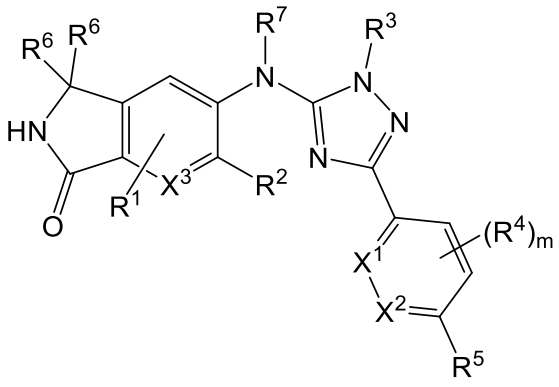
[0006] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity or increased solubility relative to prior art compounds and existing therapies.

[0007] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0008] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0008a] In a first aspect of the present disclosure, there is provided a compound of formula (I) and pharmaceutically acceptable salts thereof:



(**I**)

X^1 and X^2 are each independently selected from carbon and nitrogen; wherein at least one of X^1 and X^2 is carbon;

X^3 is selected from carbon and nitrogen;

R^1 and R^2 are each independently selected from H, halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10},and cyclopropyl;

R^3 is independently selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_0-C_3-alkylene-R^{3a}, and C_2-C_4-alkylene-R^{3b}; wherein R^{3a} is independently at each occurrence selected from cyclopropyl and azetidinyl, said cyclopropyl or azetidinyl groups being optionally substituted with from 1 to 4 R^{11} groups; wherein R^{3b} is independently at each occurrence selected from NR^8R^9, OR^{10} and SR^8;

R^4 and R^{12} are each independently at each occurrence selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, $CR^8R^8NR^8R^9$, $CR^8R^8OR^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^5 is independently selected from $CONR^8R^8$, unsubstituted phenyl, phenyl substituted with from 1 to 4 R^{11} groups, and 4- to 10- membered heterocyclyl, wherein said heterocyclyl group may be monocyclic or bicyclic and wherein any given ring of said heterocyclyl group may be saturated, unsaturated or partially unsaturated; wherein any saturated ring or partially unsaturated ring is optionally substituted with a single R^{13} group and/or from 1 to 4 R^{11} groups and wherein any unsaturated ring is optionally substituted with a single R^{13} group and/or from 1 to 3 R^{12} groups;

R^6 is independently at each occurrence selected from H, halo, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10}, and cyclopropyl, or the two R^6 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring;

R^7 and R^8 are each independently selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^9 is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl; or R^8 and R^9, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{11} groups;

R^{10} is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{11} is independently at each occurrence selected from =O, halo , nitro, cyano, NR^8R^9, OR^{14}, SR^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

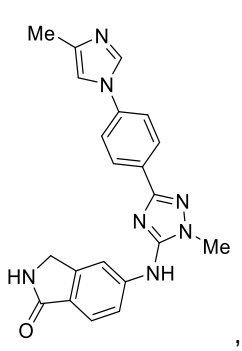
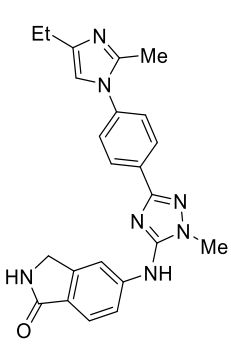
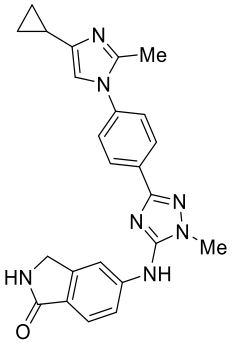
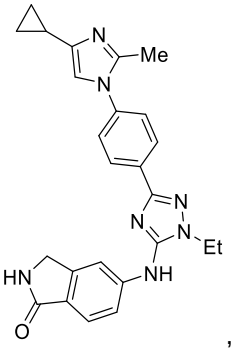
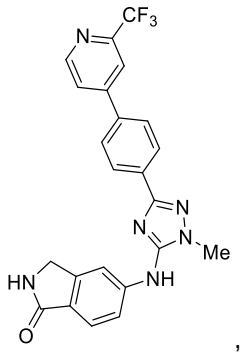
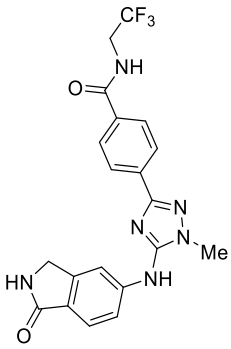
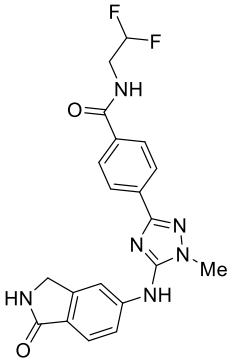
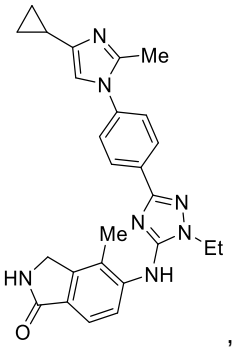
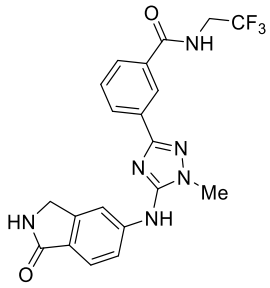
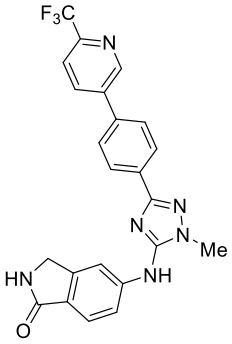
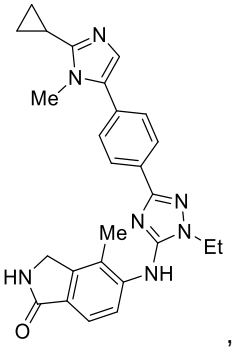
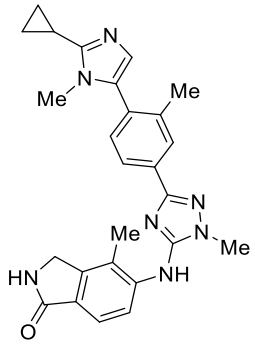
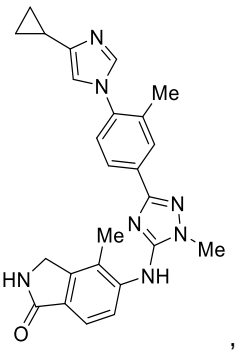
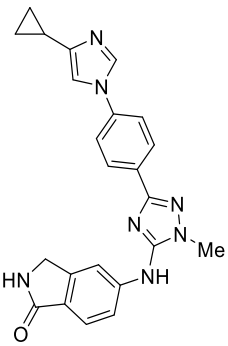
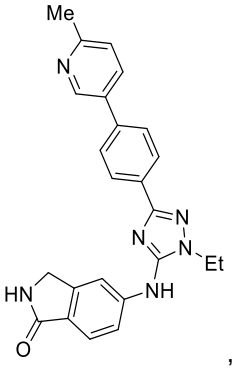
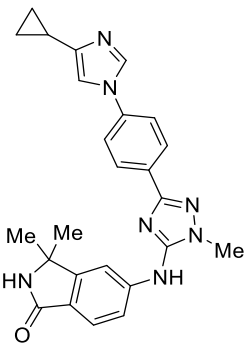
R^{13} is independently selected from C_3-C_6-cycloalkyl, 3- to 6-membered-heterocycloalkyl, $CR^8R^8NR^8R^9$ and $CR^8R^8OR^8$; wherein where R^{13} is cycloalkyl or heterocycloalkyl, R^{13} is optionally substituted with from 1 to 4 R^{11} groups;

R^{14} is independently at each occurrence selected from H, C_1-C_4-alkyl; C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl; and

m is an integer selected from 0, 1, 2, 3 and 4;

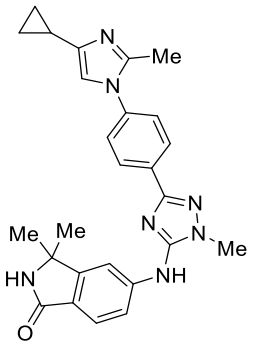
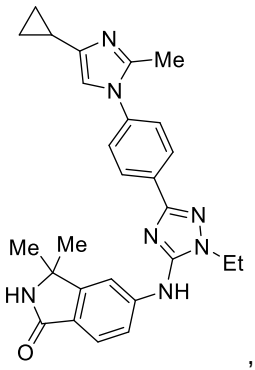
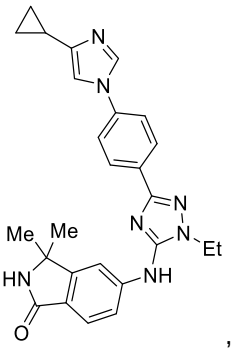
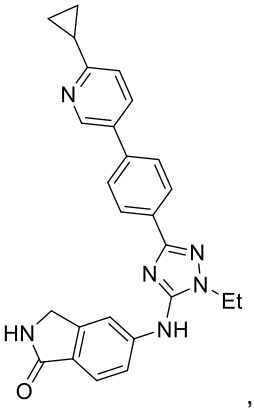
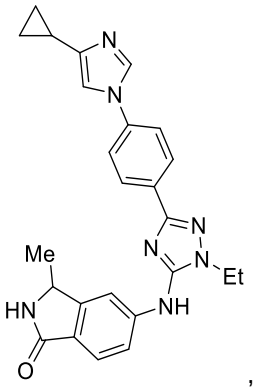
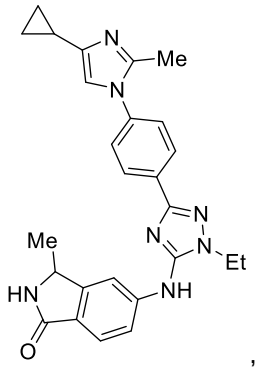
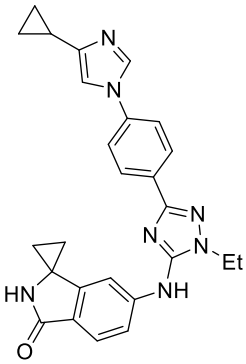
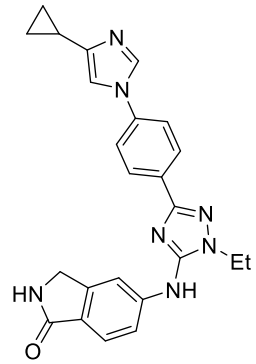
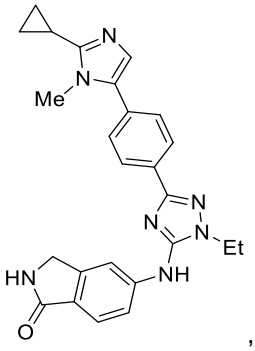
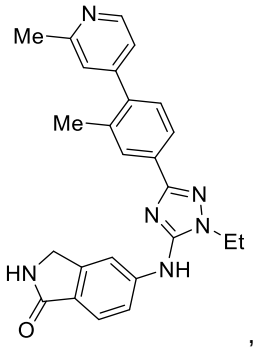
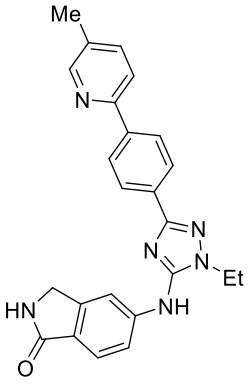
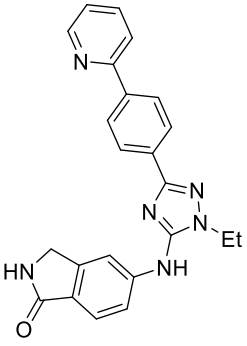
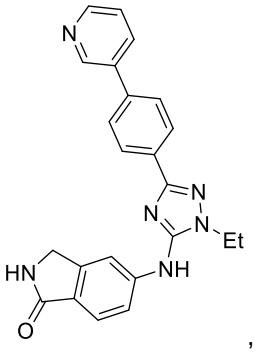
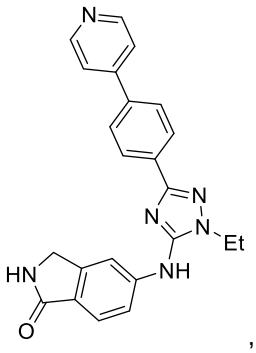
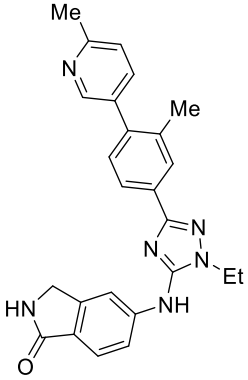
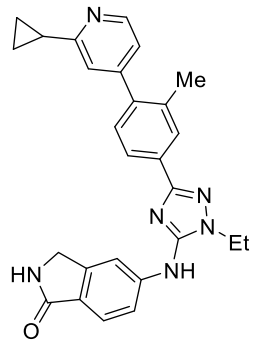
wherein any of the aforementioned alkyl or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl,; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

[0008b] In another aspect of the present disclosure, there is provided a compound of formula (**I**) may be selected from:

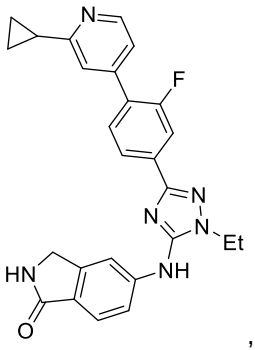
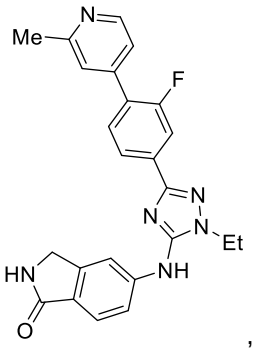
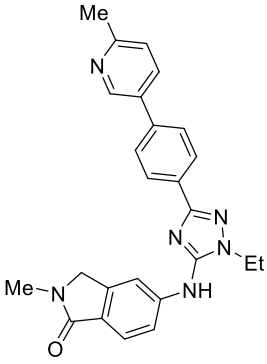
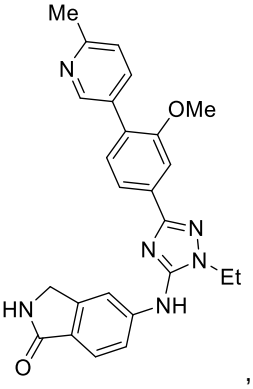
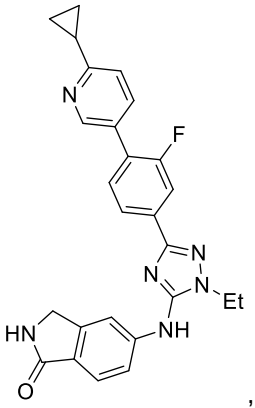
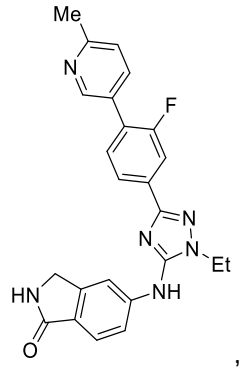
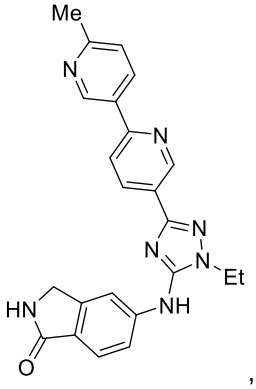
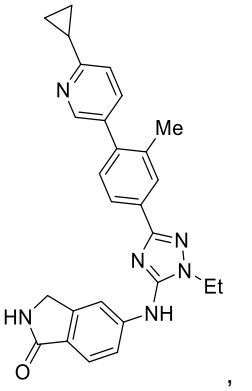
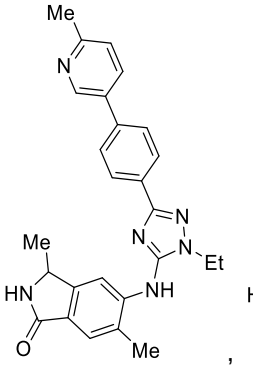
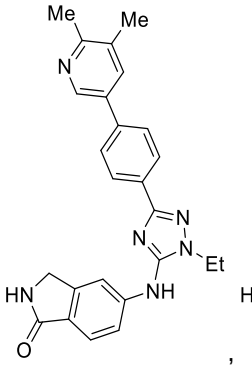
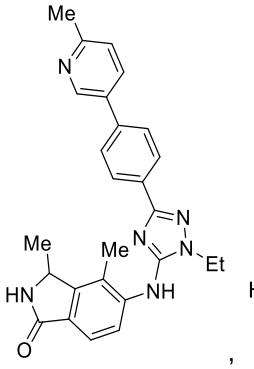
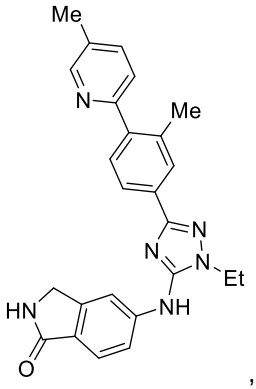
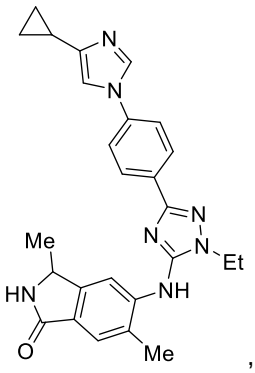
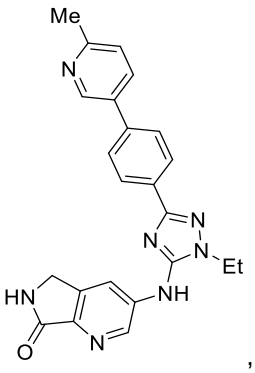
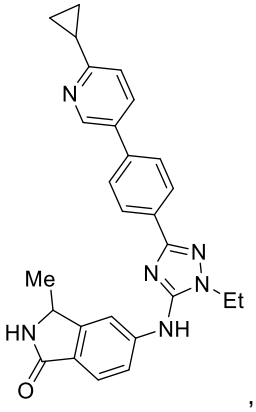
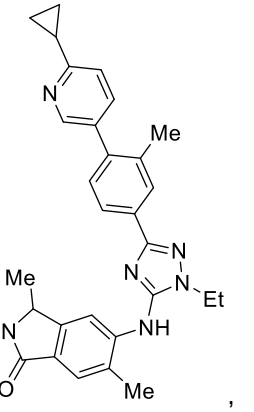

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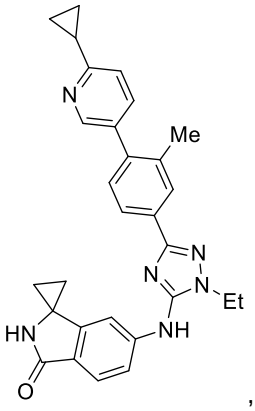
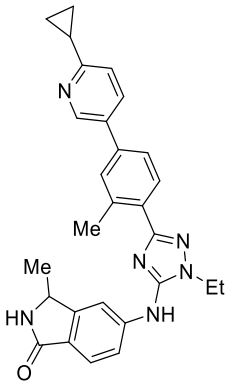
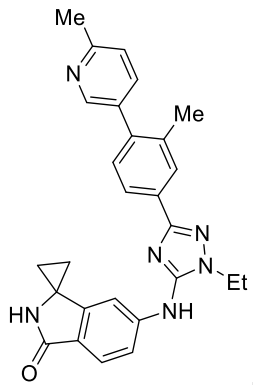
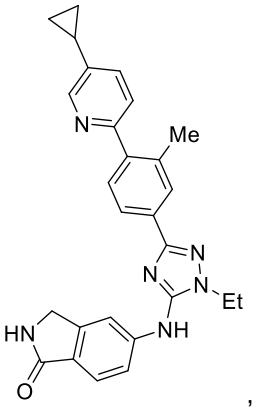
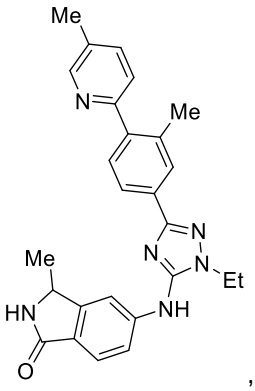
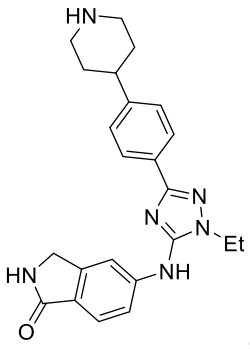
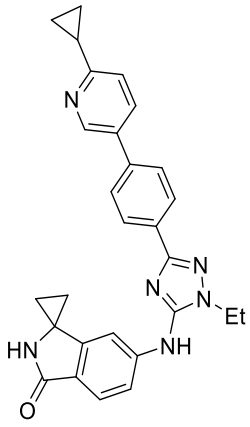
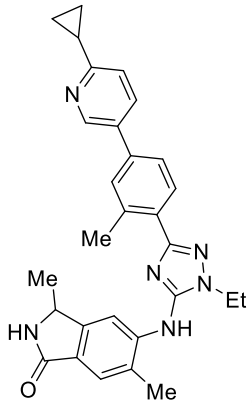
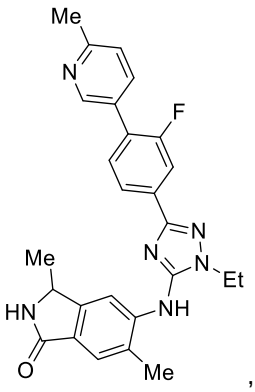
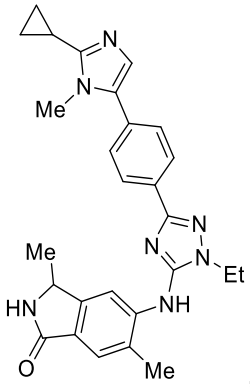
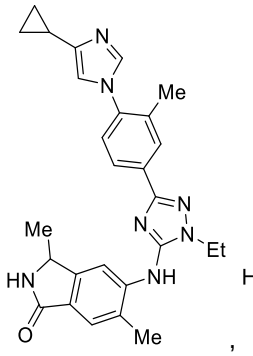
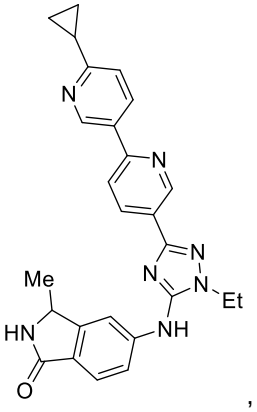
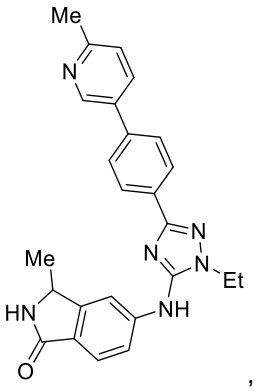
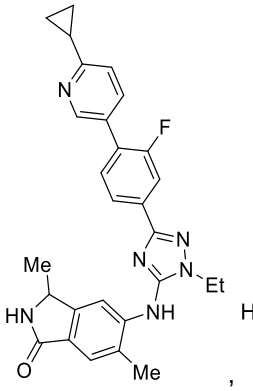
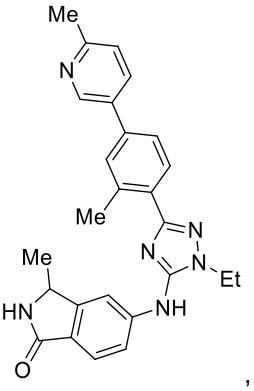
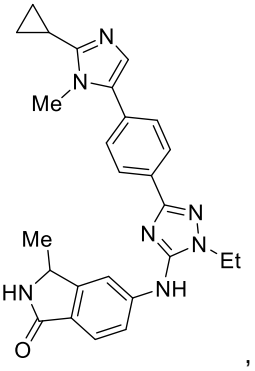
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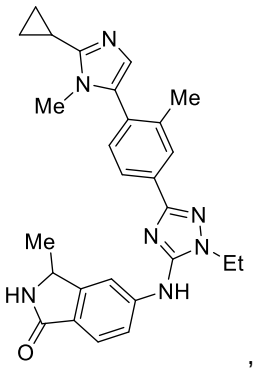
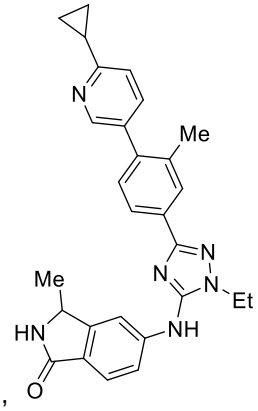
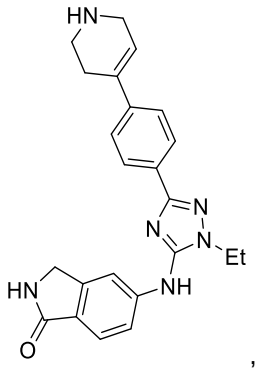
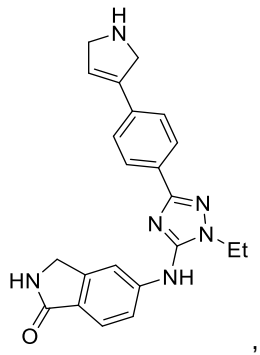
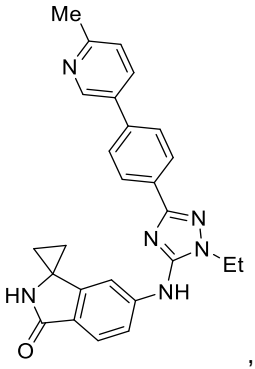
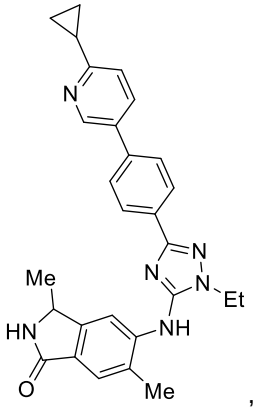
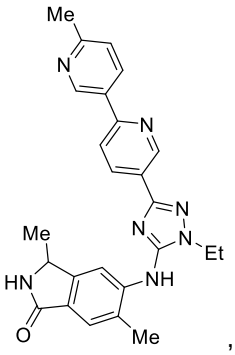
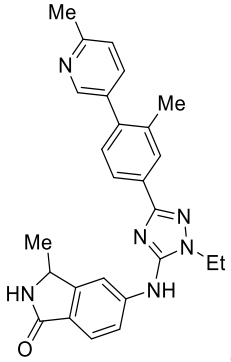
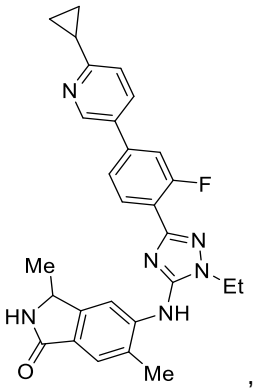
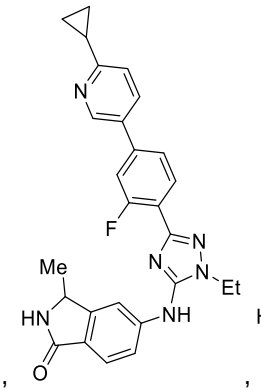
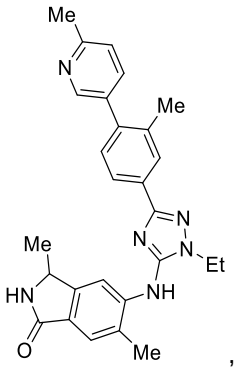
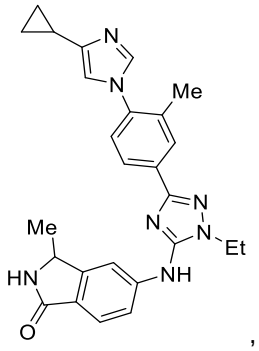
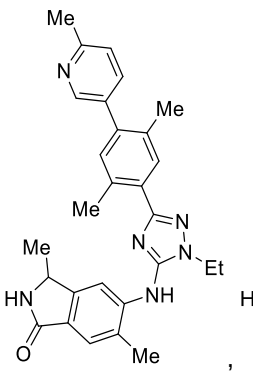
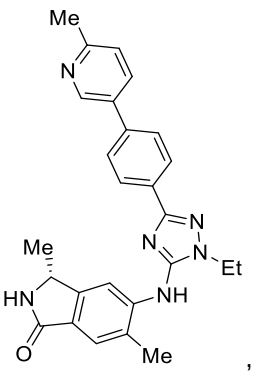
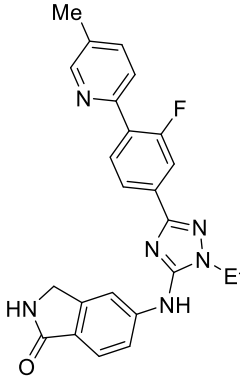
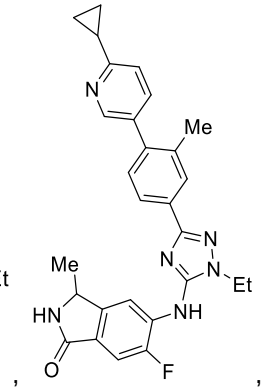
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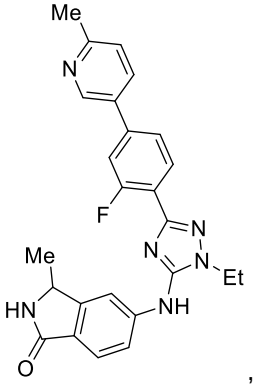
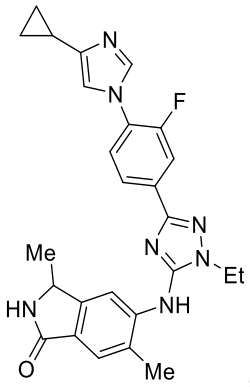
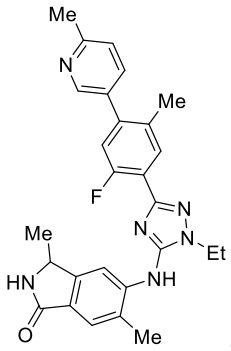
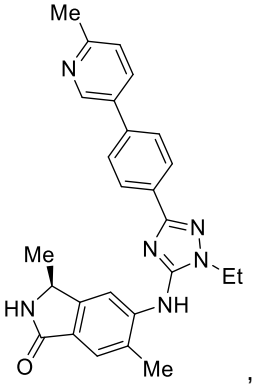
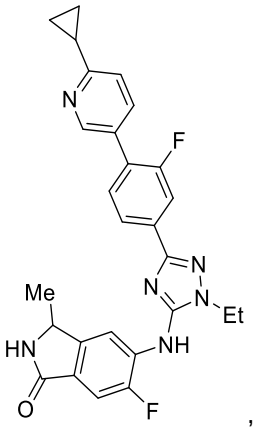
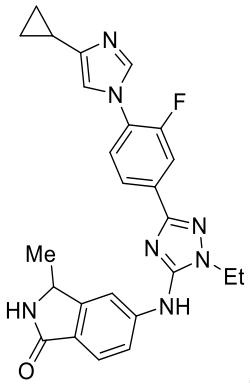
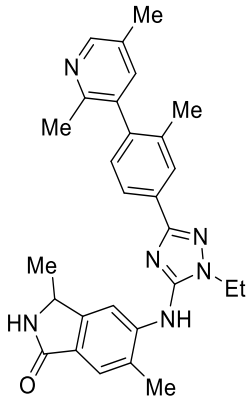
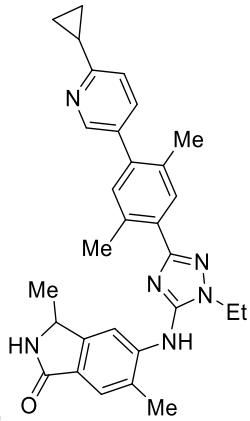
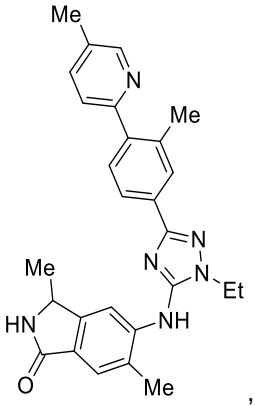
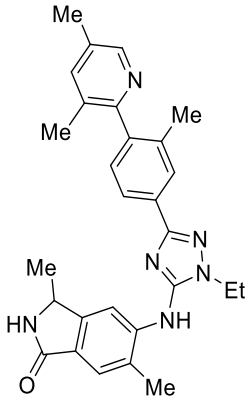
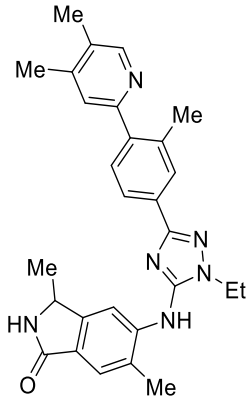
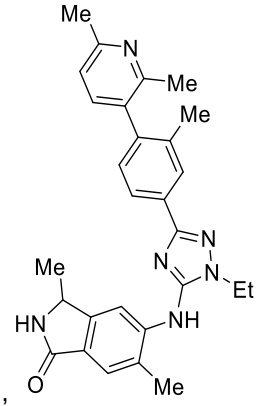
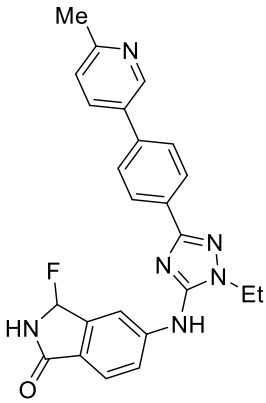
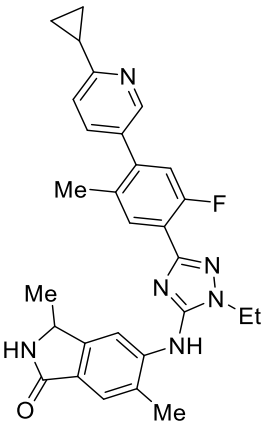
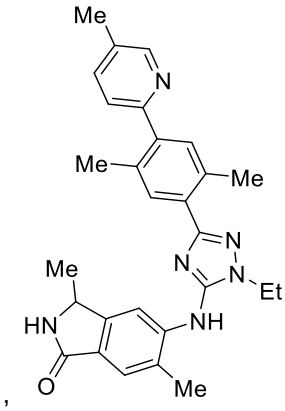
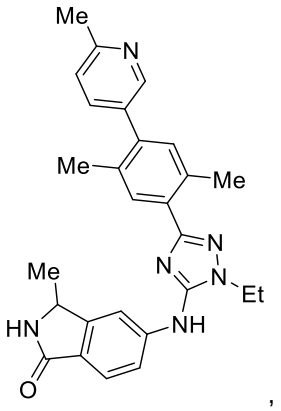
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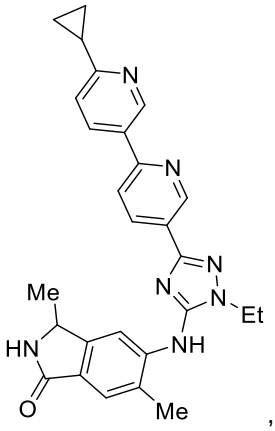
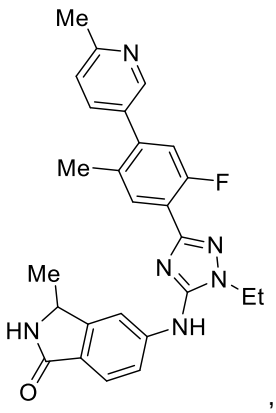
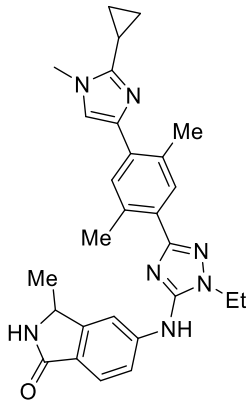
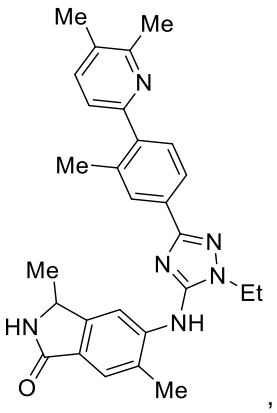
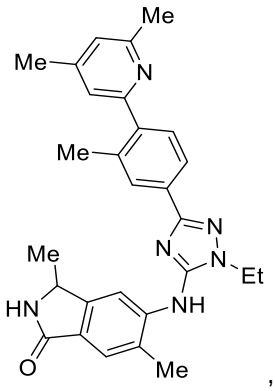
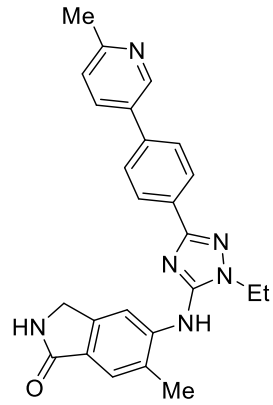
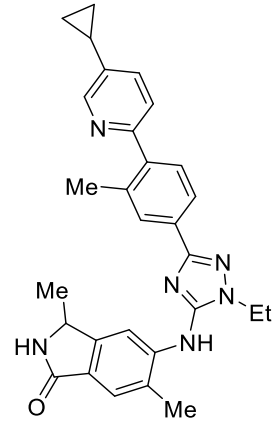
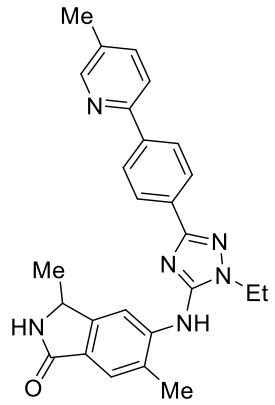
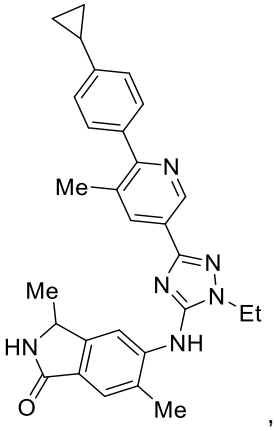
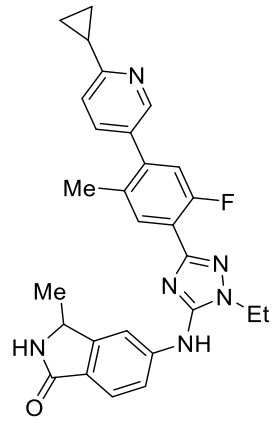
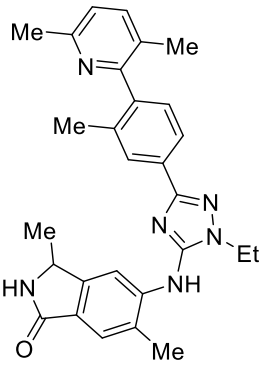
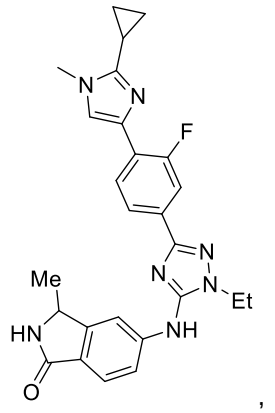
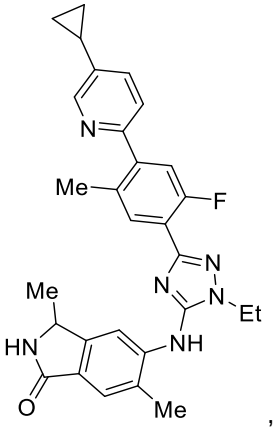
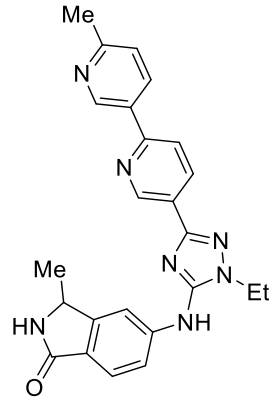
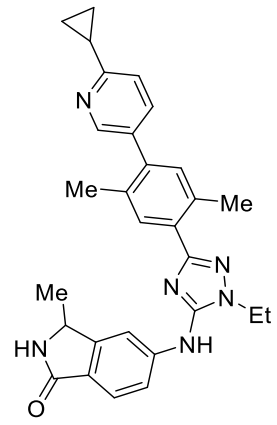
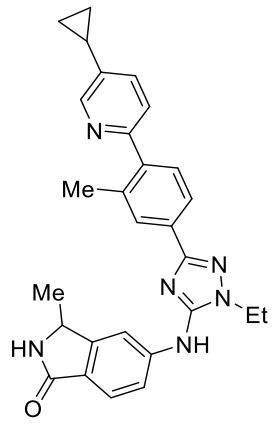
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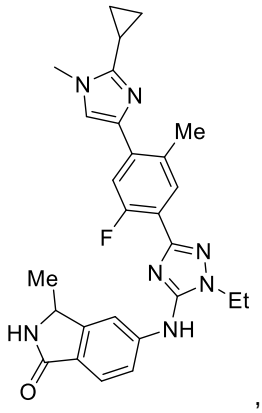
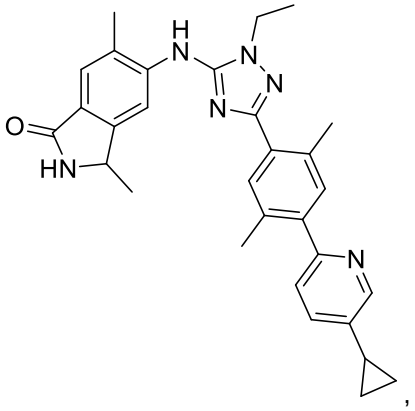
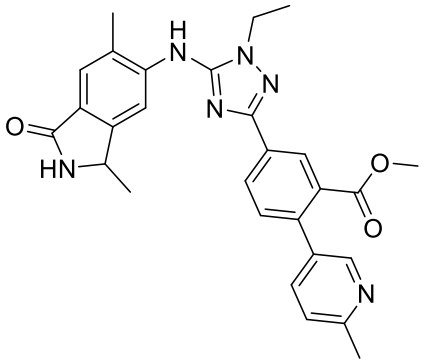
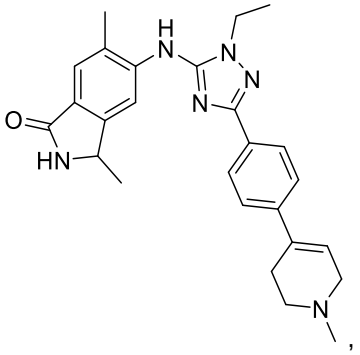
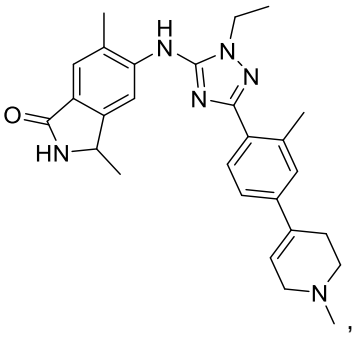
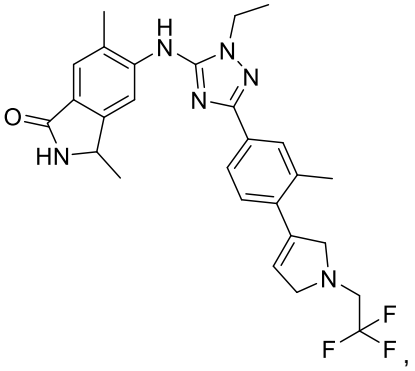
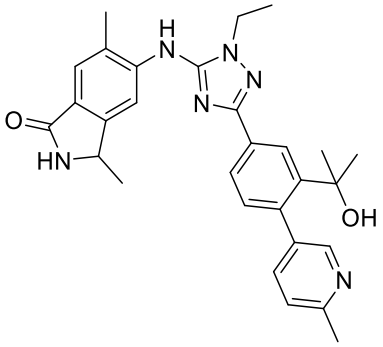
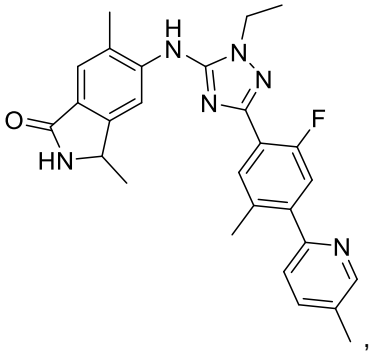
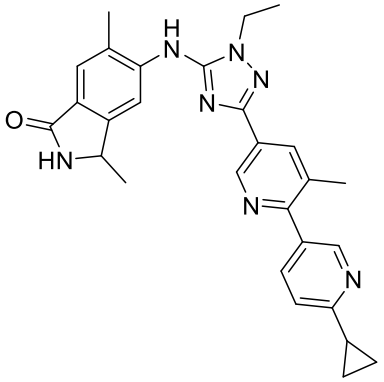
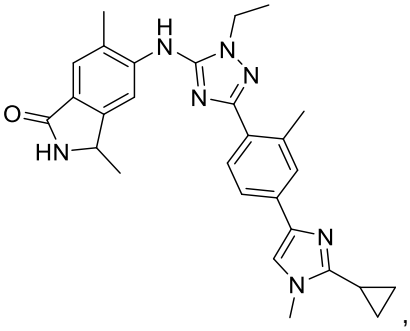
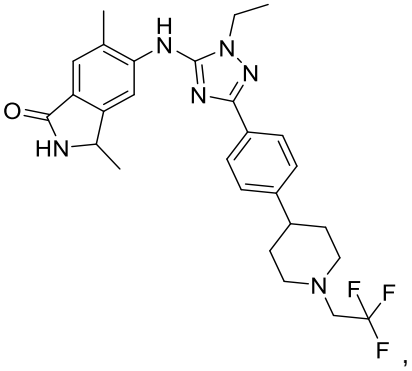
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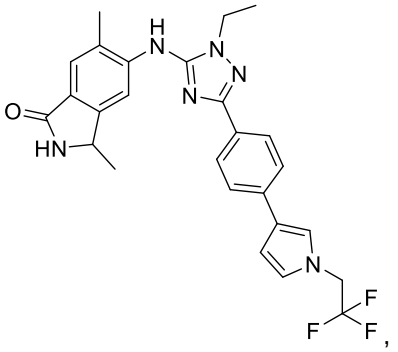
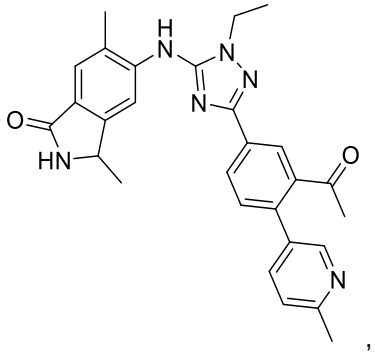
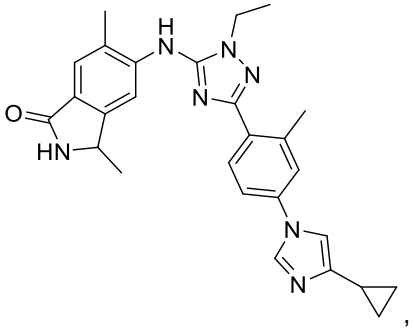
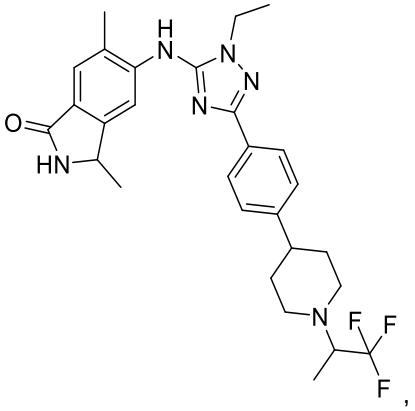
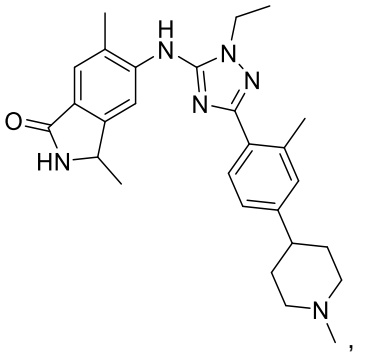
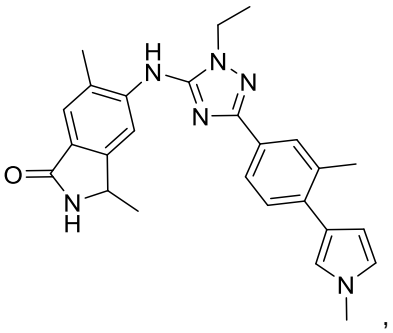
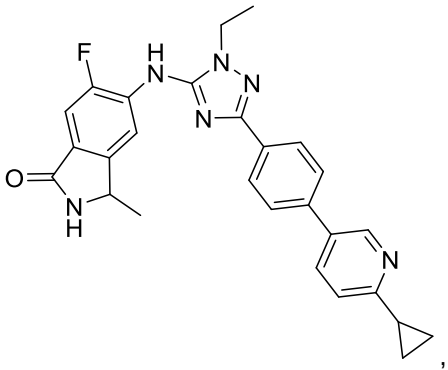
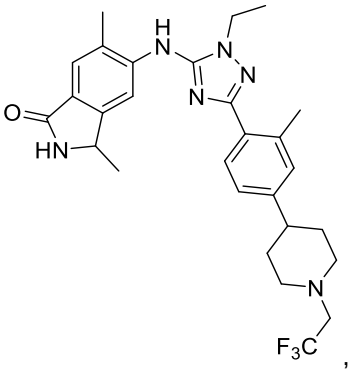
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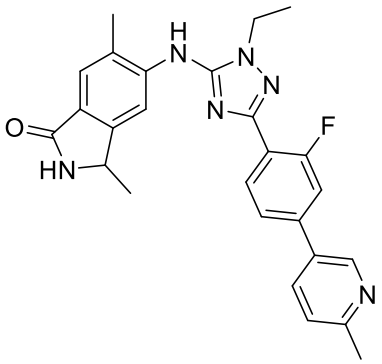
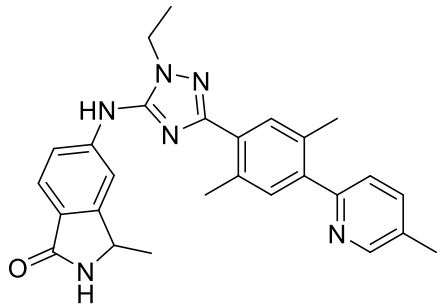
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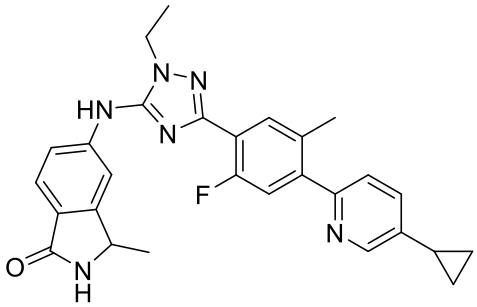
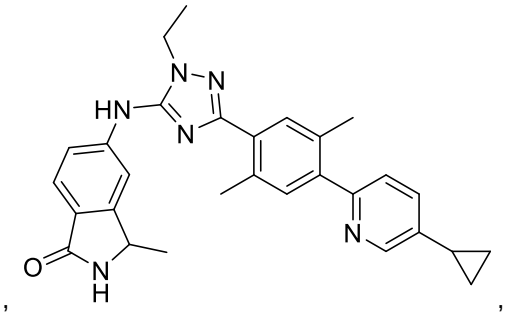

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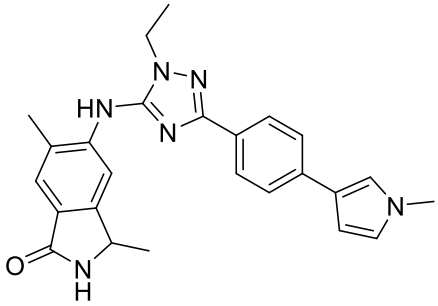
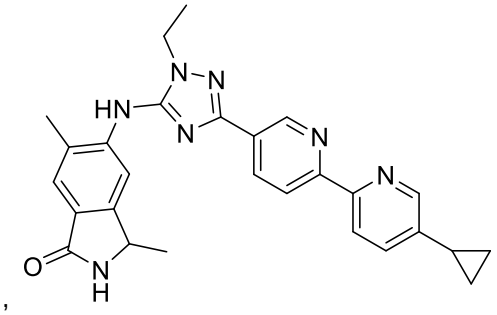
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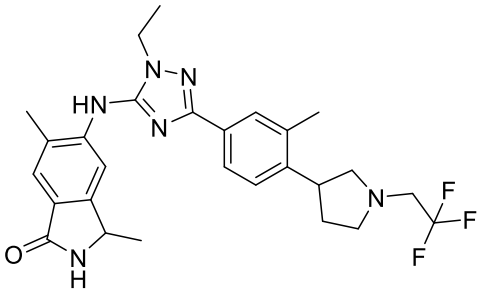
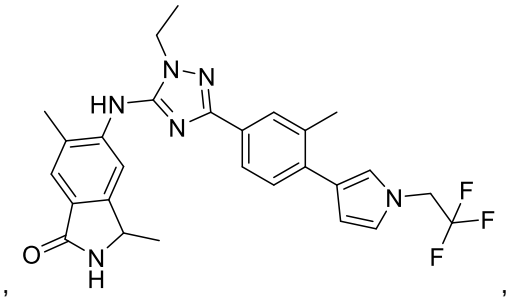

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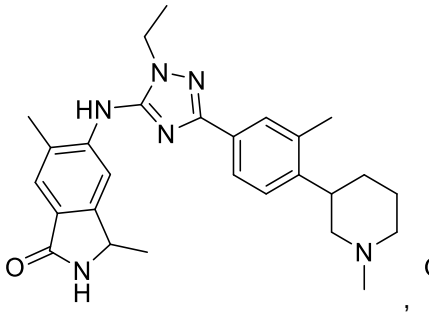
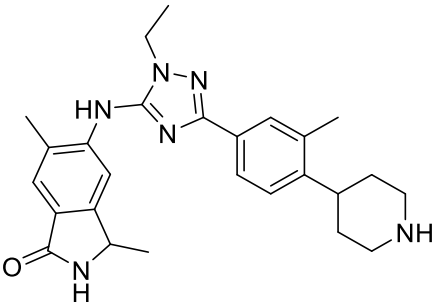
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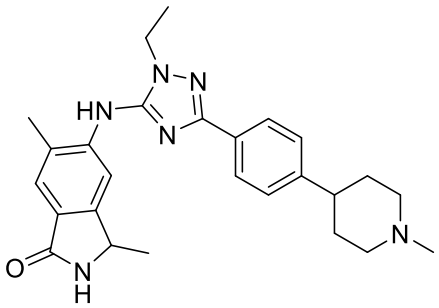
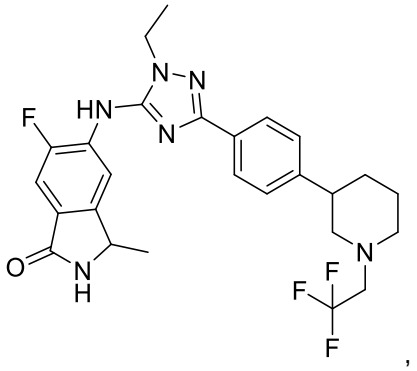
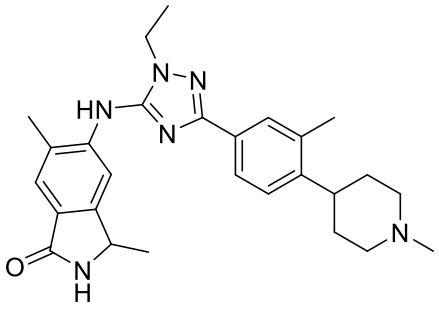
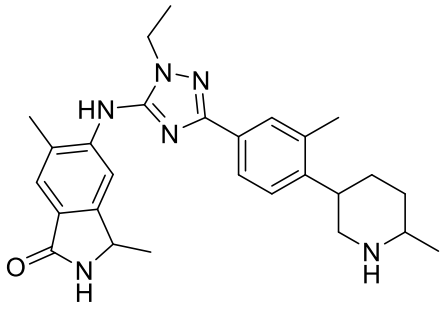
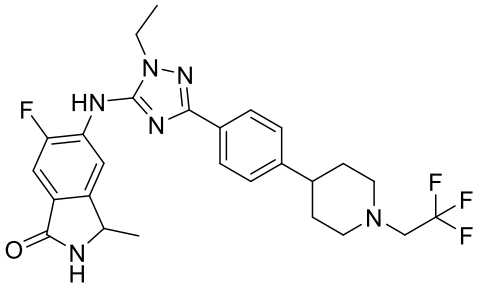
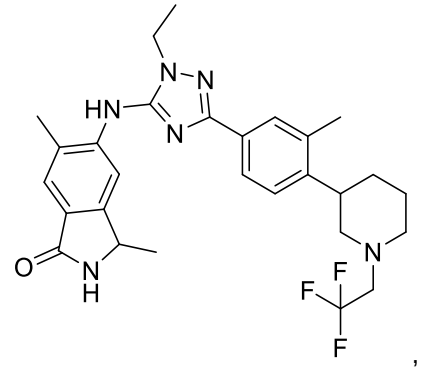
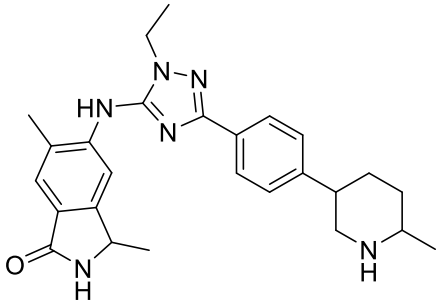
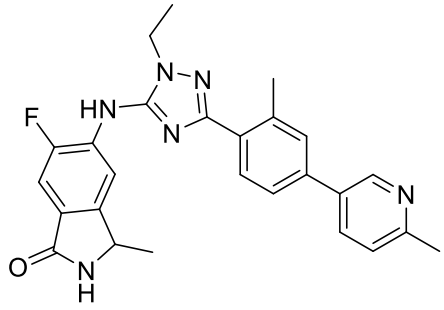
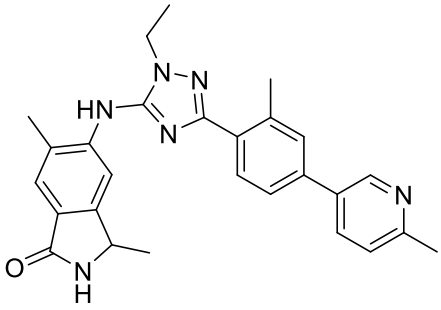
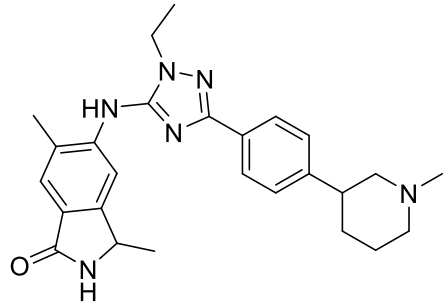


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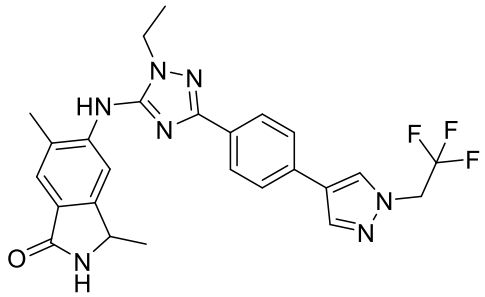
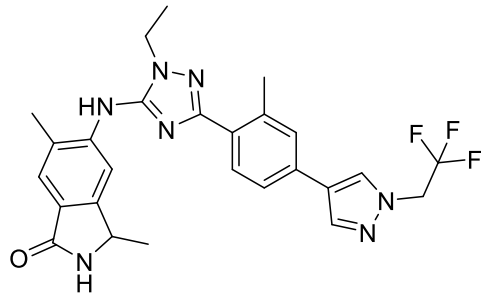
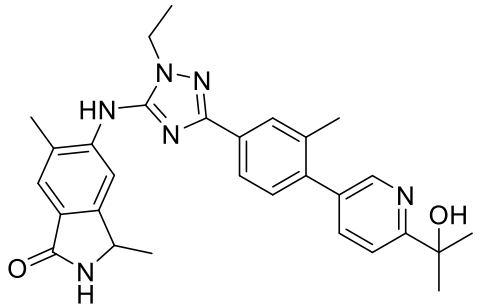
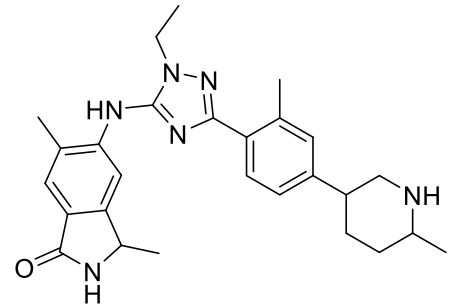
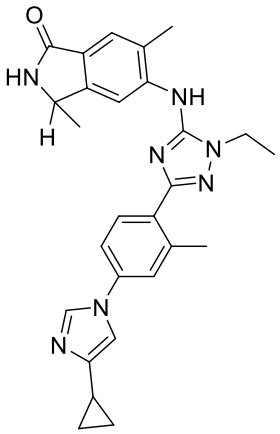
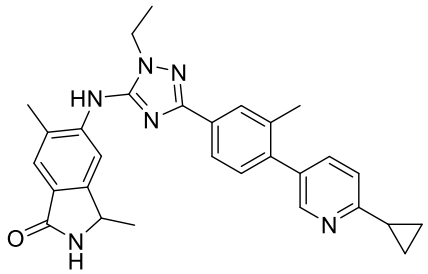
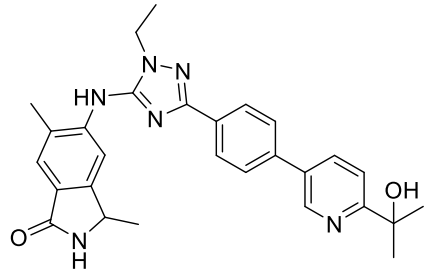
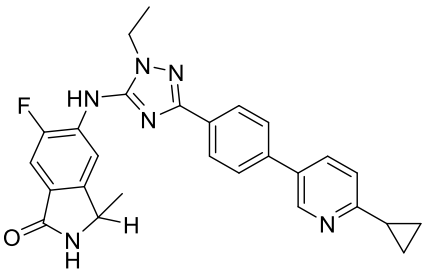
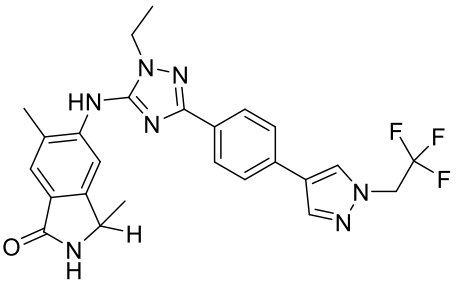

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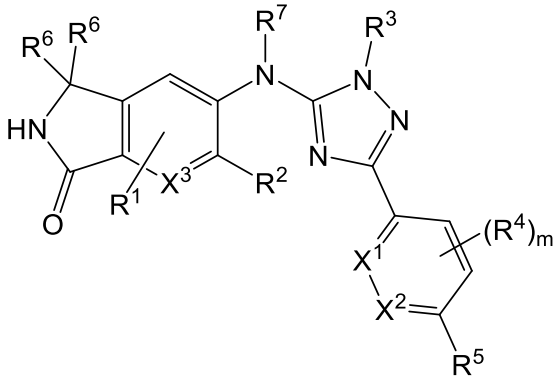
[0008c] In yet another aspect of the present disclosure, there is provided a pharmaceutical formulation comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

[0008d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutical formulation as disclosed herein, for use as a medicament.

[0008e] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutical formulation as disclosed herein, for use in treating a a disease or disorder selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

[0008f] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutical formulation as disclosed herein, in the manufacture of a medicament for treating a a disease or disorder selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

[0009] The present disclosure provides a compound of formula (I) and pharmaceutically acceptable salts thereof:



(**I**)

X^1 and X^2 are each independently selected from carbon and nitrogen; wherein at least one of X^1 and X^2 is carbon;

X^3 is selected from carbon and nitrogen;

R^1 and R^2 are each independently selected from H, halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10},and cyclopropyl;

R^3 is independently selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_0-C_3-alkylene-R^{3a}, and C_2-C_4-alkylene-R^{3b}; wherein R^{3a} is independently at each occurrence selected from cyclopropyl and azetidinyl, said cyclopropyl or azetidinyl groups being optionally substituted with from 1 to 4 R^{11} groups; wherein R^{3b} is independently at each occurrence selected from NR^8R^9, OR^{10} and SR^8;

R^4 and R^{12} are each independently at each occurrence selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, $CR^8R^8NR^8R^9$, $CR^8R^8OR^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^5 is independently selected from $CONR^8R^8$, unsubstituted phenyl, phenyl substituted with from 1 to 4 R^{11} groups, and 4- to 10- membered heterocyclyl, wherein said heterocyclyl group may be monocyclic or bicyclic and wherein any given ring of said heterocyclyl group may be saturated, unsaturated or partially unsaturated; wherein any saturated ring or partially unsaturated ring is

optionally substituted with a single R^{13} group and/or from 1 to 4 R^{11} groups and wherein any unsaturated ring is optionally substituted with a single R^{13} group and/or from 1 to 3 R^{12} groups;

R^6 is independently at each occurrence selected from H, halo, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10}, and cyclopropyl, or the two R^6 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring;

R^7 and R^8 are each independently selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^9 is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl; or R^8 and R^9, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{11} groups;

R^{10} is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{11} is independently at each occurrence selected from =O, halo , nitro, cyano, NR^8R^9, OR^{14}, SR^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

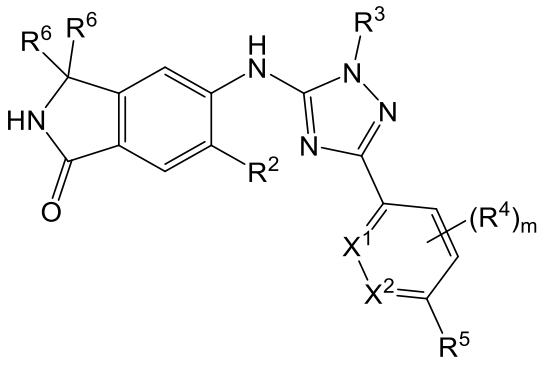
R^{13} is independently selected from C_3-C_6-cycloalkyl, 3- to 6-membered-heterocycloalkyl, $CR^8R^8NR^8R^9$ and $CR^8R^8OR^8$; wherein where R^{13} is cycloalkyl or heterocycloalkyl, R^{13} is optionally substituted with from 1 to 4 R^{11} groups;

R^{14} is independently at each occurrence selected from H, C_1-C_4-alkyl; C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl; and

m is an integer selected from 0, 1, 2, 3 and 4;

wherein any of the aforementioned alkyl or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl,; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

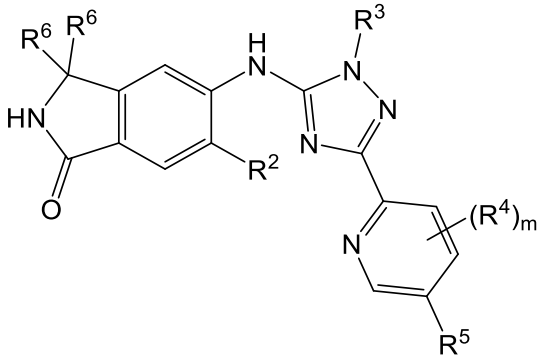
[0010] In an example, the compound of formula (**I**) is a compound of formula (**II**):



(**II**)

wherein X^1, X^2, R^2, R^3, R^4, R^5, R^6 and m are as described above for compounds of formula (**I**).

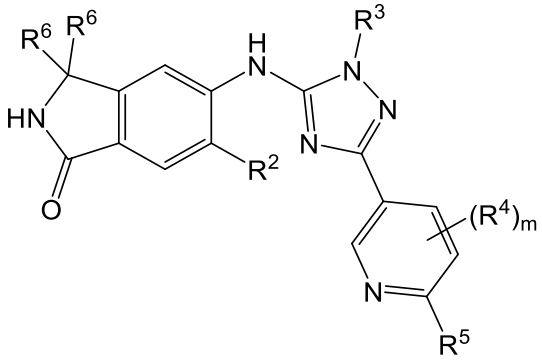
[0011] In an example, the compound of formula (**I**) is a compound of formula (**III**):



(**III**)

wherein R^2, R^3, R^4, R^5, R^6 and m are as described above for compounds of formula (**I**).

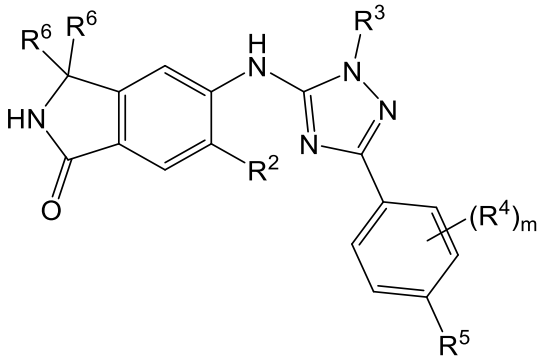
[0012] In an example, the compound of formula (**I**) is a compound of formula (**IV**):



(**IV**)

wherein R^2, R^3, R^4, R^5, R^6 and m are as described above for compounds of formula (**I**).

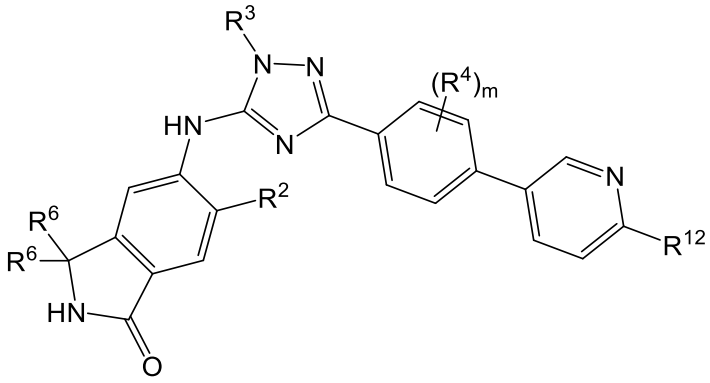
[0013] In an example, the compound of formula (**I**) is a compound of formula (**V**):



(**V**)

wherein R^2, R^3, R^4, R^5, R^6 and m are as described above for compounds of formula (**I**).

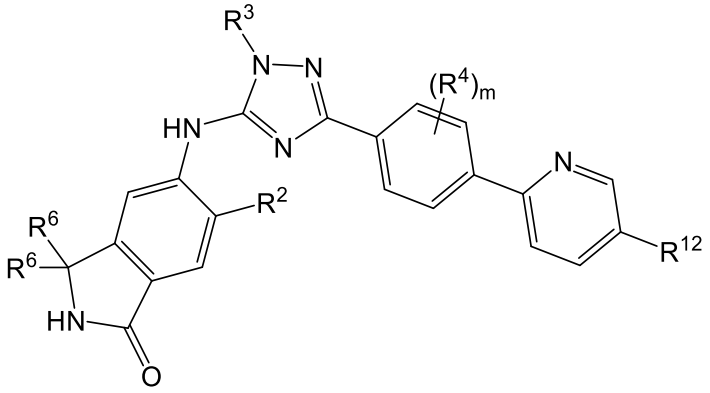
[0014] In an example, the compound of formula (**I**) is a compound of formula (**VI**):



(**VI**)

wherein R^2, R^3, R^4, R^6, R^{12} and m are as described above for compounds of formula (**I**).

[0015] In an example, the compound of formula (**I**) is a compound of formula (**VII**):



(**VII**)

wherein R^2, R^3, R^4, R^6, R^{12} and m are as described above for compounds of formula (**I**).

[0016] The following examples apply to compounds of any of formulae (**I**)-(**VII**). These examples are independent and interchangeable. Any one example may be combined with any other example, where chemically allowed. In other words, any of the features described in the following examples may (where chemically allowable) be combined with the features described in one or more other examples. In particular, where a compound is exemplified or illustrated in this specification, any two or more of the examples listed below, expressed at any level of generality, which encompass that compound may be combined to provide a further example which forms part of the present disclosure.

[0017] It may be that X^1 is carbon and X^2 is nitrogen. It may be that X^1 is nitrogen and X^2 is carbon. It may be that X^1 is CR^{4a} and X^2 is nitrogen; wherein R^{4a} is independently selected from halo, nitro, cyano, OR^{10}, C_1-C_4-alkyl and C_1-C_4-haloalkyl and cyclopropyl. It may be that X^1 is nitrogen and X^2 is CR^{4a}; wherein R^{4a} is independently selected from halo, nitro, cyano, OR^{10}, C_1-C_4-alkyl and C_1-C_4-haloalkyl and cyclopropyl.

[0018] It may be that X^3 is carbon. It may be that X^3 is nitrogen.

[0019] It may be that R^1, if present, is attached to X^3. For the absence of doubt, this example applies where X^3 is carbon.

[0061] In an example there is provided compounds of the present disclosure having a ROCK2 binding affinity within category +++ or ++++ as defined elsewhere herein. In an example there is provided compounds of the present disclosure having a ROCK2 binding affinity IC50 value of < 3 µM. In an example there is provided compounds of the present disclosure having a ROCK2 binding affinity IC50 value of < 0.3 µM. Optionally, the binding activity is determined using the assay for ROCK2 inhibition defined in the examples.

[0062] In an example of the disclosure there is provided the compounds of the present disclosure for use as a medicament.

[0063] In accordance with another example, the present disclosure provides a pharmaceutical formulation comprising a compound of the present disclosure and a pharmaceutically acceptable excipient.

[0064] In an example, the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti-cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors.

[0065] In accordance with another example, there is provided a compound of the present disclosure for use in the treatment of a condition which is modulated by ROCK1 and/or ROCK2. Usually conditions that are modulated by ROCKs (please note that ROCKs refer to either or both of ROCK1 and ROCK2) are conditions that would be treated by the inhibition of ROCKs using a compound of the present disclosure. A compound of any formula disclosed herein may be for use in the treatment of a condition treatable by the inhibition of ROCKs. As discussed above, ROCK signalling is instrumental in a number of conditions.

[0066] In another example of the disclosure, there is provided a compound of the present disclosure for use in the treatment of a disease or disorder selected from: fibrotic diseases, auto-immune diseases, muscular dystrophy, inflammatory conditions, central nervous system disorders, or cancer.

[0067] In an example of the disclosure there is provided a method of treating a disease or disorder which is modulated by ROCK1 and/or ROCK2 wherein the method comprises administering a therapeutic amount of a compound of the disclosure, to a patient in need thereof.

[0068] The method of treatment may be a method of treating a condition treatable by the inhibition of ROCK1 and/or ROCK2.

[0069] The disclosure also provides a method of treating a disease or disorder selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer, wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

saturnine gout, Scheuermann's osteochondritis, scleroderma, septic arthritis, seronegative arthritis, shigella arthritis, shoulder-hand syndrome, sickle cell arthropathy, Sjogren's syndrome, slipped capital femoral epiphysis, spinal stenosis, spondylolysis, staphylococcus arthritis, Stickler syndrome, subacute cutaneous lupus, Sweet's syndrome, Sydenham's chorea, syphilitic arthritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, tarsal tunnel syndrome, tennis elbow, Tietse's syndrome, transient osteoporosis, traumatic arthritis, trochanteric bursitis, tuberculosis arthritis, arthritis of Ulcerative colitis, undifferentiated connective tissue syndrome (UCTS), urticarial vasculitis, viral arthritis, Wegener's granulomatosis, Whipple's disease, Wilson's disease, yersinial arthritis and conditions involving vascularization and/or inflammation, include atherosclerosis, rheumatoid arthritis (RA), hemangiomas, angiofibromas, and psoriasis. Other non-limiting examples of angiogenic disease are retinopathy of prematurity (retrolental fibroplastic), corneal graft rejection, corneal neovascularization related to complications of refractive surgery, corneal neovascularization related to contact lens complications, corneal neovascularization related to pterygium and recurrent pterygium , corneal ulcer disease, and non-specific ocular surface disease, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Chrorfs disease, autoimmune nephritis, primary biliary cirrhosis, acute pancreatitis, allograph rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osier- Weber syndrome, restinosis, and fungal, parasitic and viral infections, including cytomegalo viral infections.

[0071] Any of the conditions disclosed above as being treatable by ROCK1 and/or ROCK2 inhibition may be treated by a compound of the disclosure, or may be treated in a method comprising administering a compound of the disclosure, or may be treated by a medicament manufactured through the use of a compound of the present disclosure.

[0072] In examples, the disease or disorder may be selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney. glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren’s syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE, cGVHD, inflammatory bowel disease, stenosis of the bowel, disorders involving neuronal degeneration or physical injury to neural tissue, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), multiple sclerosis, liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft

tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma, wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof.

[0073] In certain examples, the disease or disorder is selected from: Idiopathic Pulmonary Fibrosis (IPF); systemic sclerosis (SSC); interstitial lung disease (ILD); type 1 and type 2 diabetes; diabetic nephropathy; Nonalcoholic Steatohepatitis (NASH); Nonalcoholic fatty liver disease (NAFLD); hypertension, atherosclerosis, restenosis, stroke, heart failure, coronary vasospasm, cerebral vasospasm, peripheral circulatory disorder, peripheral artery occlusive disease, ischemia/reperfusion injury, pulmonary hypertension and angina, and erectile dysfunction, fibroid lung, fibroid liver and fibroid kidney.

[0074] In certain examples the disease or disorder is selected from: glaucoma, ocular hypertension, retinopathy, rheumatoid arthritis, psoriasis, psoriatic arthritis, Sjogren’s syndrome, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), SLE and cGVHD, inflammatory bowel disease and stenosis of the bowel.

[0075] In certain examples, compounds of the disclosure are for use in the treatment of or are used in a method of treatment of central nervous system disorders. Such disorders may involve neuronal degeneration or physical injury to neural tissue, including without limitation, Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), or multiple sclerosis.

[0076] In certain examples compounds of the disclosure are for use in the treatment of or are used in a method of treatment of cancer. Examples include but are not limited to: liver cancer, bladder cancer, hepatoma, squamous carcinoma of the lung, non-small cell lung cancer, adenocarcinoma of the lung, small-cell lung cancer, , various types of head and neck cancer, breast cancer, colon cancer, colorectal cancer, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, esophageal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, squamous cell cancer, pituitary cancer, astrocytoma, soft tissue sarcoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer and melanoma.

[0077] In another example of the disclosure there is provided a pharmaceutical composition, wherein the composition comprises a compound of the disclosure and pharmaceutically acceptable excipients.

[0078] In an example the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be one disclosed elsewhere herein.

[0079] In an example of the present disclosure there is provided the use of a compound of the disclosure in the manufacture of a medicament for use in the treatment of any condition disclosed herein.

DETAILED DESCRIPTION

[0080] Given below are definitions of terms used in this application. Any term not defined herein takes the normal meaning as the skilled person would understand the term.

[0081] The term “halo” refers to one of the halogens, group 17 of the periodic table. In particular, the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to chlorine or fluorine.

[0082] The term “alkyl” refers to a linear or branched hydrocarbon chain. For example, the term “C_{1-6} alkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl and *n*-hexyl. “Alkylene” groups may likewise be linear or branched and is divalent, i.e. it attached at two positions to other portions of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or more substituents.

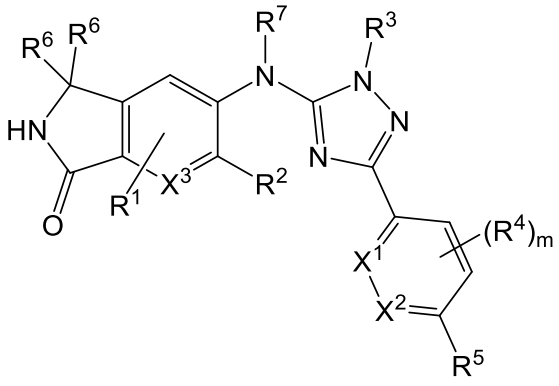
[0083] The term “haloalkyl” refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. For example, the term “C_{1-6} haloalkyl” refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms substituted with at least one halogen. The halogen atom may be present at any position on the hydrocarbon chain. For example, C_{1-6} haloalkyl may refer to chloromethyl, fluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl. The term “fluoroalkyl” refers to a hydrocarbon chain substituted with at least one fluorine atom..

[0084] The term “alkenyl” refers to a branched or linear hydrocarbon chain containing at least one double bond. For example, the term “C_{2-6} alkenyl” refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the “C_{2-6} alkenyl” may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[0085] The term “alkynyl” refers to a branched or linear hydrocarbon chain containing at least one triple bond. For example, the term “C_{2-6} alkynyl” refers to a branched or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at any possible position of the hydrocarbon chain. For example, the “C_{2-6} alkynyl” may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

CLAIMS

1. A compound of formula (I) and pharmaceutically acceptable salts thereof:



(**I**)

X^1 and X^2 are each independently selected from carbon and nitrogen; wherein at least one of X^1 and X^2 is carbon;

X^3 is selected from carbon and nitrogen;

R^1 and R^2 are each independently selected from H, halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10},and cyclopropyl;

R^3 is independently selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_0-C_3-alkylene-R^{3a}, and C_2-C_4-alkylene-R^{3b}; wherein R^{3a} is independently at each occurrence selected from cyclopropyl and azetidinyl, said cyclopropyl or azetidinyl groups being optionally substituted with from 1 to 4 R^{11} groups; wherein R^{3b} is independently at each occurrence selected from NR^8R^9, OR^{10} and SR^8;

R^4 and R^{12} are each independently at each occurrence selected from halo, nitro, cyano, NR^8R^9, OR^{10}, SR^8, SO_2R^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, $CR^8R^8NR^8R^9$, $CR^8R^8OR^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^5 is independently selected from $CONR^8R^8$, unsubstituted phenyl, phenyl substituted with from 1 to 4 R^{11} groups, and 4- to 10- membered heterocyclyl, wherein said heterocyclyl group may be monocyclic or bicyclic and wherein any given ring of said heterocyclyl group may be saturated, unsaturated or partially unsaturated; wherein any saturated ring or partially unsaturated ring is optionally substituted with a single R^{13} group and/or from 1 to 4 R^{11} groups and wherein any unsaturated ring is optionally substituted with a single R^{13} group and/or from 1 to 3 R^{12} groups;

R^6 is independently at each occurrence selected from H, halo, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with NR^8R^9, C_1-C_4-alkyl substituted with OR^{10}, and cyclopropyl, or the two R^6 groups and the carbon atom to which they are attached may together form a C_3-C_6 cycloalkyl ring;

R^7 and R^8 are each independently selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^9 is independently at each occurrence selected from H, C_1-C_4-alkyl, $C(O)$-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl; or R^8 and R^9, together with the nitrogen atom to which they are attached together form a C_5-C_8-heterocycloalkyl group optionally substituted with from 0 to 4 R^{11} groups;

R^{10} is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and C_1-C_4-haloalkyl;

R^{11} is independently at each occurrence selected from =O, halo , nitro, cyano, NR^8R^9, OR^{14}, SR^8, $SO_2NR^8R^8$, CO_2R^8, $C(O)R^8$, $CONR^8R^8$, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{13} is independently selected from C_3-C_6-cycloalkyl, 3- to 6-membered-heterocycloalkyl, $CR^8R^8NR^8R^9$ and $CR^8R^8OR^8$; wherein where R^{13} is cycloalkyl or heterocycloalkyl, R^{13} is optionally substituted with from 1 to 4 R^{11} groups;

R^{14} is independently at each occurrence selected from H, C_1-C_4-alkyl; C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl; and

m is an integer selected from 0, 1, 2, 3 and 4;

wherein any of the aforementioned alkyl or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: halo, oxo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl,; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl..

2. A compound of claim 1, wherein X^3 is CR^1.

3. A compound of claim 2, wherein R^1 is H.

4. A compound of any one of claims 1 to 3, wherein R^2 is independently selected from H, fluoro, C_1-C_3-alkyl, C_1-C_3-fluoroalkyl and cyclopropyl.

5. A compound of any one of claims 1 to 3, wherein R^2 is H.

6. A compound of any one of claims 1 to 5, wherein R^7 is H.

7. A compound of any one of claims 1 to 6, wherein R^3 is independently selected from C_1-C_4-alkyl and cyclopropyl.

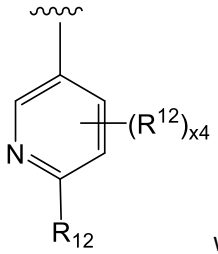
8. A compound of any one of claims 1 to 7, wherein m is 1.

9. A compound of claim 8, wherein R^4 is selected from C_1-C_3-alkyl and cyclopropyl.

10. A compound of any one of claims 1 to 9, wherein R^5 is imidazole, optionally substituted with a single R^{13} group and/or from 1 to 3 R^{12} groups.

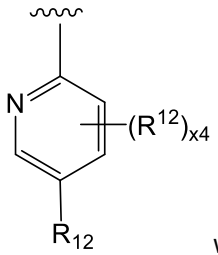
11. A compound of any one of claims 1 to 9, wherein R^5 is pyridine, optionally substituted with a single R^{13} group and/or from 1 to 3 R^{12} groups.

12. A compound of claim 11, wherein R^5 has the structure:



wherein x4 is an integer independently selected from 0, 1 and 2.

13. A compound of claim 11, wherein R^5 has the structure

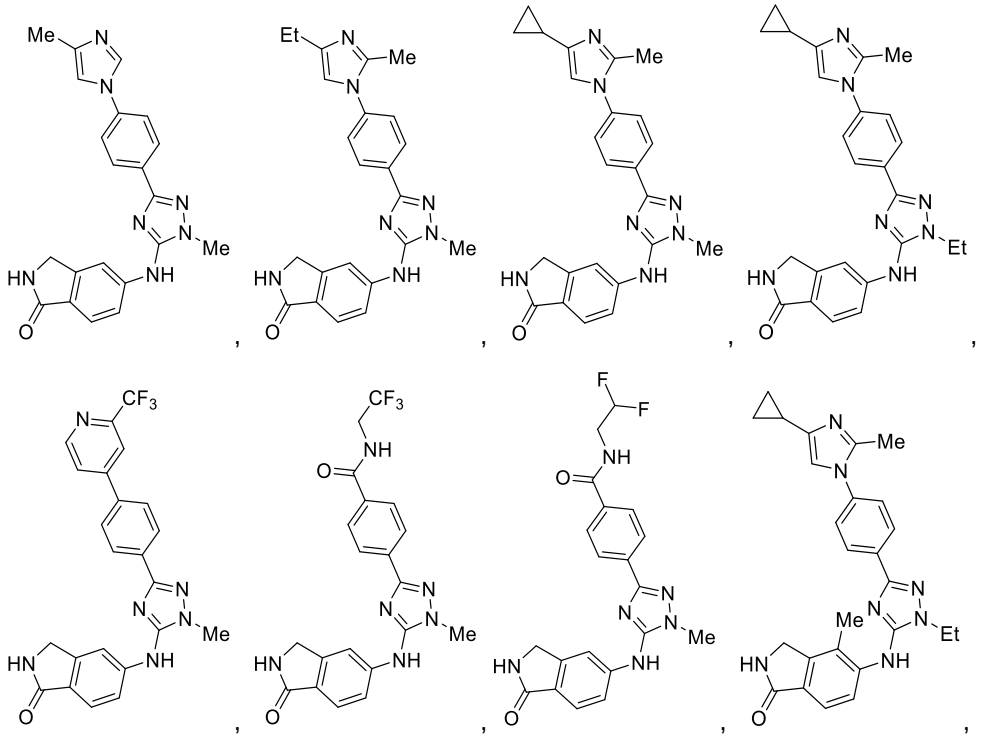


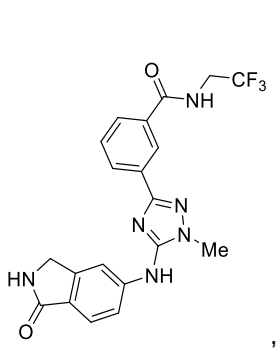
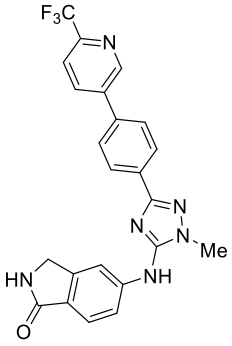
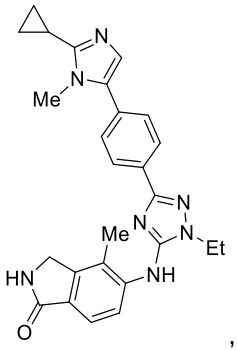
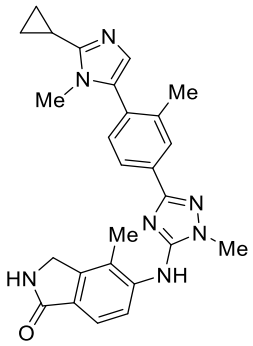
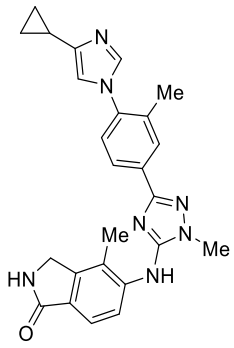
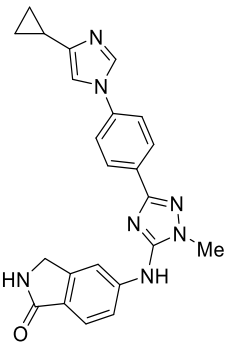
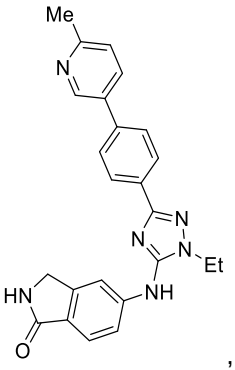
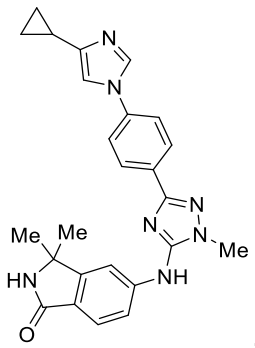
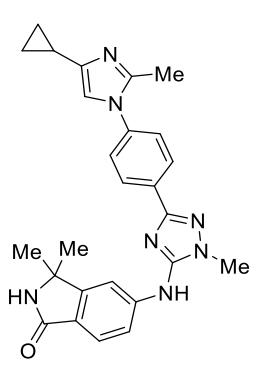
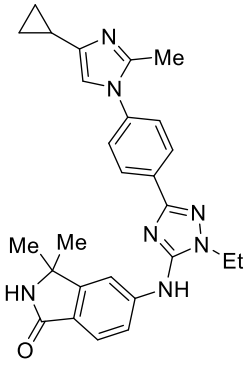
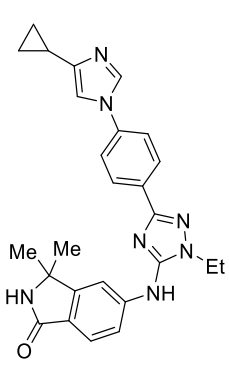
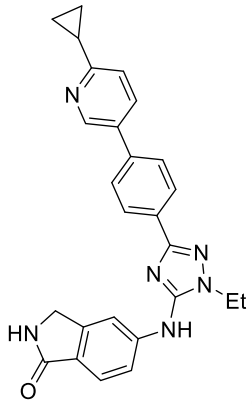
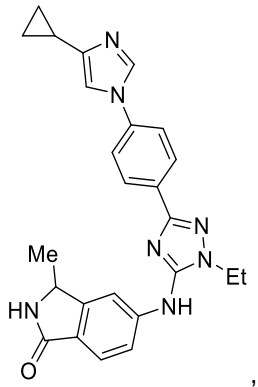
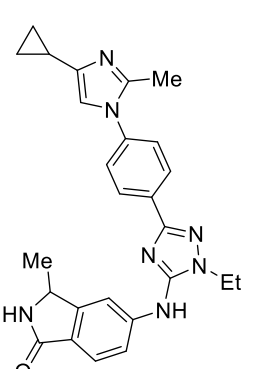
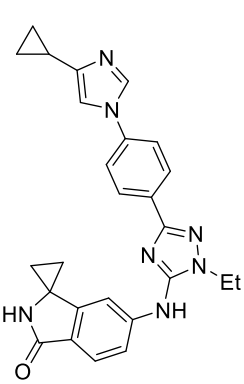
wherein x4 is an integer independently selected from 0, 1 and 2.

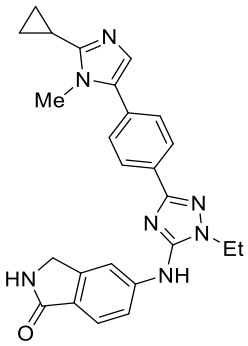
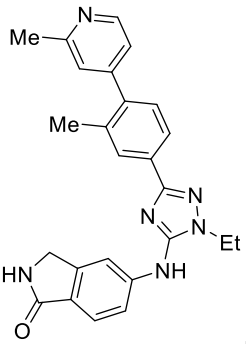
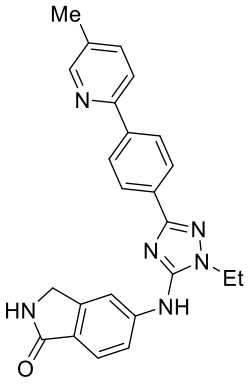
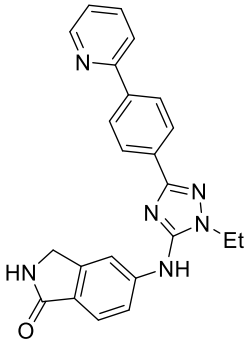
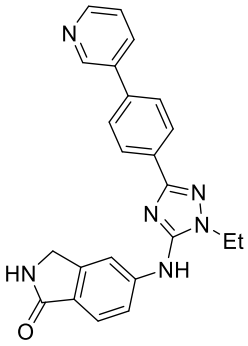
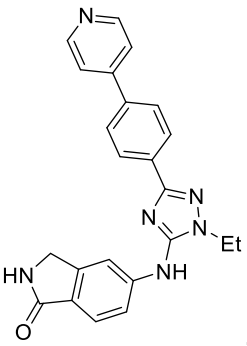
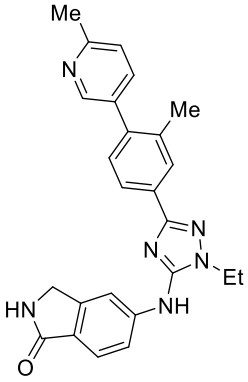
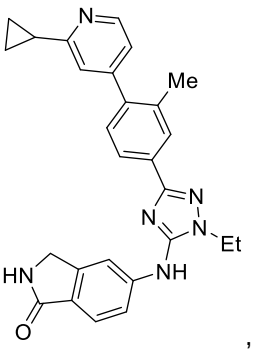
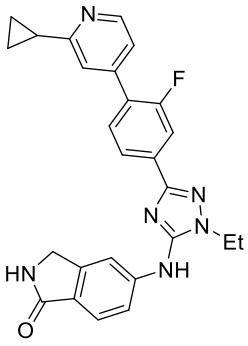
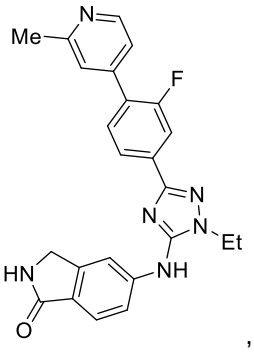
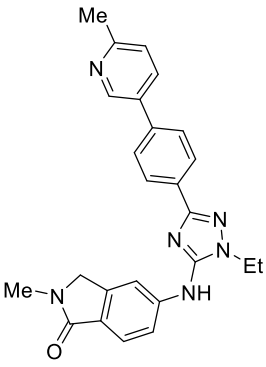
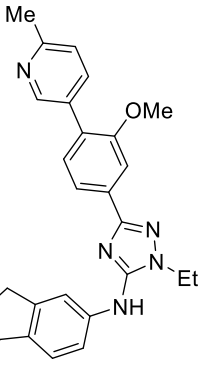
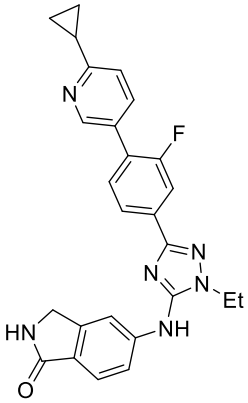
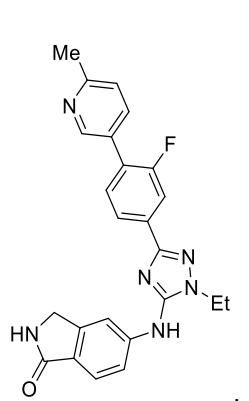
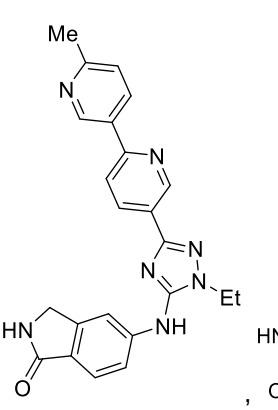
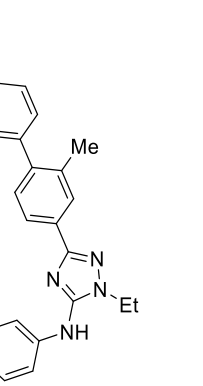
14. A compound of any one of claims 1 to 13, wherein R^6 is independently at each occurrence selected from H and C_1-C_4-alkyl.

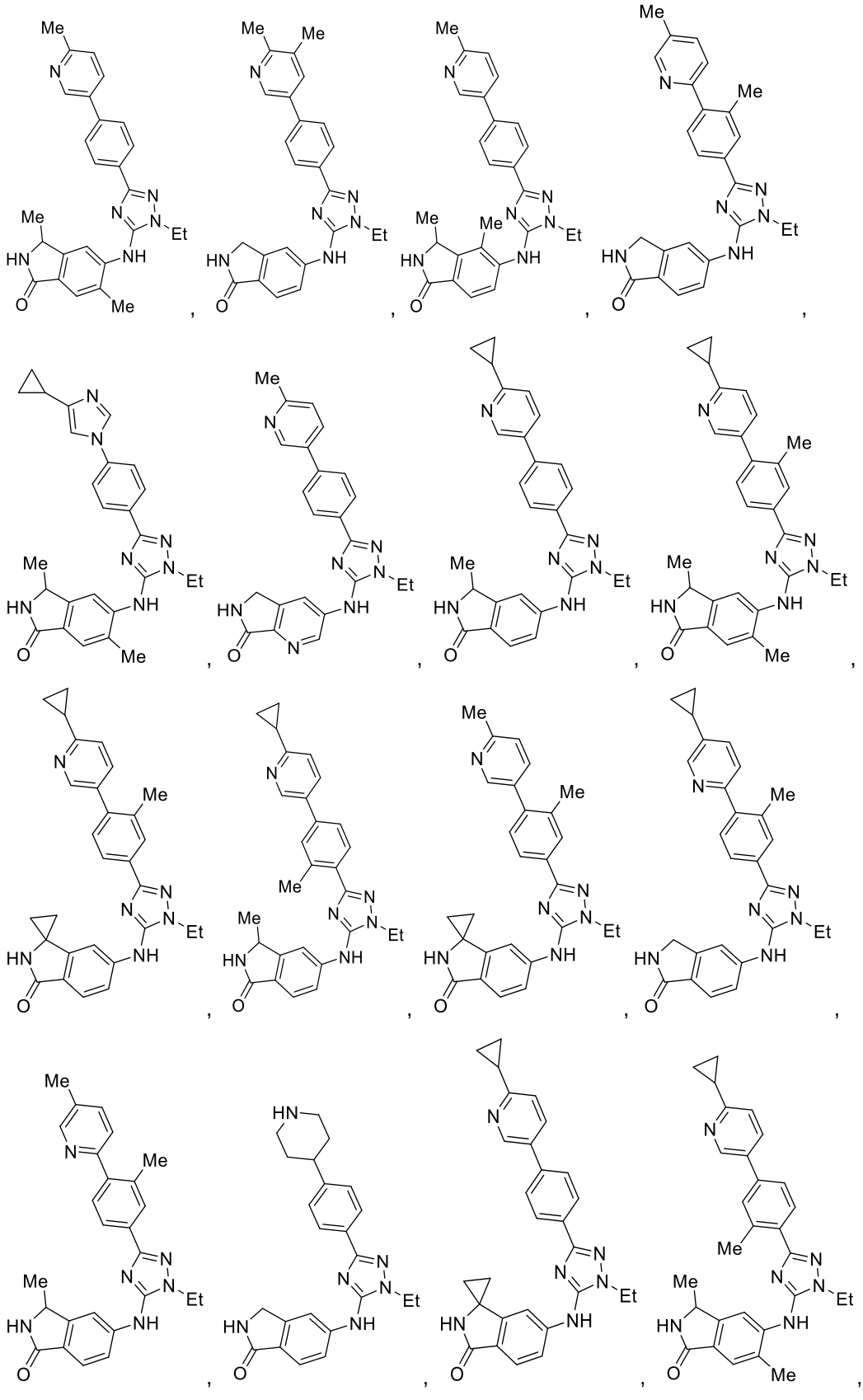
15. A compound of any one of claims 1 to 13, wherein the two R^6 groups and the carbon atom to which they are attached together form a C_3-C_6 cycloalkyl ring.

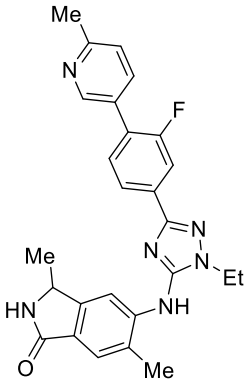
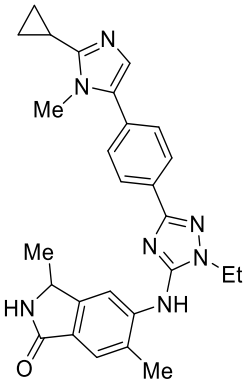
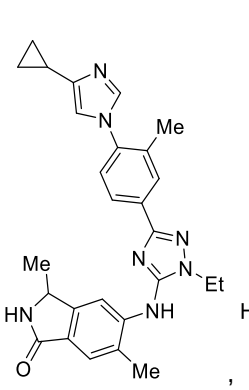
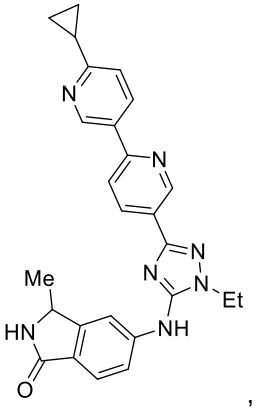
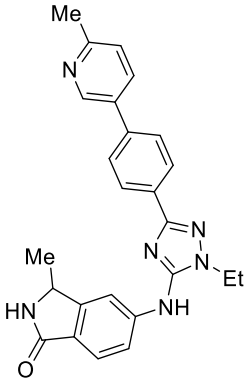
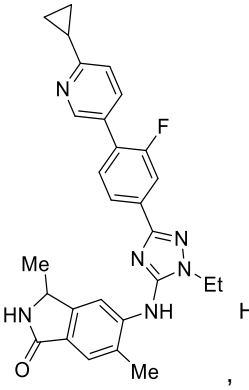
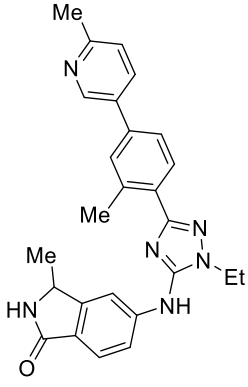
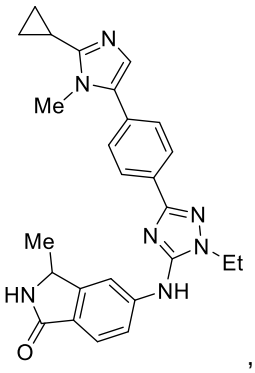
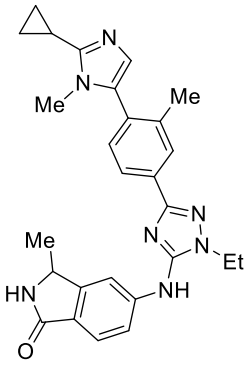
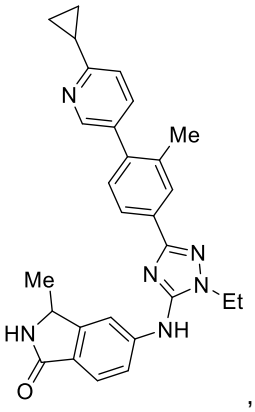
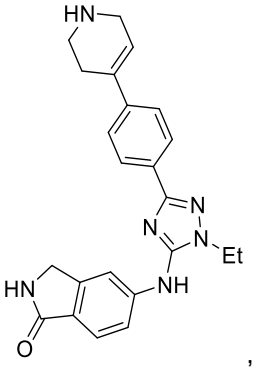
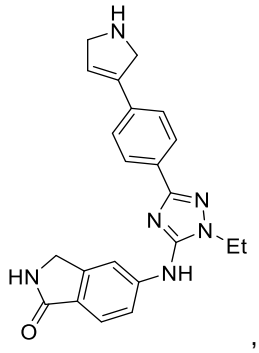
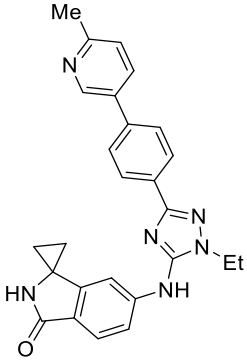
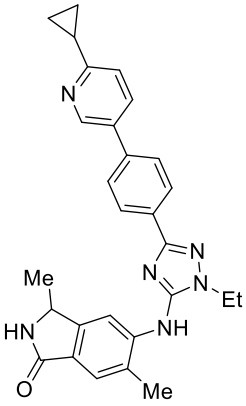
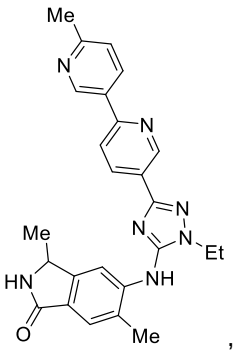
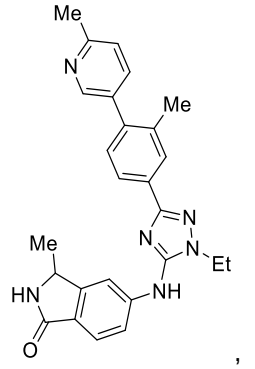
16. A compound of formula (**I**) may be selected from:





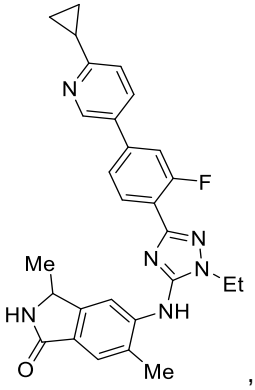
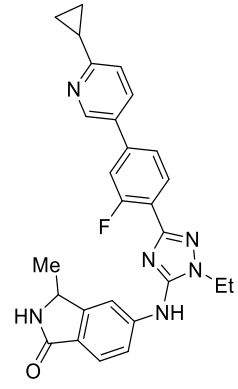
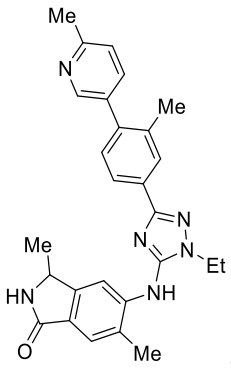
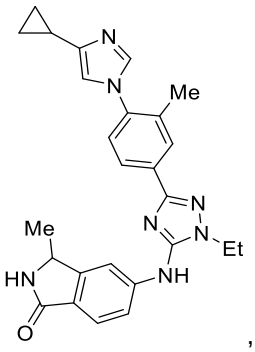
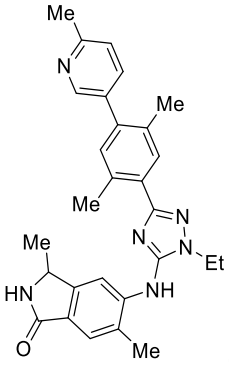
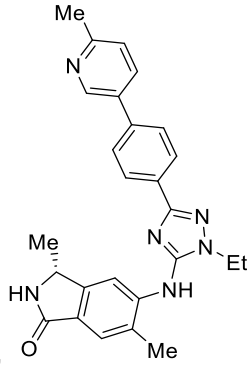
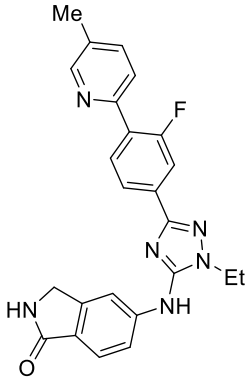
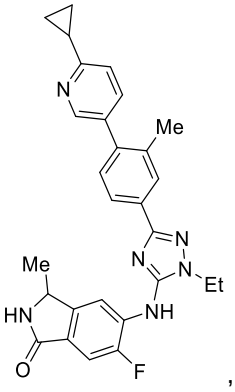
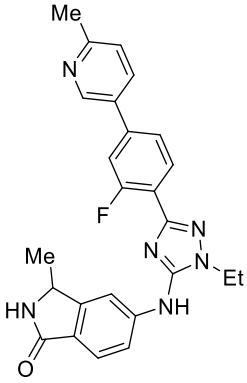
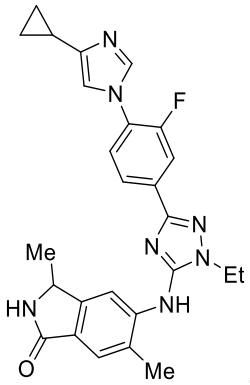
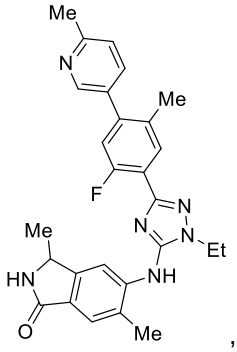
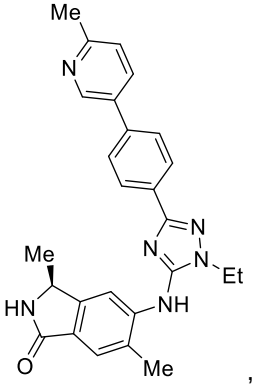
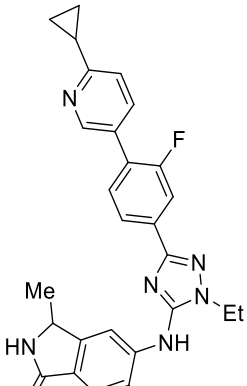
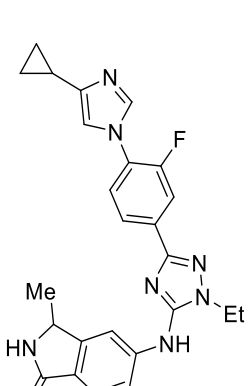
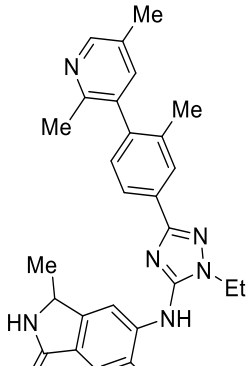
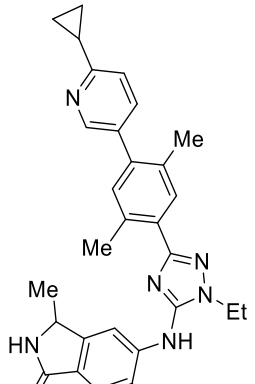

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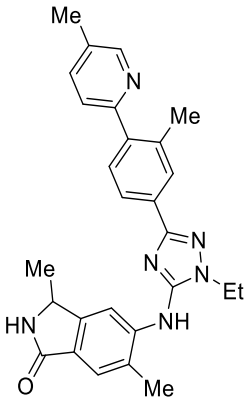
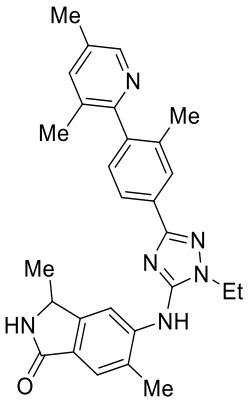
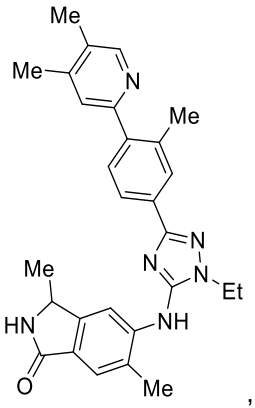
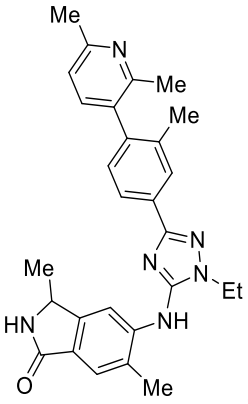
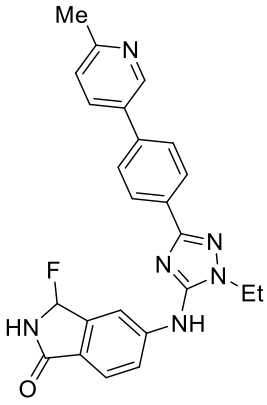
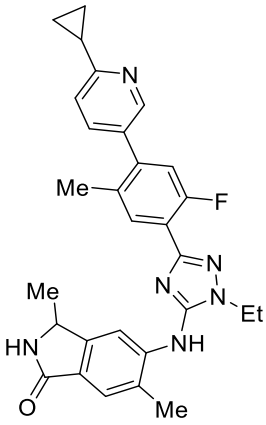
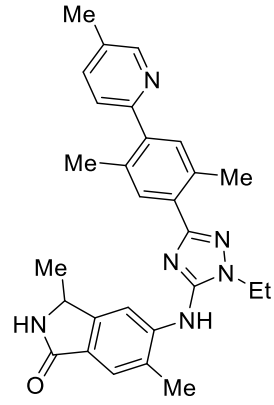
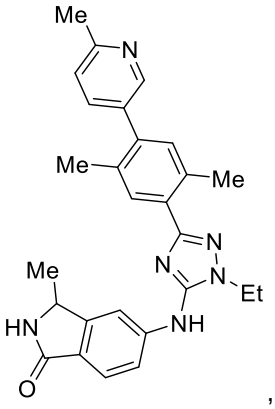
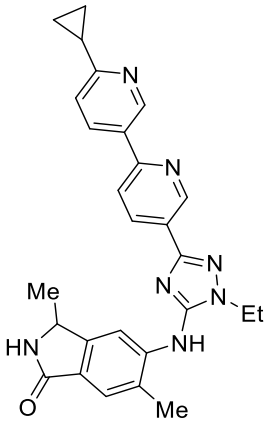
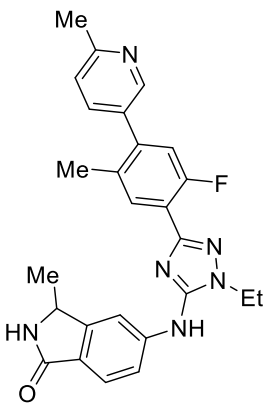
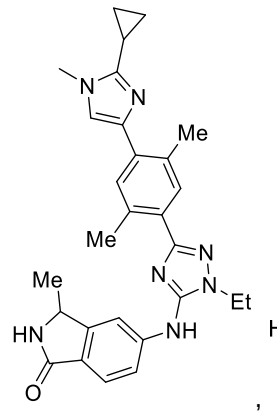
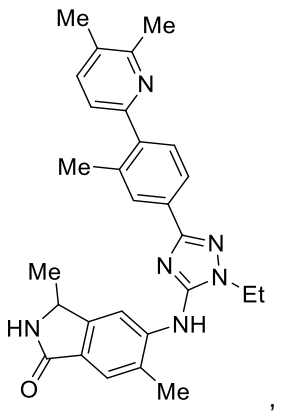

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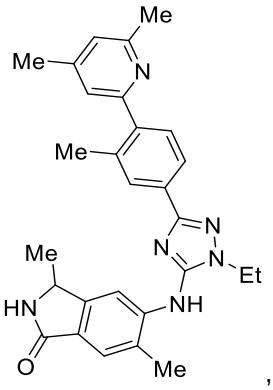
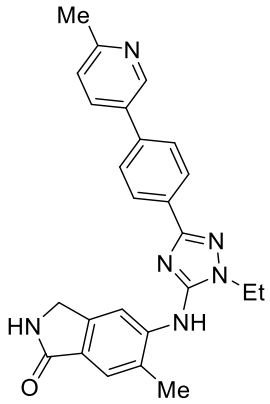
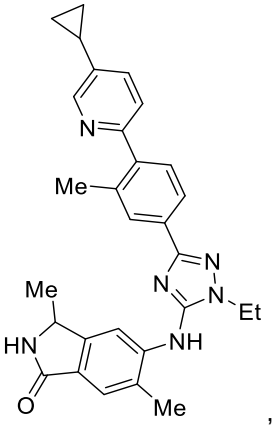
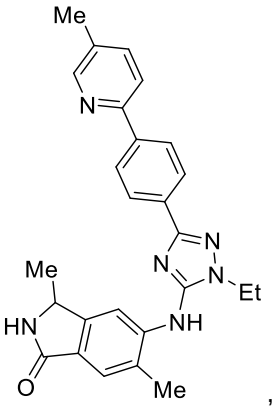
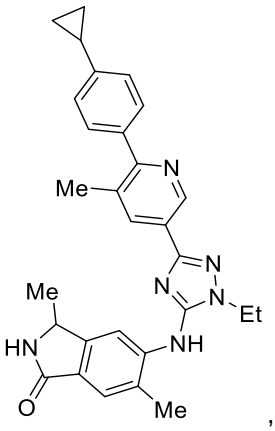
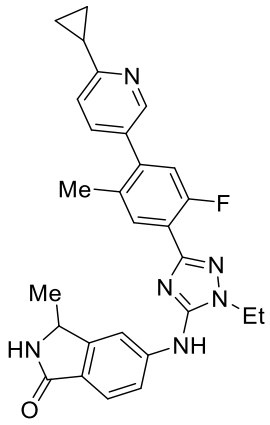
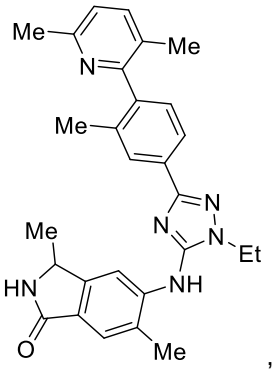
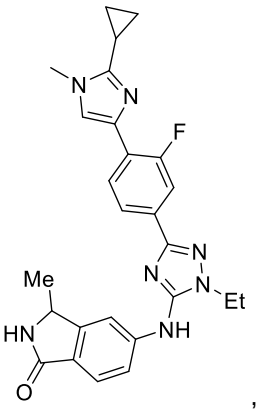
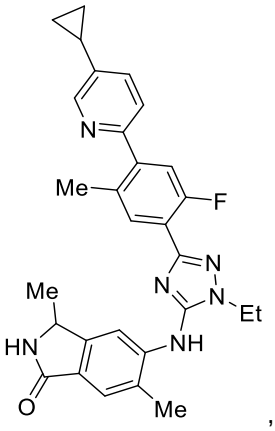
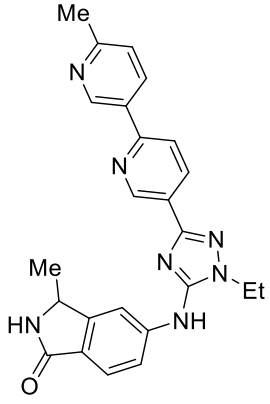
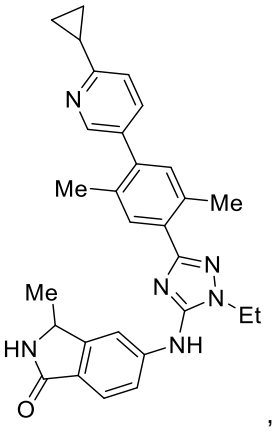
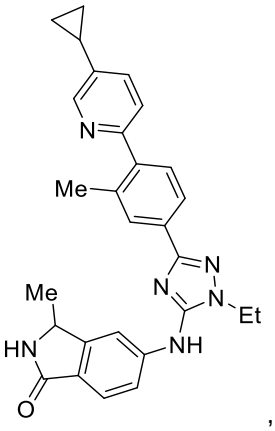
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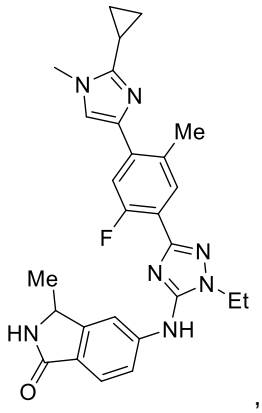
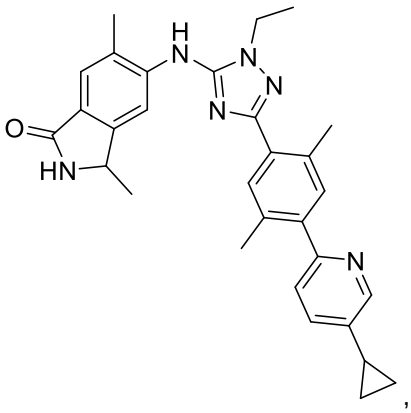
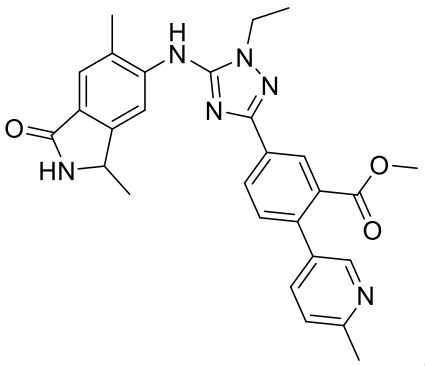
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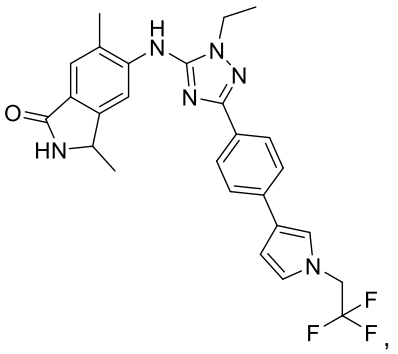
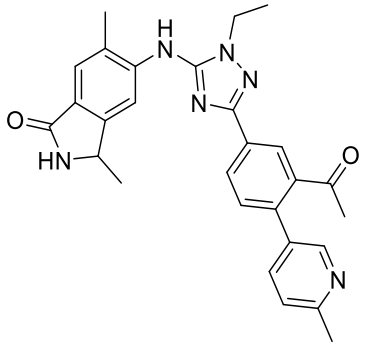
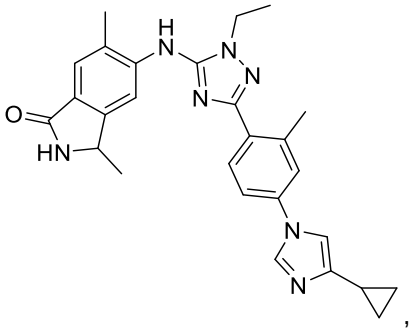
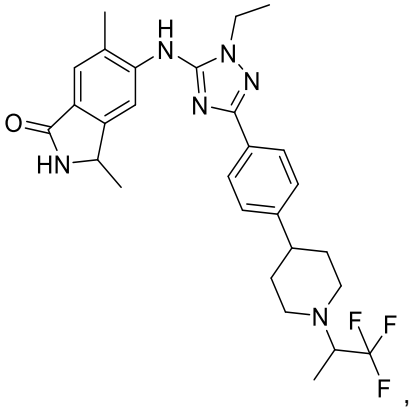
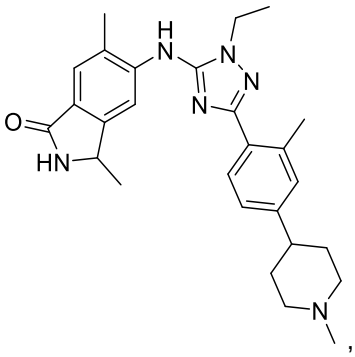
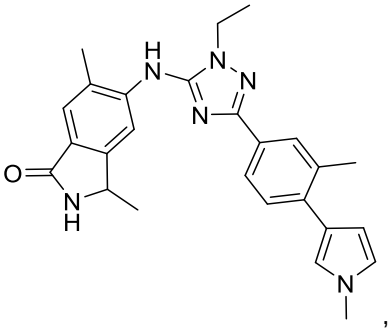
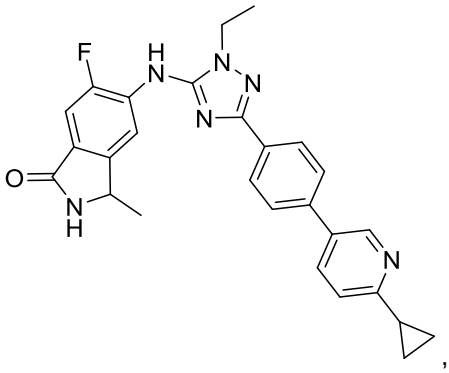
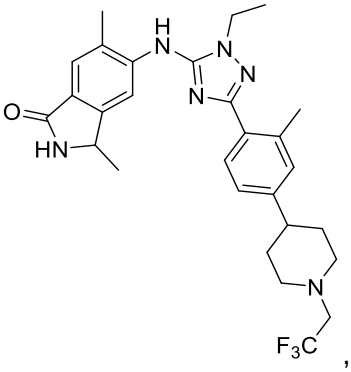
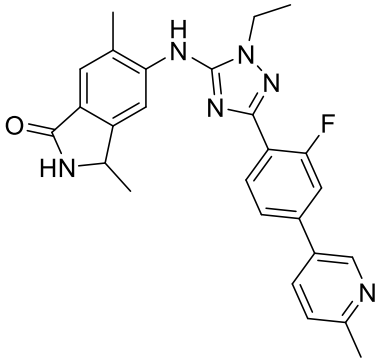
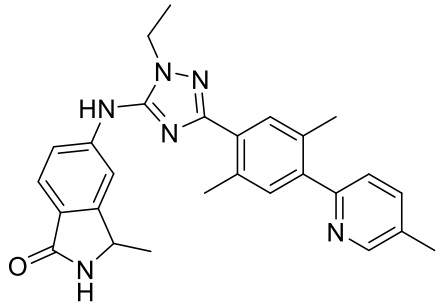
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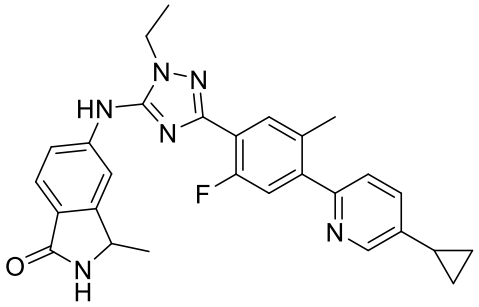
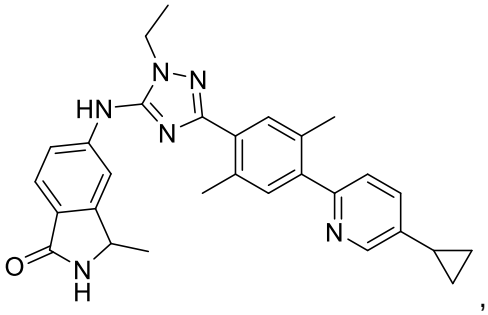
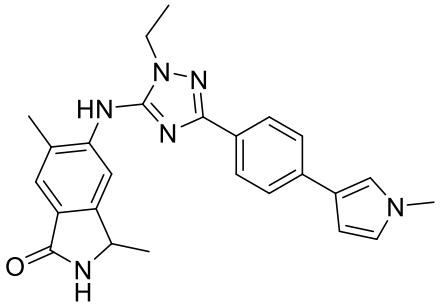
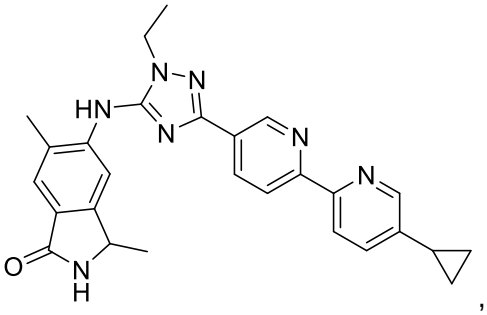
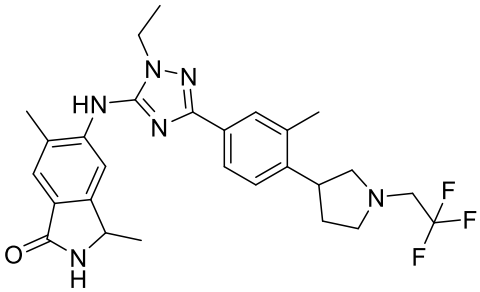
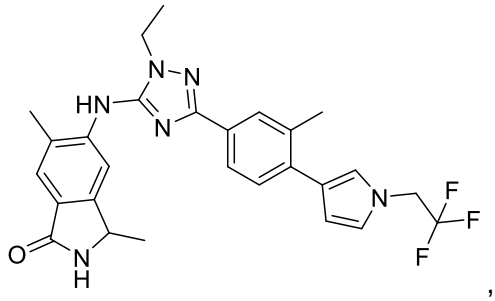
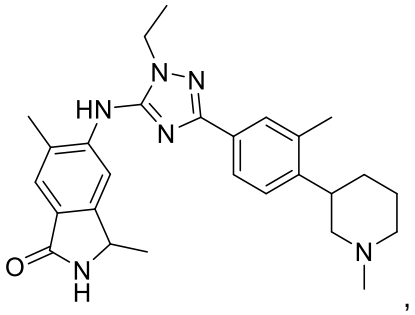
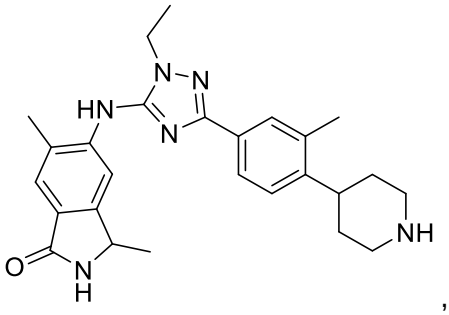
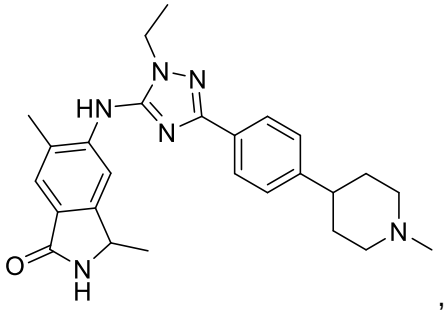
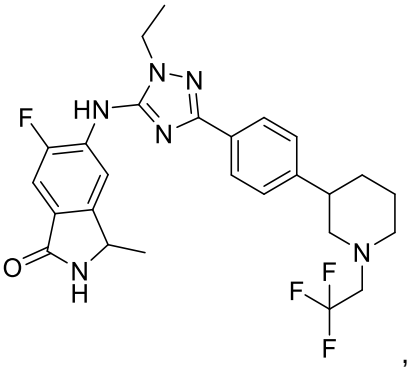
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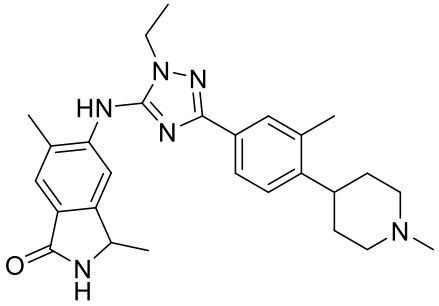
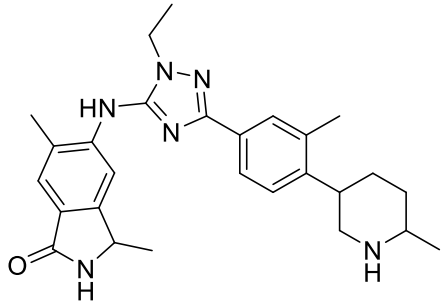
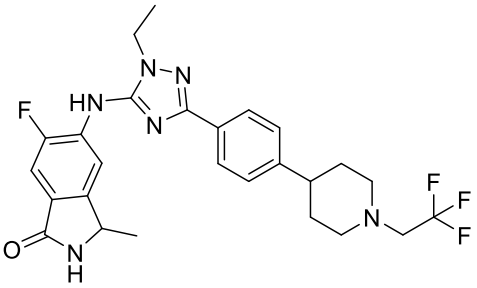
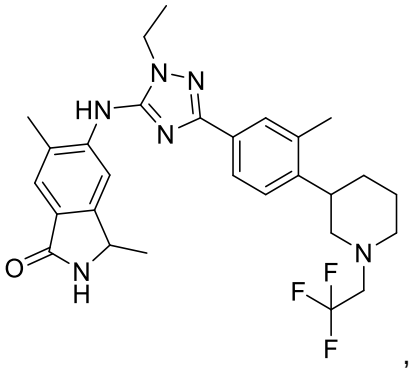
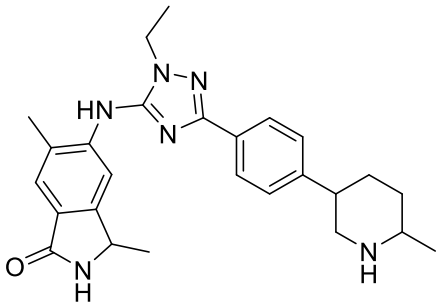
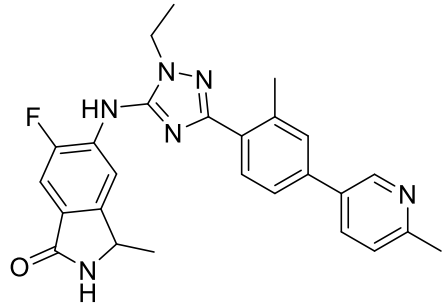
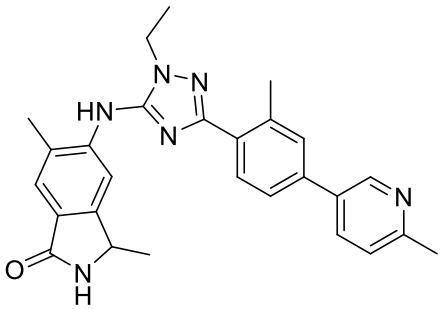
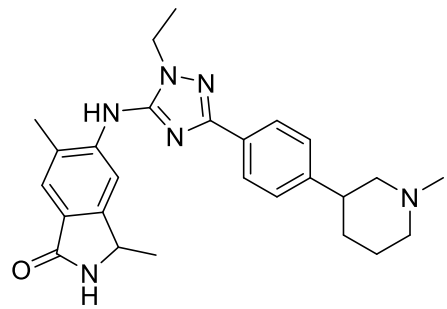
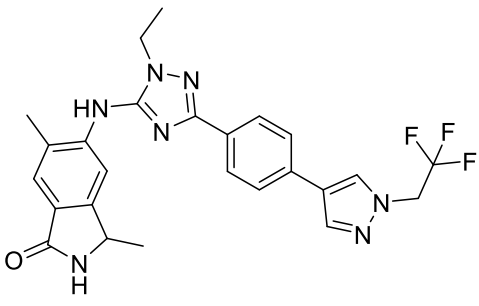
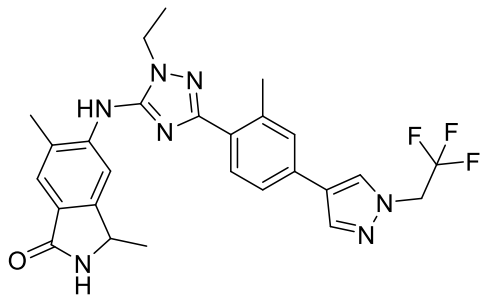

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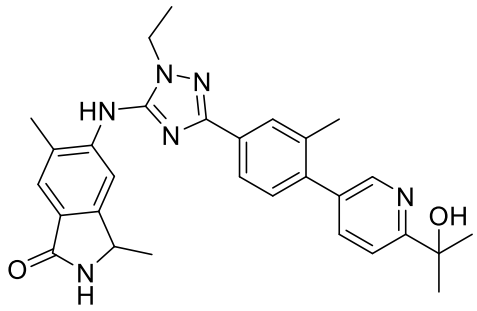
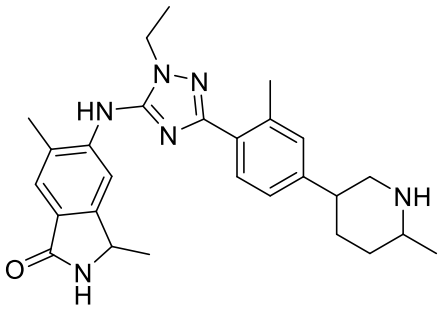
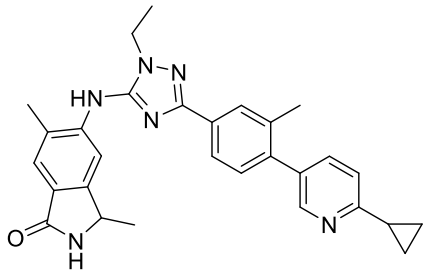
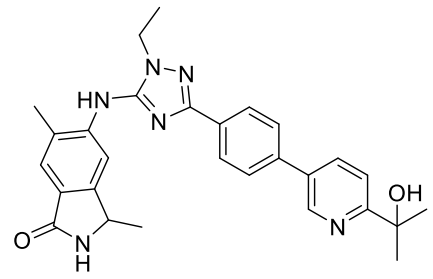
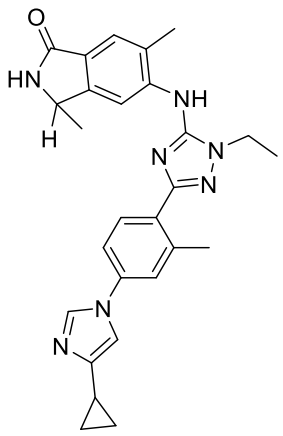
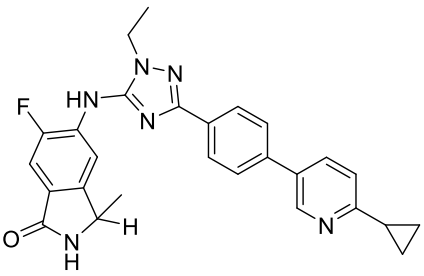
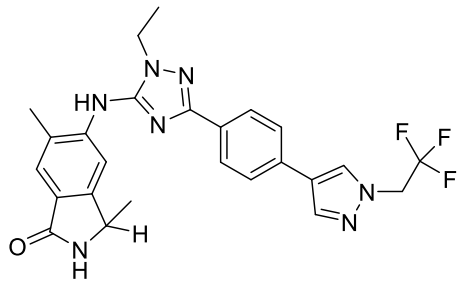














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17. A pharmaceutical formulation comprising a compound of any one of claims 1 to 16 and a pharmaceutically acceptable excipient.

18. A compound of any one of claims 1 to 16, or a pharmaceutical formulation of claim 17, for use as a medicament.

19. A compound of any one of claims 1 to 16, or a pharmaceutical formulation of claim 17, for use in treating a a disease or disorder selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.

20. Use of a compound of any one of claims 1 to 16, or a pharmaceutical formulation of claim 17, in the manufacture of a medicament for treating a a disease or disorder selected from: fibrotic diseases, auto-immune, inflammatory-fibrotic conditions, inflammatory conditions, central nervous system disorders, or cancer.