inhibitory activity. It is therefore desirable to have a BTK inhibitor with high BTK inhibition and low EGFR inhibition to reduce or avoid the gastrointestinal side effects.

[0008] Irreversible and covalent reversible BTK inhibitors specifically target a cysteine residue C481 within BTK. Following treatment with ibrutinib, cases of primary and secondary resistance have emerged. Mutations within BTK such as C481S, C481Y, C481R, C481F have been reported in the literature and clearly interfere with drug binding (Woyach 2014; Maddocks 2015). It has been predicted that the incidence of observed resistance will increase as clinical use outside clinical trials expands over time (Zhang 2015).

[0009] Therefore, an aim of the present invention is to provide BTK inhibitors with a different binding mode more specifically reversible inhibitors. In addition, the invention aims to provide BTK inhibitors with high selectivity for BTK inhibition over EGFR and ITK inhibition.

[0010] Furthermore, it is an aim of certain embodiments of this invention to provide new cancer treatments. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing cancer treatments but are also effective against mutations. One of the aspects of the invention focus on providing BTK inhibitors effective against the C481 mutations.

[0011] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

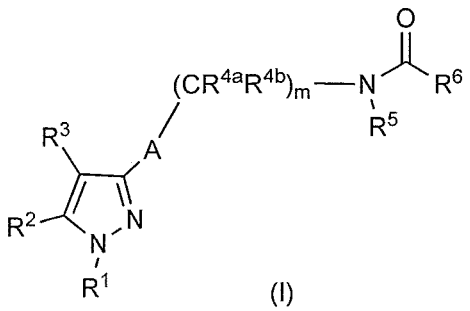
[0012] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0013] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0014] In accordance with the present disclosure there is provided compounds as disclosed below. Furthermore, the disclosure provides compounds capable of inhibiting Bruton's tyrosine kinase (BTK) and the use of these compounds in inhibiting BTK. In accordance with the disclosure there is provided a method of treating conditions modulated by BTK. The disclosure provides compounds for use in treating a condition which is modulated by BTK.

[0015] In a first aspect of the invention there is provided a compound according to formula (**I**) or pharmaceutically acceptable salts thereof:



(I)

wherein

A represents a ring selected from the group consisting of: unsubstituted or substituted: phenyl, pyridine, pyridazine, pyrimidine, or pyrazine, wherein when substituted A is substituted with from 1 to 4 R^7;

R^1 represents a group selected from: C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{2-8} alkyl ether, $-C(O)R^A$, C_{3-10} carbocyclic group, 3 to 10 membered heterocyclic group, C_{1-8} alkyl substituted with C_{3-10} carbocyclic group, and C_{1-8} alkyl substituted with 3 to 10 membered heterocyclic group, wherein each of the aforementioned groups are unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkyl ether, $-OR^A$, $-NR^AR^B$, -CN, =O, $-OC(O)R^A$, $-C(O)R^A$, $-C(O)OR^A$, $-NR^AC(O)R^B$, $-C(O)NR^AR^B$, $-NR^AS(O)_2R^B$, $-S(O)_2NR^AR^B$, benzoyl, a 5 or 6 membered heterocycloaryl, a 3 to 6 membered heterocycloalkyl ring, C_{1-4} alkyl substituted with $-OR^A$ and C_{1-4} alkoxy substituted with $-OR^A$, or a single atom of R^1 is substituted twice so as to form a 3 to 6 membered heterocycloalkyl or cycloalkyl ring;

R^2 represents a group selected from the group consisting of: -OH, halo, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 3 to 10 membered heterocyclic group, alkyl substituted with $-OR^C$, C_{1-8} alkyl substituted with C_{3-10} carbocyclic group, alkyl substituted with 3 to 10 membered heterocyclic group, and $-NR^CR^D$;

R^3 represents $-C(O)NR^ER^F$, C_{1-6} alkyl substituted with $-OR^G$, or C_{1-6} haloalkyl;

R^{4a} and R^{4b} are independently at each occurrence selected from the group consisting of: H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl substituted with $-OR^H$;

R^5 is H or C_{1-4} alkyl;

R^6 is a group selected from a substituted or unsubstituted: phenyl or a 5 or 6 membered heteroaryl ring, wherein, when substituted, R^6 contains from 1 to 5 substituents independently selected at each occurrence from: halo, $-OR^I$, $-NR^IR^J$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with $-OR^I$;

R^7 is selected from the group consisting of: H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} alkyl substituted with $-OR^H$;

m is 1 or 2;

R^A and R^B are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, phenyl, benzyl, or C_{1-4} alkyl substituted with $-OR^H$;

R^C, R^D, R^E and R^F are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, unsubstituted C_{3-10} carbocyclic group, C_{1-4} alkyl substituted with unsubstituted C_{3-10} carbocyclic group, C_{1-4} alkyl substituted with C_{3-10} carbocyclic group substituted with 1 or 2 R^H or $-OR^H$, and 3 to 10 membered heterocyclic group;

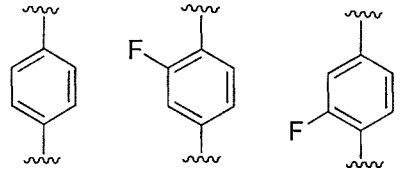
R^G, R^I, and R^J are independently at each occurrence selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy and C_{1-4} alkyl substituted with $-OR^H$; and

R^H is selected from H or C_{1-4} alkyl.

[0016] In an embodiment A is unsubstituted phenyl, unsubstituted pyridine, phenyl substituted by from 1 to 4 R^7, or pyridine substituted by from 1 to 4 R^7.

[0017] Preferably, A is unsubstituted phenyl, unsubstituted pyridine, unsubstituted pyridazine, unsubstituted pyrimidine, unsubstituted pyrazine, or phenyl substituted with 1 or 2 R^7.

[0029] In preferred embodiments, A is selected from:



[0030] In embodiments R^6 is a group selected from a substituted or unsubstituted: phenyl or 6 membered heteroaryl ring. Preferably, R^6 is a group selected from a substituted: phenyl or 6 membered heteroaryl ring, substituted with 1 or 2 (preferably 1) methoxy (-OMe) group.

[0031] In embodiments R^6 is a group selected from a substituted or unsubstituted: phenyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, or thiodiazolyl.

[0032] Preferably, R^6 is a group selected from a substituted: phenyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, or thiodiazolyl, wherein R^6 contains from 1, 2 or 3 substituents independently selected at each occurrence from: halo, $-OR^I$, -CN, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, and $C_{1\text{-}6}$ alkyl substituted with $-OR^I$, optionally R^I is selected from: H, methyl, ethyl, $-CF_3$, $-CH_2-OR^H$ and $-CH_2CH_2-OR^H$. Preferably, R^I is H or methyl.

[0033] As the skilled person will be aware, based on the depiction of the structural formula of compounds of the disclosure, R^6 is attached to the remainder of the compound of the disclosure via a carbonyl (-C(=O)-) group. When R^6 is substituted by 1, 2 or 3 substituents R^6 is substituted by the carbonyl group (connecting R^6 to the remainder of the compound) and a further 1, 2 or 3 substituents. In preferred embodiments one of the substituents is substituted adjacent to the -C(=O)-. In other words, one of the substituents is substituted ortho to the carbonyl group (-C(=O)-). Preferably, the substituent of the 1, 2 or 3 substituents that is substituted on R^6 ortho to the carbonyl group is methoxy.

[0034] In embodiments R^6 is substituted or unsubstituted: phenyl or pyridyl (preferably substituted. In particularly preferred embodiments R^6 is substituted phenyl.

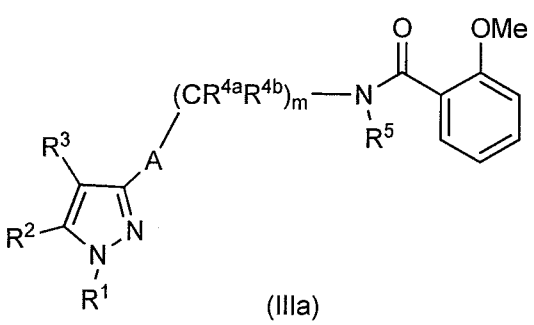
[0035] Preferably, R^6 contains from 1, 2 or 3 substituents independently selected at each occurrence from: fluoro, chloro, methoxy, ethoxy, isopropoxy, -CN, methyl, ethyl, trifluoromethyl, trifluoroethyl or $-OCF_3$. In embodiments, R^6 contains 1 or 2 substituents independently selected at each occurrence from: fluoro, methoxy or methyl. Preferably, R^6 contains 1 methoxy substituent or 2 substituents that are fluoro and methoxy.

[0036] A particularly preferred substituent for R^6 is methoxy. Accordingly, in preferred embodiments R^6 is a group selected from a methoxy substituted: phenyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, or thiodiazolyl. Optionally, R^6 is a group selected from a methoxy substituted: phenyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl.

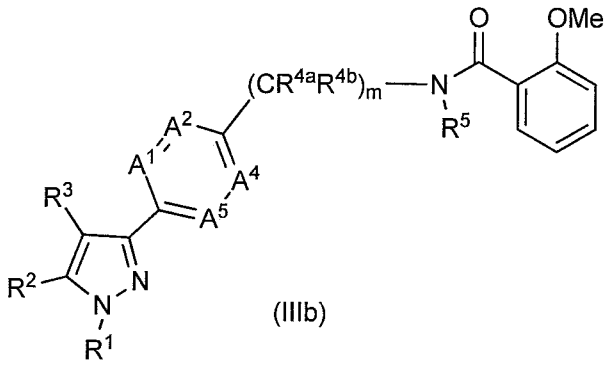
[0037] Particularly preferred substituents for R^6 are methoxy and fluoro. Accordingly, in preferred embodiments R^6 is a group selected from a fluoro and methoxy substituted: phenyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, furanyl, thiophenyl, oxazolyl, thiazolyl, isoxazolyl,

isothiazolyl, triazolyl, oxadiazolyl, or thiodiazolyl. Optionally, R^6 is a group selected from a fluoro and methoxy substituted: phenyl, pyridyl, pyridazinyl, pyrazinyl or pyrimidinyl.

[0038] R^6 may be methoxyphenyl or fluoromethoxyphenyl. R^6 may be methoxyphenyl. As the skilled person will be aware R^6 is attached to the remainder of the compound of the disclosure via a carbonyl (-C(=O)-) group. When R^6 is methoxy phenyl the phenyl group of R^6 is substituted by the carbonyl group (connecting the phenyl ring to the remainder of the compound) and a methoxy group. In preferred embodiments where R^6 is methoxy phenyl, the methoxy group is substituted adjacent to the -C(=O)-. In other words, the methoxy group is substituted ortho to the carbonyl group (-C(=O)-) Accordingly, in an embodiment compounds according to formula (I) are compounds of formulae (IIIa) and (IIIb):



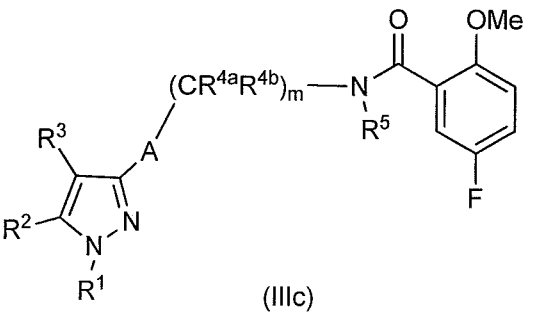
(IIIa)



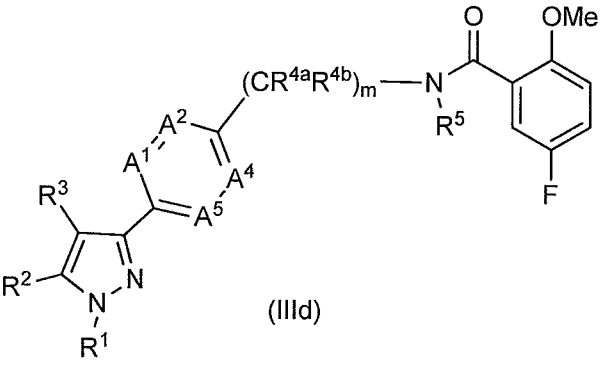
(IIIb)

[0039] Hence, in preferred embodiments R^6 is 2-methoxyphen-1-yl.

[0040] R^6 may be fluoromethoxyphenyl. As the skilled person will be aware R^6 is attached to the remainder of the compound of the disclosure via a carbonyl (-C(=O)-) group. When R^6 is fluoromethoxyphenyl the phenyl group of R^6 is substituted by the carbonyl group (connecting the phenyl ring to the remainder of the compound), a fluoro group and a methoxy group. In preferred embodiments where R^6 is fluoromethoxyphenyl, the methoxy group is substituted adjacent to the -C(=O)- and the fluoro group is substituted opposite the methoxy group. In other words, the methoy group is substituted ortho to the carbonyl group (-C(=O)-) and the fluoro group is attached para to the methoxy group. Accordingly, in an embodiment compounds according to formula (I) are compounds of formulae (IIIc) and (IIId):



(IIIc)

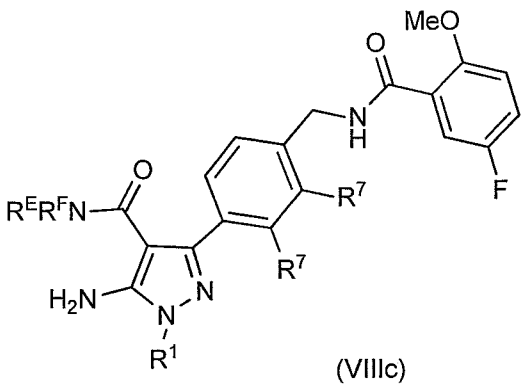


(IIId)

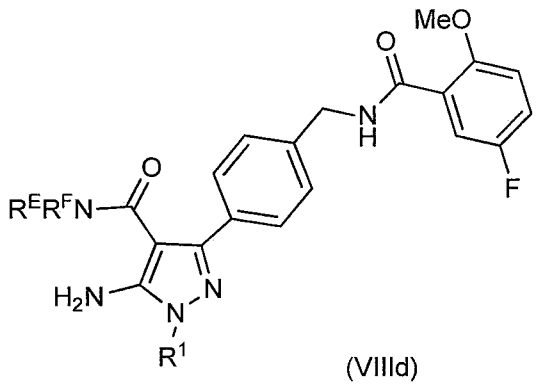
[0041] Hence, in preferred embodiments R^6 is 5-fluoro-2-methoxyphen-1-yl.

[0042] In embodiments R^6 is 2-methoxyphen-1-yl or 5-fluoro-2-methoxyphen-1-yl.

[0043] R^5 may be H or methyl. Preferably, R^5 is H.

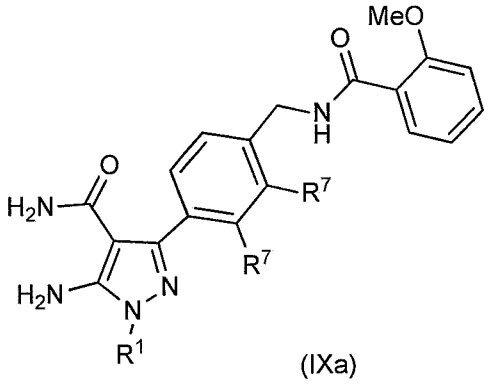


(VIIIc)

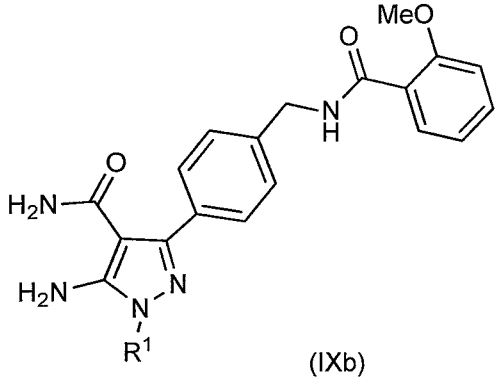


(VIIId)

[0091] In an embodiment the compound according to formula (I) may be compounds of formulae (IXa) and (IXb) or pharmaceutically acceptable salts thereof

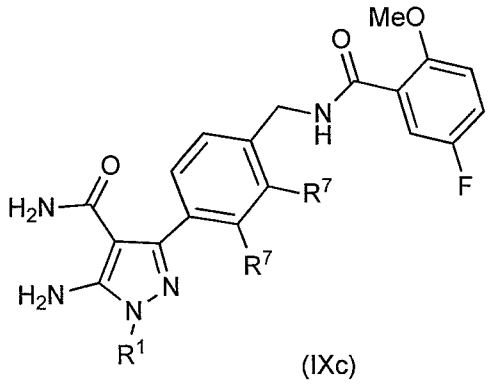


(IXa)

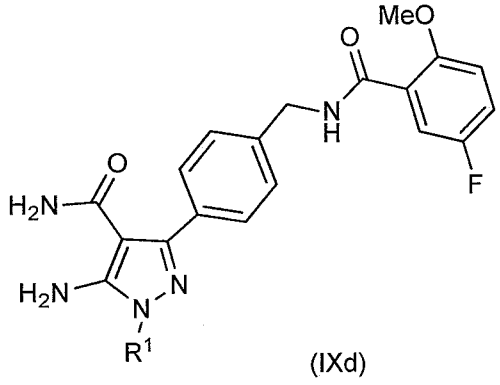


(IXb)

[0092] Alternativley, the compound according to formula (I) may be compounds of formulae (IXc) and (IXd) or pharmaceutically acceptable salts thereof

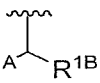


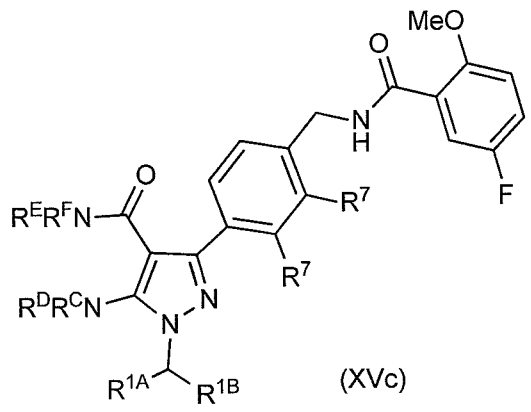
(IXc)



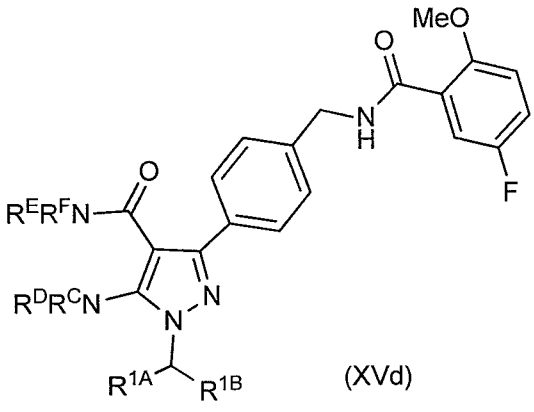
(IXd)

[0093] For the compounds of formulae (VIa), (VIIa), (VIIIa), (IXa), (VIc), (VIIc), (VIIIc), and (IXc) R^7 may be as defined elsewhere herein, preferably R^7 may be selected from: H, fluoro, methyl, methoxy, and -CH_2OH.

[0094] In a particulary preferred embodiment of the disclosure R^1 is . Accordingly, the compound according to formula (I) may be a compound of formula (X) or a pharmaceutically acceptable salt thereof:



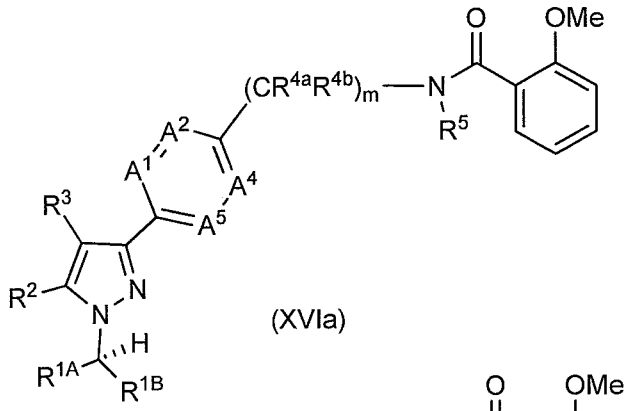
(XVc)



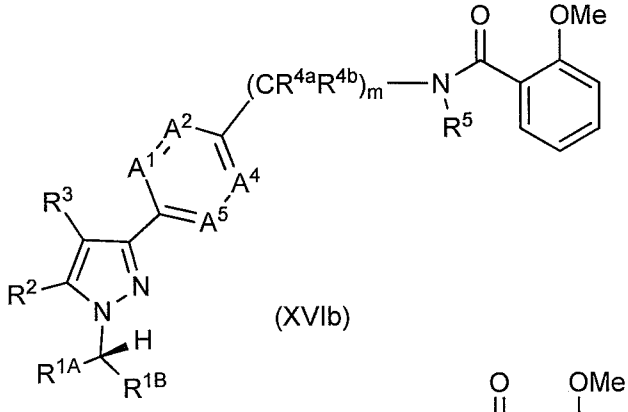
(XVd)

[00102] In the compounds of formulae (XVa), (XVb), (XVc) and (XVd) R^C and R^D may be H. In the compounds of formulae (XVa), (XVb), (XVc) and (XVd) R^E and R^F may be H. In the compounds of formulae (XVa), (XVb), (XVc) and (XVd) R^C and R^D may be H and R^E and R^F may be H.

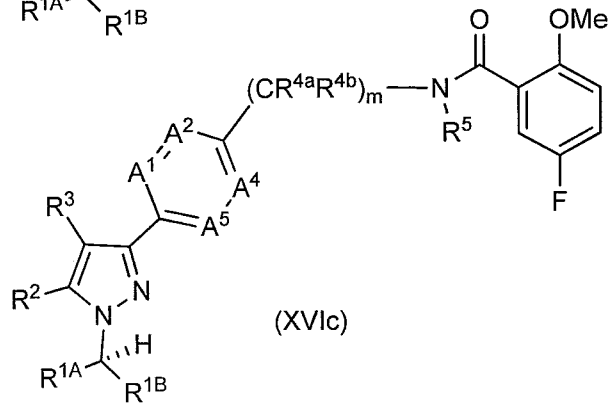
[00103] In an embodiment the compound according to formula (I) may be compounds of formulae (XVa), (XVb), (XVc) and (XVd) or pharmaceutically acceptable salts thereof:



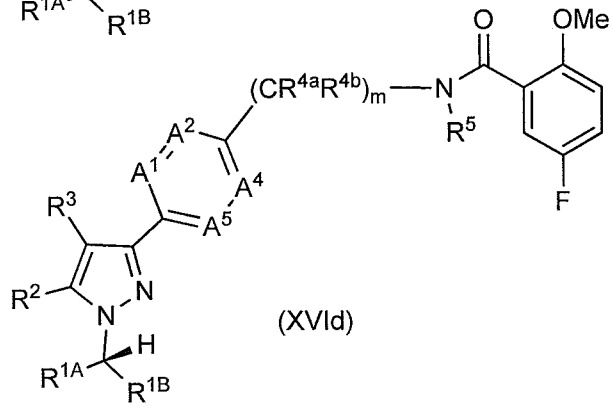
(XVIa)



(XVIb)



(XVIc)



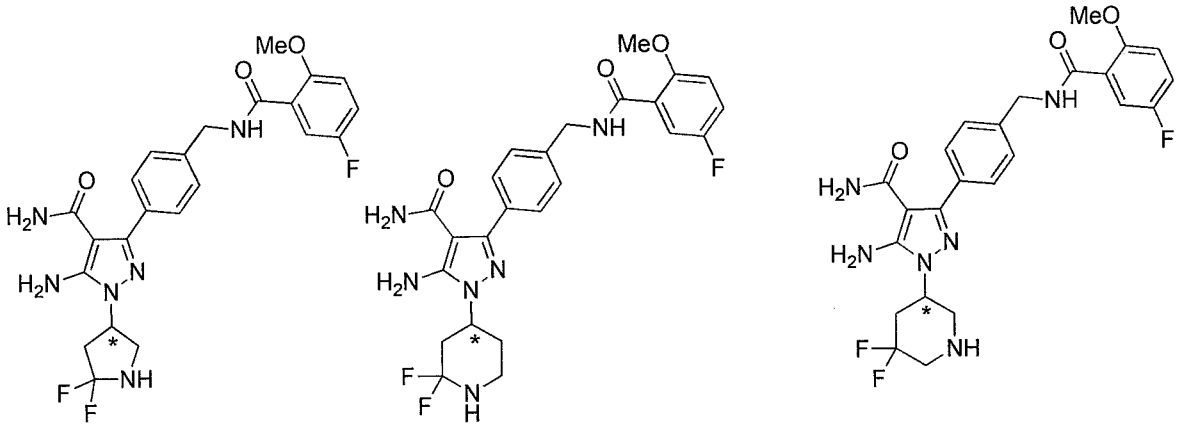
(XVId)

[00104] In embodiments of the compounds of formula (XVIa), (XVIb), (XVIc) and (XVId) A^1, A^2, A^4 and A^5 are CH, or A^1, A^4 and A^5 are CH and A^2 is CH, or A^2, A^4 and A^5 are CH and A^1 is CF.

[00105] In embodiments of the compounds of formula (XVIa), (XVIb), (XVIc) and (XVId) R^2 represents $-NR^CR^D$ and R^3 represents $-C(O)NR^ER^F$. Optionally, R^C and R^D are H and R^E and R^F are H.

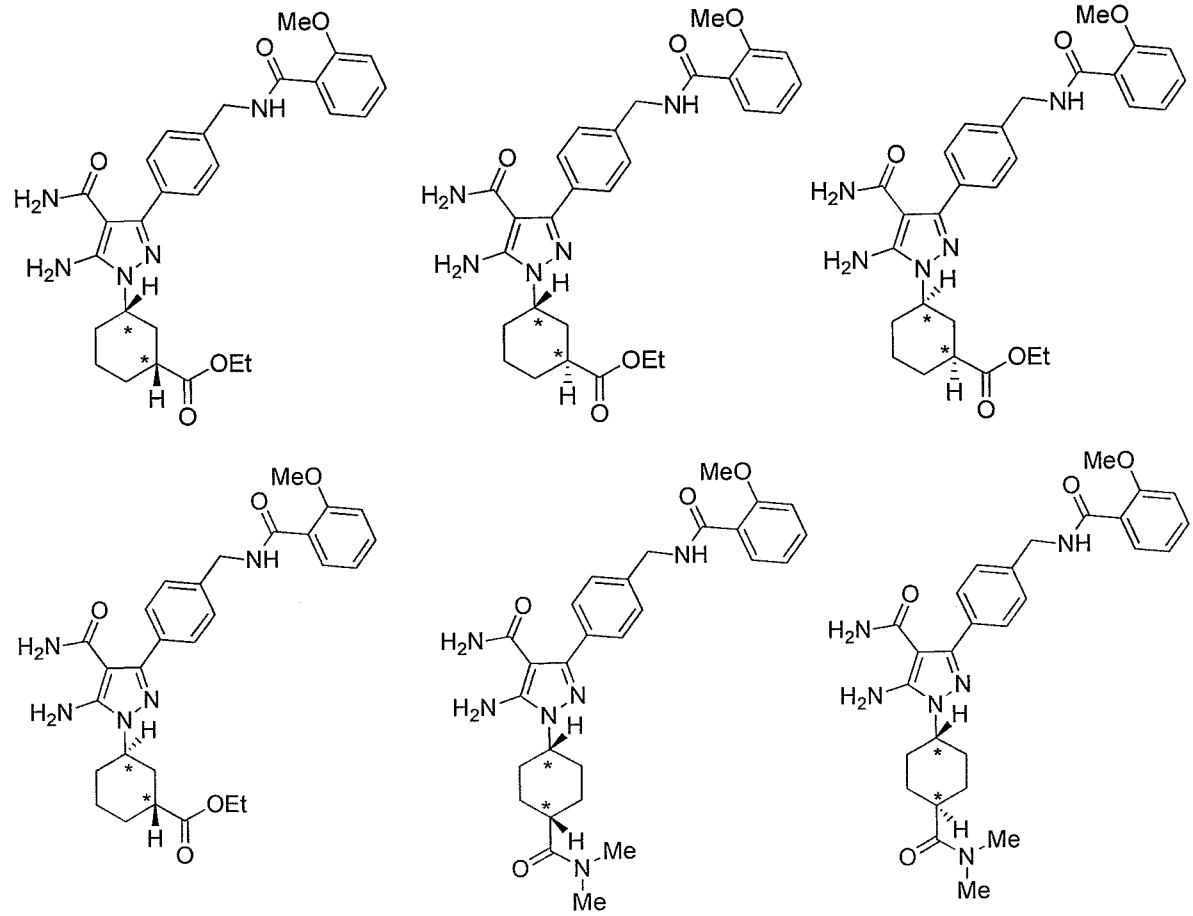
[00106] The genus of compounds represented by formula (X), i.e. where R^1 is $-CHR^{1A}R^{1B}$, is an active genus.

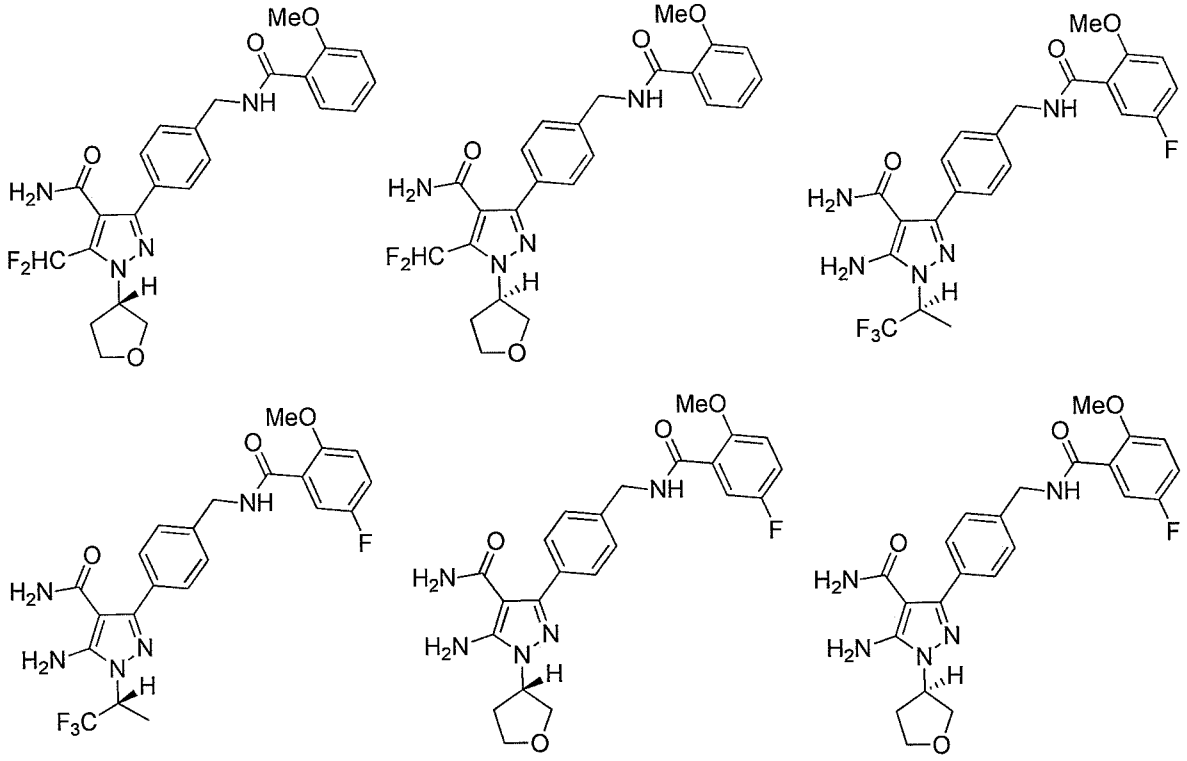
[00107] Preferred compounds of the disclosure include:



[00110] Some of the above compounds have one or more chiral centres, for example one or two chiral centres. All enantiomers and diastereomers of the above compounds are contemplated by the disclosure. Certain chiral centres are indicated on the compounds above with a * symbol. The cmpounds may have chiral centres in addition to those indicated with a *. In one embodiment the compounds of the disclosure have the (*R*)-configuration at the stereocentre. In an alternative embodiment the compounds of the disclosure have the (*S*)-configuration at the stereocentre. Where compounds have two stereocentres the stereocentres may have (*R*),(*R*) configuration, (*S*),(*R*) configuration, (*R*),(*S*) configuration or (*S*),(*S*) configuration. The disclosure also contemplates racemic mixtures of these compounds.

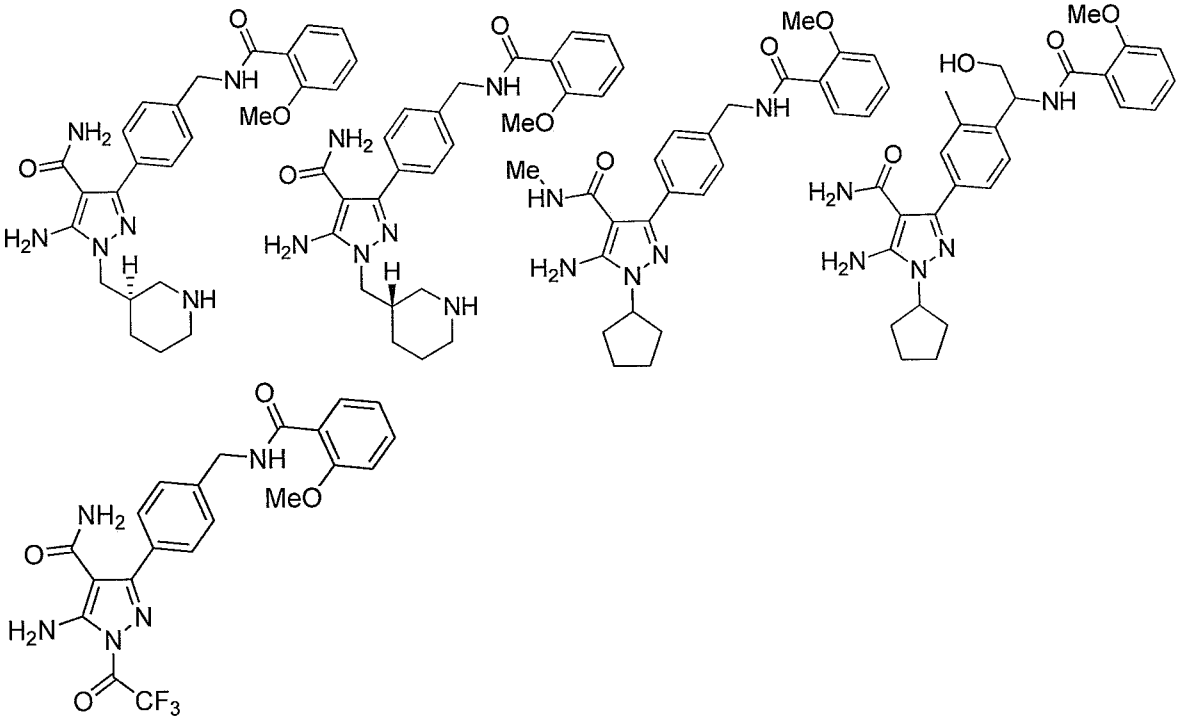
[00111] The compounds of formula (I) may be compounds selected from:





[00112] Any compound described in the examples also forms part of the disclosure. This includes the compounds falling under the scope of formula (I) and in another embodiment any and all novel intermediates in the synthesis of the compounds of formula (I).

[00113] Less preferred compounds of formula (I) are given below. In certain emboidments the compounds shown below do not form part of the disclosure.



[00114] In another aspect of the invention there is provided a compound of any formula disclosed herein for use as a medicament.

[00115] In another embodiment a compound of any formula disclosed herein is for use in the treatment of a condition which is modulated by Bruton's tyrosine kinase (BTK). Usually conditions that are modulated by BTK are conditions that would be treated by the inhibition of BTK 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 Bruton's tyrosine kinase (BTK).

[00116] BTK inhibition is a novel approach for treating many different human diseases associated with the inappropriate activation of B-cells, including B-cell proliferative disorders, B-cell malignancies, immunological disease for example, autoimmune, heteroimmune conditions, and inflammatory disorders, or fibrosis. In particular, BTK inhibition is a novel approach for treating many different human diseases associated with the inappropriate activation of B-cells, including B-cell malignancies, immunological disease for example, autoimmune and inflammatory disorders.

[00117] In embodiments the condition treatable by the inhibition of BTK may be selected from: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimune conditions, or fibrosis. Specific conditions treatable by the inhibition of BTK may be selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, follicular lymphoma, chronic lymphocytic lymphoma, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma/, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, vulvodynia, graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, vulvitis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiolitis obliterans,

fibrosis (e.g. chronic kidney fibrosis), nephropathies associated with injury/fibrosis (e.g., chronic nephropathies associated with diabetes (e.g. diabetic nephropathy)), lupus, scleroderma of the kidney, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathyrenal fibrosis associated with human chronic kidney disease (CKD), chronic progressive nephropathy (CPN), tubulointerstitial fibrosis, ureteral obstruction, chronic uremia, chronic interstitial nephritis, radiation nephropathy, glomerulosclerosis, progressive glomerulonephrosis (PGN), endothelial/thrombotic microangiopathy injury, HIV-associated nephropathy, or fibrosis associated with exposure to a toxin, an irritant, a chemotherapeutic agent, fibrosis associated with scleroderma; radiation induced gut fibrosis; fibrosis associated with a foregut inflammatory disorder such as Barrett's esophagus and chronic gastritis, and/or fibrosis associated with a hindgut inflammatory disorder, such as inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease, age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity and neovascular glaucoma are examples of fibrosis treatable by BTK inhibition.

[00125] Arthritis, multiple sclerosis, osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and lupus are examples of immunological diseases treatable by BTK inhibition. Arthritis is an example of an inflammatory disorder treatable by BTK inhibition. Lupus and Sjögren's syndrome is an example of an autoimmune disease treatable by BTK inhibition.

[00125a] In one aspect, there is provided use of a compound disclosed herein for the manufacture of a medicament for the treatment of a condition which is modulated by BTK.

[0125b] In another aspect, there is provided use of a compound disclosed herein for the manufacture of a medicament for the treatment of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

[00125c] In yet another aspect, there is provided use of a compound disclosed herein for the manufacture of a medicament for the treatment of a condition selected from the group consisting of: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, follicular lymphoma, chronic lymphocytic lymphoma, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma/, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, vulvodynia, graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, vulvitis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiolitis obliterans, bronchiectasis, fatty liver disease, steatosis (e.g., nonalcoholic steatohepatitis

(NASH), cholestatic liver disease (e.g., primary biliary cirrhosis (PBC), cirrhosis, alcohol-induced liver fibrosis, biliary duct injury, biliary fibrosis, cholestasis or cholangiopathies. In some embodiments, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, e.g., hepatitis (e.g., hepatitis C, B or D), autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (e.g., alcohol, pharmaceutical drugs and environmental toxins), renal fibrosis (e.g., chronic kidney fibrosis), nephropathies associated with injury/fibrosis (e.g., chronic nephropathies associated with diabetes (e.g., diabetic nephropathy)), lupus, scleroderma of the kidney, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathyrenal fibrosis associated with human chronic kidney disease (CKD), chronic progressive nephropathy (CPN), tubulointerstitial fibrosis, ureteral obstruction, chronic uremia, chronic interstitial nephritis, radiation nephropathy, glomerulosclerosis, progressive glomerulonephrosis (PGN), endothelial/thrombotic microangiopathy injury, HIV-associated nephropathy, or fibrosis associated with exposure to a toxin, an irritant, or a chemotherapeutic agent, fibrosis associated with scleroderma; radiation induced gut fibrosis; fibrosis associated with a foregut inflammatory disorder such as Barrett's esophagus and chronic gastritis, and/or fibrosis associated with a hindgut inflammatory disorder, such as inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease, age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity and neovascular glaucoma.

[00125d] In a further aspect, there is provided use of a compound disclosed herein for the manufacture of a medicament for the treatment of cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis, wherein the compound is formulated to be administered simultaneously, sequentially or separately with an additional anti-tumour agent.

[00125e] In one aspect, there is provided use of a compound disclosed herein, for the manufacture of a medicament for the treatment of a condition which is modulated by BTK in a patient in need thereof.

[00125f] In one aspect, there is provided use of a compound disclosed herein, for the manufacture of a combination product, wherein the combination product comprises a compound of any formula disclosed herein for use simultaneously, sequentially or separately with an anti-tumor agent.

[00125g] In one aspect, there is provided use of a compound disclosed herein in a combination therapy with an anti-tumor agent.

[00126] Any of the conditions disclosed above as being treatable by BTK 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.

[00127] In embodiments, a compound of the disclosure may be for use in the treatment of: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders. The compound of the disclosure may be for use in the treatment of specific conditions selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis

osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome and lupus. The compounds may also be used for the treatment of disorders associated with renal transplant.

[00128] In an embodiment the compound of the disclosure may be for use in the treatment of specific conditions selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, lupus and arthritis.

[00129] In an embodiment there is provided a method of treatment of a condition which is modulated by Bruton's tyrosine kinase, wherein the method comprises administering a therapeutic amount of a compound of the disclosure, to a patient in need thereof.

[00130] The method of treatment may be a method of treating a condition treatable by the inhibition of Bruton's tyrosine kinase.

[00131] The disclosure also provides a method of treating a condition selected from: cancer, lymphoma, leukemia, immunological diseases autoimmune diseases and inflammatory disorders, wherein the method comprises administering a therapeutic amount of a compound of the disclosure, to a patient in need thereof. The disclosure also provides a method of treating a specific condition selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome and lupus, wherein the method comprises administering a therapeutic amount of a compound of any formula disclosed herein, to a patient in need thereof. The method may also treat disorders associated with renal transplant.

[00132] In an embodiment the method may be for treating a specific condition selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, arthritis and lupus.

[00133] In another aspect of the invention there is provided a pharmaceutical composition, wherein the pharmaceutical composition comprises a compound disclosed herein and pharmaceutically acceptable excipients.

[00134] In an embodiment the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be an anti-tumor agent described below

DETAILED DESCRIPTION

[00135] 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.

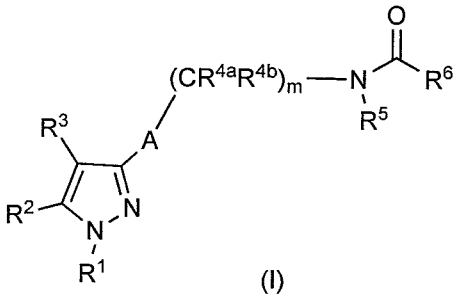
[00136] The term "halo" refers to one of the halogens, group 17 of the periodic table. In particular the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to fluorine or chlorine.

[00137] The term "alkyl" refers to a linear or branched hydrocarbon chain. For example, the terms "C_{1-8} alkyl" or "C_{1-6} alkyl" refer to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms or 1, 2, 3, 4, 5, 6, 7, or 8 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 may have two places of attachment to the remainder 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. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, =O, or C_{1-6} alkoxy.

[00138] The term "alkoxy" refers to an alkyl group which is attached to a molecule via oxygen. This includes moieties where the alkyl part may be linear or branched. For example, the term "C_{1-6} alkoxy"

CLAIMS

1. A compound according to formula (I) or pharmaceutically acceptable salts thereof:



(I)

wherein

A represents a ring selected from the group consisting of: unsubstituted or substituted: phenyl, pyridine, pyridazine, pyrimidine, or pyrazine, wherein when substituted A is substituted with from 1 to 4 R^7;

R^1 represents a group selected from: C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{2-8} alkyl ether, $-C(O)R^A$, C_{3-10} carbocyclic group, 3 to 10 membered heterocyclic group, C_{1-8} alkyl substituted with C_{3-10} carbocyclic group, and C_{1-8} alkyl substituted with 3 to 10 membered heterocyclic group, wherein each of the aforementioned groups are unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkyl ether, $-OR^A$, $-NR^AR^B$, -CN, =O, $-OC(O)R^A$, $-C(O)R^A$, $-C(O)OR^A$, $-NR^AC(O)R^B$, $-C(O)NR^AR^B$, $-NR^AS(O)_2R^B$, $-S(O)_2NR^AR^B$, benzoyl, a 5 or 6 membered heterocycloaryl, a 3 to 6 membered heterocycloalkyl ring, C_{1-4} alkyl substituted with $-OR^A$ and C_{1-4} alkoxy substituted with $-OR^A$, or a single atom of R^1 is substituted twice so as to form a 3 to 6 membered heterocycloalkyl or cycloalkyl ring;

R^2 represents a group selected from the group consisting of: -OH, halo, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 3 to 10 membered heterocyclic group, alkyl substituted with $-OR^C$, C_{1-8} alkyl substituted with C_{3-10} carbocyclic group, alkyl substituted with 3 to 10 membered heterocyclic group, and $-NR^CR^D$;

R^3 represents $-C(O)NR^ER^F$, C_{1-6} alkyl substituted with $-OR^G$, or C_{1-6} haloalkyl;

R^{4a} and R^{4b} are independently at each occurrence selected from the group consisting of: H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{1-6} alkyl substituted with $-OR^H$;

R^5 is H or C_{1-4} alkyl;

R^6 is a group selected from a substituted or unsubstituted: phenyl or a 5 or 6 membered heteroaryl ring, wherein, when substituted, R^6 contains from 1 to 5 substituents independently selected at each occurrence from: halo, $-OR^I$, $-NR^IR^J$, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with $-OR^I$;

R^7 is selected from the group consisting of: H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} alkyl substituted with $-OR^H$;

m is 1 or 2;

R^A and R^B are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, phenyl, benzyl, or C_{1-4} alkyl substituted with $-OR^H$;

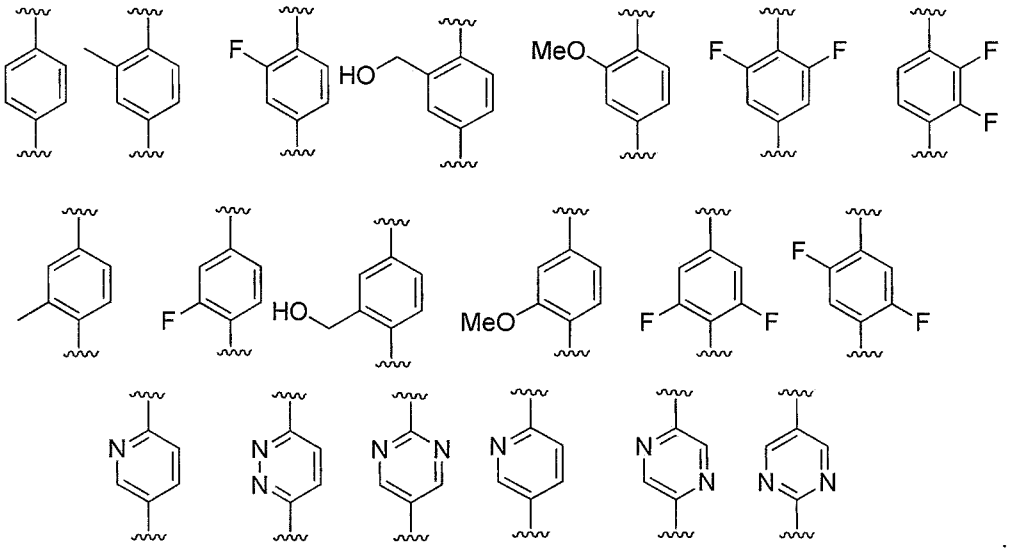
R^C, R^D, R^E and R^F are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, unsubstituted C_{3-10} carbocyclic group, C_{1-4} alkyl substituted with unsubstituted C_{3-10} carbocyclic group, C_{1-4} alkyl substituted with C_{3-10} carbocyclic group substituted with 1 or 2 R^H or $-OR^H$, and 3 to 10 membered heterocyclic group;

R^G, R^I, and R^J are independently at each occurrence selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy and C_{1-4} alkyl substituted with $-OR^H$; and

R^H is selected from H or C_{1-4} alkyl.

2. The compound of claim 1, wherein A is unsubstituted phenyl, unsubstituted pyridine, phenyl substituted by from 1 to 4 R^7, or pyridine substituted by from 1 to 4 R^7.

3. The compound of claim 1, wherein A is selected from:



4. The compound of any preceding claim, wherein R^6 is a group selected from a substituted: phenyl or 6 membered heteroaryl ring, optionally wherein R^6 is substituted with 1 or 2 groups independently selected from: methyl, fluoro, or methoxy.

5. The compound of any preceding claim, wherein R^6 is 2-methoxyphen-1-yl or 5-fluoro-2-methoxyphen-1-yl.

6. The compound of any preceding claim, wherein R^5 is H.

7. The compound of any preceding claim, wherein R^{4a} and R^{4b} are independently selected at each occurrence from the group consisting of: H, methyl, ethyl, cyclopropyl, or $-CH_2OH$.

8. The compound of any preceding claim, wherein R^{4a} and R^{4b} are H.

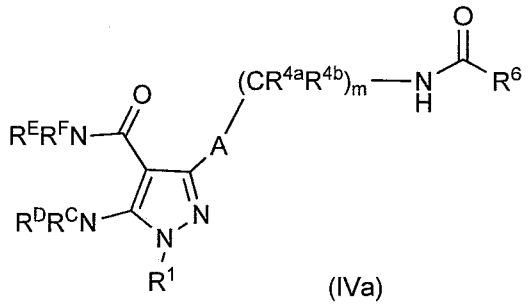
9. The compound of any preceding claim, wherein m is 1.

10. The compound of claim 1, wherein m is 1, R^{4a} and R^{4b} are H, R^5 is H, R^6 is methoxyphenyl or methoxyfluorophenyl, and A is unsubstituted phenyl or phenyl substituted by one or two R^7, optionally wherein R^7 is selected from: fluoro, methyl, methoxy, and $-CH_2OH$.

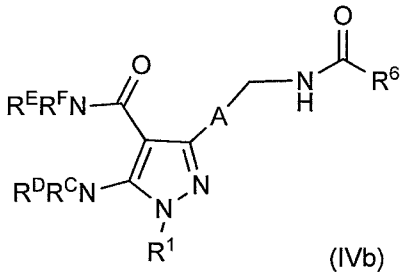
11. The compound of any preceding claim, wherein R^2 represents a group selected from: halo, C_{1-8} alkyl, C_{1-8} haloalkyl, or $-NR^CR^D$, wherein R^C and R^D are, at each occurrence, independently selected from the group consisting of: H or C_{1-4} alkyl.

12. The compound of any preceding claim, wherein R^3 represents $-C(O)NH_2$, $-C(O)NHMe$, $-CH_2OH$, $CH(OH)CH_3$, $-CF_3$, or $-CHF_2$.

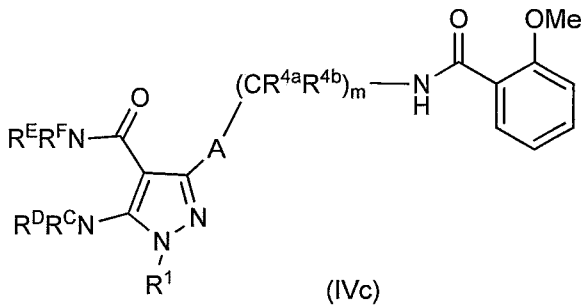
13. The compound of claim 1, wherein the compound is a compound according to formulae (IVa), (IVb), (IVc), (IVd), (IVe) or (IVf) or pharmaceutically acceptable salts thereof:



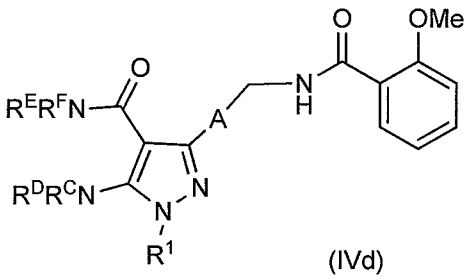
(IVa)



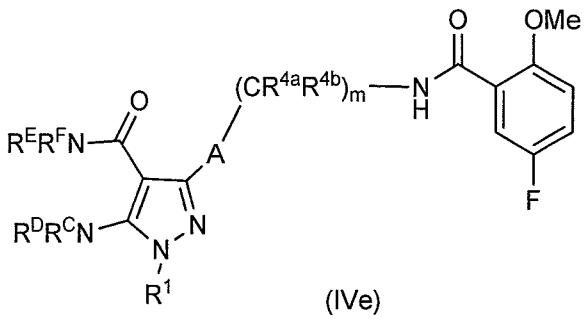
(IVb)



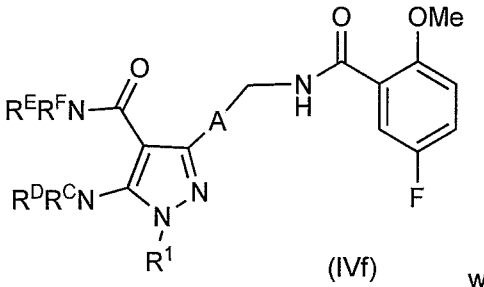
(IVc)



(IVd)



(IVe)



(IVf)

wherein

R^C and R^D are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, unsubstituted C_{3-10} carbocyclic group (optionally C_{3-6} carbocyclic group), 3 to 10 membered heterocyclic group (optionally 3 to 6 membered heterocyclic group); and

R^E and R^F are, at each occurrence, independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, unsubstituted C_{3-10} carbocyclic group (optionally C_{3-6} carbocyclic group), 3 to 10 membered heterocyclic group (optionally 3 to 6 membered heterocyclic group).

14. The compound of claim 13, wherein R^C, R^D, R^E and R^F are H.

15. The compound of any preceding claim, wherein R^1 represents a group selected from: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkyl ether, $-C(O)R^A$, C_{3-10} cycloalkyl (preferably C_{3-6} cycloalkyl), C_{6-10} aryl (preferably phenyl), 3 to 10 membered heterocycloalkyl (optionally 3 to 6 membered), 3 to 10 membered heteroaryl (optionally 3 to 6 membered), C_{1-6} alkyl substituted with C_{3-10} cycloalkyl (preferably C_{3-6} cycloalkyl), C_{1-6}

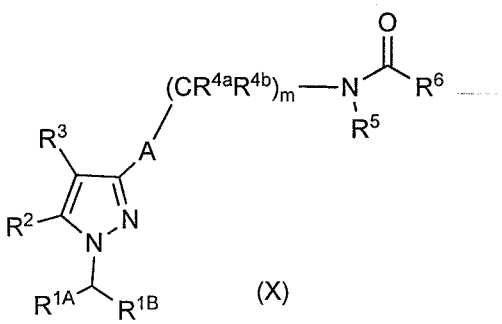
alkyl substituted with C_{6-10} aryl (preferably phenyl), C_{1-6} alkyl substituted with 3 to 10 membered heterocycloalkyl (optionally 3 to 6 membered), and C_{1-6} alkyl substituted with 3 to 10 membered heteroaryl (optionally 3 to 6 membered), wherein each of the aforementioned groups are unsubstituted or substituted with 1 to 5 substituents selected from: halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{2-4} alkyl ether, $-OR^A$, -CN, =O, $-C(O)OR^A$, $-C(O)NR^AR^B$, 5 or 6 membered heteroaryl, a 3 to 6 membered heterocycloalkyl ring, C_{1-4} alkyl substituted with $-OR^A$, C_{1-4} alkoxy substituted with $-OR^A$ or a single atom of R^1 is substituted twice so as to form a 3 to 6 membered heterocycloalkyl or cycloalkyl ring.

16. The compound of any preceding claim, wherein R^A is selected from: H, C_{1-4} alkyl, C_{1-4} haloalkyl, benzyl or C_{1-4} alkyl substituted with $-OR^H$.

17. The compound of any of claims 1 to 14, wherein R^1 is selected from substituted or unsubstituted: methyl, ethyl, iso-propyl, tert-hexyl, tert-butyl, trifluoroethyl, propyl ether, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, indanyl, bicyclo[3.1.0]hexyl, oxetane, tetrahydropyranyl, phenyl, pyridyl, C_{1-8} alkyl (preferably methyl or ethyl) substituted with oxetane, C_{1-8} alkyl (preferably methyl or ethyl) substituted with morpholine, C_{1-8} alkyl (preferably methyl or ethyl) substituted with tetrazole, C_{1-8} alkyl (preferably methyl or ethyl) substituted with piperidine, and C_{1-8} alkyl (preferably methyl or ethyl) substituted with cyclohexyl,

wherein R^1 is substituted with1 to 5 substituents selected from: -OH, =O, -OMe, -CN, methyl, CF_3, Cl, F, -OBn, or $-CO_2Et$.

18. The compound of claim 1, wherein the compound is a compound of formula (X) or a pharmaceutically acceptable salt thereof:



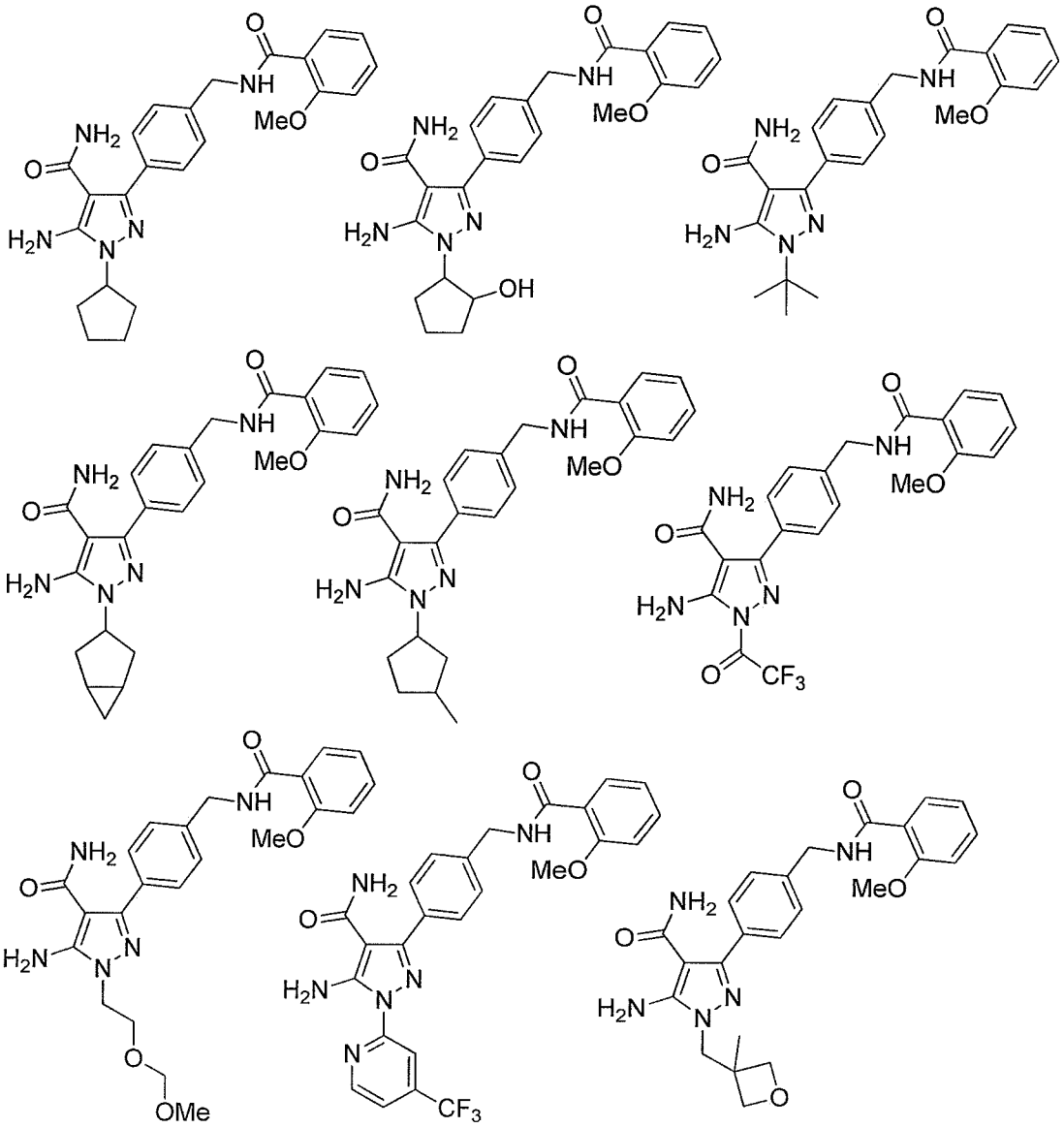
(X)

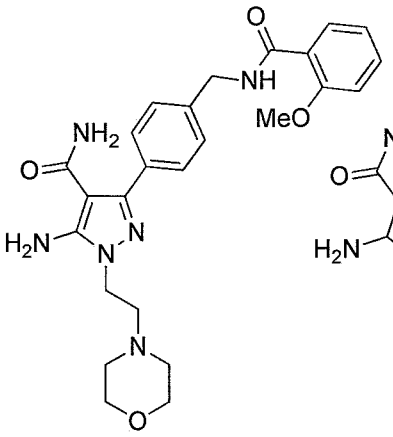
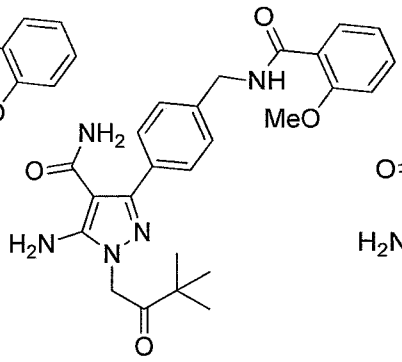
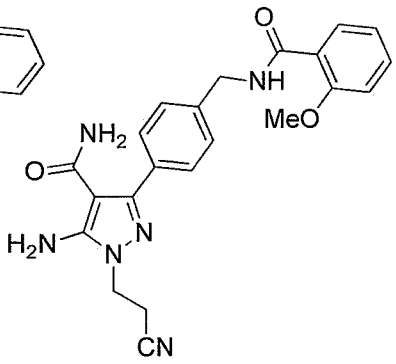
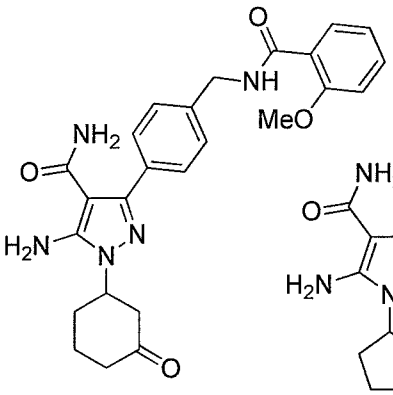
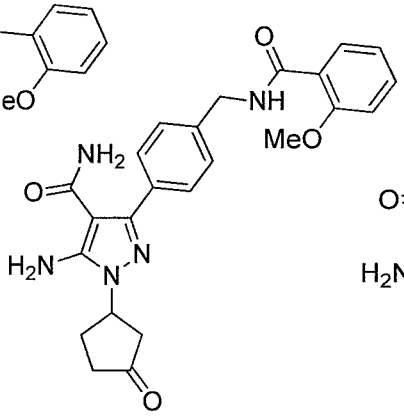
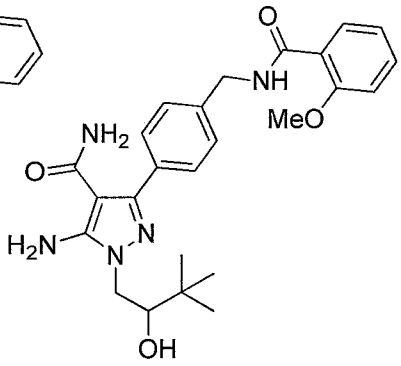
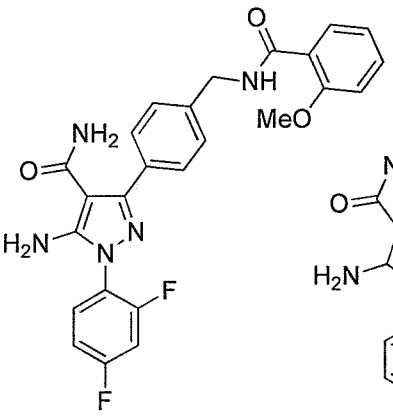
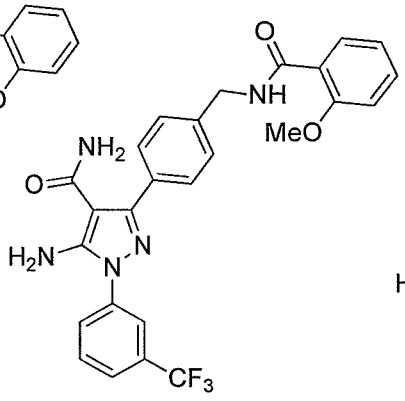
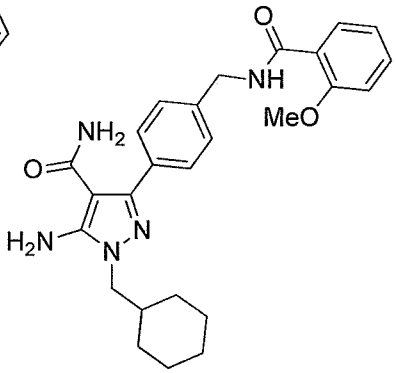
wherein R^{1A} is selected from C_{1-2} alkyl or C_{1-2} haloalkyl and R^{1B} is selected from unsubstituted C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyl substituted with OH, C_{1-4} alkyl substituted with OMe, 5 or 6 membered heteroaryl, 3 to 6 membered heterocycloalkyl ring, phenyl, or C_{3-10} carbocyclic group; provided that when R^{1A} is C_{1-2} alkyl then R^{1B} is not unsubstituted C_{1-4} alkyl.

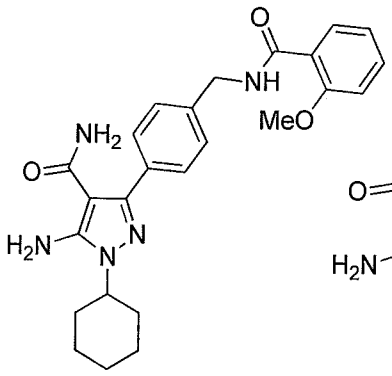
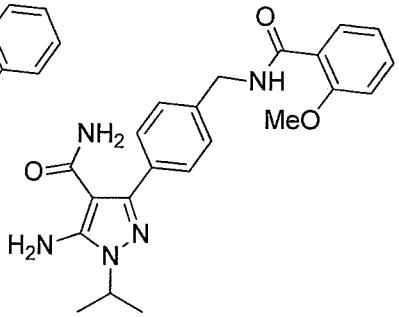
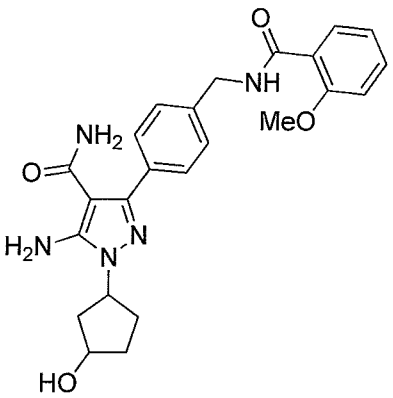
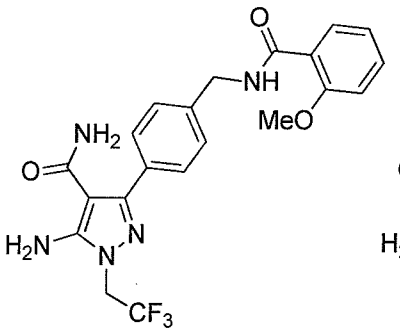
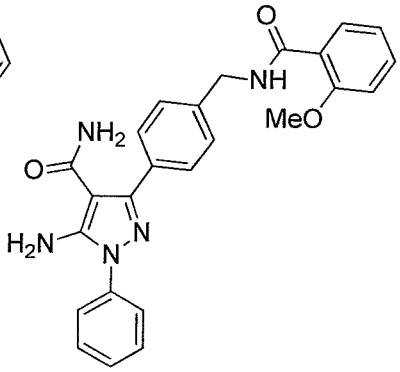
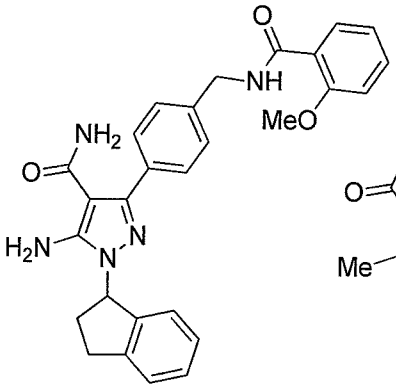
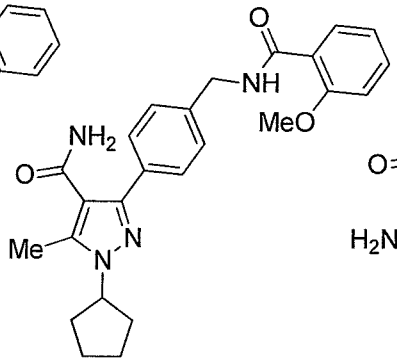
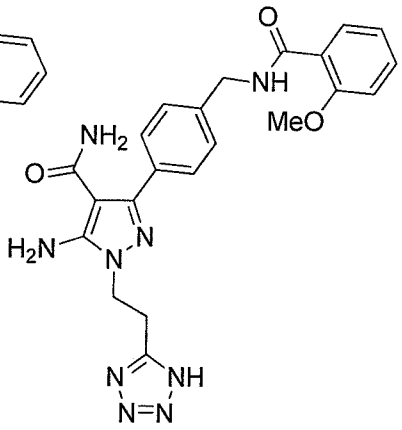
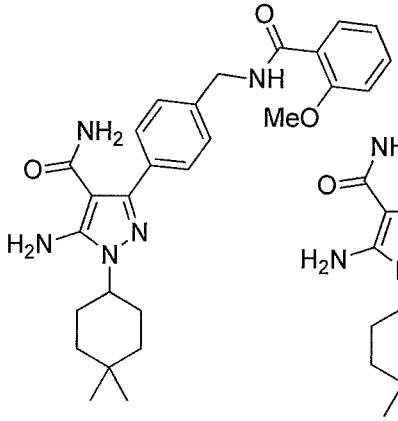
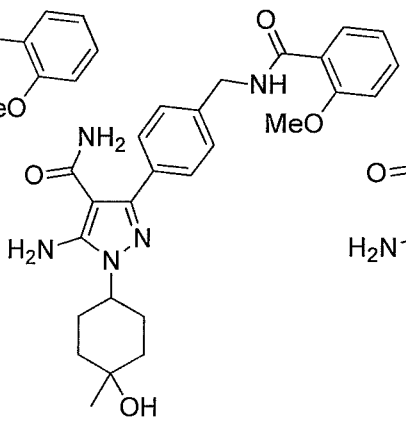
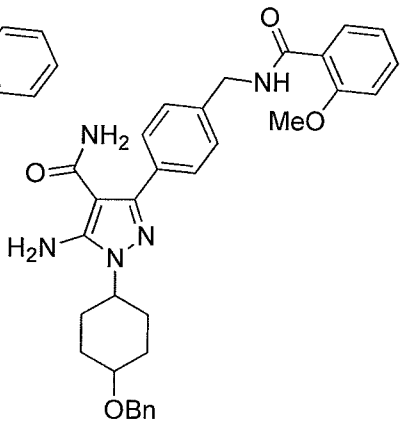
19. The compound of claim 18, wherein R^{1A} is selected from methyl, difluoromethyl or trifluoromethyl, and R^{1B} is selected from methyl, ethyl, propyl, trifluoromethyl, difluormethyl, trifluorethyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OMe$, pyrrolidinyl, piperidinyl, tetrhydrofuranyl, tetrahydropyranyl, pyridinyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; provided that when R^{1A} is not methyl then R^{1B} is not methyl, ethyl, or propyl.

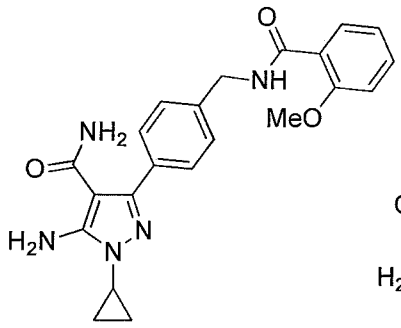
20. The compound of claim 18 or claim 19, wherein R^{1A} is trifluoromethyl.

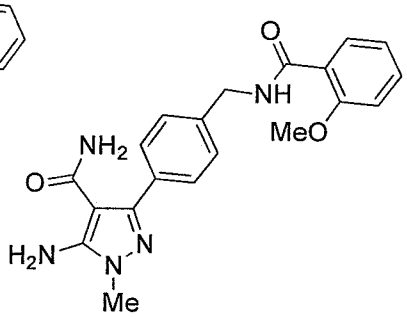
21. The compound of claim 1, wherein the compound is selected from the group consisting of:

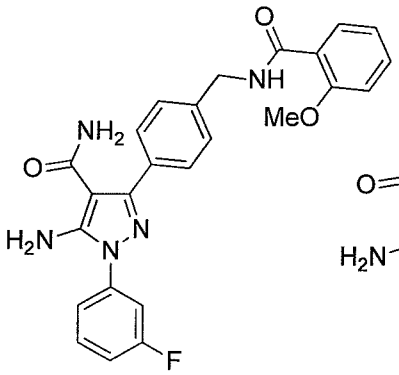


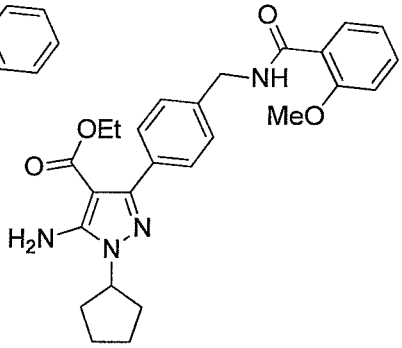










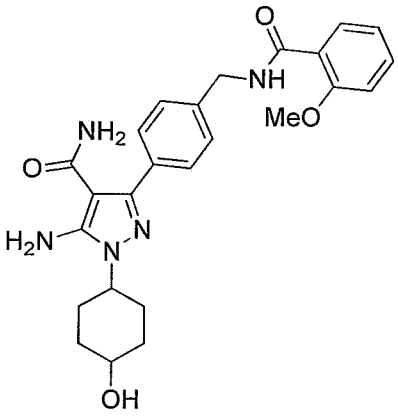












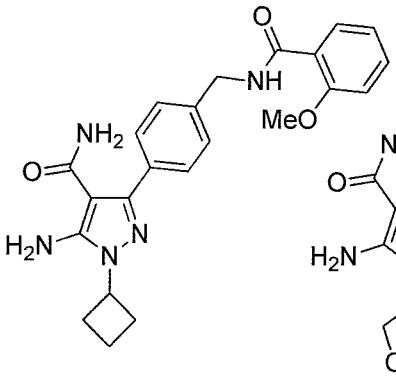


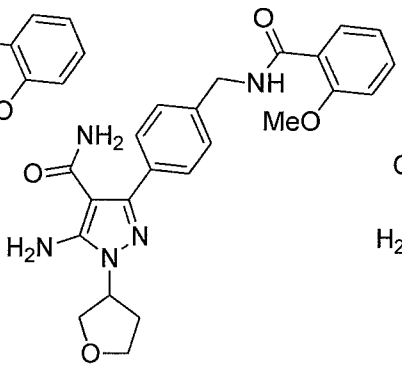


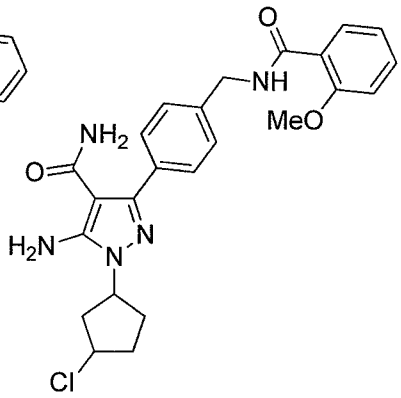


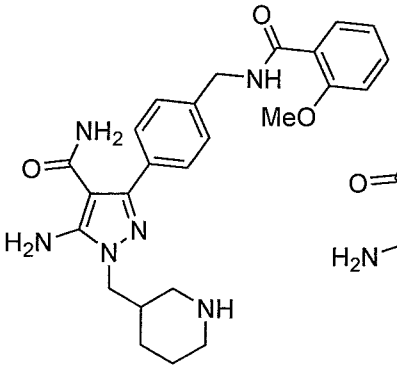


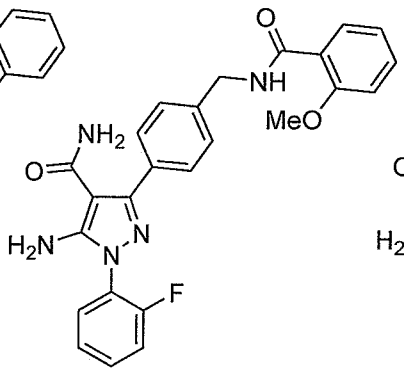


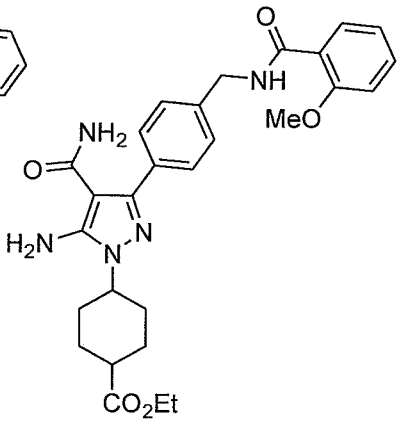


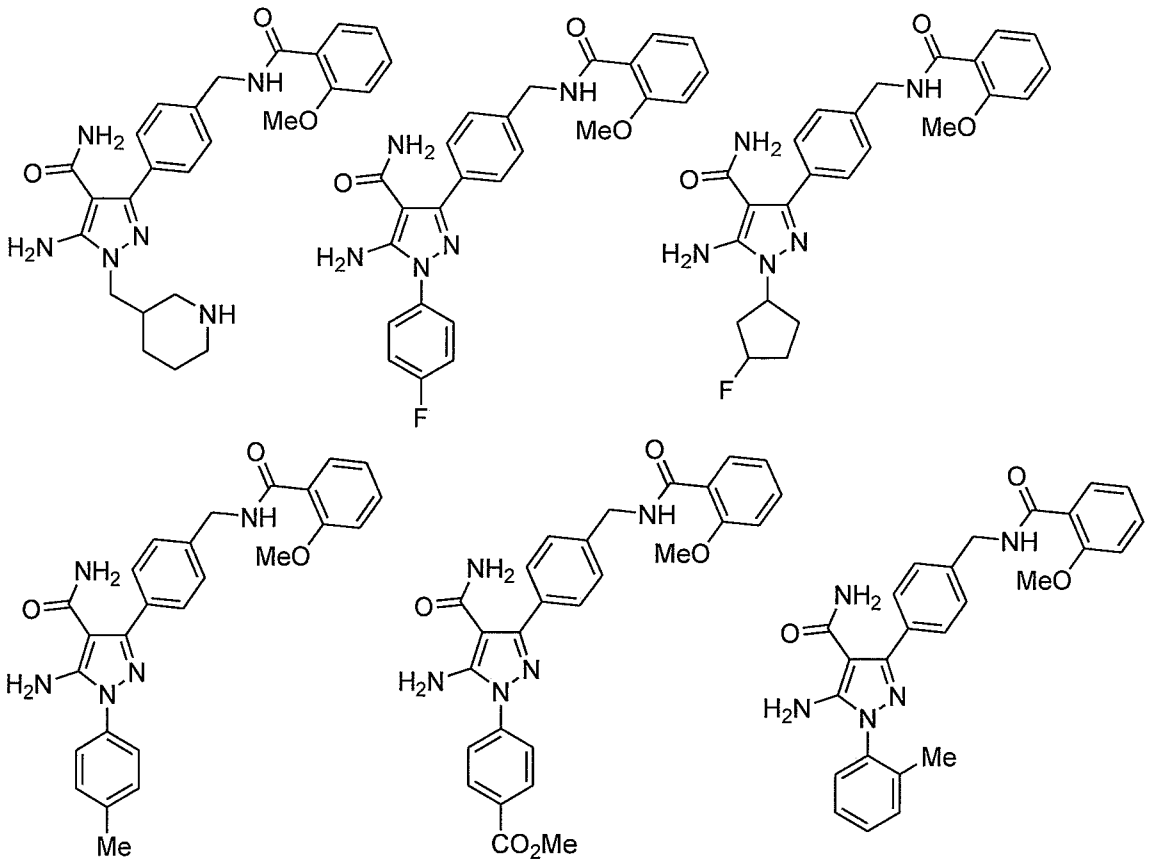


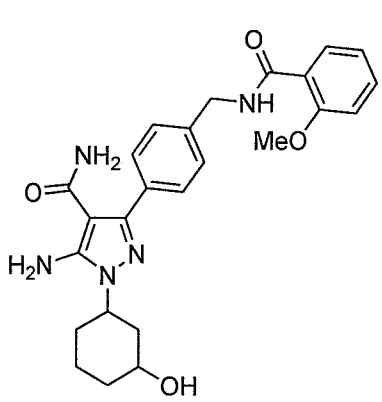


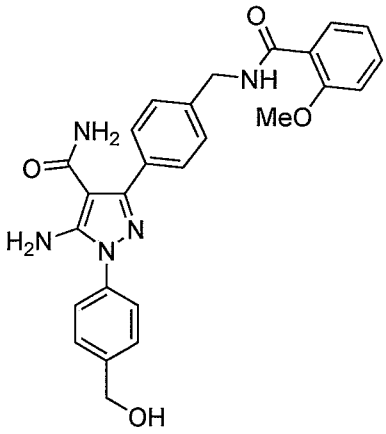


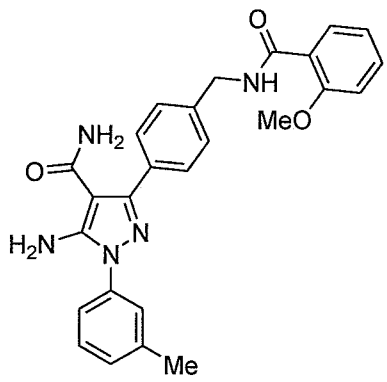


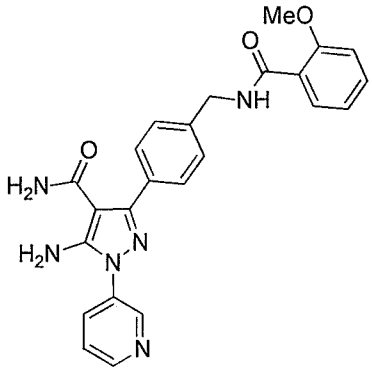


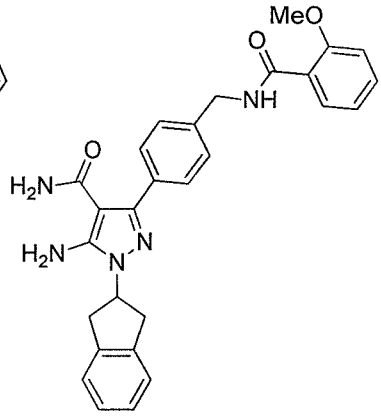


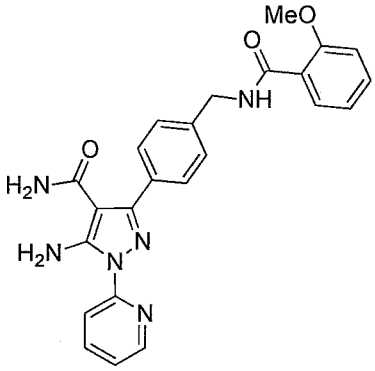


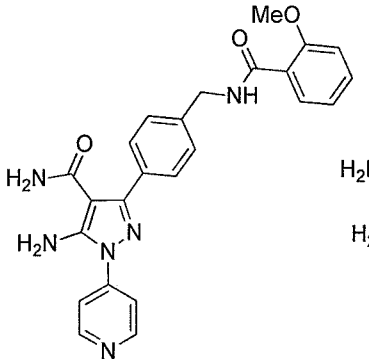


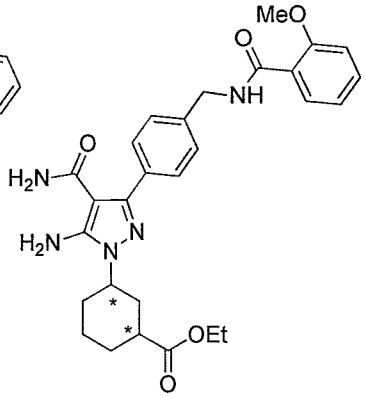


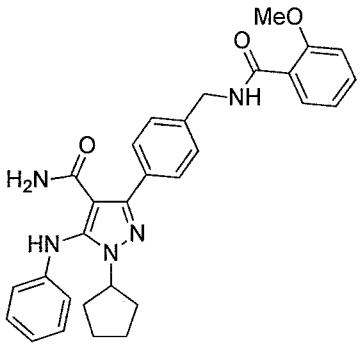


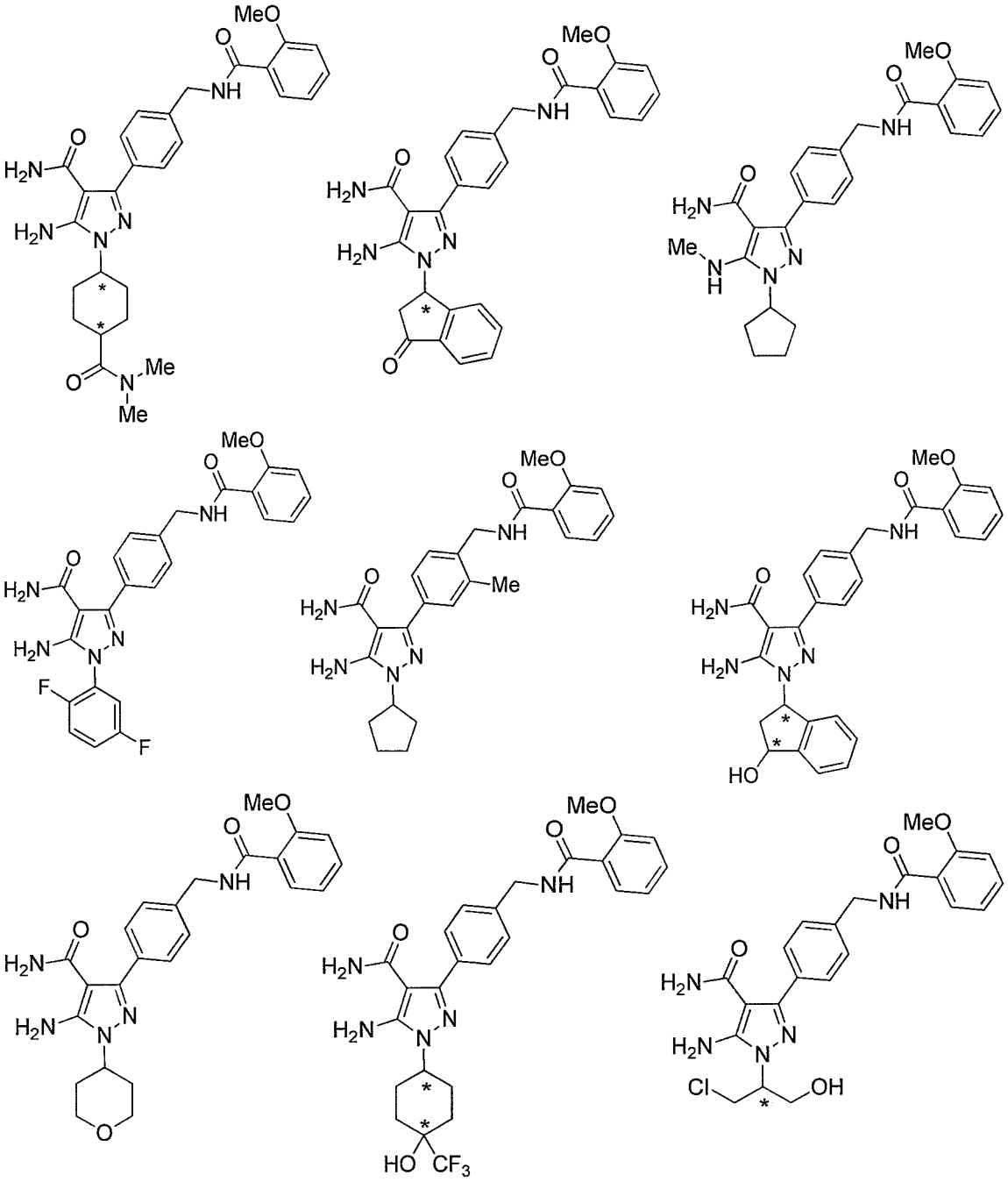


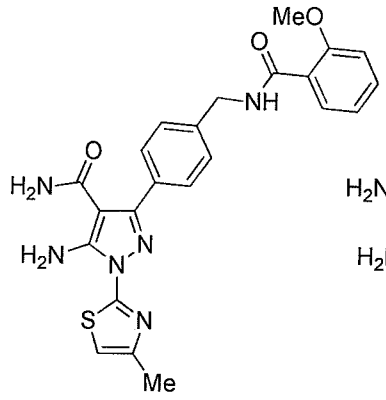
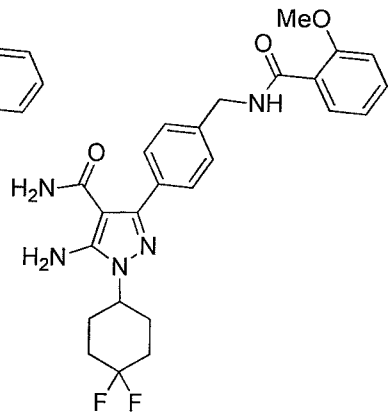
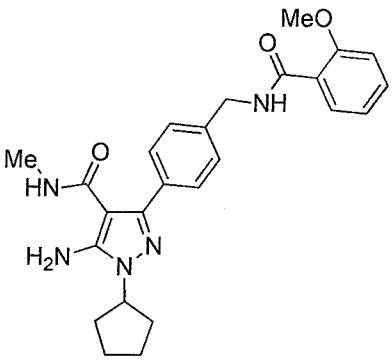
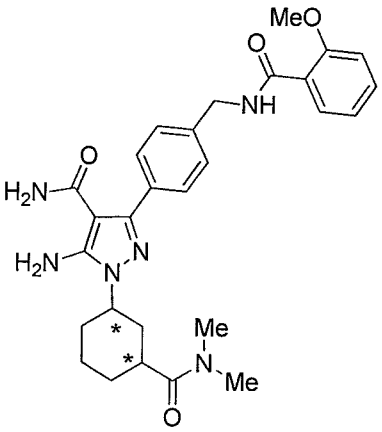
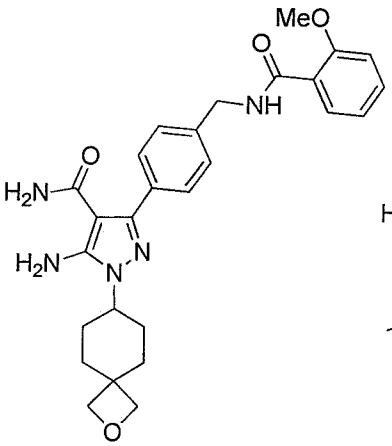
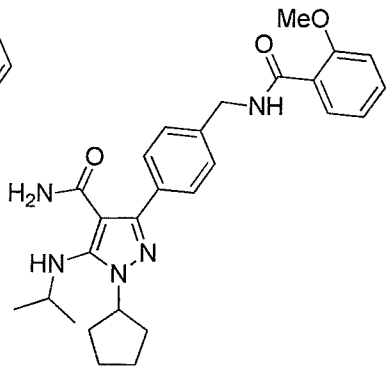
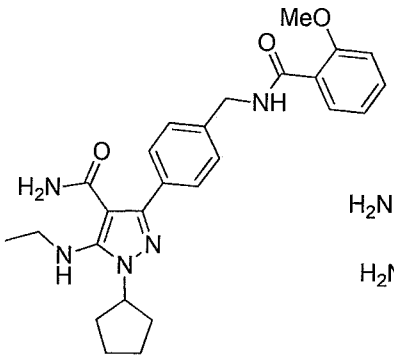
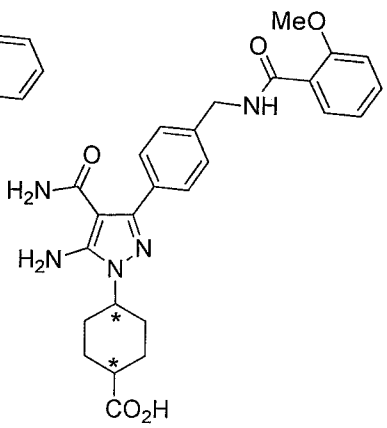
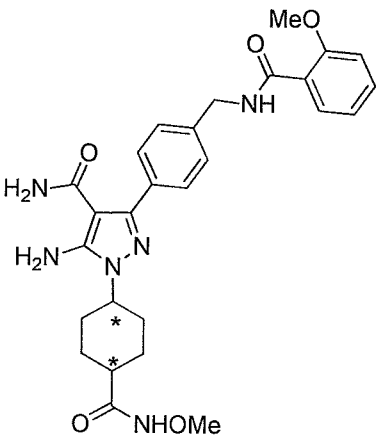
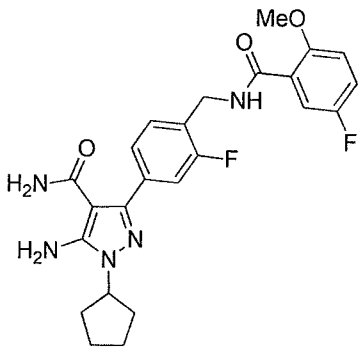
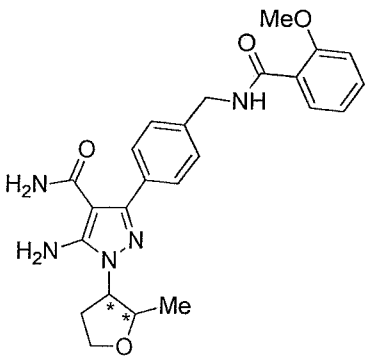
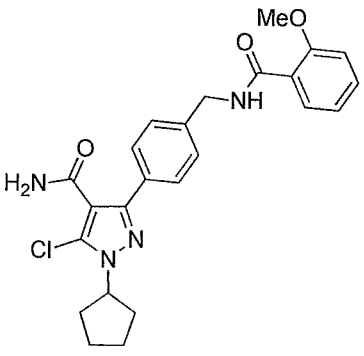


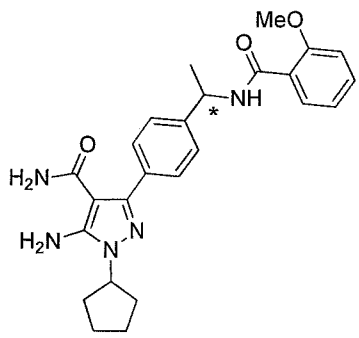
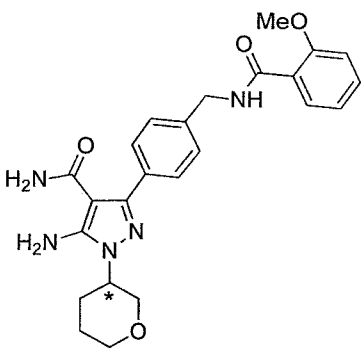
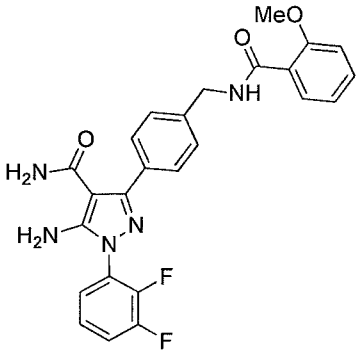
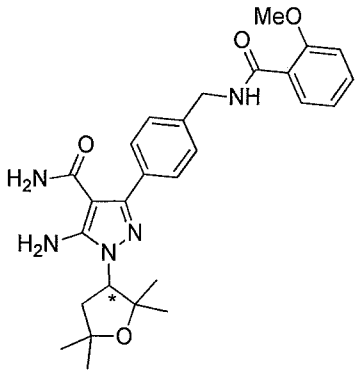
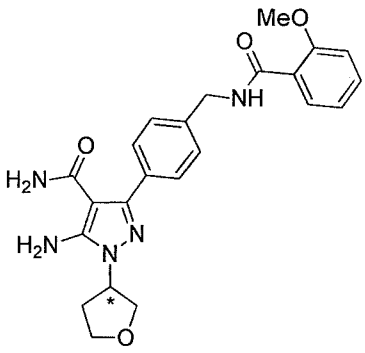
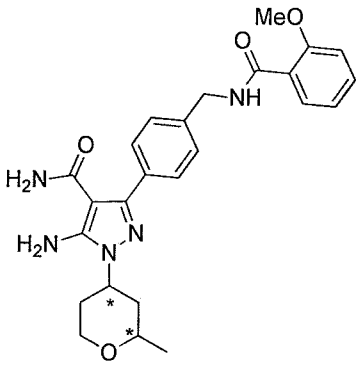
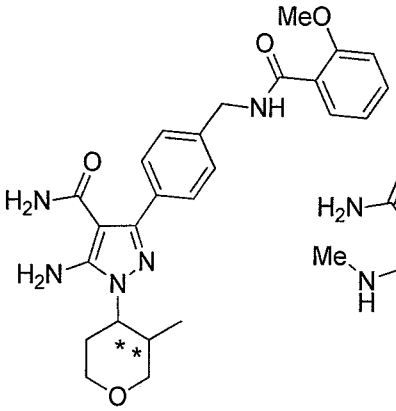
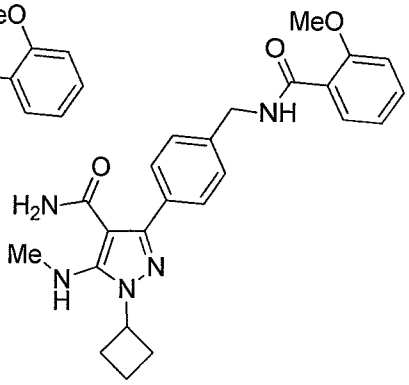
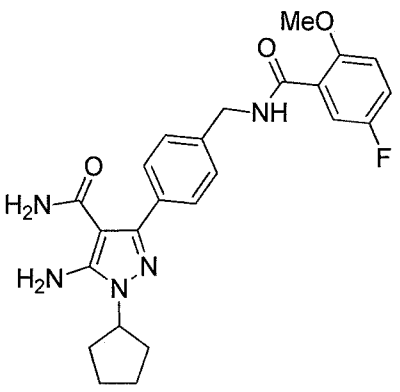
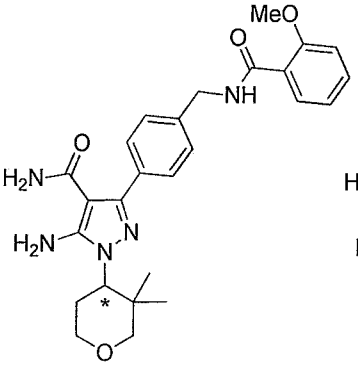
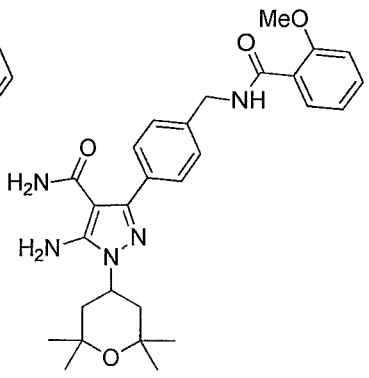
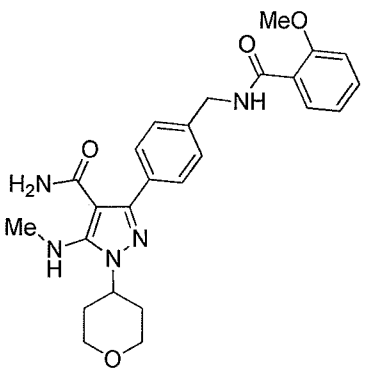


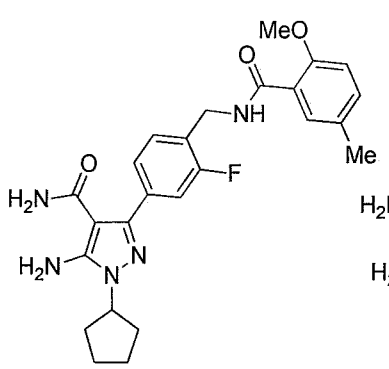
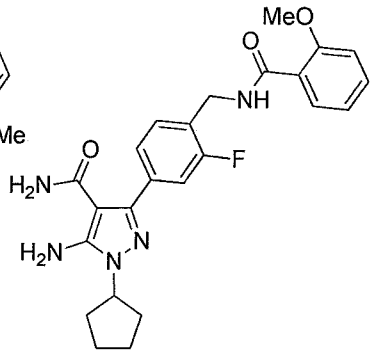
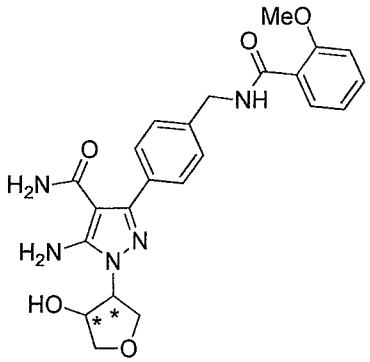
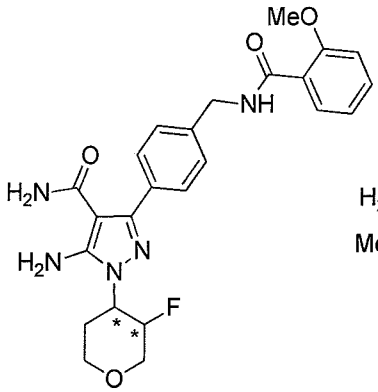
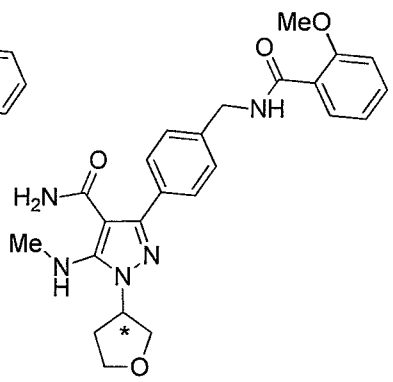
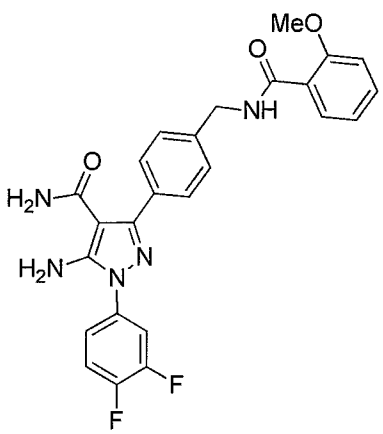
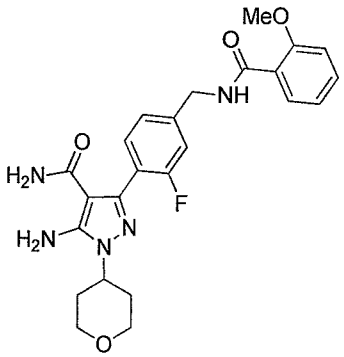
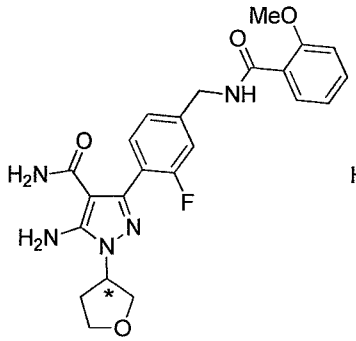
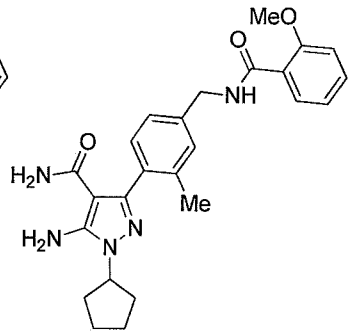
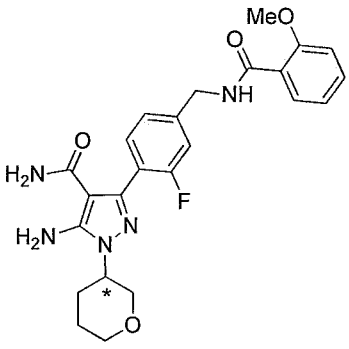
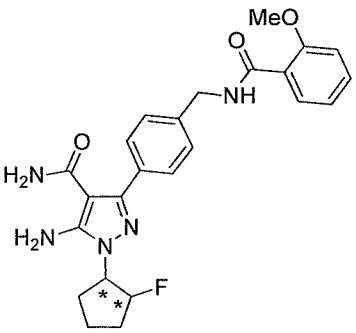
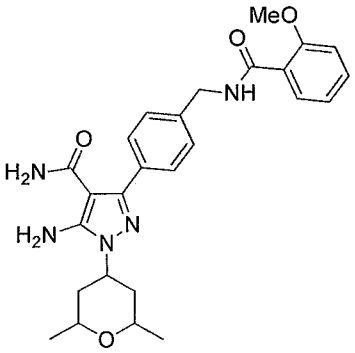


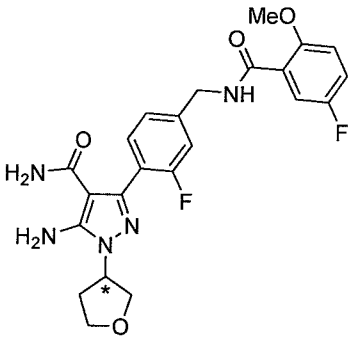
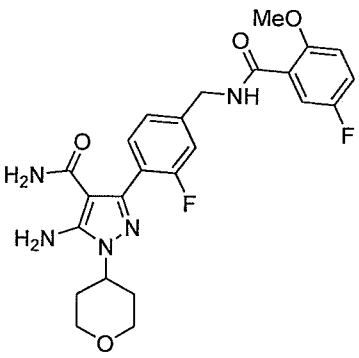
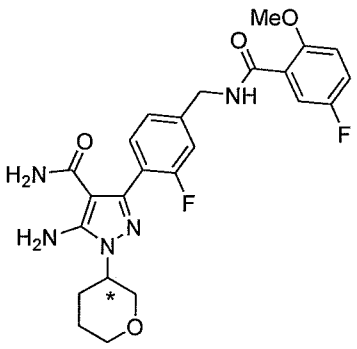
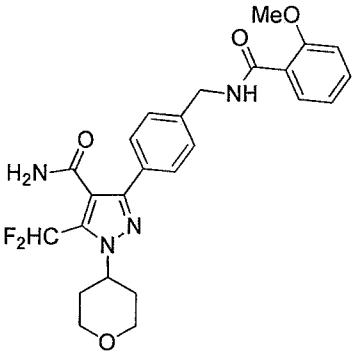
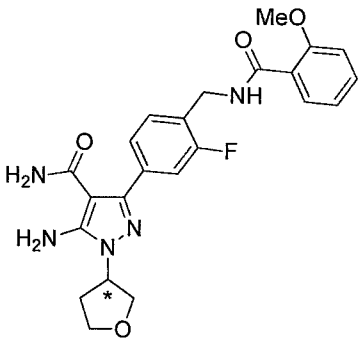
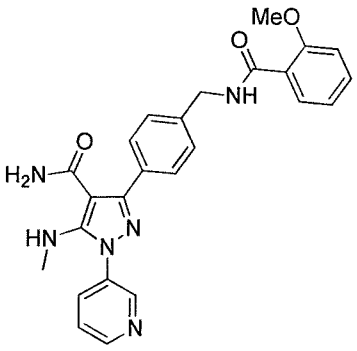
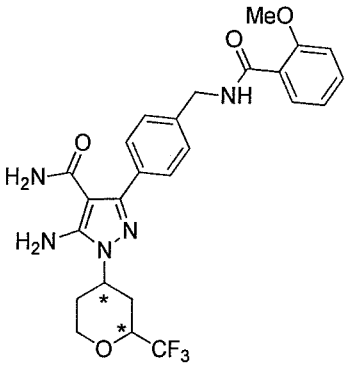
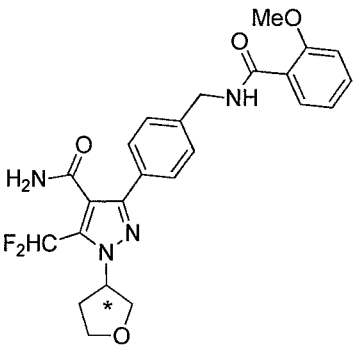
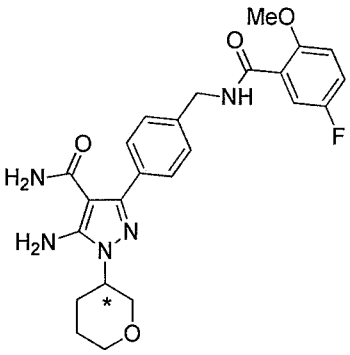
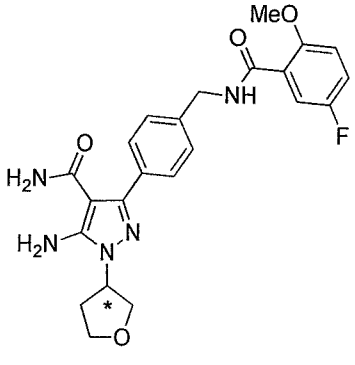
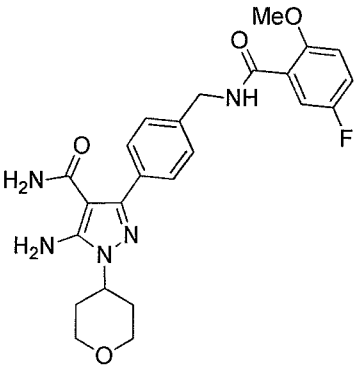
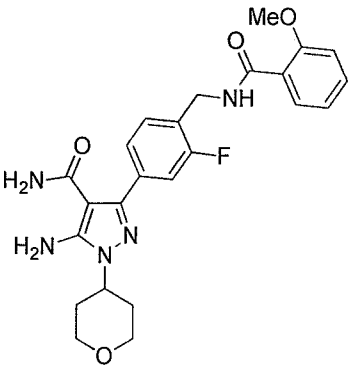


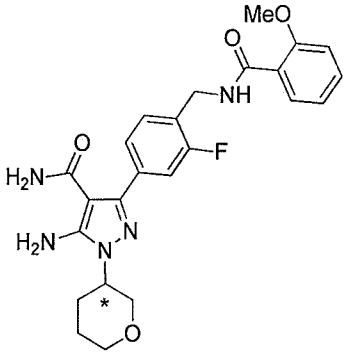
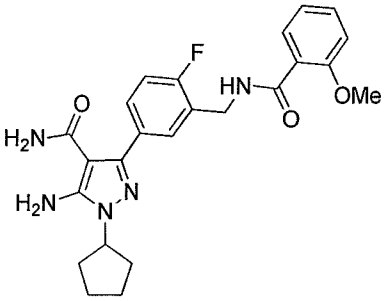
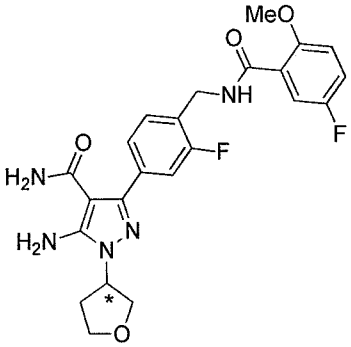
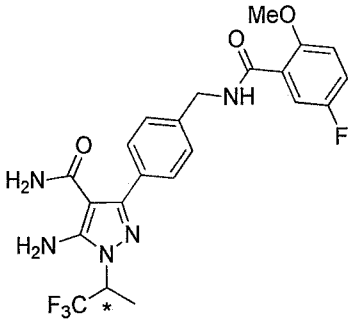
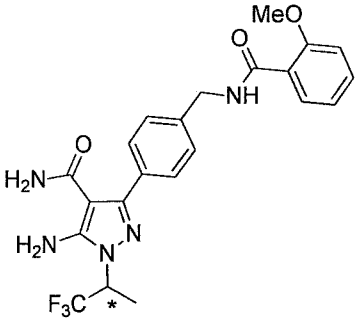
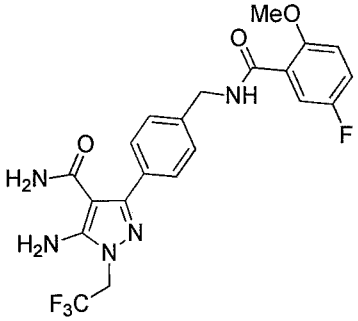
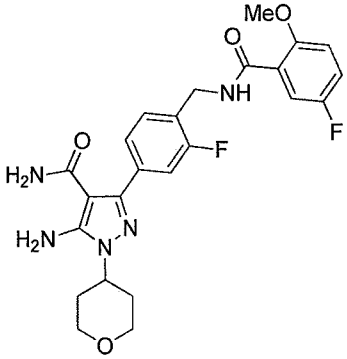
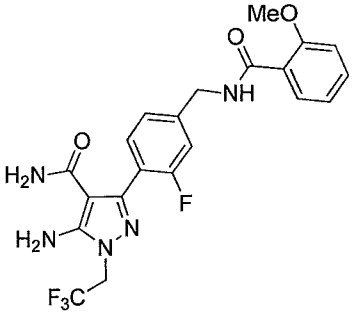
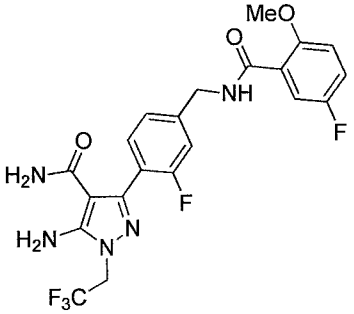
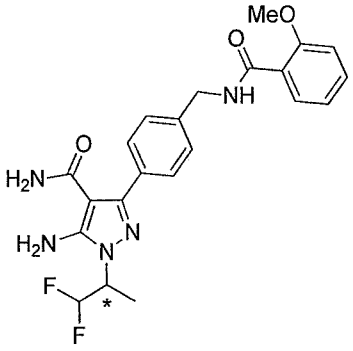
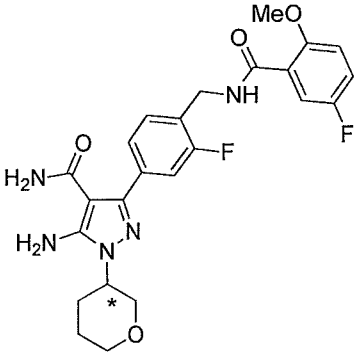
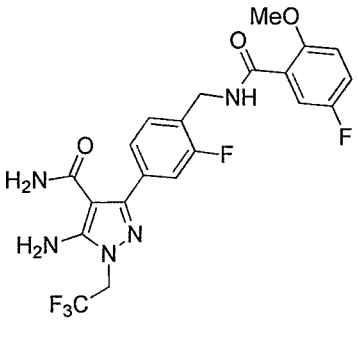


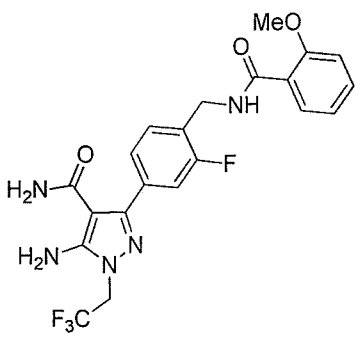













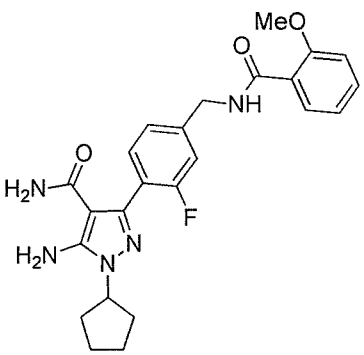













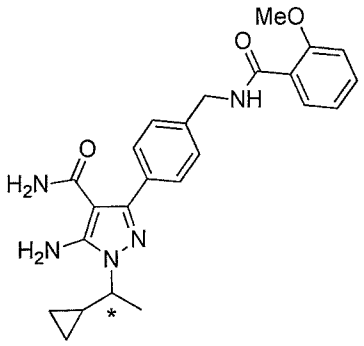













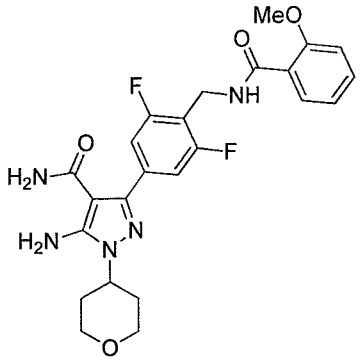













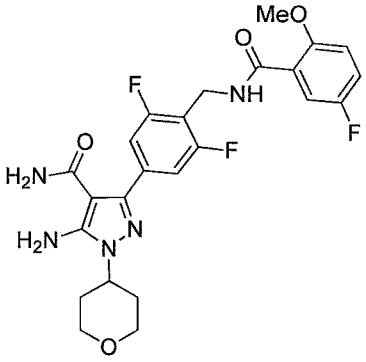













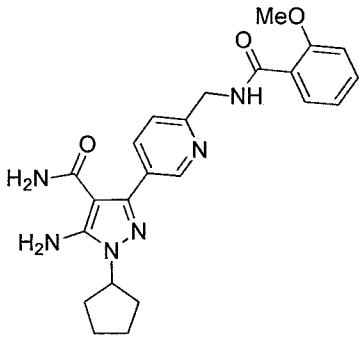


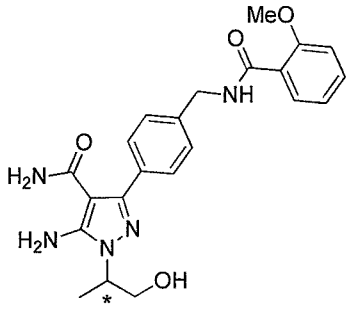


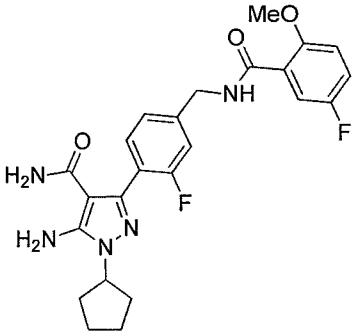


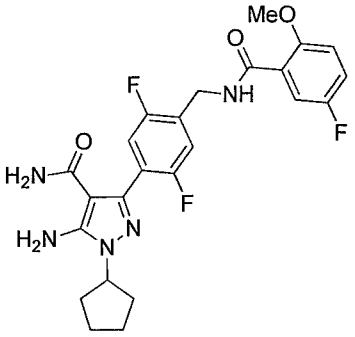


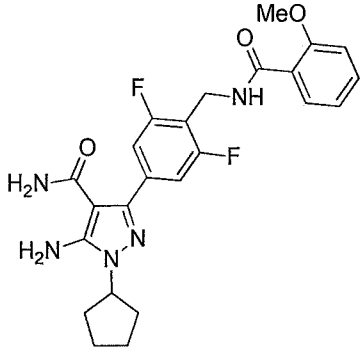


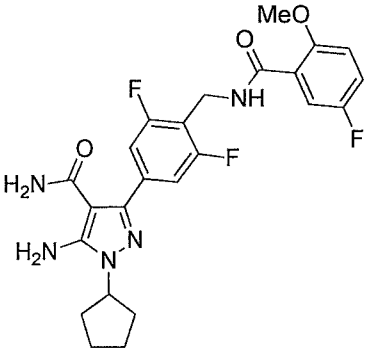


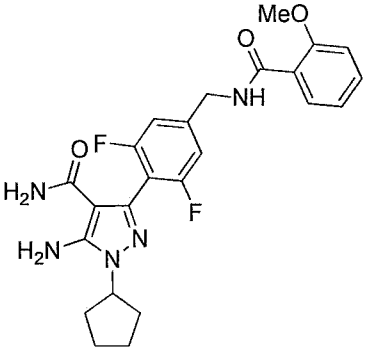


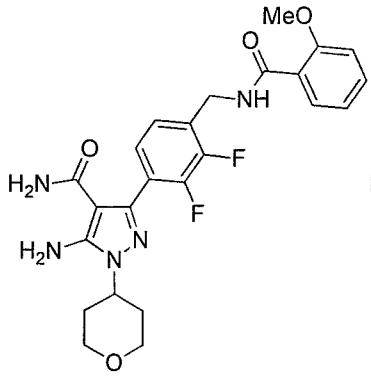
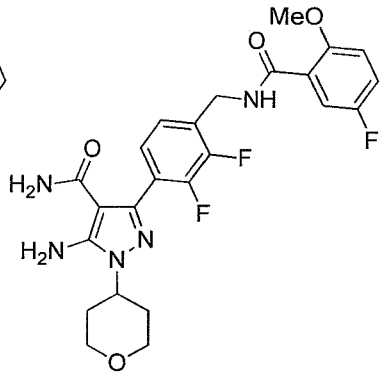
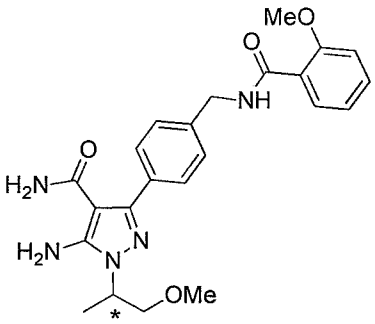
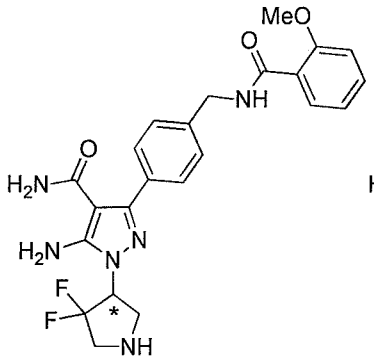
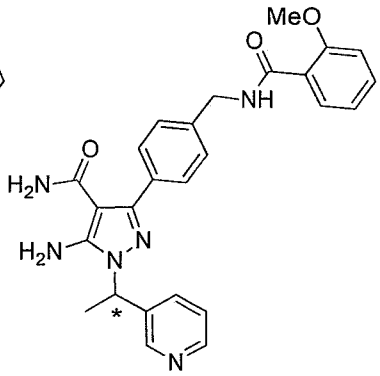
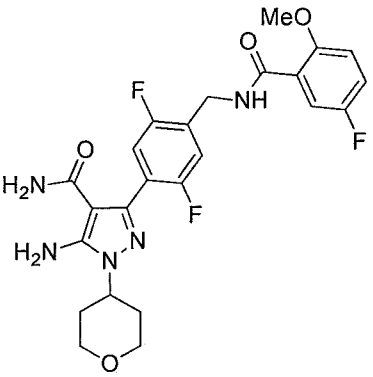
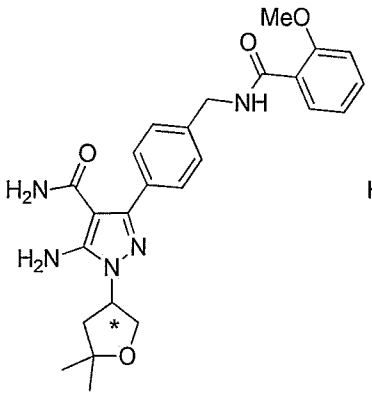
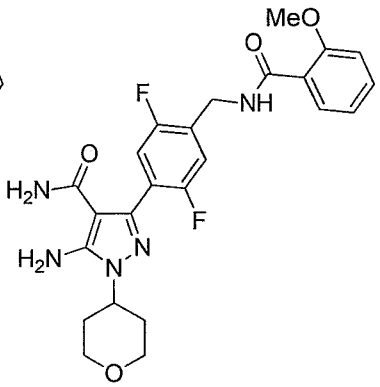
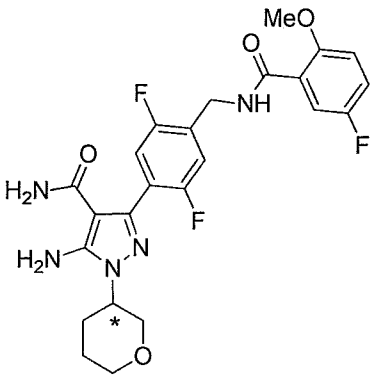
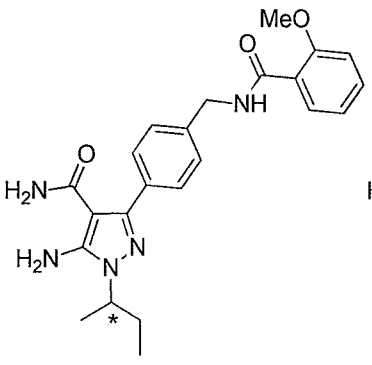
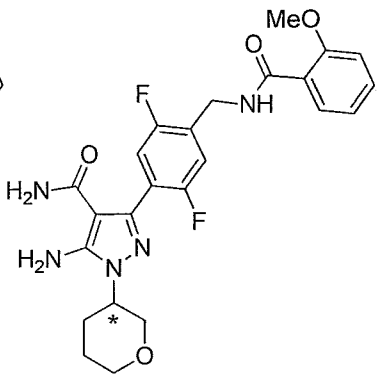
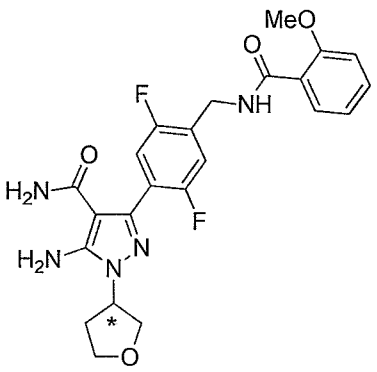


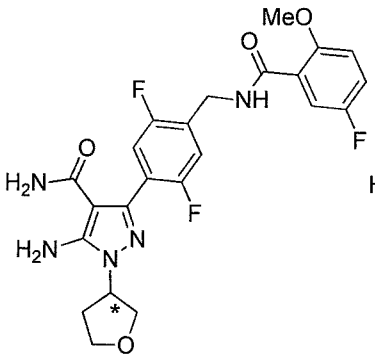
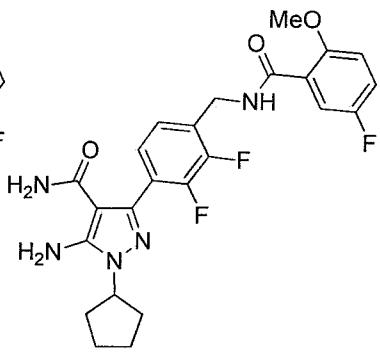
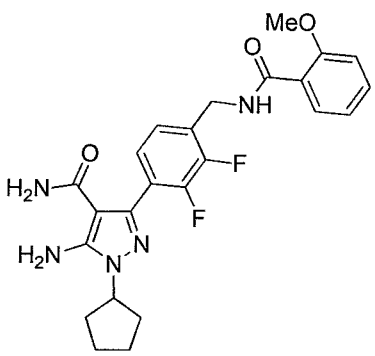
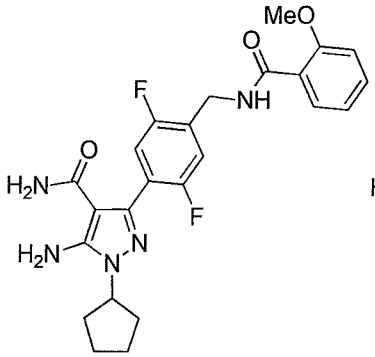
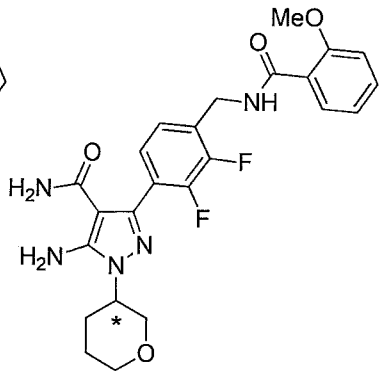
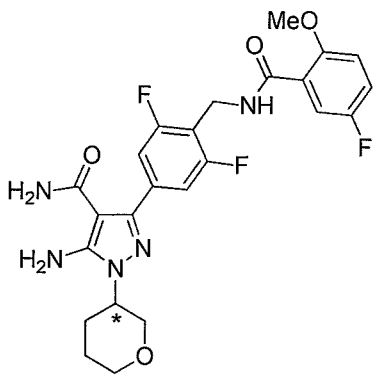
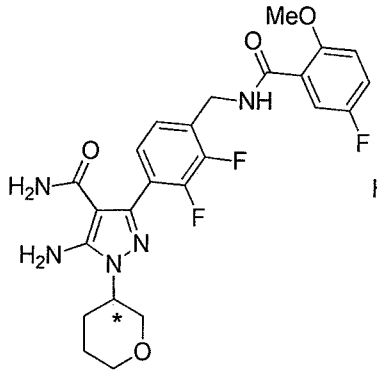
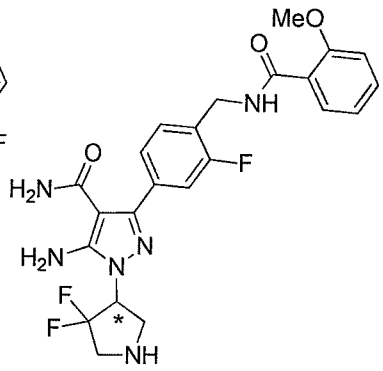
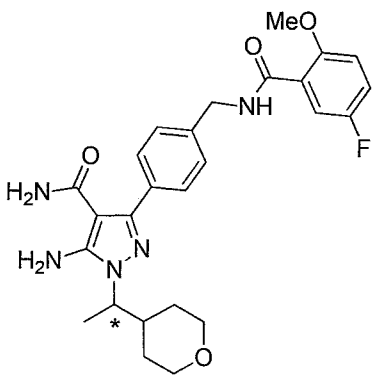
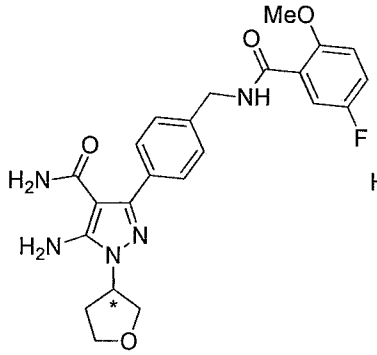
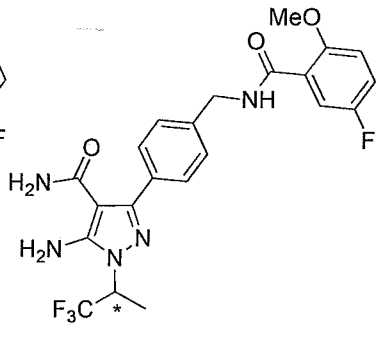
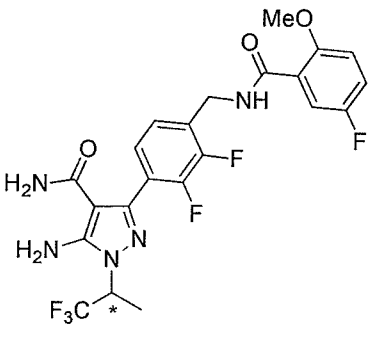


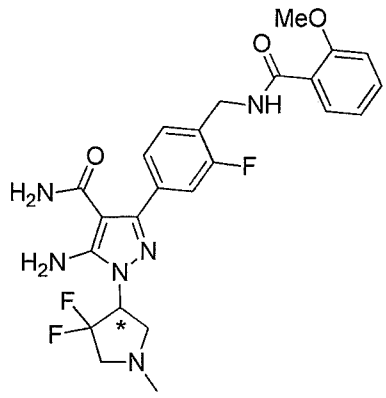
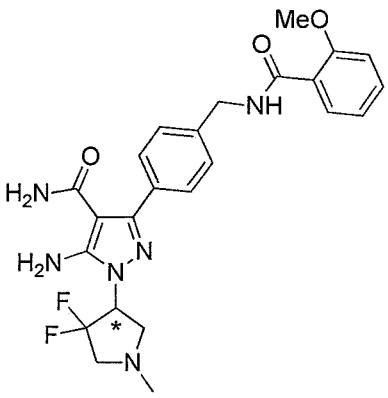
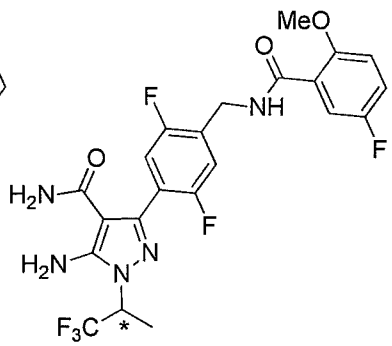
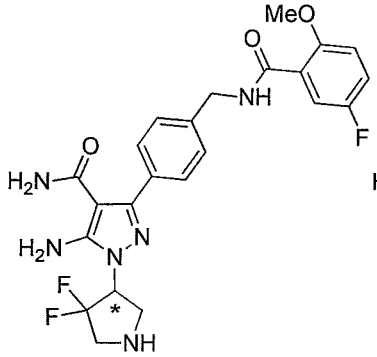
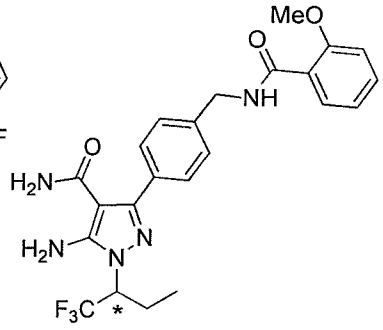
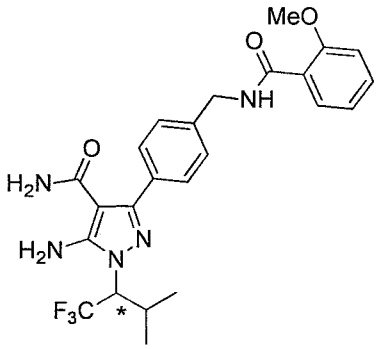
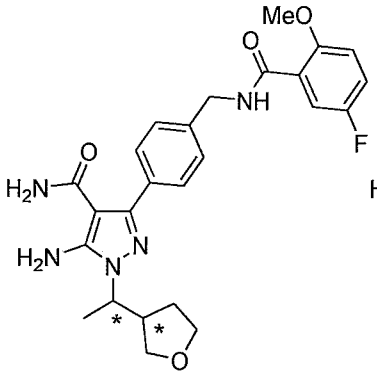
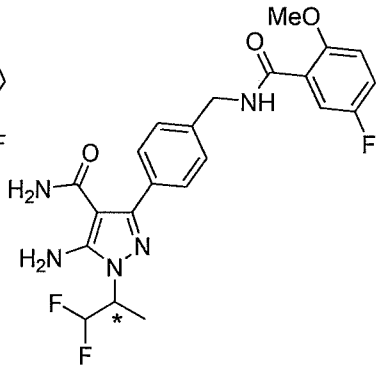
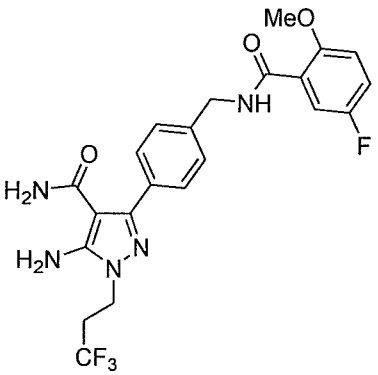
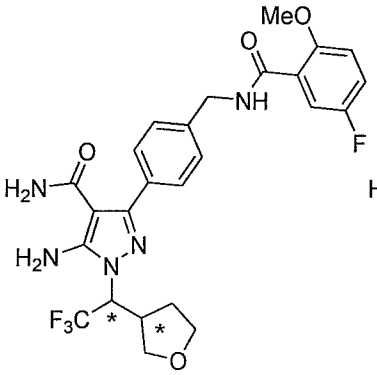
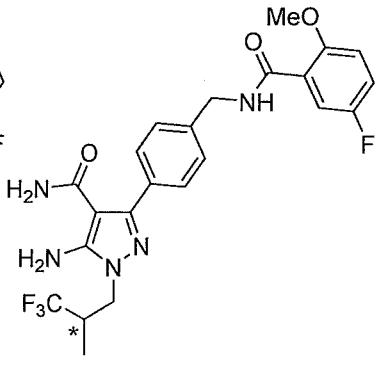
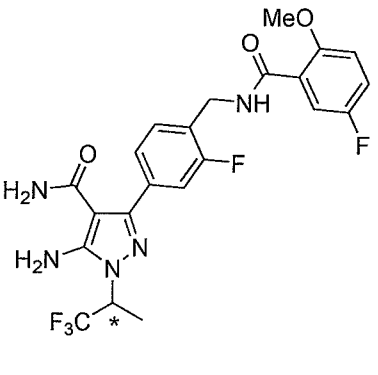


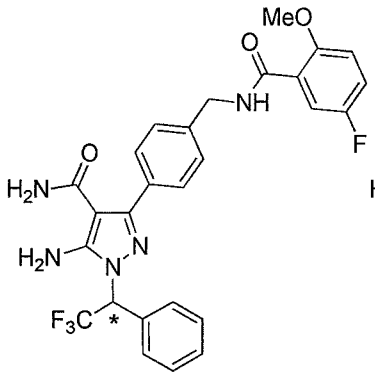
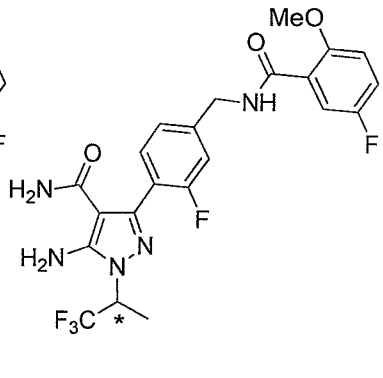
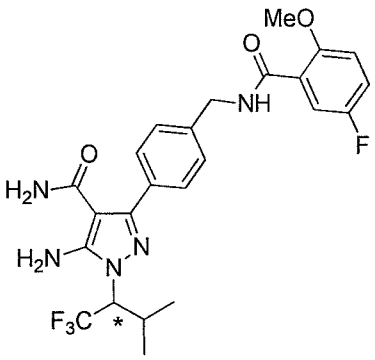
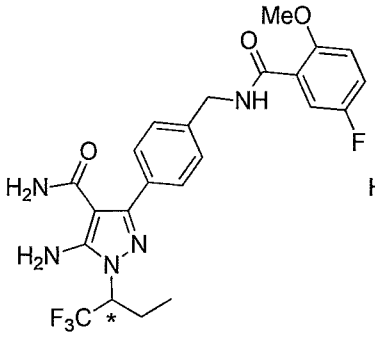
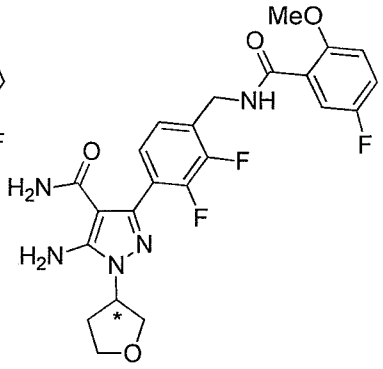
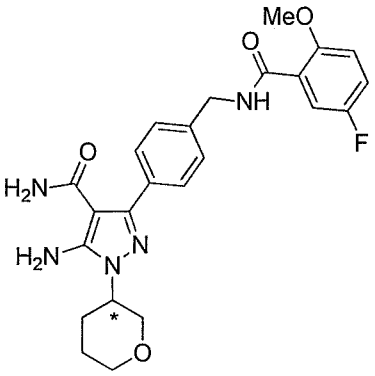
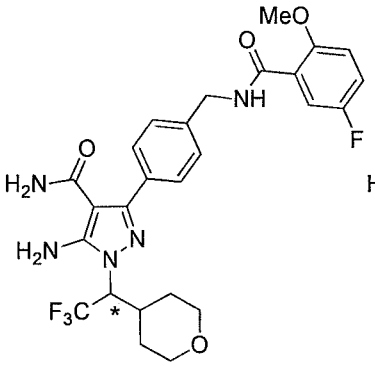
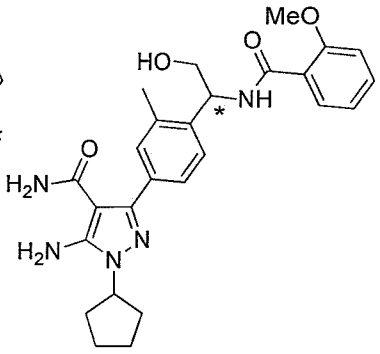
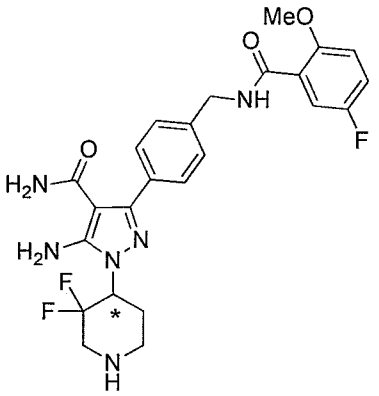
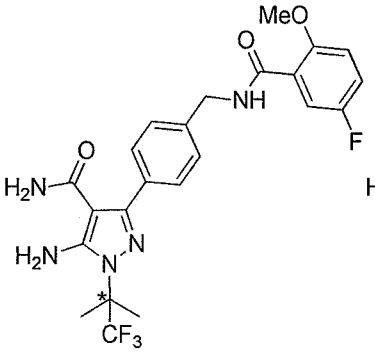
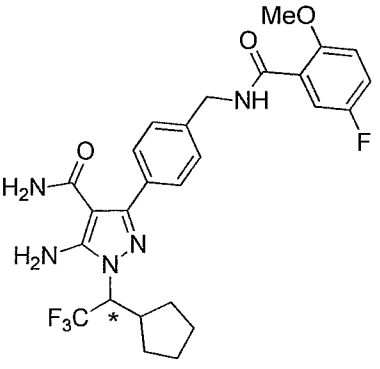
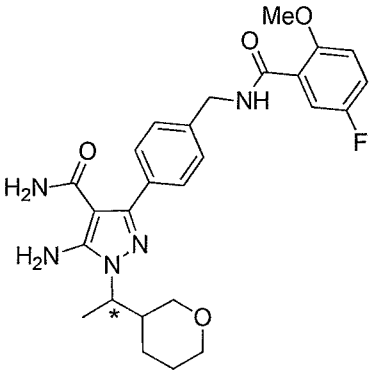


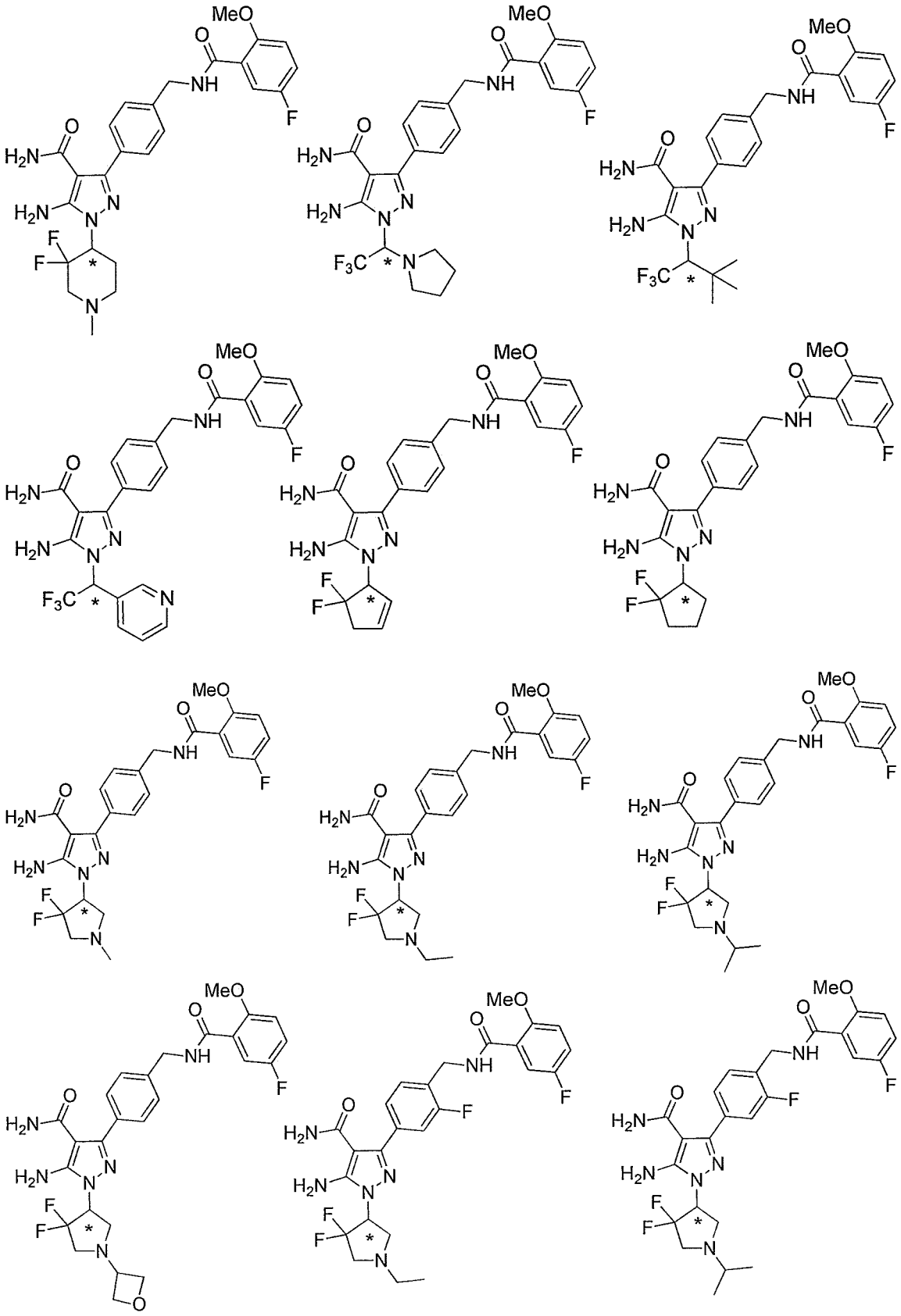


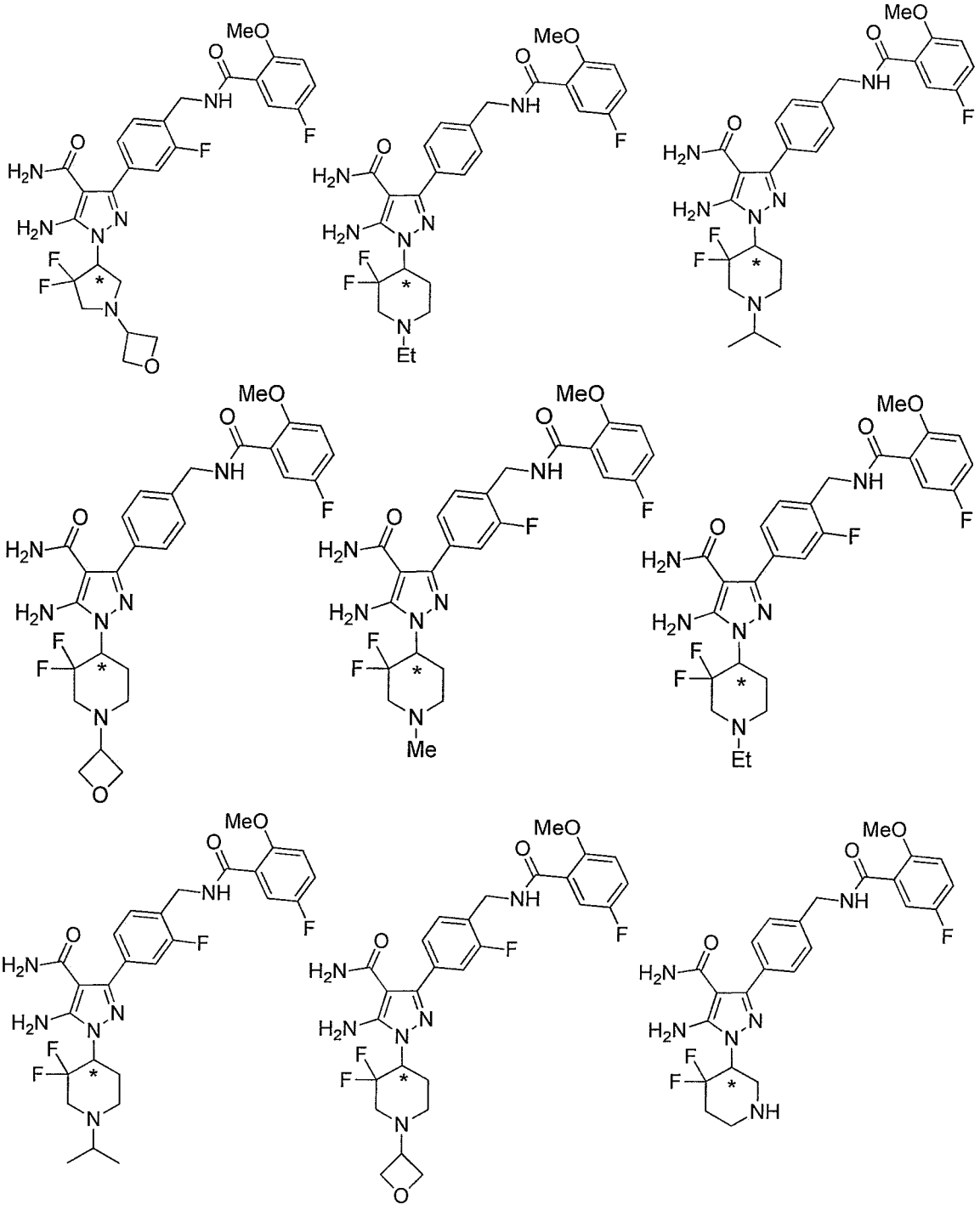













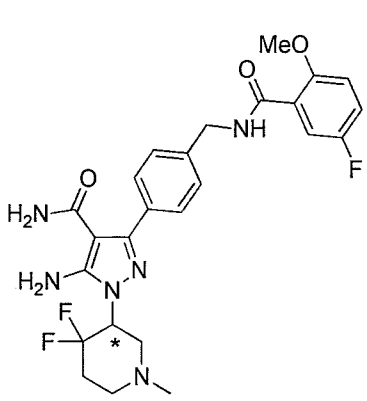
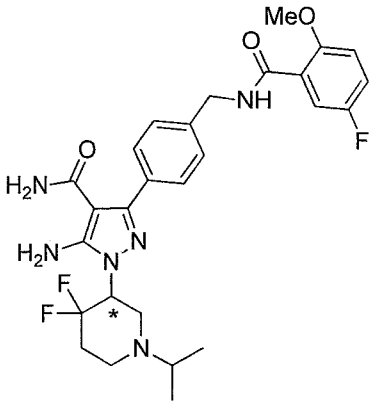
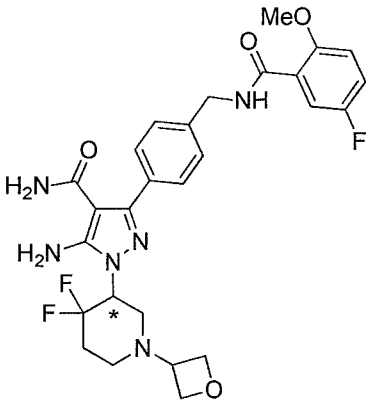
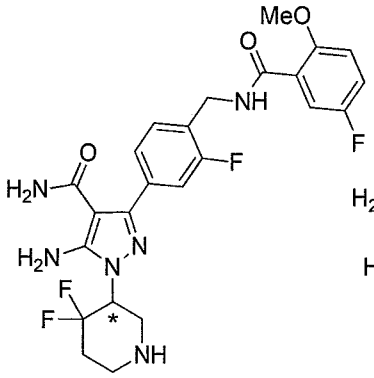
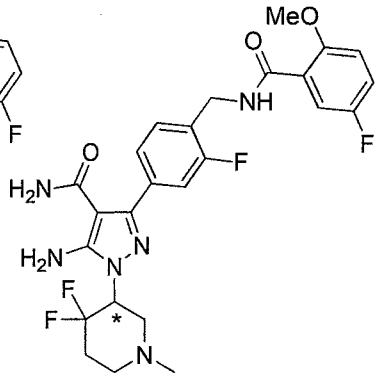
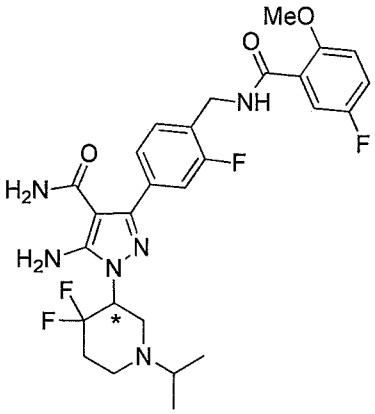
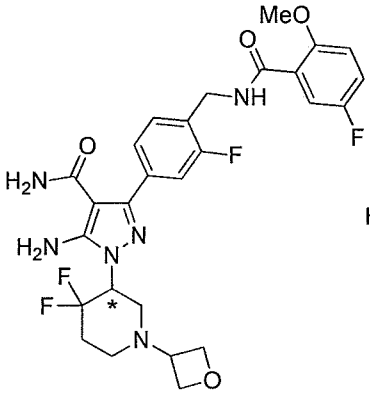
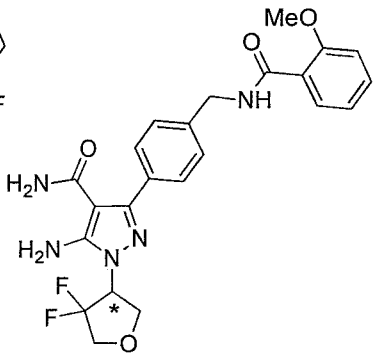
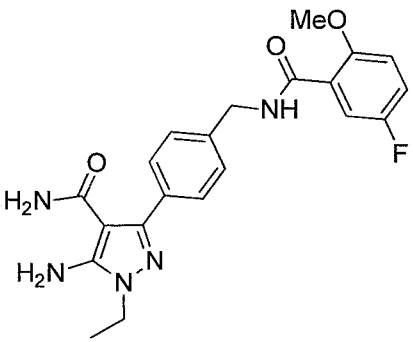
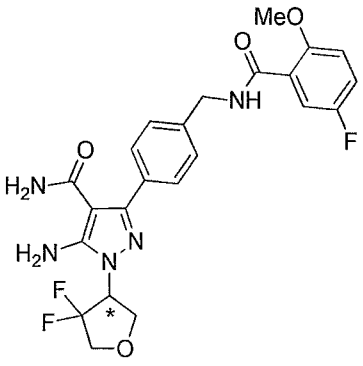
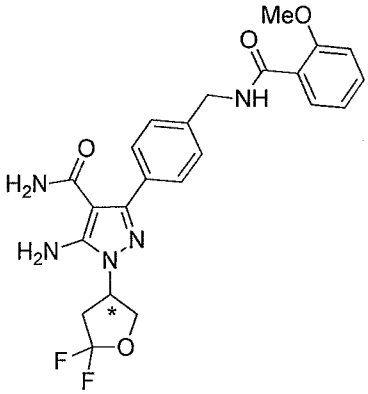
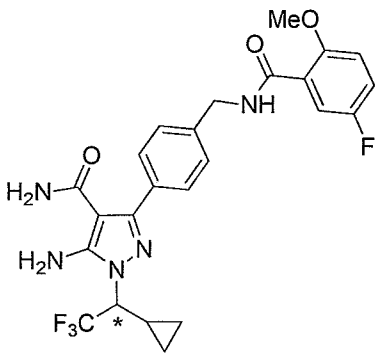













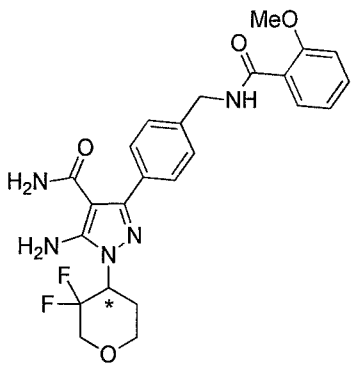
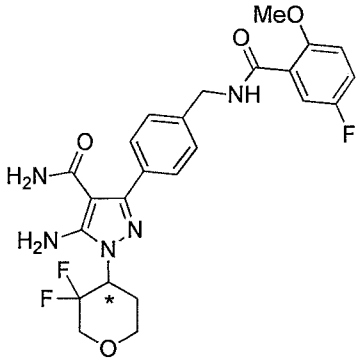
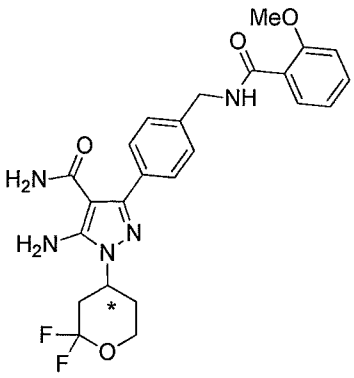
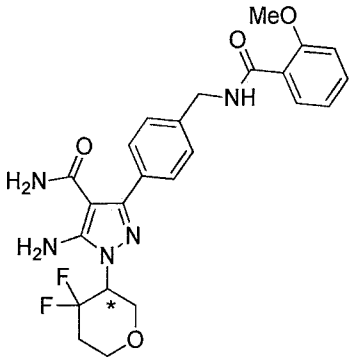
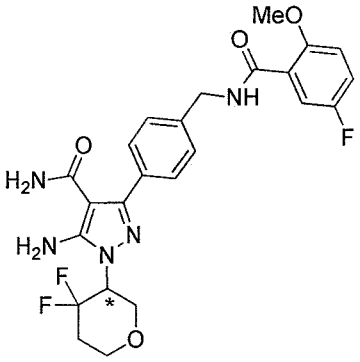
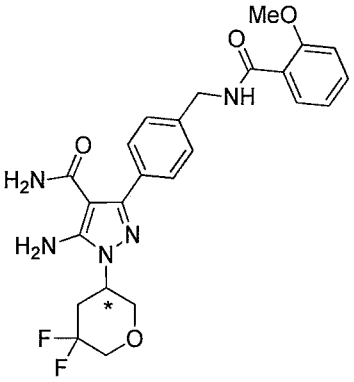
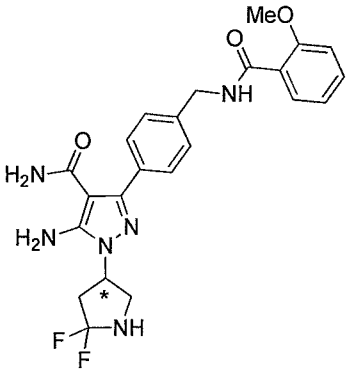
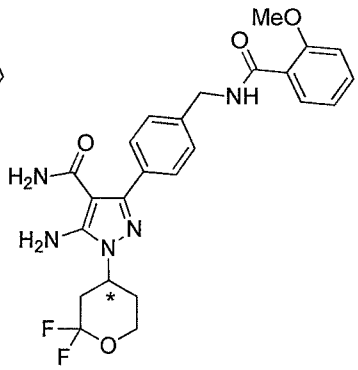
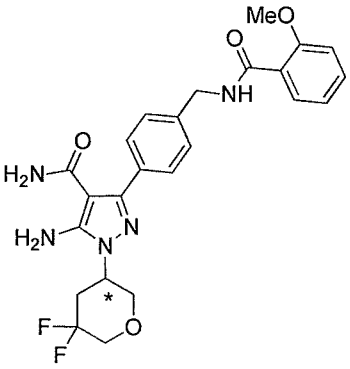
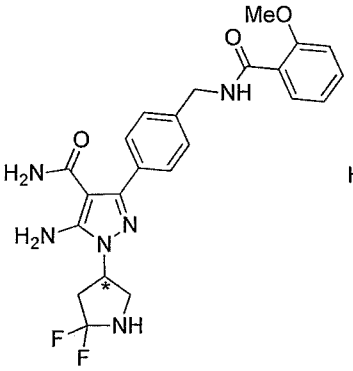
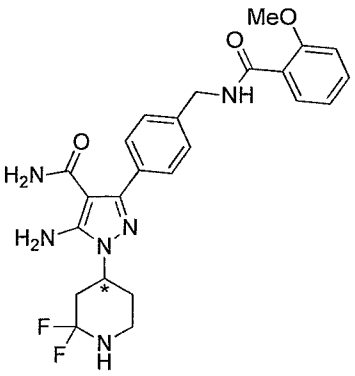
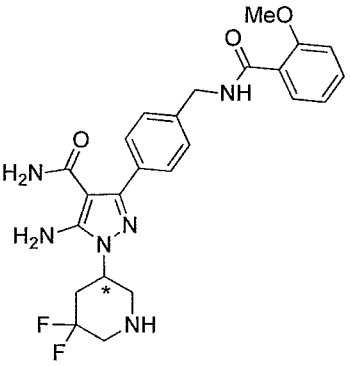













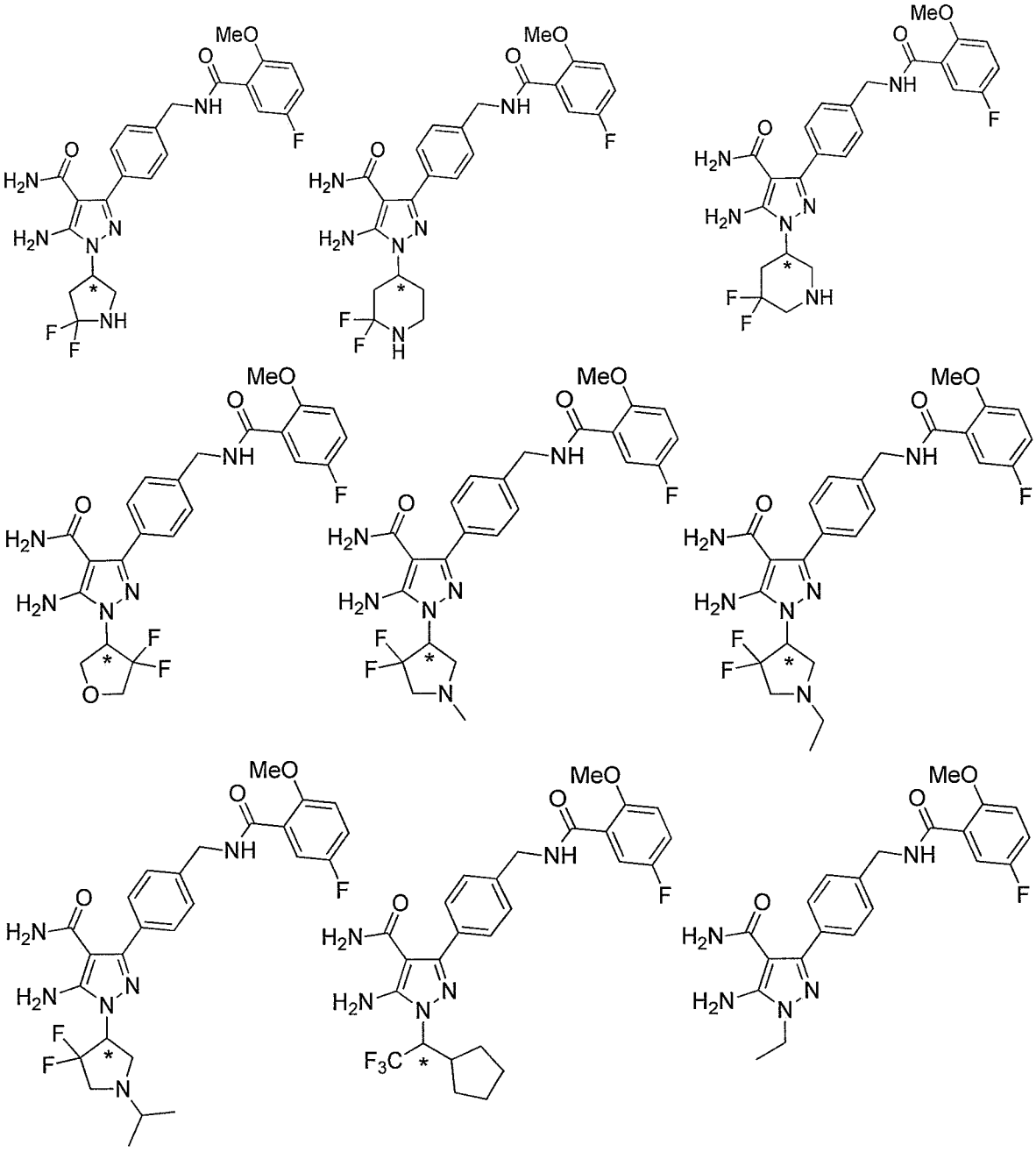













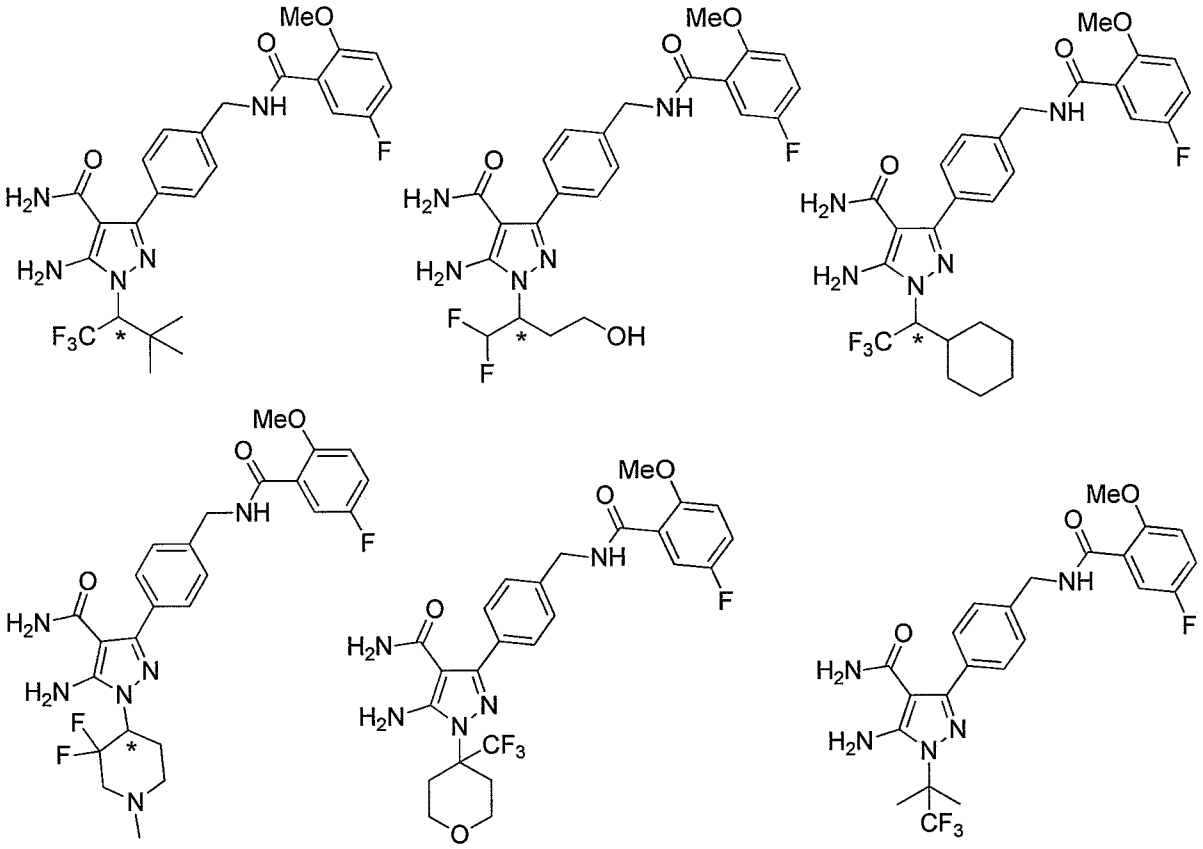








or a pharmaceutically acceptable salt thereof.

22. A compound of any preceding claim for use as a medicament.

23. Use of a compound of any of claims 1 to 21 for the manufacture of a medicament for the treatment of a condition which is modulated by BTK.

24. The use of claim 23, wherein the condition modulated by BTK is selected from the group consisting of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

25. The use of claim 23 or claim 24, wherein the condition modulated by BTK is selected from the group consisting of: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia, B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia,

multiple myeloma, bone cancer, bone metastasis, arthritis, multiple sclerosis, osteoporosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome, and lupus.

26. Use of a compound of any of claims 1 to 21 for the manufacture of a medicament for the treatment of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

27. Use of a compound of any of claims 1 to 21 for the manufacture of a medicament for the treatment of a condition selected from the group consisting of: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma for example ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, bone cancer, bone metastasis, follicular lymphoma, chronic lymphocytic lymphoma, B-cell prolymphocyte leukemia, lymphoplasmacytic lymphoma/, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitisis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, vulvodynia, graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, vulvitis, pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), usual interstitial pneumonitis (UIP), interstitial lung disease, cryptogenic fibrosing alveolitis (CFA), bronchiolitis obliterans, bronchiectasis, fatty liver disease, steatosis (e.g., nonalcoholic steatohepatitis (NASH),

cholestatic liver disease (e.g., primary biliary cirrhosis (PBC), cirrhosis, alcohol-induced liver fibrosis, biliary duct injury, biliary fibrosis, cholestasis or cholangiopathies. In some embodiments, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, e.g., hepatitis (e.g., hepatitis C, B or D), autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (e.g., alcohol, pharmaceutical drugs and environmental toxins), renal fibrosis (e.g., chronic kidney fibrosis), nephropathies associated with injury/fibrosis (e.g., chronic nephropathies associated with diabetes (e.g., diabetic nephropathy)), lupus, scleroderma of the kidney, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathyrenal fibrosis associated with human chronic kidney disease (CKD), chronic progressive nephropathy (CPN), tubulointerstitial fibrosis, ureteral obstruction, chronic uremia, chronic interstitial nephritis, radiation nephropathy, glomerulosclerosis, progressive glomerulonephrosis (PGN), endothelial/thrombotic microangiopathy injury, HIV-associated nephropathy, or fibrosis associated with exposure to a toxin, an irritant, or a chemotherapeutic agent, fibrosis associated with scleroderma; radiation induced gut fibrosis; fibrosis associated with a foregut inflammatory disorder such as Barrett's esophagus and chronic gastritis, and/or fibrosis associated with a hindgut inflammatory disorder, such as inflammatory bowel disease (IBD), ulcerative colitis and Crohn's disease, age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity and neovascular glaucoma.

28. Use of a compound of any of claims 1 to 21 in a combination therapy with an anti-tumor agent.

29. Use of a compound of any of claims 1 to 21 for the manufacture of a medicament for the treatment of cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis, wherein the compound is formulated to be administered simultaneously, sequentially or separately with an additional anti-tumour agent.

30. A pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of any of claims 1 to 21 and pharmaceutically acceptable excipients.

31. A pharmaceutical composition of claim 30, wherein the composition is a combination product and comprises an additional pharmaceutically active agent.

32. Use of a compound of any one of claims 1 to 21, for the manufacture of a medicament for the treatment of a condition which is modulated by BTK in a patient in need thereof.

33. The use of claim 32, wherein the condition modulated by BTK is selected from the group consisting of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, and fibrosis.

34. Use of a compound of any one of claims 1-21, for the manufacture of a combination product, wherein the combination product comprises a compound of any of claims 1 to 21 for use simultaneously, sequentially or separately with an anti-tumor agent.