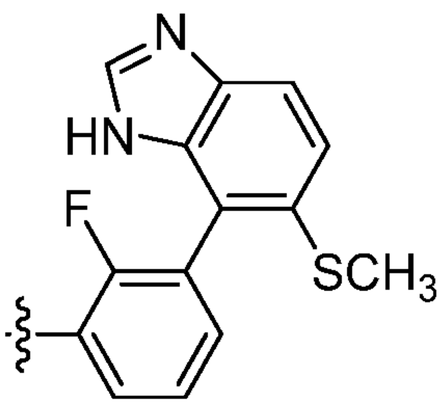
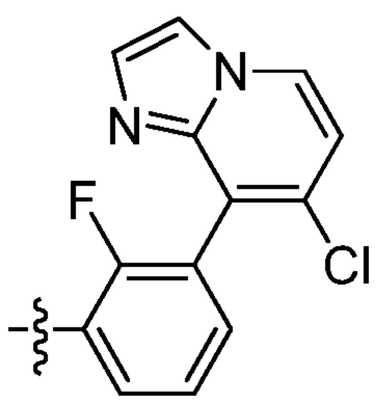
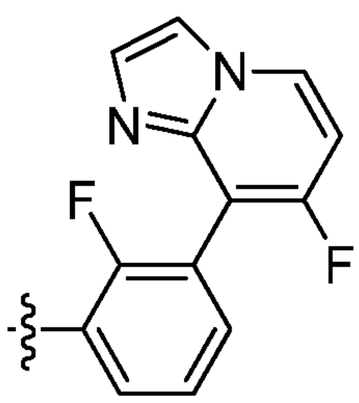
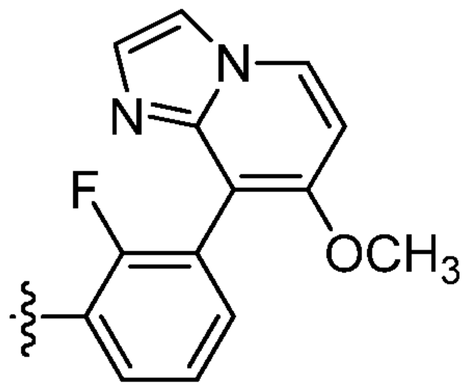
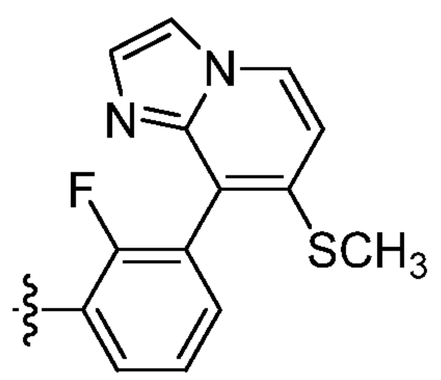
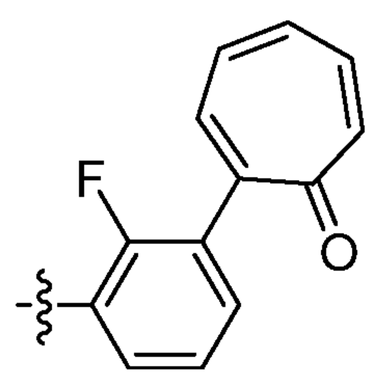
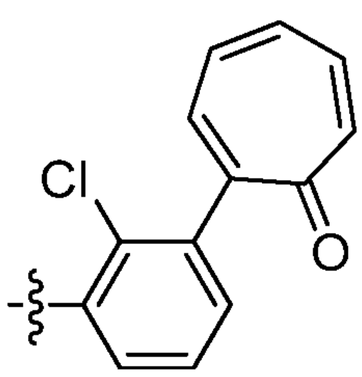
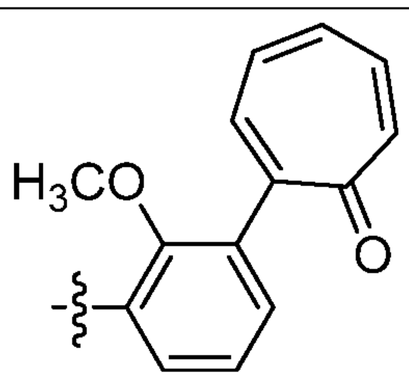
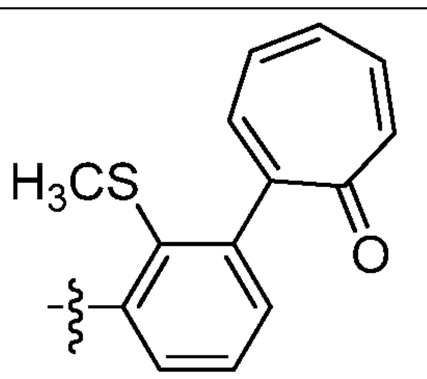
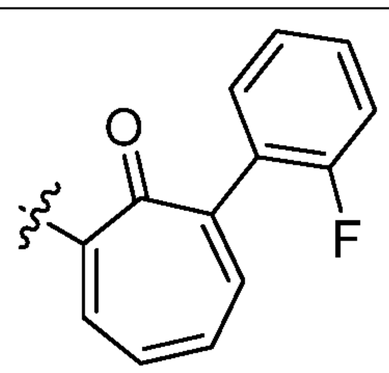
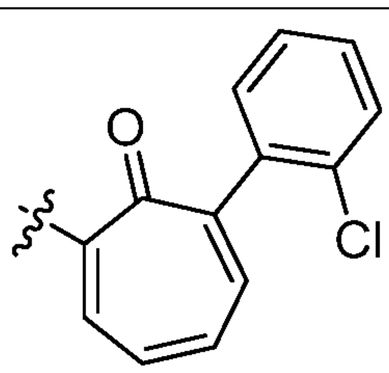
m is 0 or 1; and

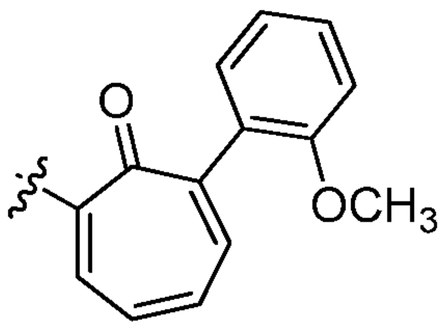
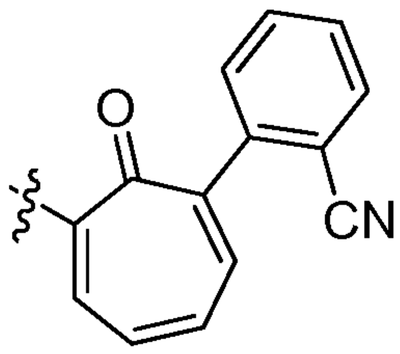
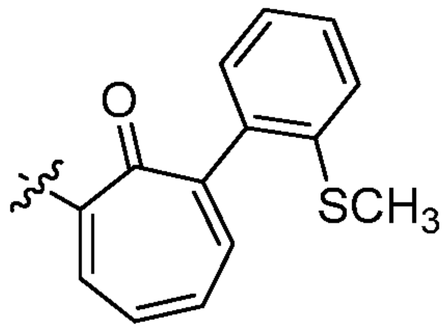
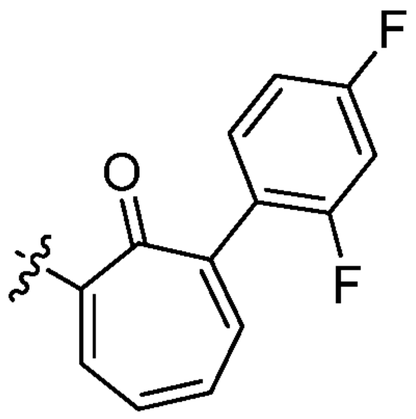
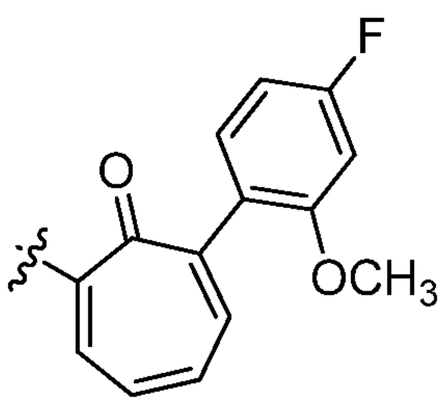
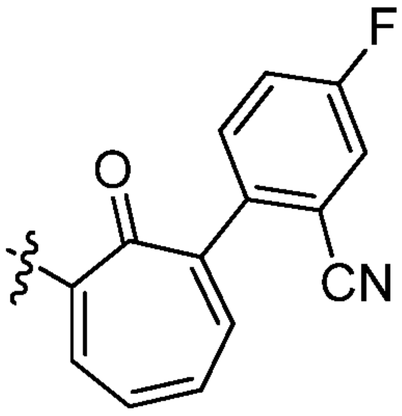
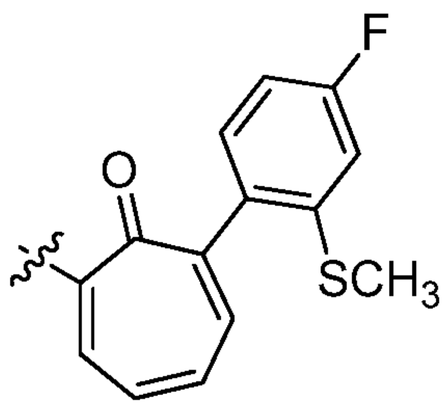
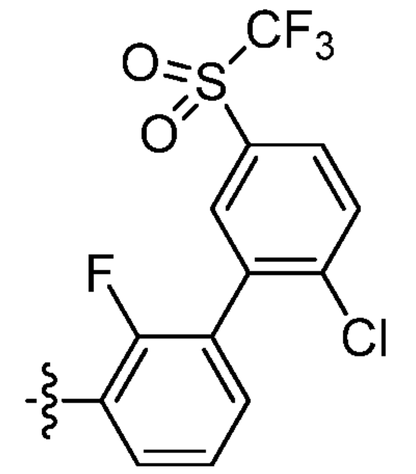
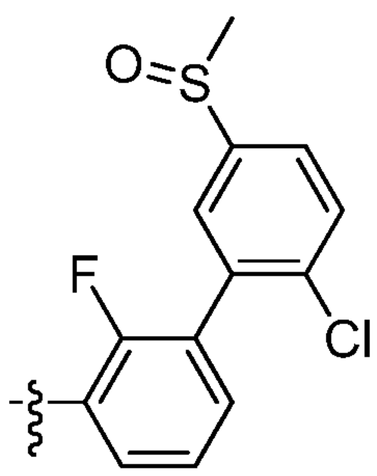
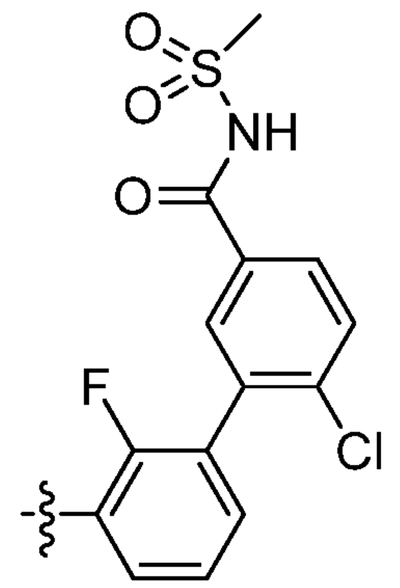
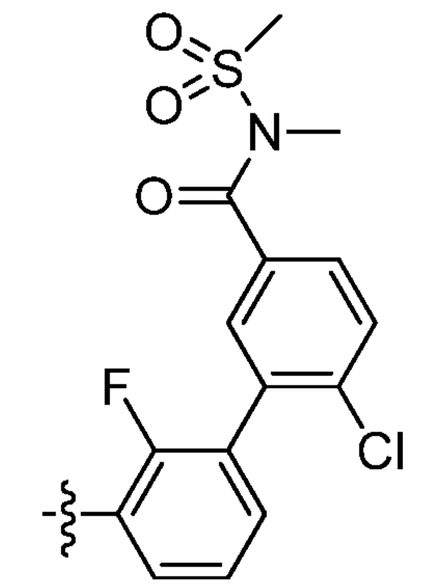
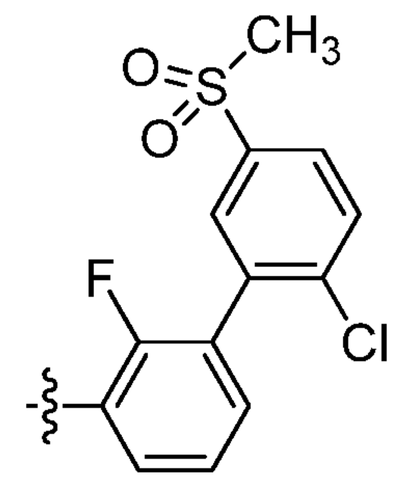
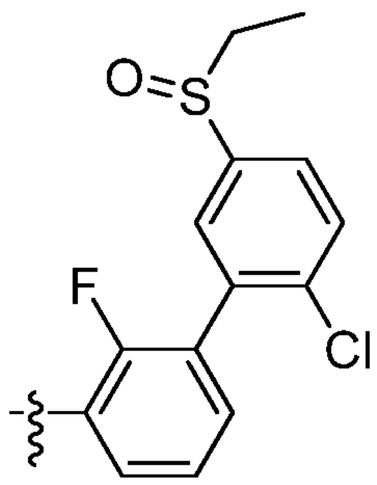
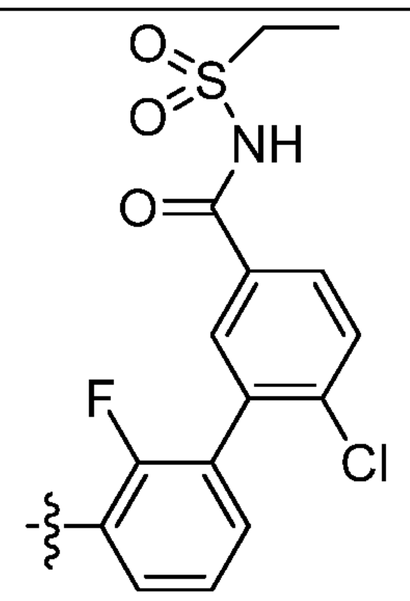
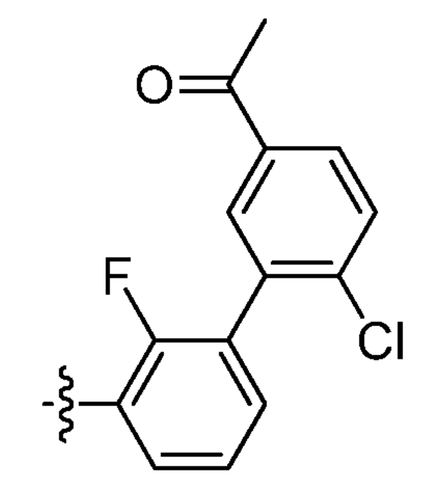
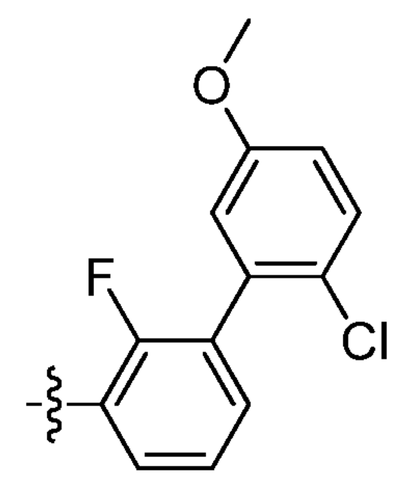
R^{26}, R^{27}, and R^{28} are independently chosen from hydrogen, halogen, hydroxyl, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkanoyl, C_1-C_6alkoxy, C_1-C_6thioalkyl, (mono- and di-C_1-C_6alkylamino)C_0-C_4alkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl, (aryl)C_0-C_4alkyl-, (heteroaryl)C_0-C_4alkyl-, and -C_0-C_4alkoxy(C_3-C_7cycloalkyl); each of which R^{26}, R^{27}, and R^{28} other than hydrogen, halogen, hydroxyl, nitro, cyano, is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, C_1-C_2alkoxy, C_1-C_2haloalkyl, (C_3-C_7cycloalkyl)C_0-C_4alkyl-, and C_1-C_2haloalkoxy; and R^{29} is hydrogen, C_1-C_2alkyl, C_1-C_2haloalkyl or $–Si(CH_3)_2C(CH_3)_3$.

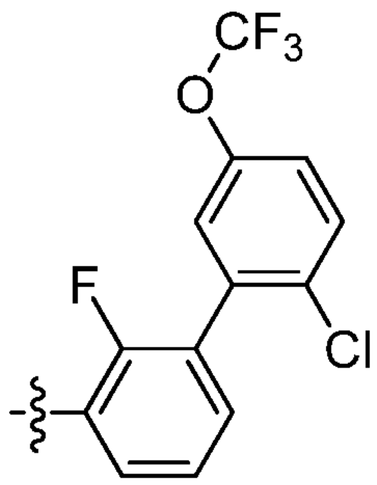
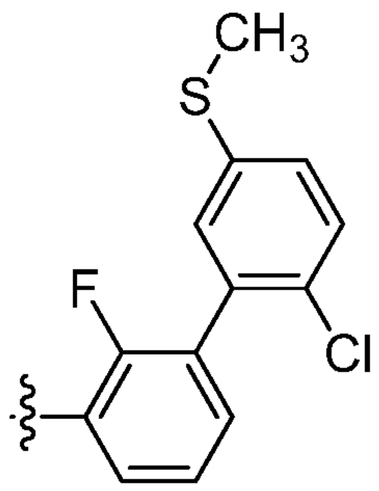
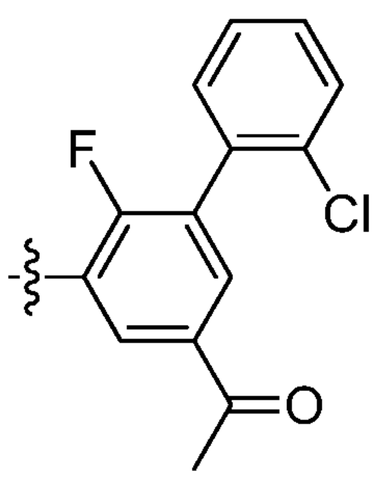
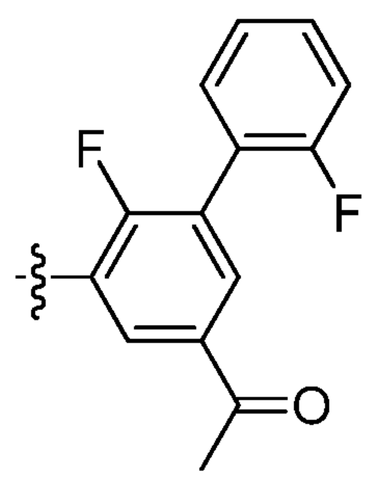
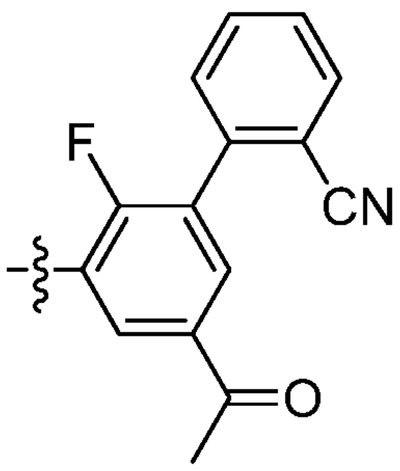
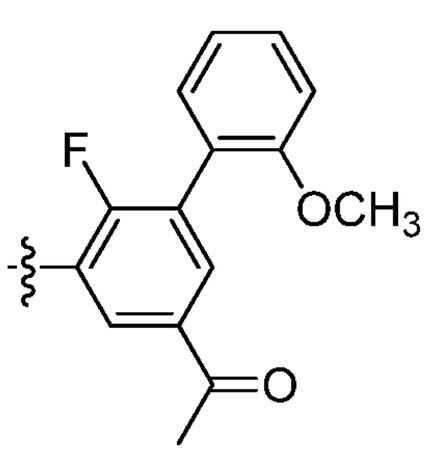
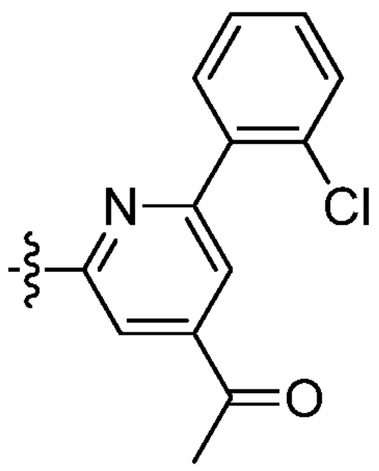
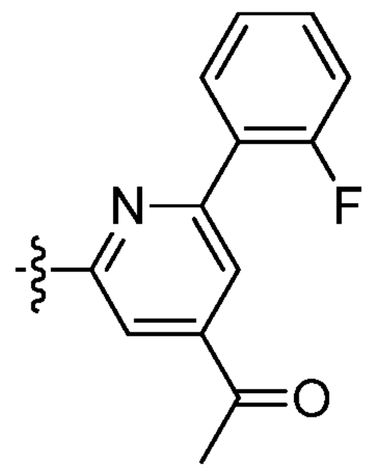
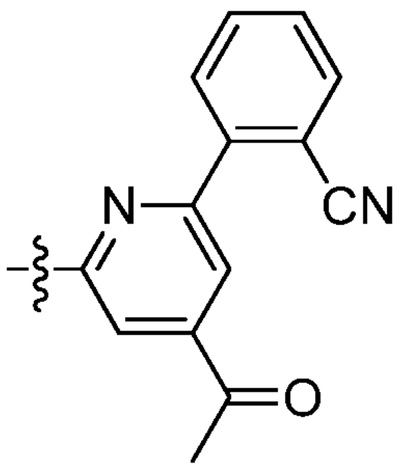
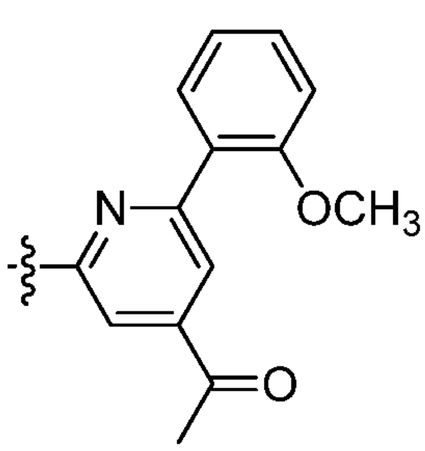
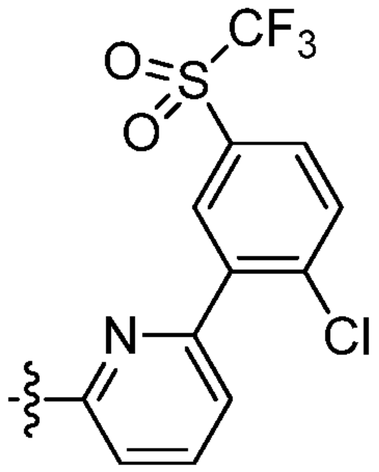
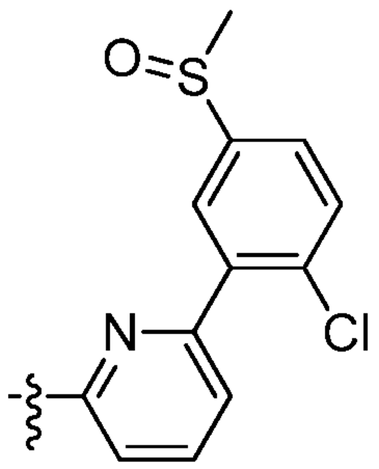
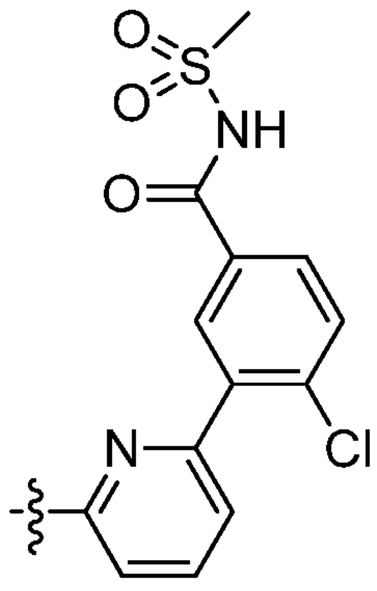
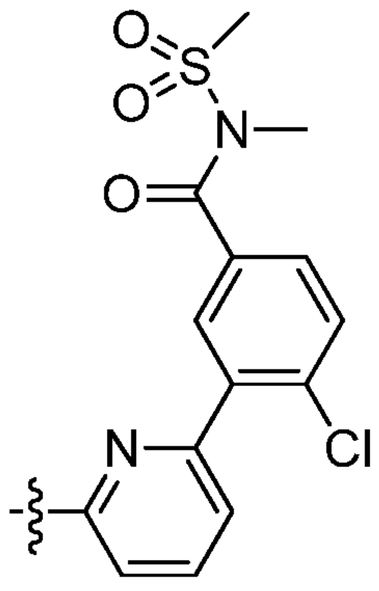
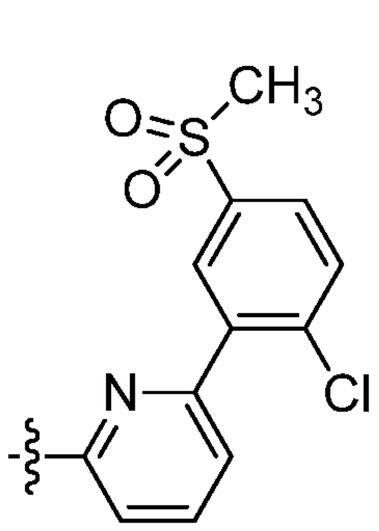
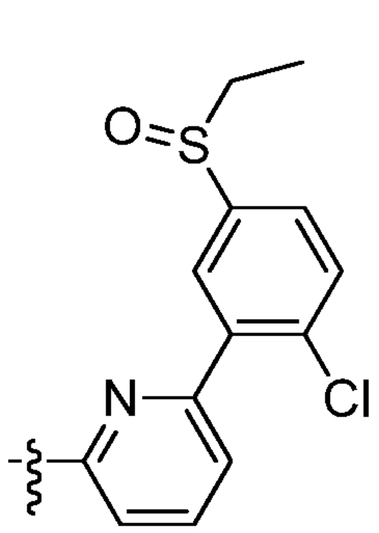
17. The compound of claim 1, wherein B is selected from:

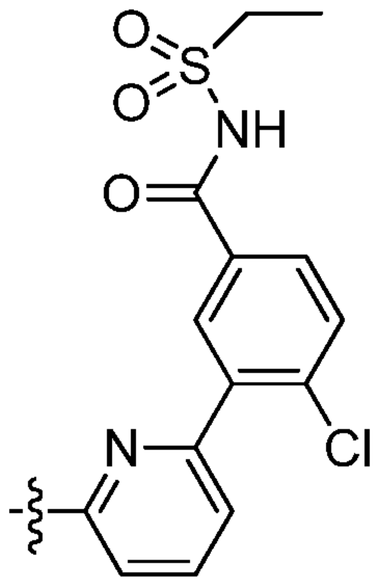
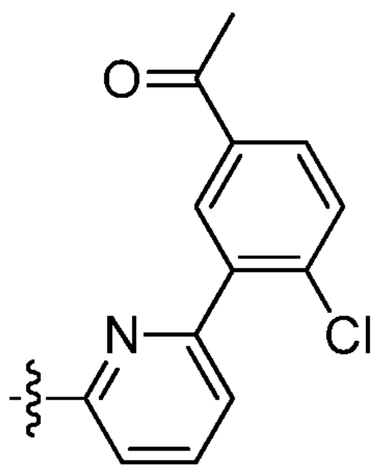
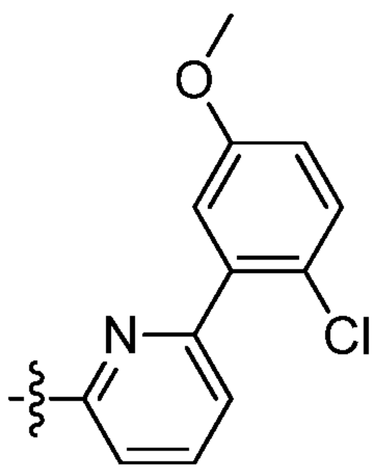
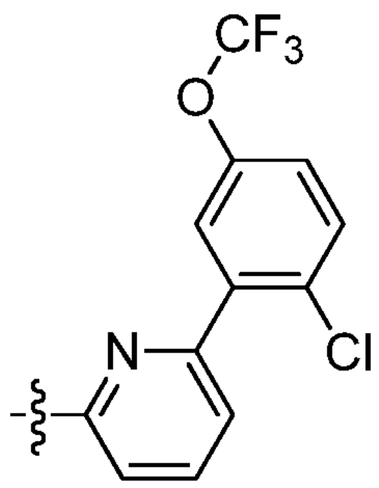
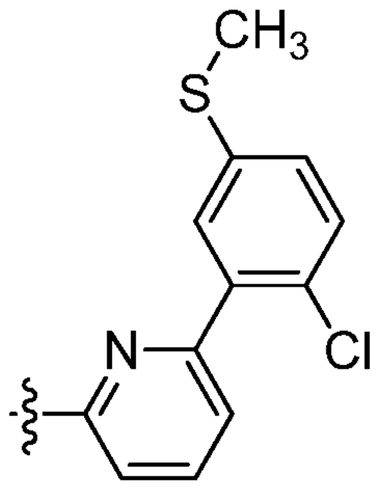
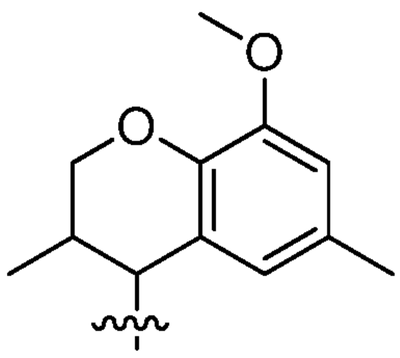
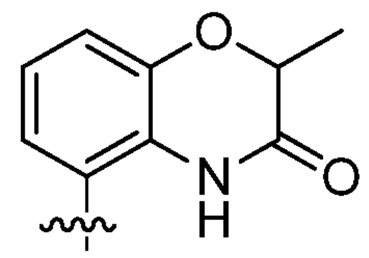
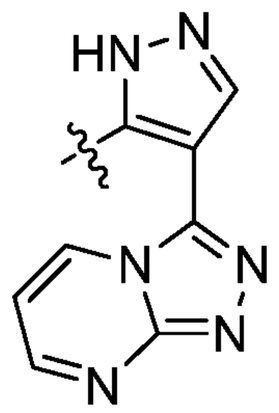
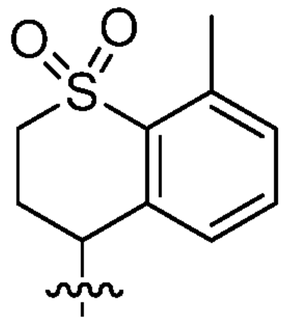
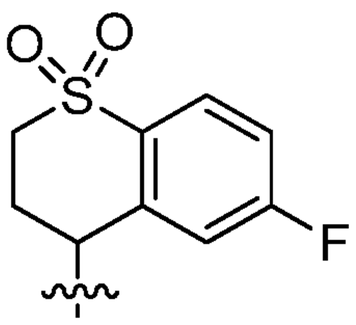
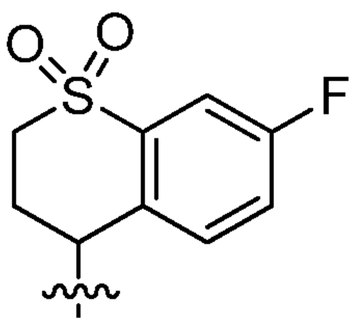
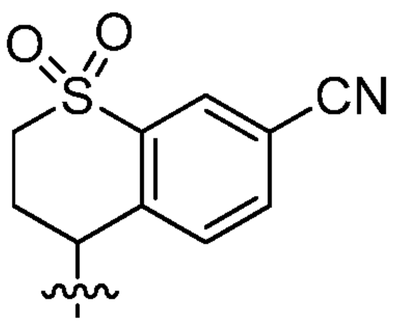
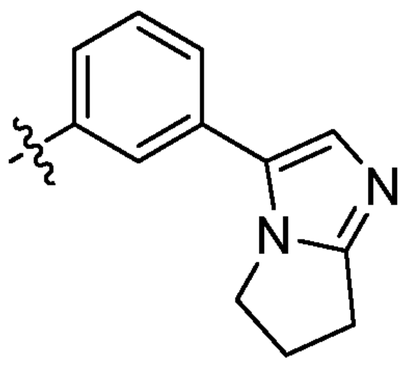
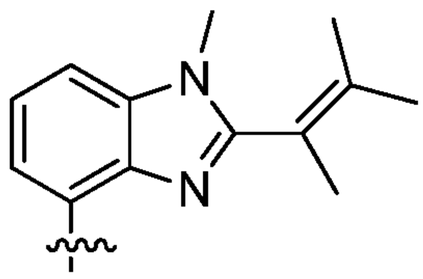
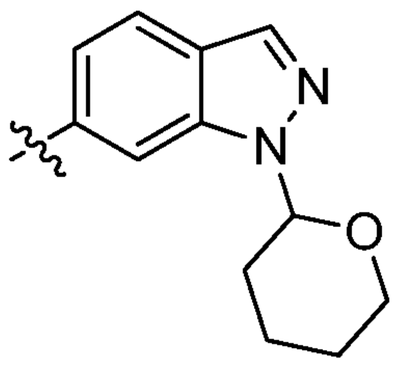
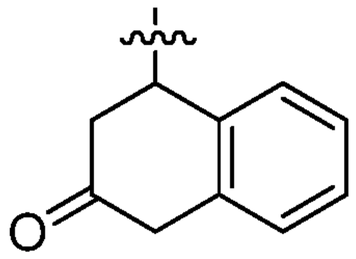
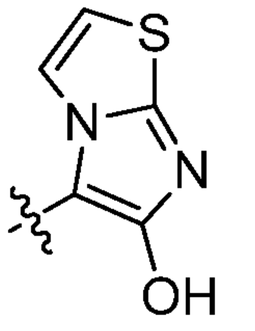
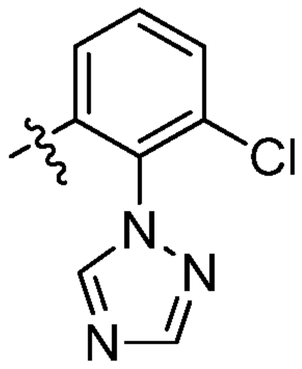
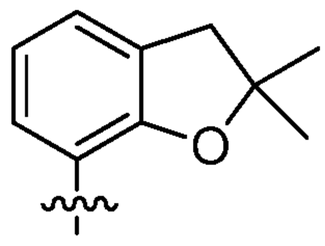
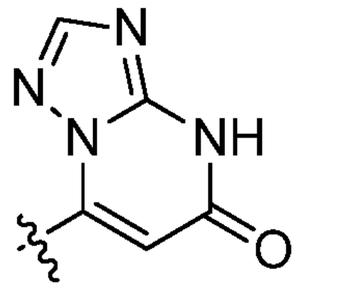
			
			

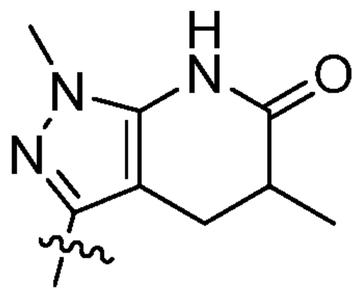
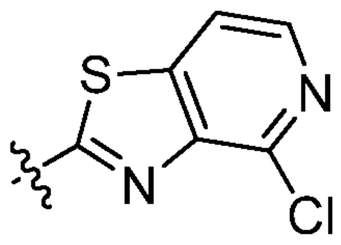
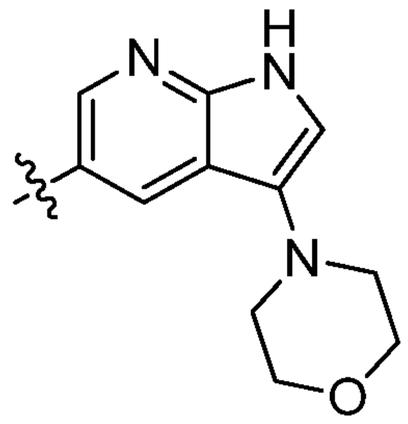
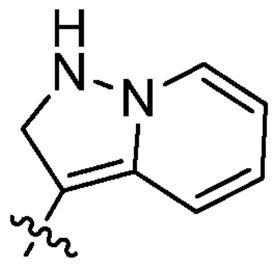
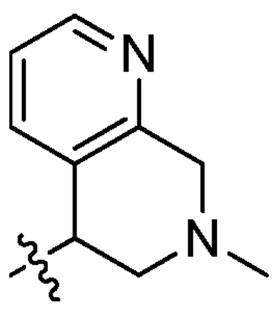
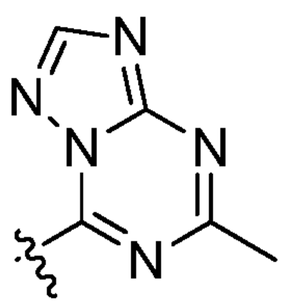
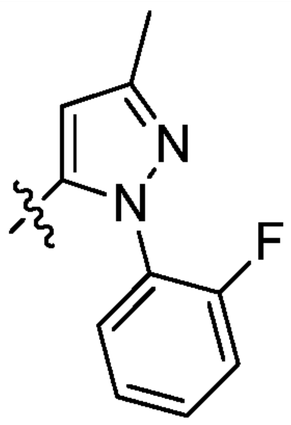
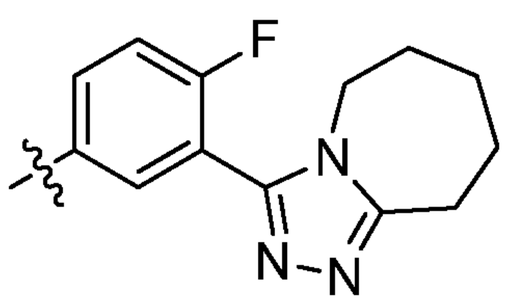
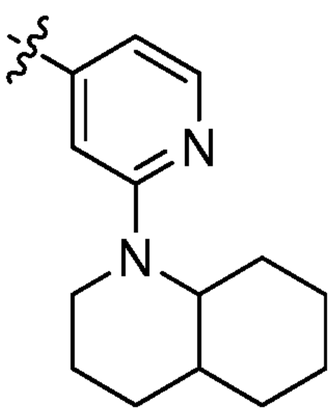
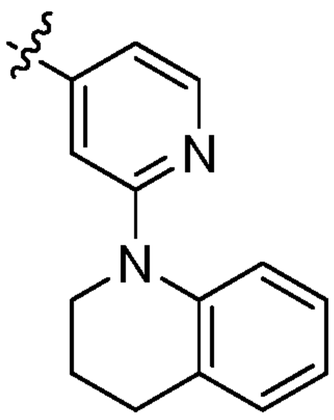
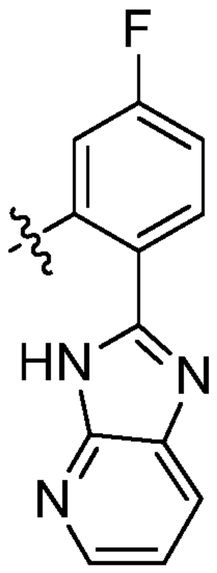
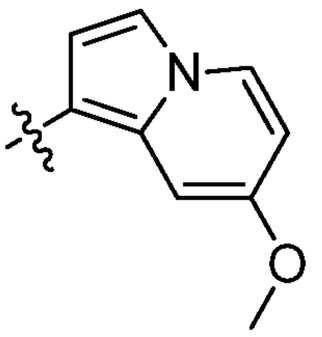
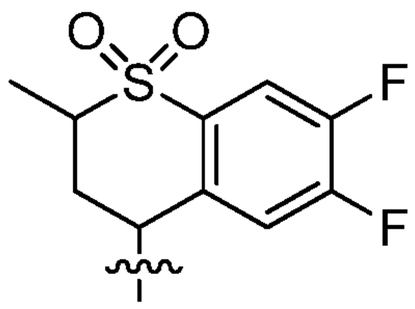
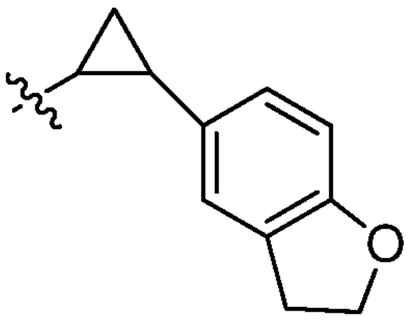
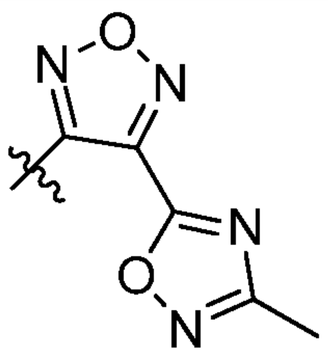
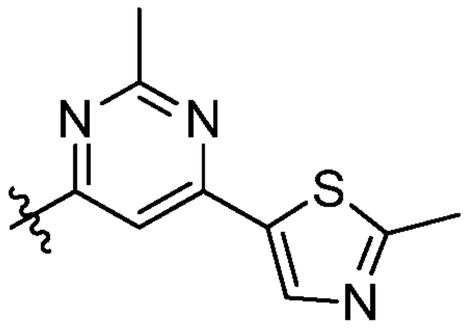
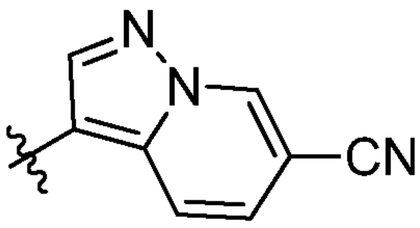
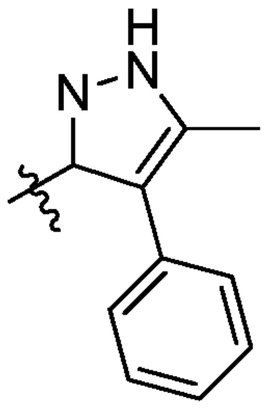
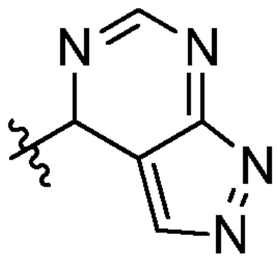
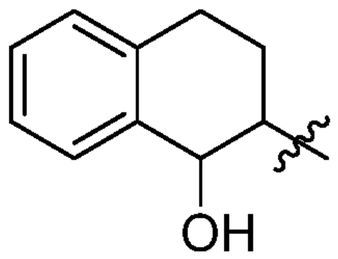
			
			
			
			
			

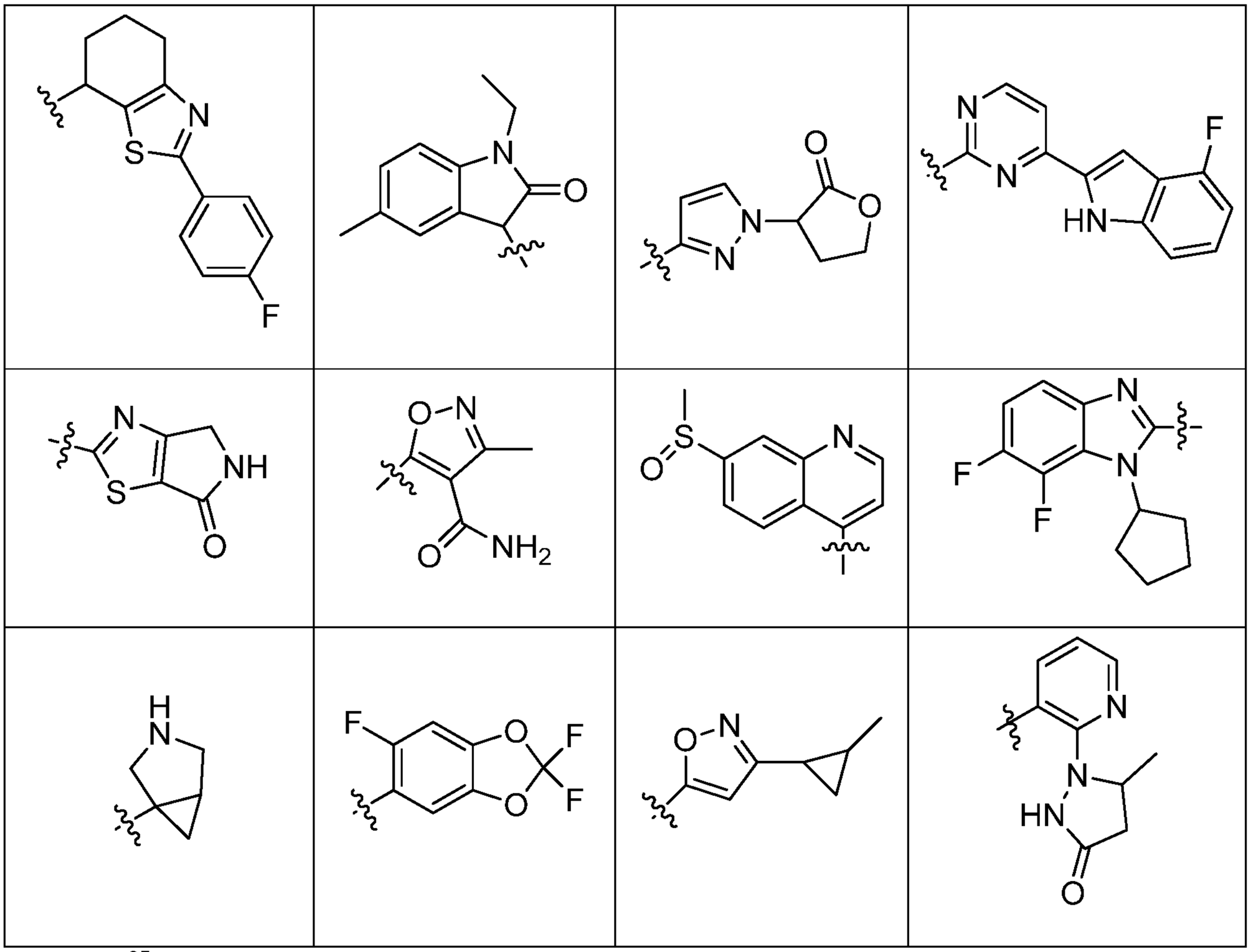
			
			
			
			
			

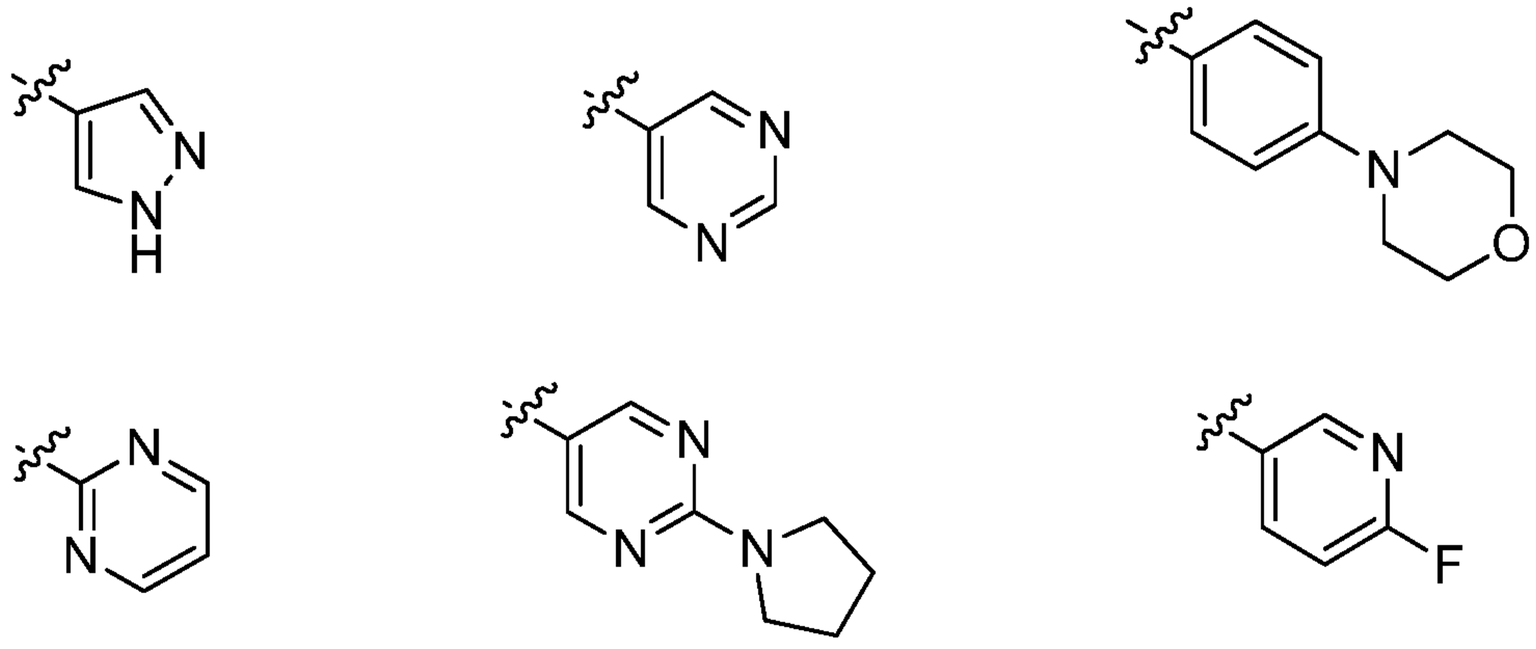


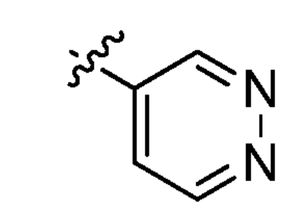
wherein R^{27} is hydrogen, methyl, or trifluoromethyl;

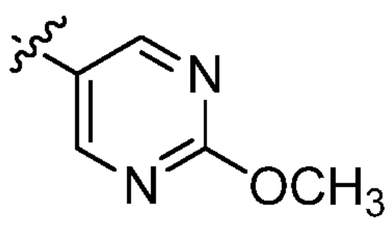
R^{28} is hydrogen or halogen; and

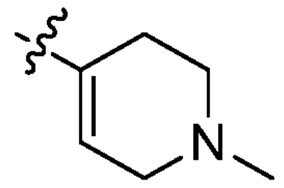
R^{29} is hydrogen, methyl, trifluoromethyl, or $–Si(CH_3)_2C(CH_3)_3$.

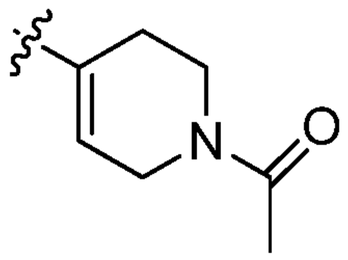
18. The compound of claim 1, wherein R^{32} is selected from

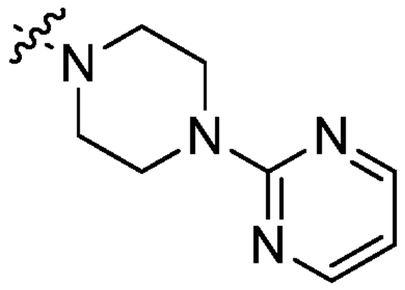


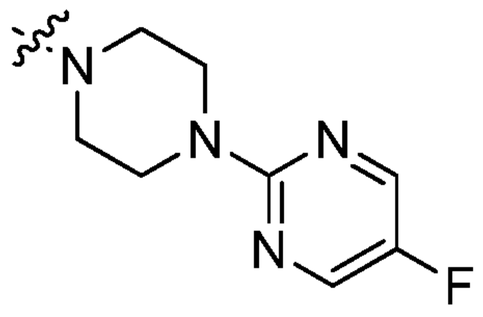


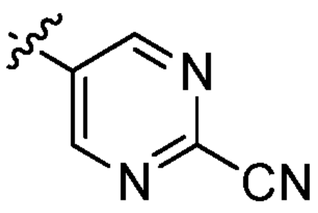


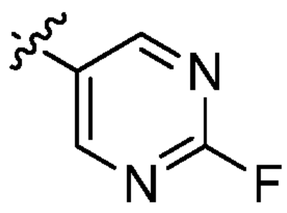


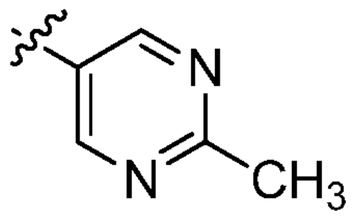


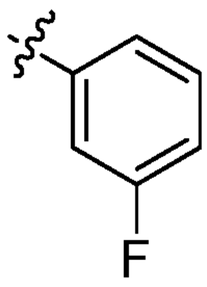


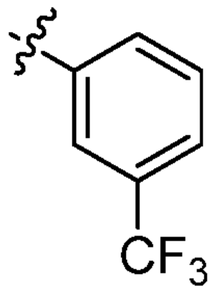


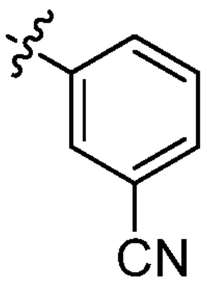


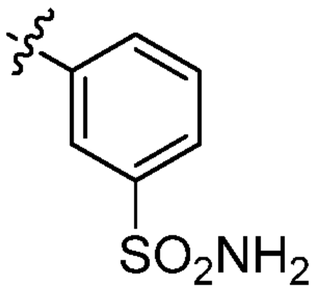


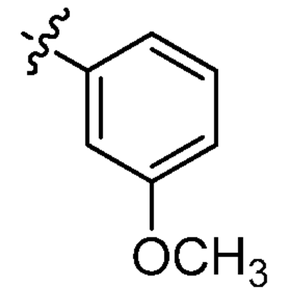


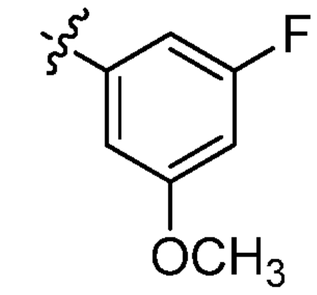


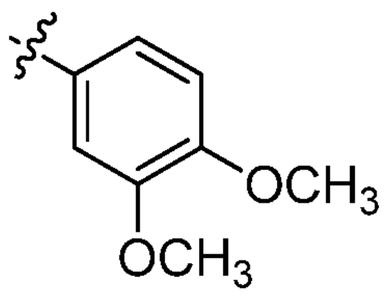


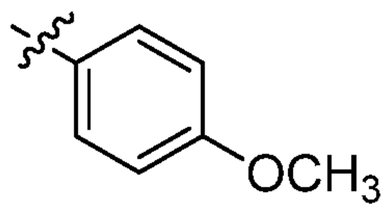


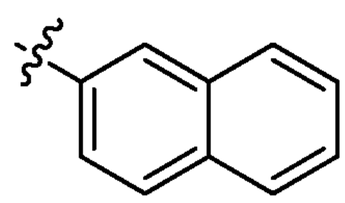


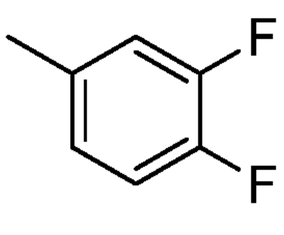


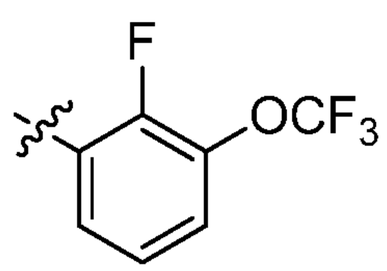


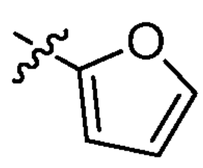


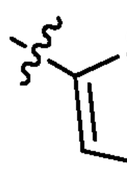


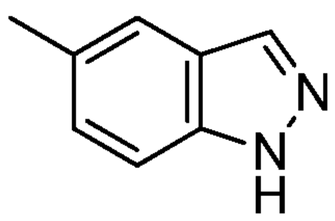


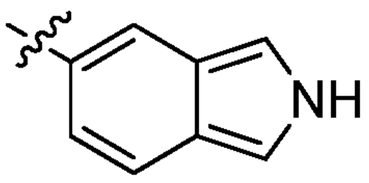


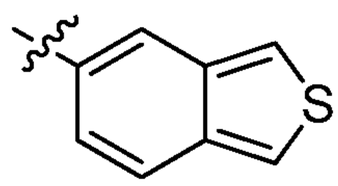
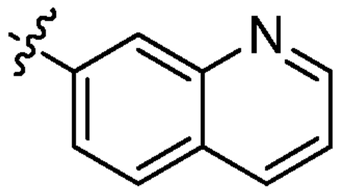
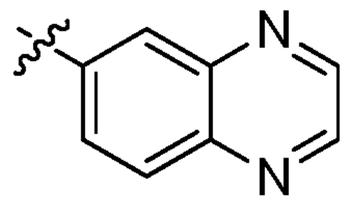
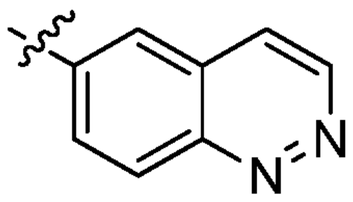
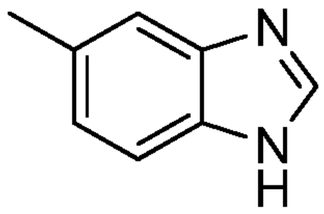
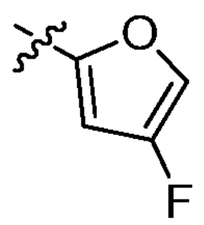















and  .

19. Use of a compound of any of claims 1, 13, 14, 15, 16, 17 or 18 in the manufacture of a medicament for the treatment of a disorder mediated by complement Factor D.

20. A compound of claim 1, 13, 14, 15, 16, 17 or 18 for use in the treatment of a disorder mediated by complement Factor D.

21. The use of claim 19, wherein the disorder is paroxysymal nocturnal hemoglobinuria (PNH).

22. The use of claim 19, method of claim 3, wherein the disorder is multiple sclerosis.

23. The use of claim 19, wherein the disorder is arthritis.

24. The use of claim 19, wherein the disorder is rheumatoid arthritis.

25. The use of claim 19, wherein the disorder is a respiratory disease or a cardiovascular disease.

26. The compound of claim 20, wherein the disorder is multiple sclerosis.

27. The compound of claim 20, wherein the disorder is arthritis.

28. The compound of claim 20, wherein the disorder is rheumatoid arthritis.

29. The compound of claim 20, wherein the disorder is a respiratory disease or a cardiovascular disease.