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.

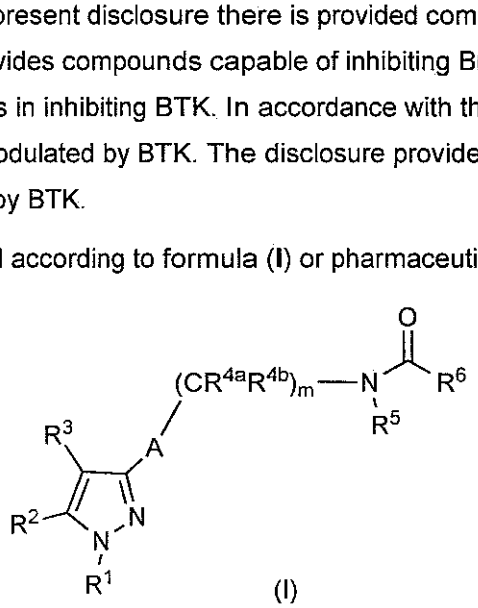
[0012] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments 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.

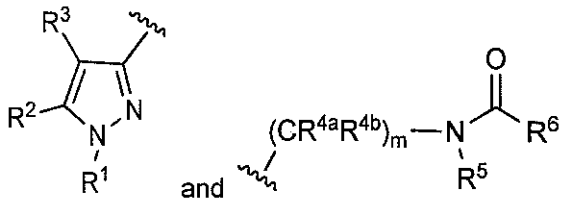
[0015] Provided is a compound according to formula (**I**) or pharmaceutically acceptable salts thereof:



(I)

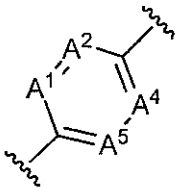
[0018] In an embodiment, A is unsubstituted phenyl, unsubstituted pyrdinyl or phenyl substituted with from 1 to 4 R^7 (optionally 1 or 2 R^7). In an embodiment, A is unsubstituted phenyl or phenyl substituted with from 1 to 4 R^7.

[0019] As the skilled person will note from the structural formula of formula (I), group "A" is substituted by two groups, shown below (it may also be optionally substituted by from 1 to 4 R^7).



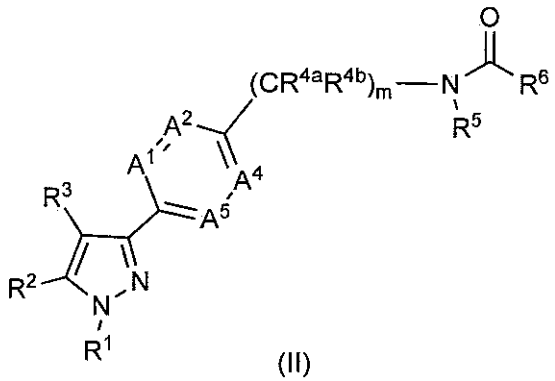
These two groups may be para substituted on A. In other words, the two groups may be 1,4-substiuted on A.

[0020] In an embodiment, A may be:



wherein 0, 1 or 2 of A^1, A^2, A^4 and A^5 are independently selected from N and the remainder are CR^7.

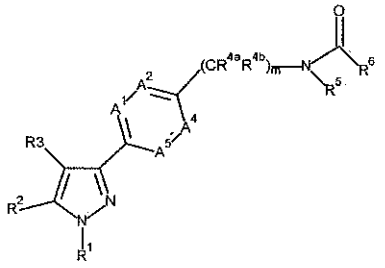
[0021] Accordingly, the compounds according to formula (I) may be compounds of formula (II) or pharmaceutically acceptable salts thereof:



(II)

wherein 0, 1 or 2 of A^1, A^2, A^4 and A^5 are independently selected from N and the remainder are CR^7.

[0021a] In one aspect, there is provided a compound according to formula (**II**) or pharmaceutically acceptable salts thereof:



(II)

wherein

0, 1 or 2 of A^1, A^2, A^4 and A^5 are independently selected from N and the remainder are C^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, $-OR^A$, $-NR^AR^B$, =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 is NH_2;

R^3 is $-C(O)NH_2$;

R^{4a} and R^{4b} are 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: 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;

R^A and R^B are, at each occurrence, independently selected from: 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: 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: 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.

[0022] In embodiments 0 or 1 of A^1, A^2, A^4 and A^5 are N, of the remaining A^1, A^2, A^4 and A^5 0 or 1 are CR^7 and the remainder are CH.

[0023] In embodiments A^1, A^4 and A^5 are CH and A^2 is CR^7 and R^7 is selected from fluoro, methyl, methoxy, or $-CH_2OH$. In embodiments A^2, A^4 and A^5 are CH and A^1 is CR^7 and R^7 is selected from H, fluoro, methyl, methoxy, or $-CH_2OH$. In embodiments A^1, A^4 and A^5 are CH and A^2 is N. In embodiments A^2, A^4 and A^5 are CH and A^1 is N. In embodiments A^1 and A^5 are CH and A^2 and A^4 are N. In embodiments A^1 and A^5 are N and A^2 and A^4 are CH. In embodiments A^1 and A^4 are CH and A^2 and A^5 are N. In embodiments A^1 and A^2 are CH and A^4 and A^5 are N.

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 in the manufacture of a medicament for the treatment of a condition which is modulated by BTK, wherein the condition modulated by BTK is selected from the group consisting of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

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

[00125c] Provided is use of a compound disclosed herein in 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 one aspect, there is provided use of a compound disclosed herein in 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 preferably 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 (preferably, nonalcoholic steatohepatitis (NASH), cholestatic liver disease (preferably, primary biliary cirrhosis (PBC), cirrhosis, alcohol-induced liver fibrosis, biliary duct injury, biliary fibrosis, cholestasis or cholangiopathies, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, preferably, hepatitis (preferably, hepatitis C, B or D), autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (preferably, alcohol, pharmaceutical drugs and environmental toxins), renal fibrosis (preferably, chronic kidney fibrosis),

nephropathies associated with injury/fibrosis (preferably, chronic nephropathies associated with diabetes (preferably, 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.

[00125e] 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 medicament is formulated to be administered simultaneously, sequentially or separately with an additional anti-tumour agent.

[00125f] Provided is 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.

[00125g] Provided is 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.

[00125h] Provided is 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.

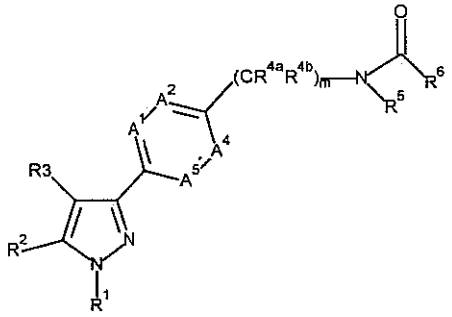
[00127] In embodiments, a compound of the disclosure may be for use in the treatment of: cancer, lymphoma, leukemia, immunological diseases, autoimmune diseases and inflammatory disorders. The compound of the disclosure may be for use in the treatment of specific conditions selected from: B-cell malignancy, 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.

CLAIMS

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



(II)

wherein

0, 1 or 2 of A^1, A^2, A^4 and A^5 are independently selected from N and the remainder are C^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, $-OR^A$, $-NR^AR^B$, =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 is NH_2;

R^3 is $-C(O)NH_2$;

R^{4a} and R^{4b} are 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: 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;

R^A and R^B are, at each occurrence, independently selected from: 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: 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: 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^2, A^4 and A^5 are CH and A^1 is CR^7 and R^7 is selected from H, fluoro, methyl methoxy or $-CH_2OH$.

3. The compound of claim 1, 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.

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

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

6. 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.

7. 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.

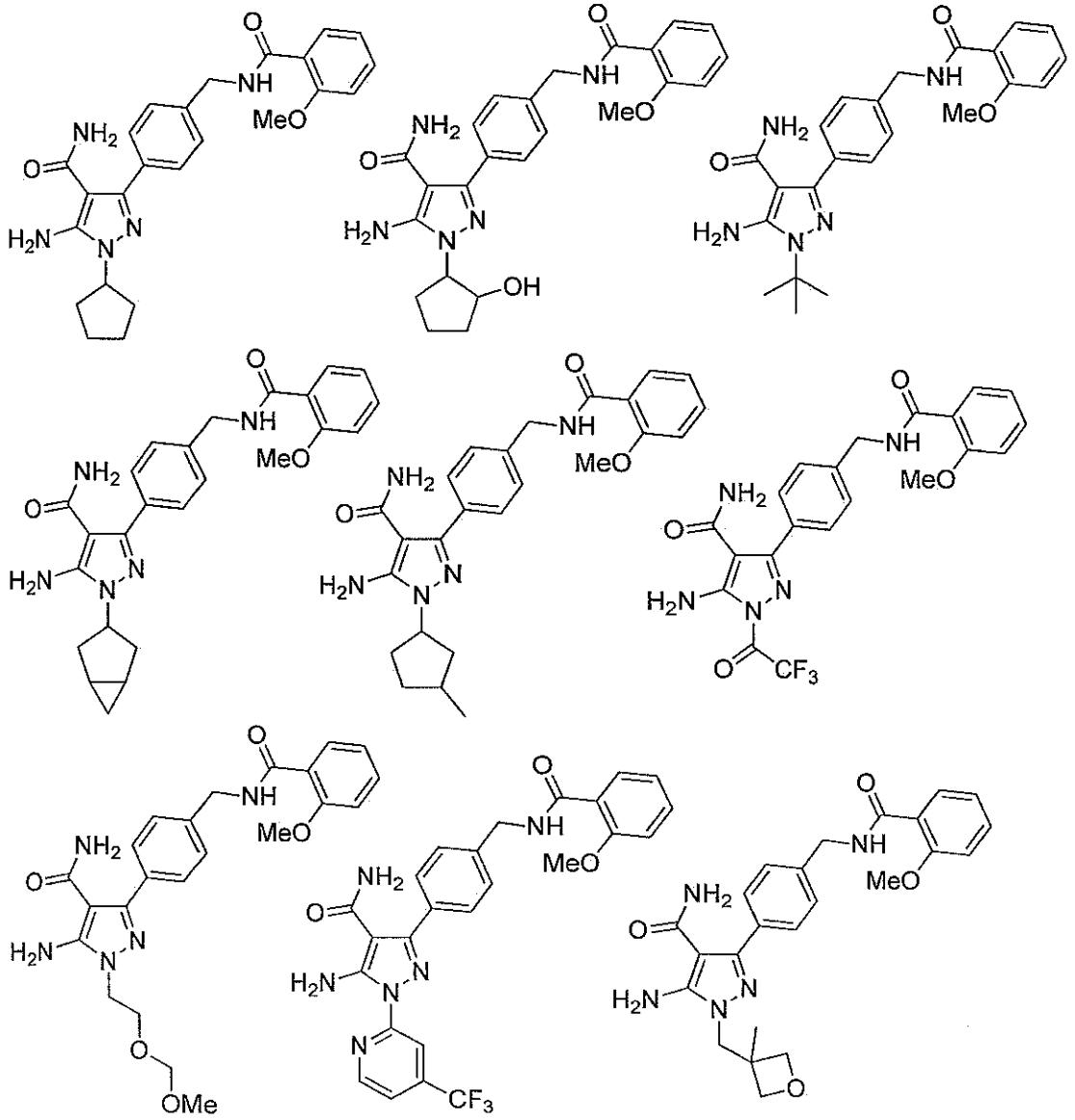
8. The compound of any of claims 1 to 7, wherein R^1 is selected from substituted or unsubstituted: methyl, ethyl, iso-propyl, tert-hexyl, tert-butyl, trifluoroethyl, propyl ether, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, indanyl, bicyclo[3.1.0]hexyl, oxetane, tetrahydropyranyl, phenyl, pyridyl, 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,

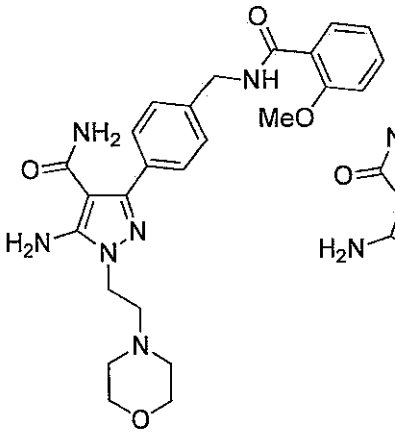
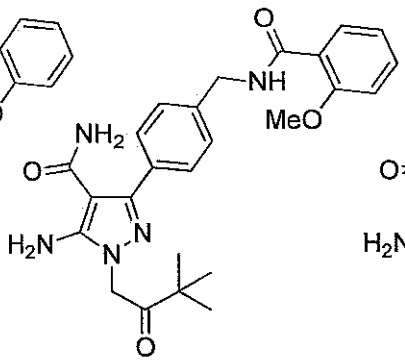
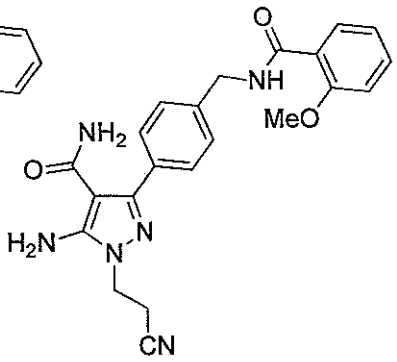
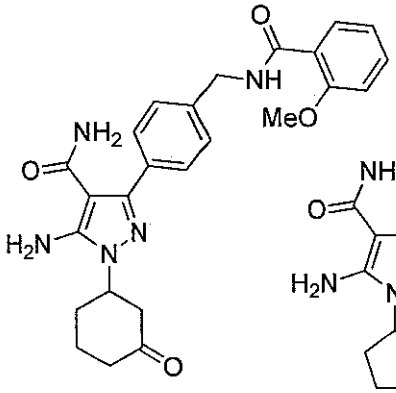
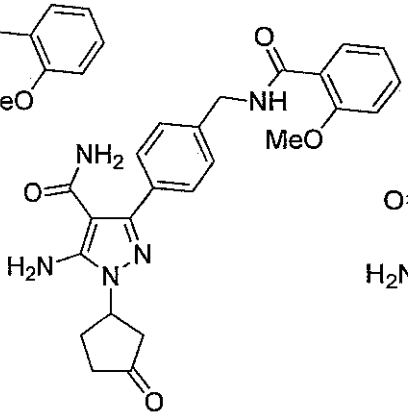
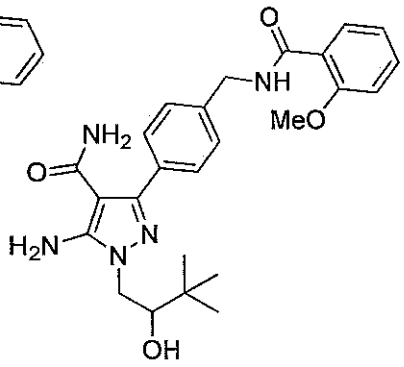
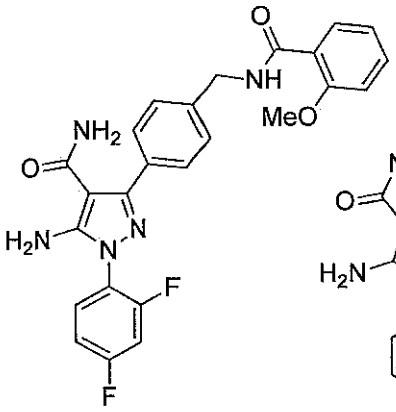
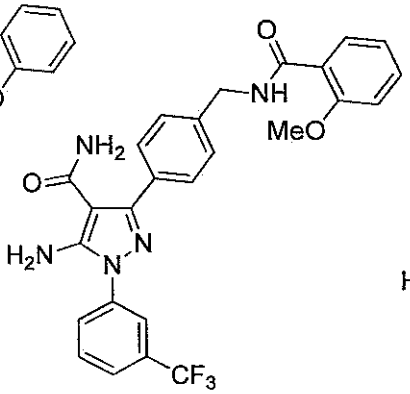
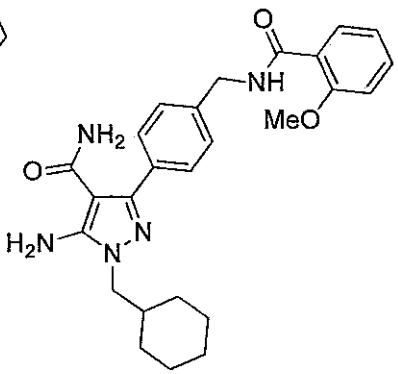
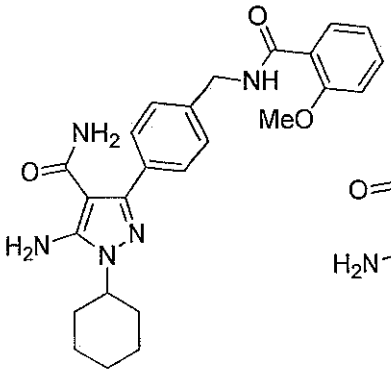
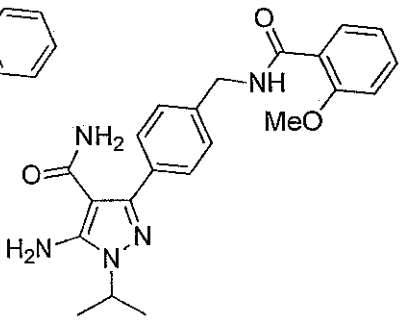
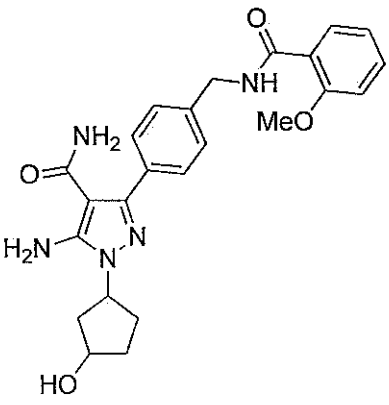
wherein R^1 is substituted with1 to 5 substituents selected from: -OH, =O, -OMe, -CN, methyl, CF_3, Cl, F, -OBn, or $-CO_2Et$.

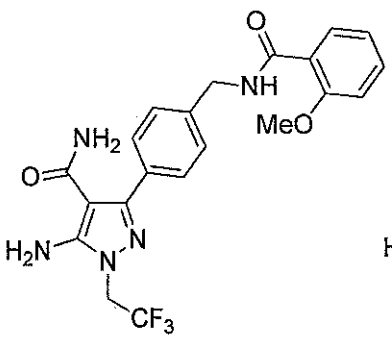
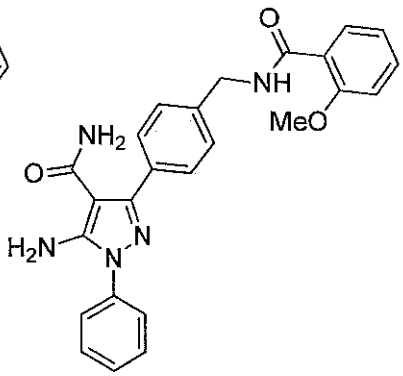
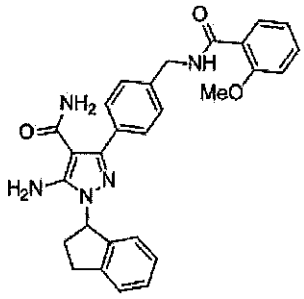
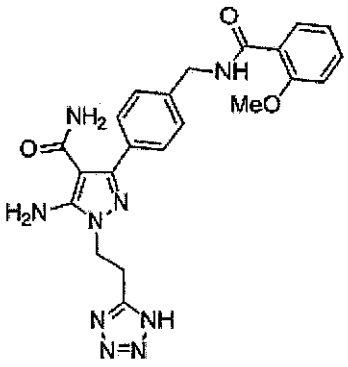
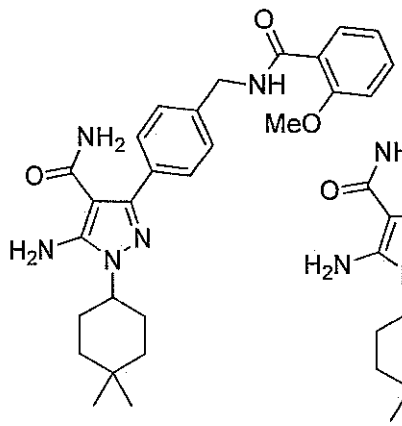
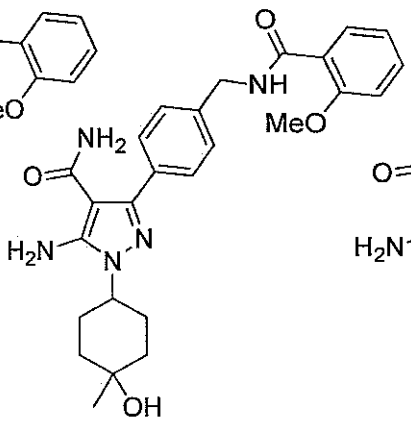
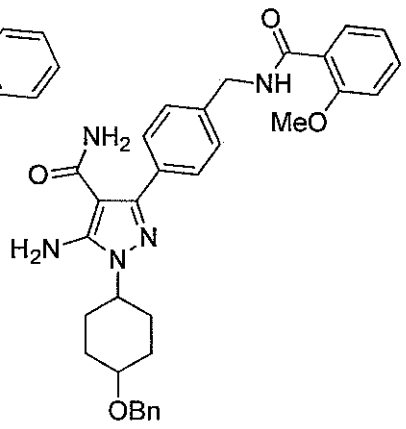
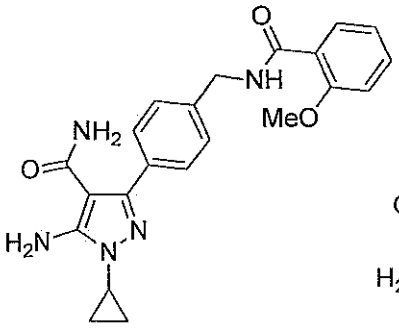
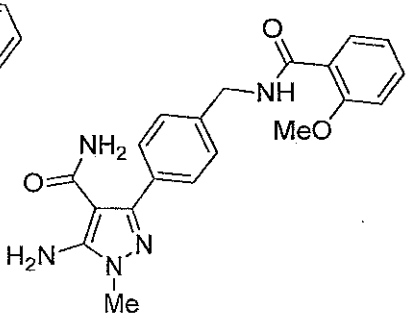
9. The compound of any of claims 1 to 5, wherein R^1 is selected from the substituted or unsubstituted: methyl, ethyl, iso-propyl, tert-hexyl, tert-butyl, trifluoroethyl, wherein R^1 is substituted with 1 to 5 substituents selected from: -OH, =O, -OMe, methyl, CF_3, Cl, F, -OBn, or $-CO_2Et$.

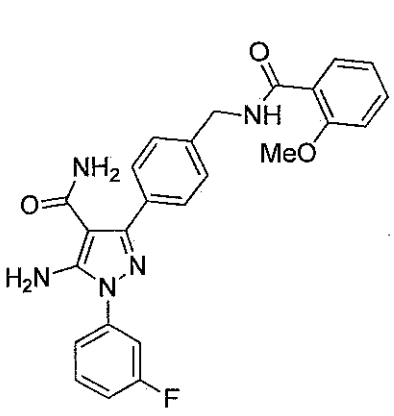
10. The compound of any of claims 1 to 5, wherein R^1 is selected from substituted or unsubstituted: cyclohexyl, phenyl, cyclobutyl, cyclopentyl, bicyclo[3.1.0]hexyl, piperidinyl, pyrolidinyl, tetrahydropyranyl,tetrahydrofuranyl, difluoroisopropyl, trifluoroisopropyl, (cyclopropyl)ethyl, or (tetrahydropyranyl)ethyl.

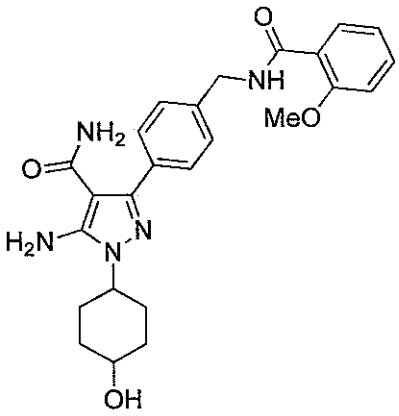
11. The compound of claim 1, wherein the compound is selected from the group consisting of:

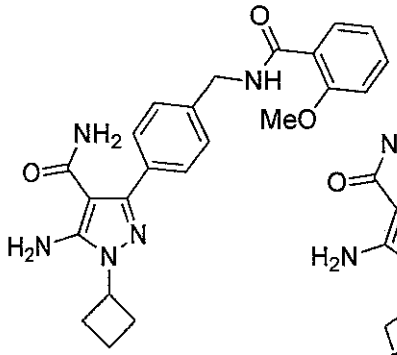


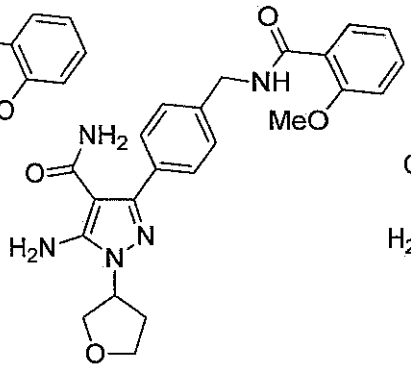













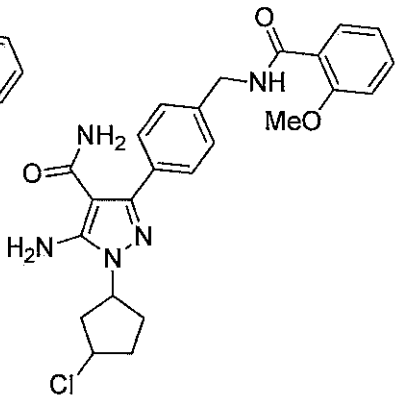










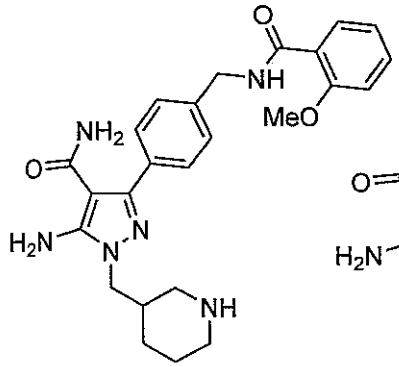


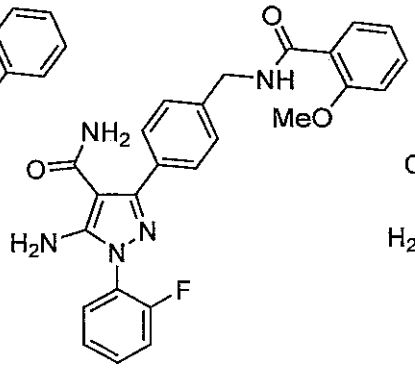


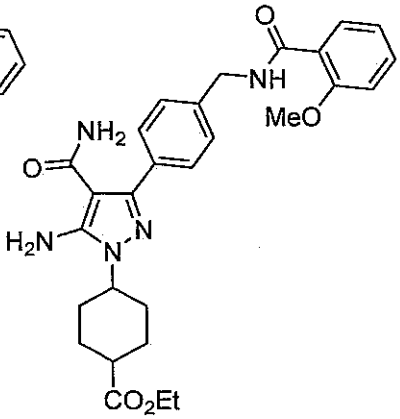


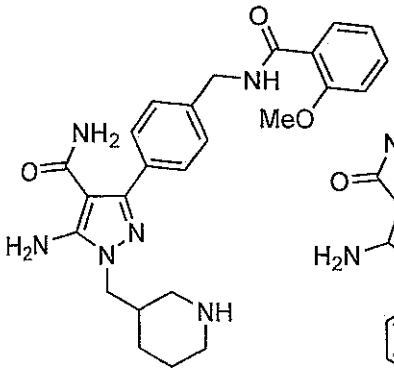


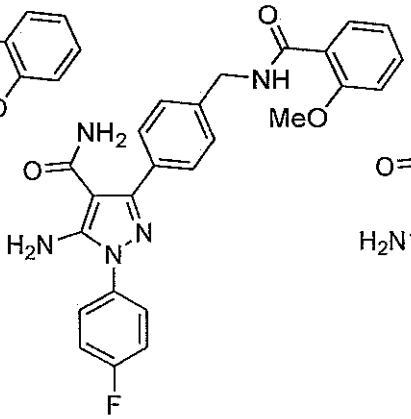


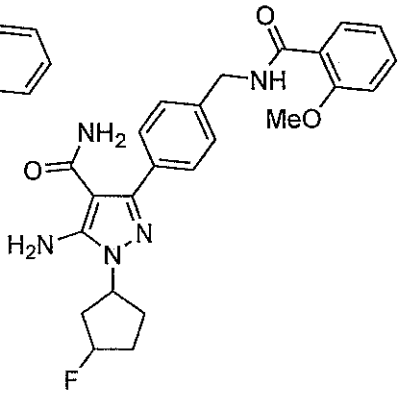


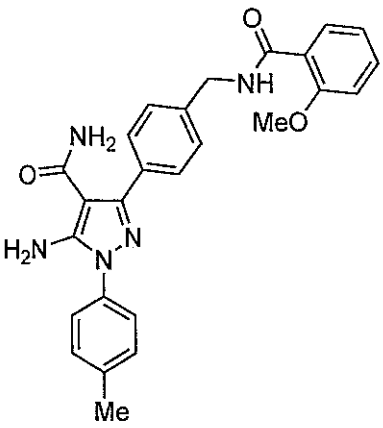


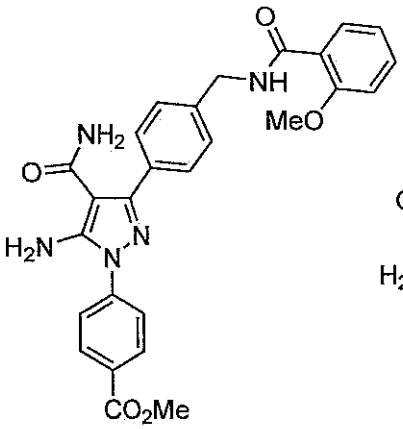


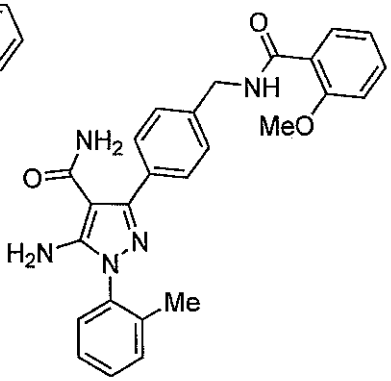


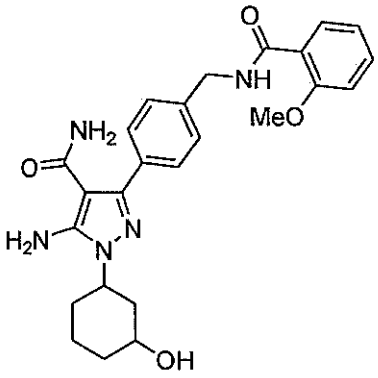


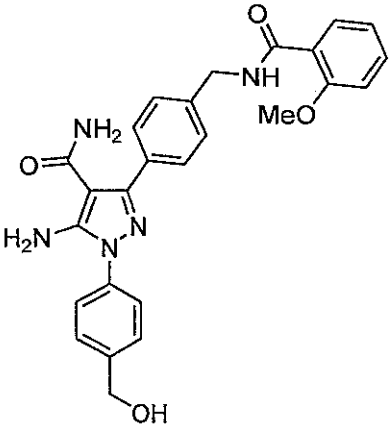


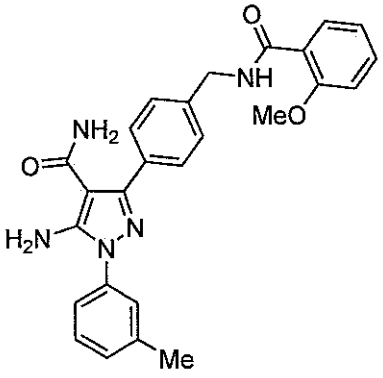


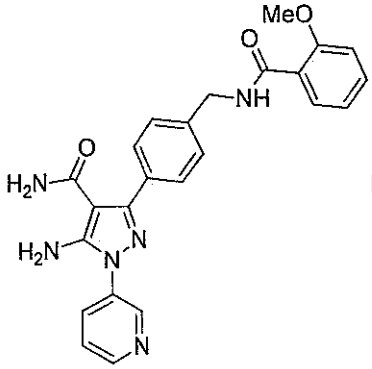


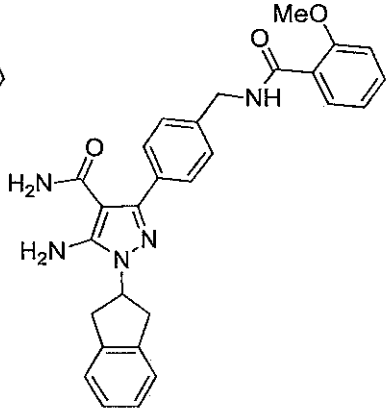


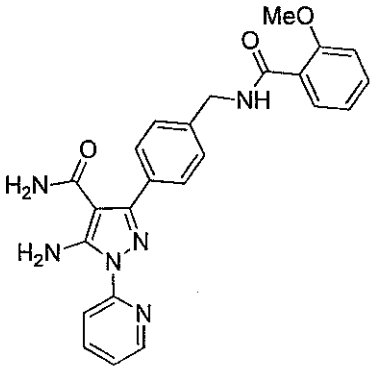


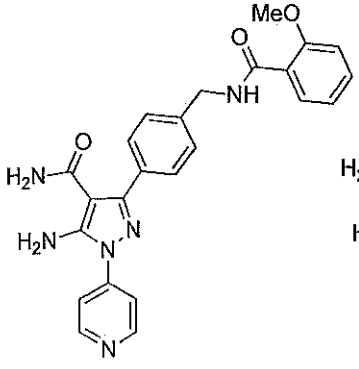


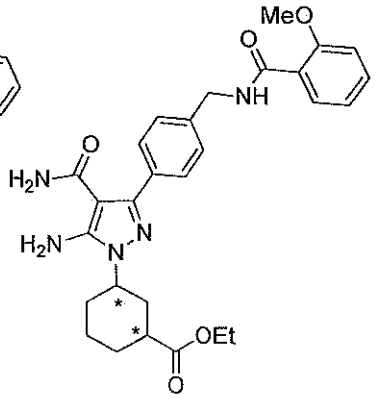


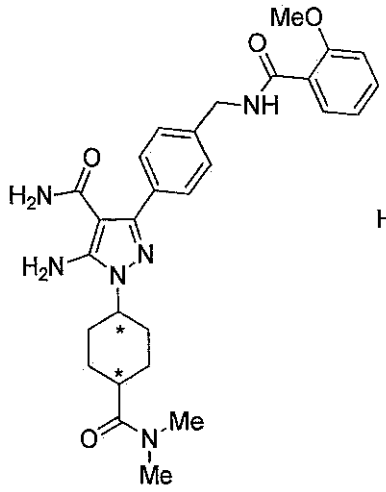
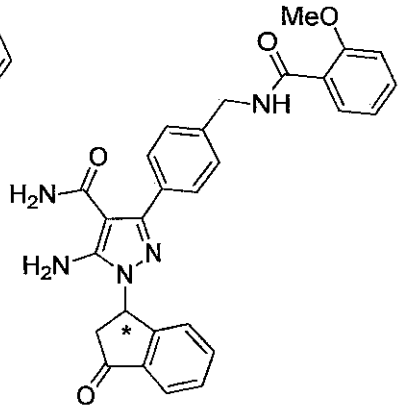
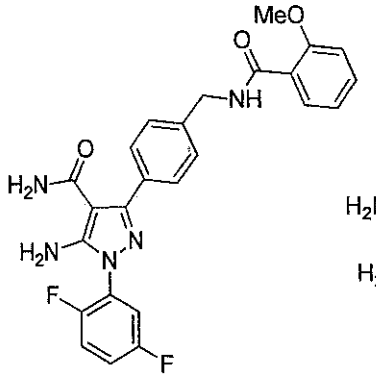
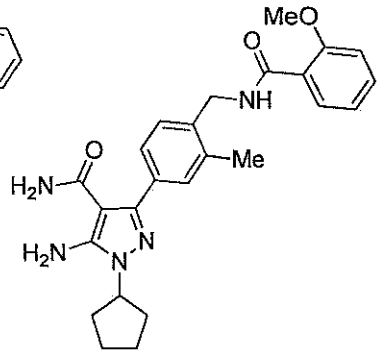
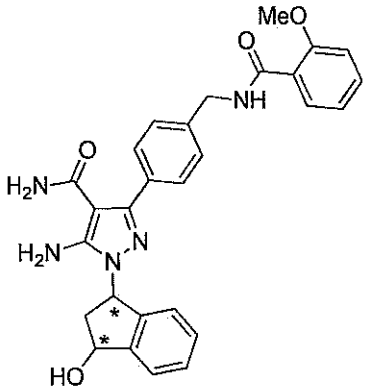
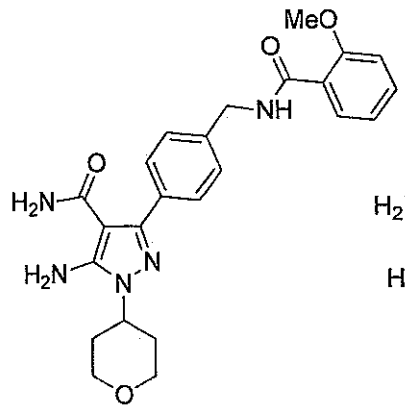
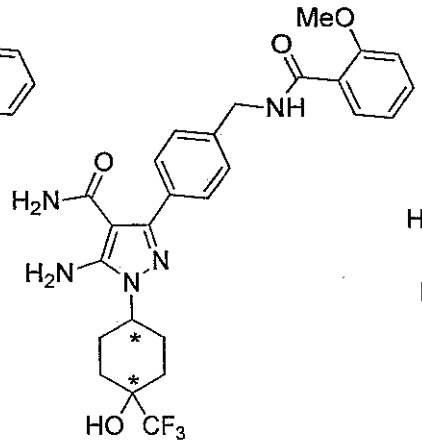
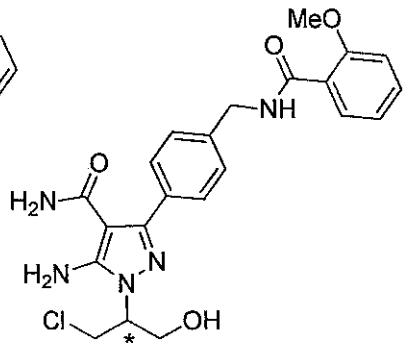


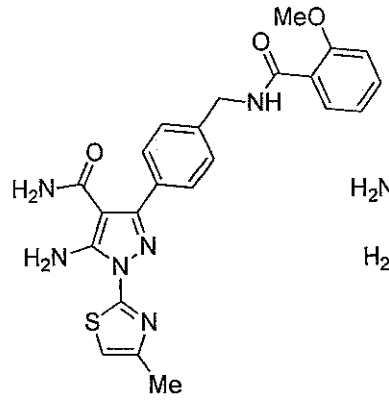






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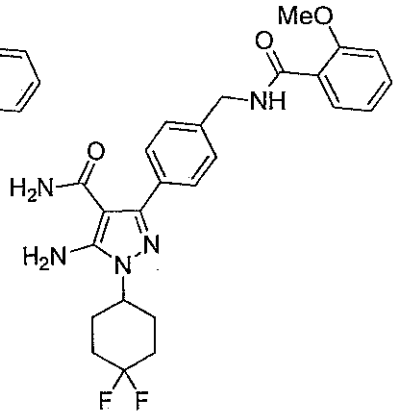
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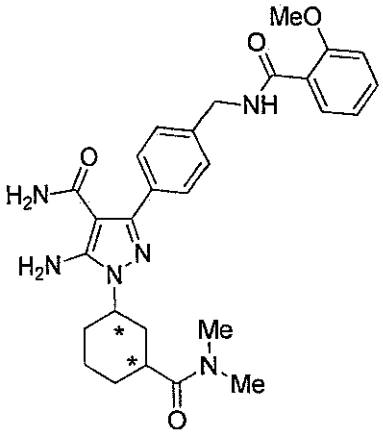
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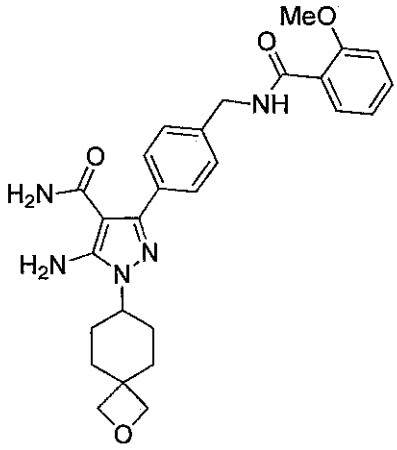
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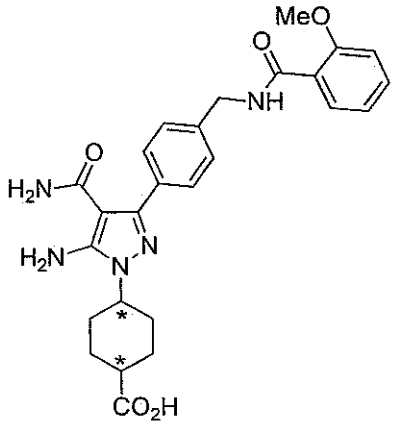
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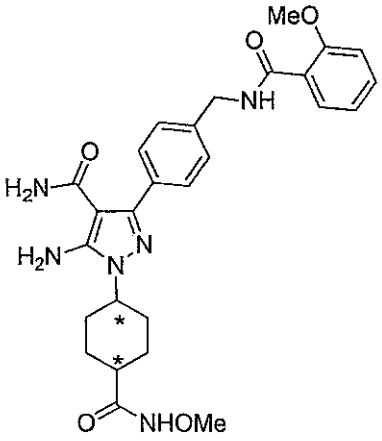
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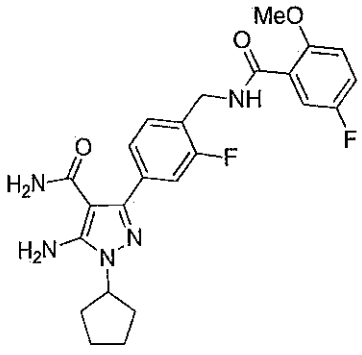
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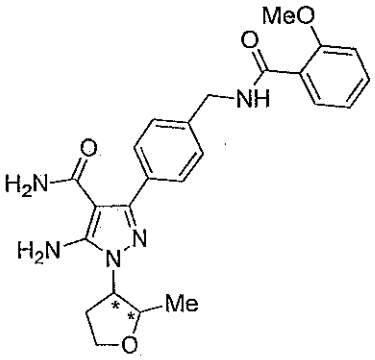
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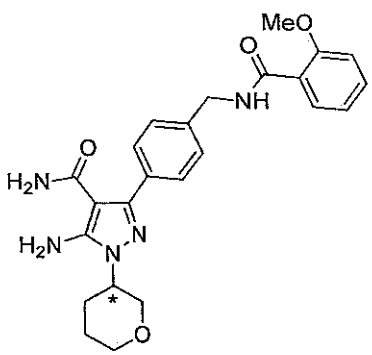
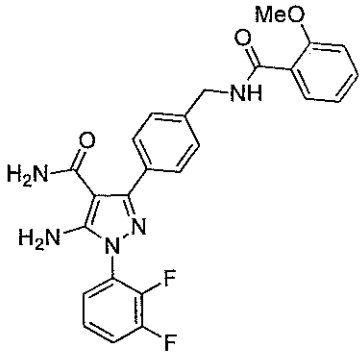
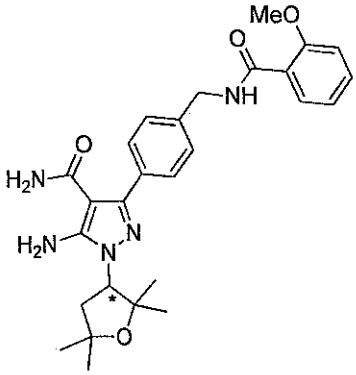
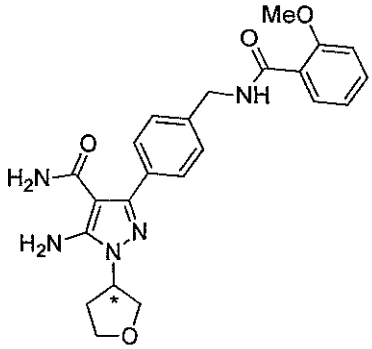
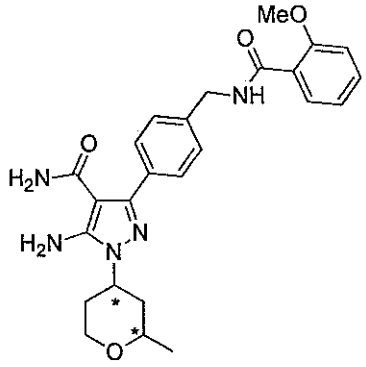
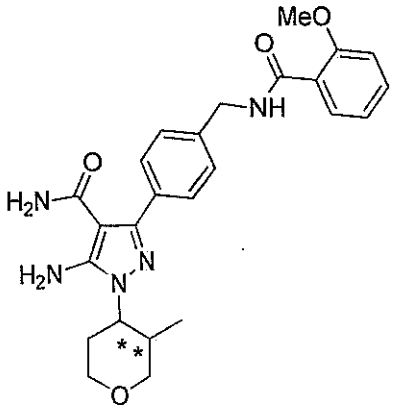


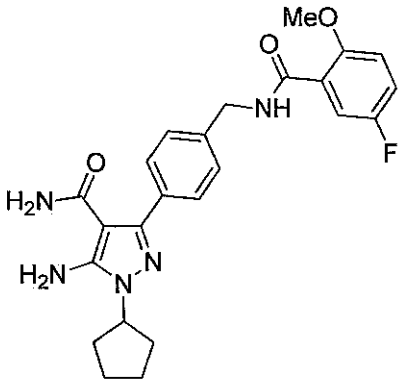


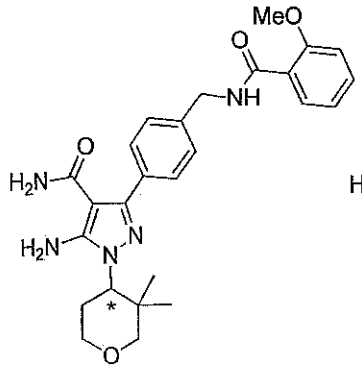


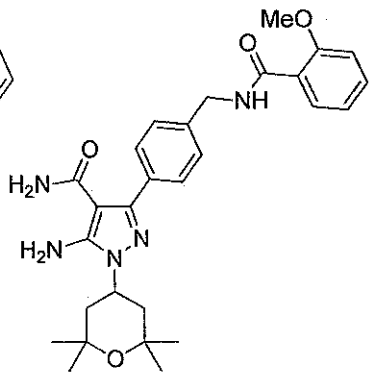


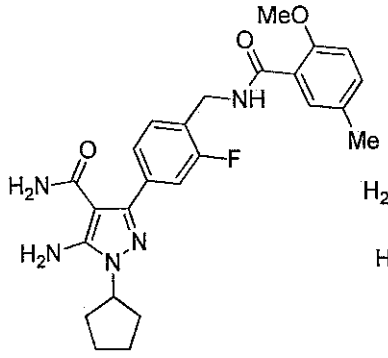
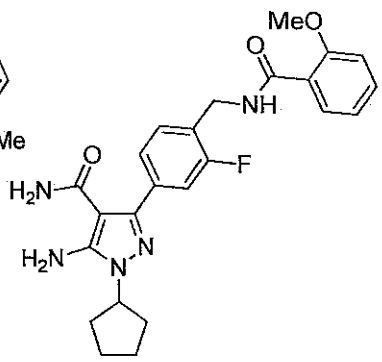
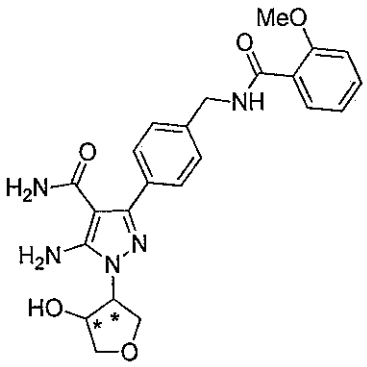
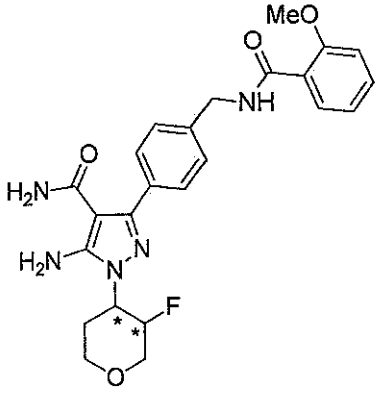
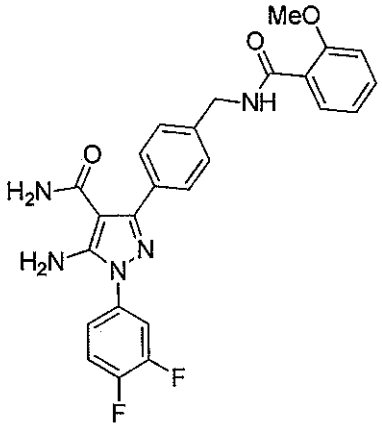
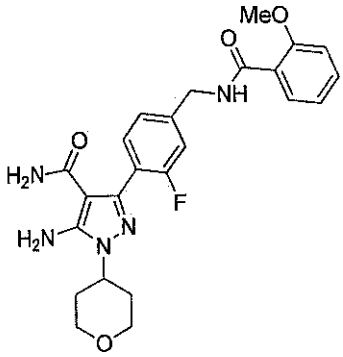
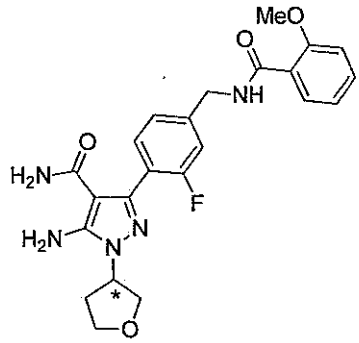
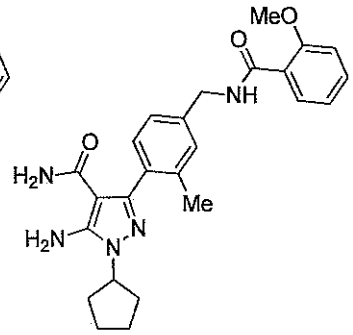
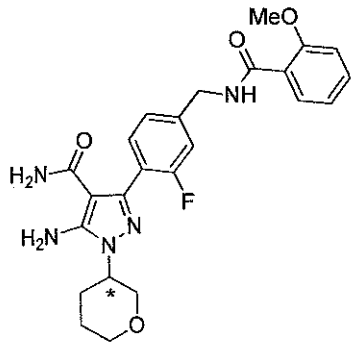
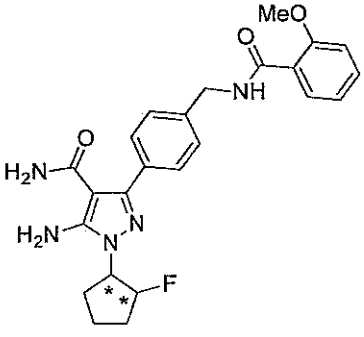
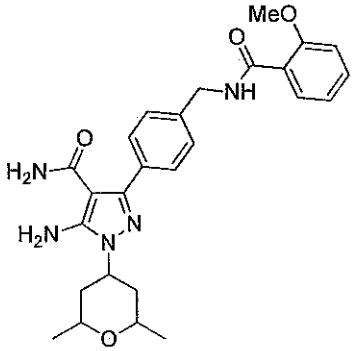


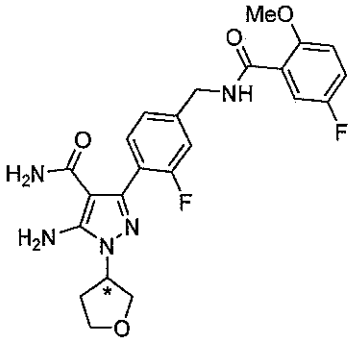
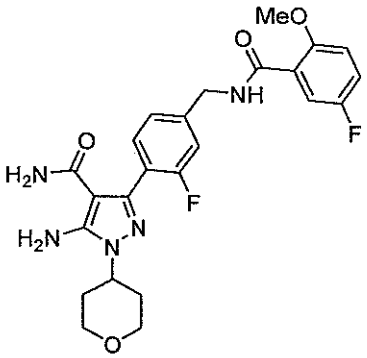
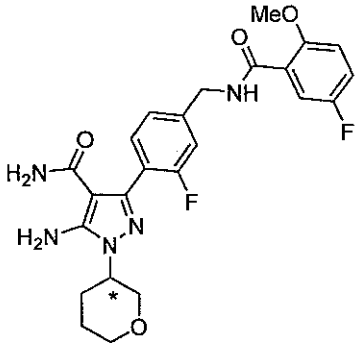
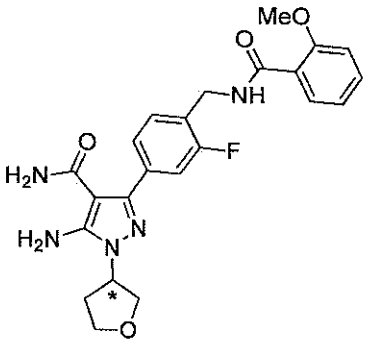
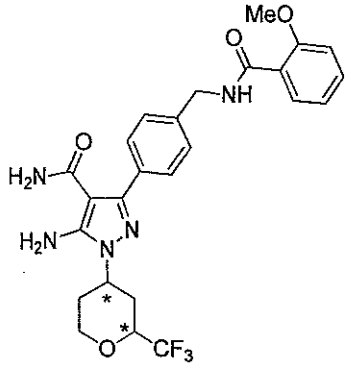
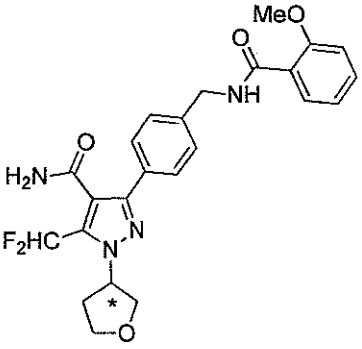
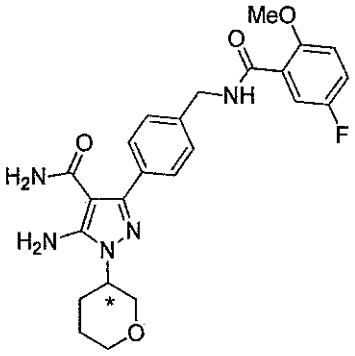
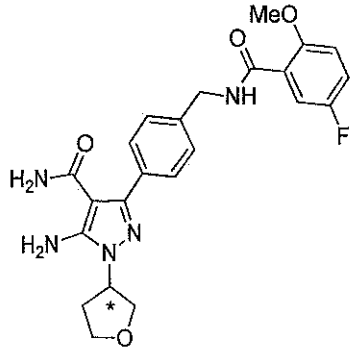
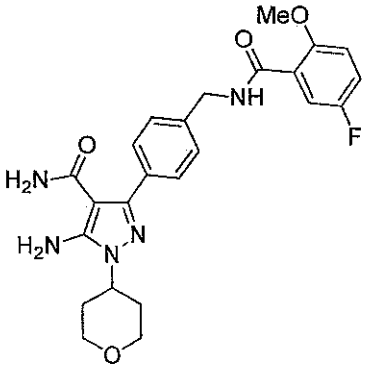
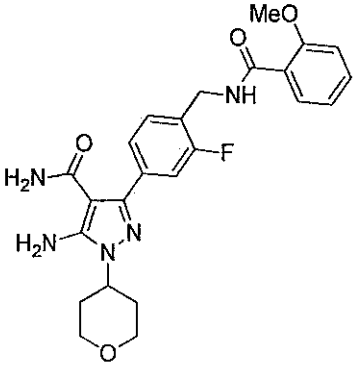


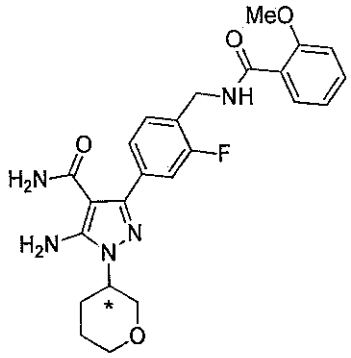
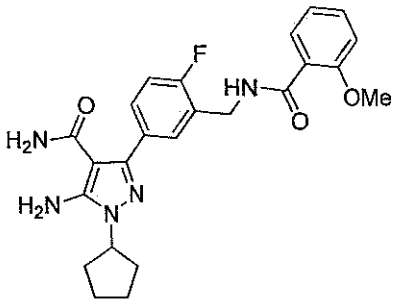
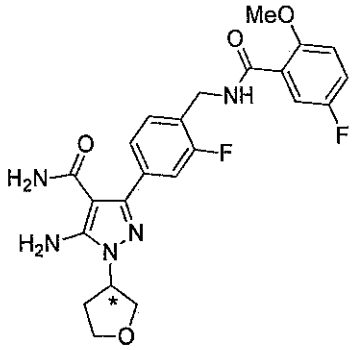
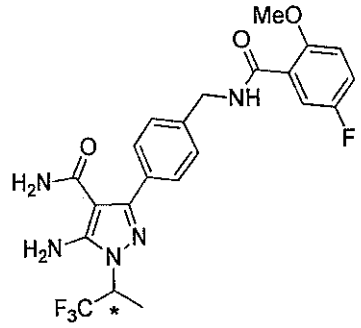
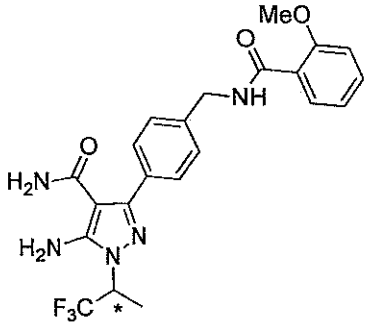
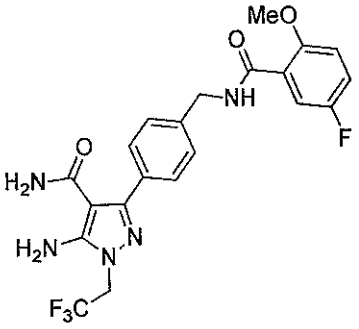
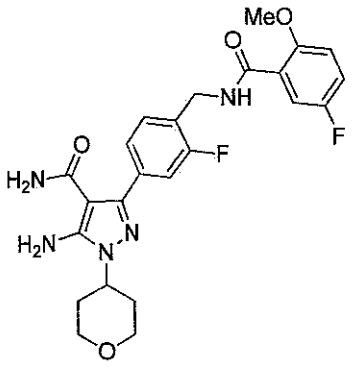
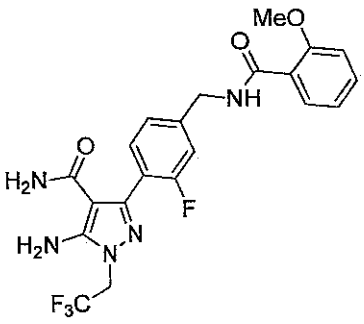
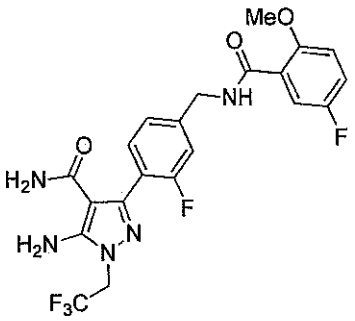
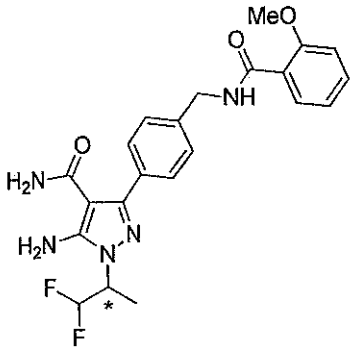
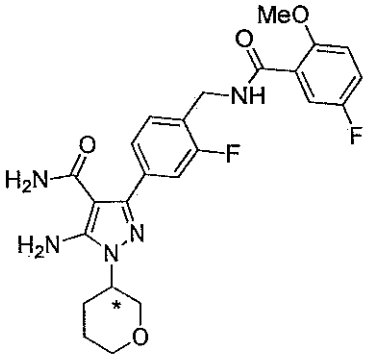
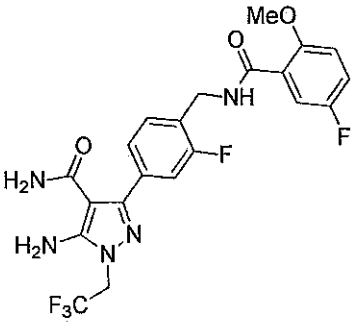


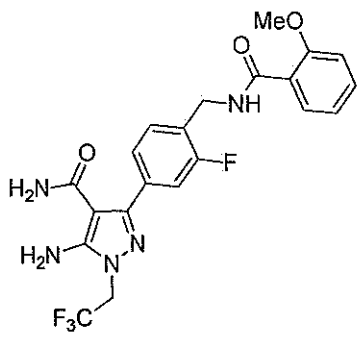
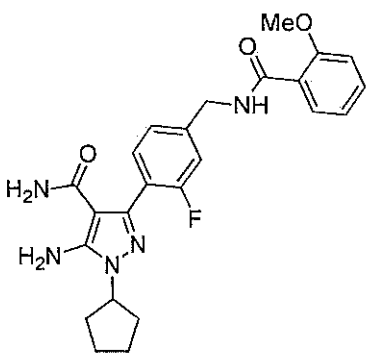
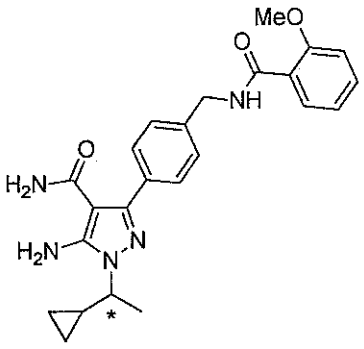
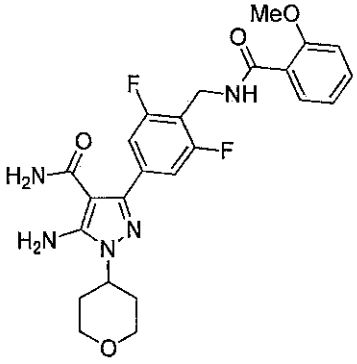
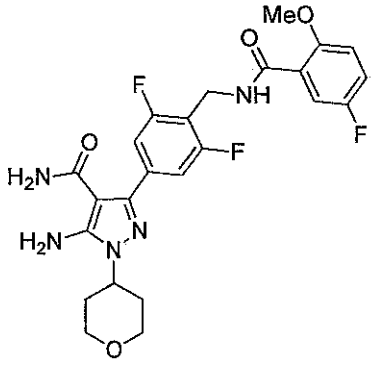
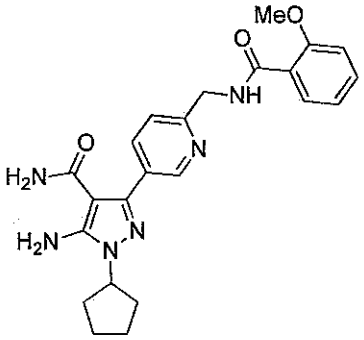
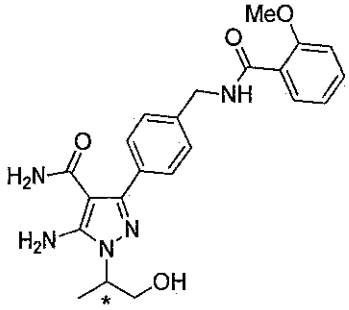
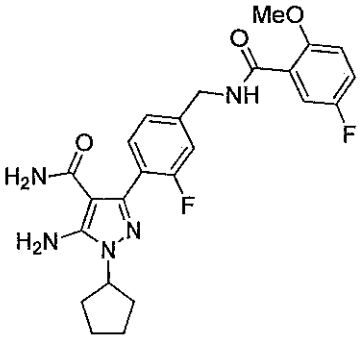
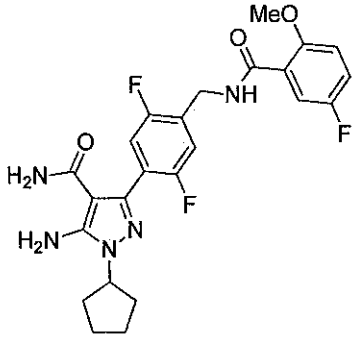
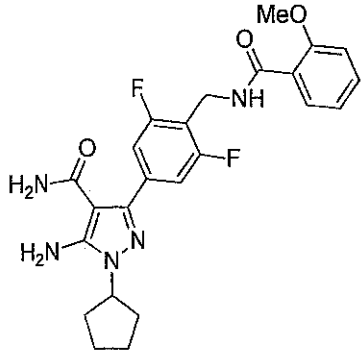
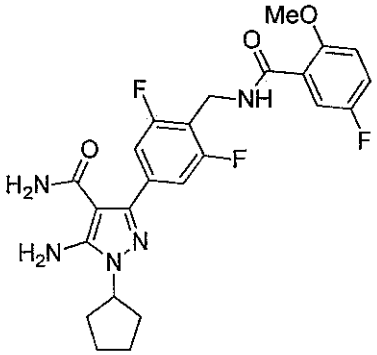
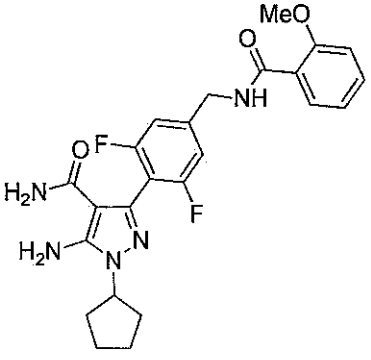


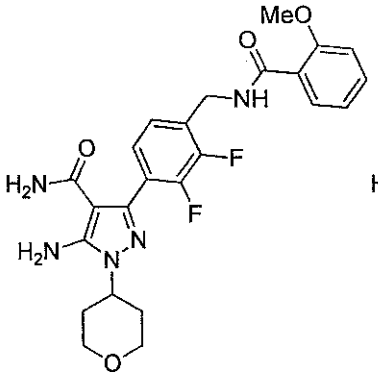
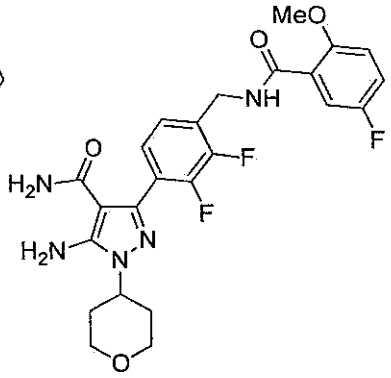
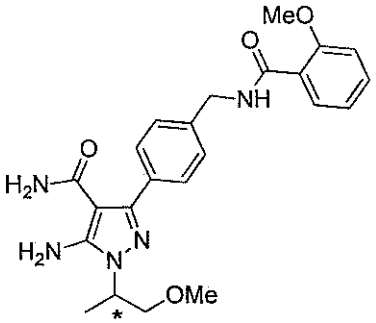
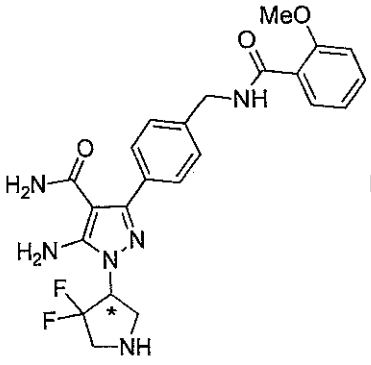
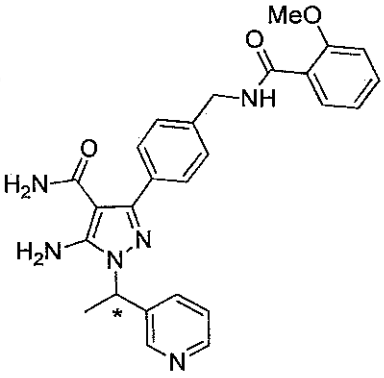
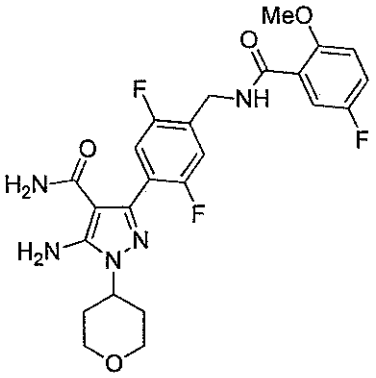
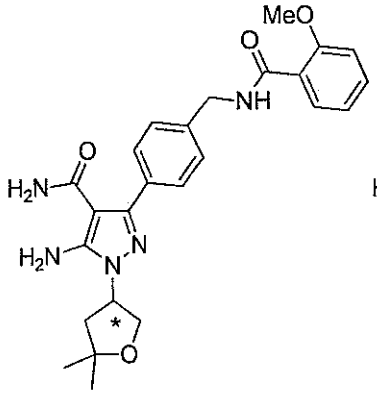
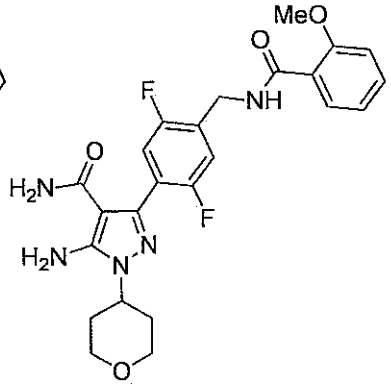
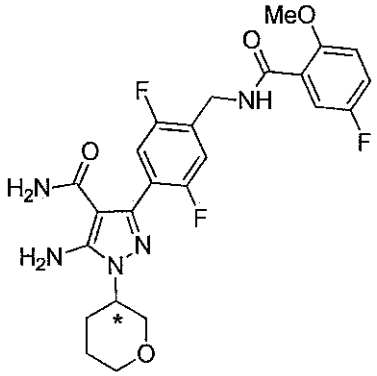
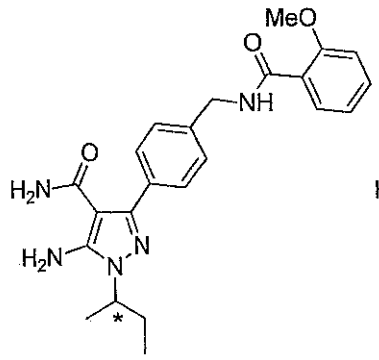
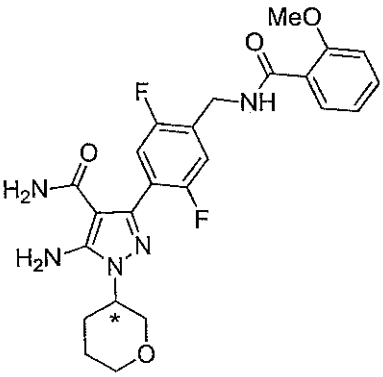
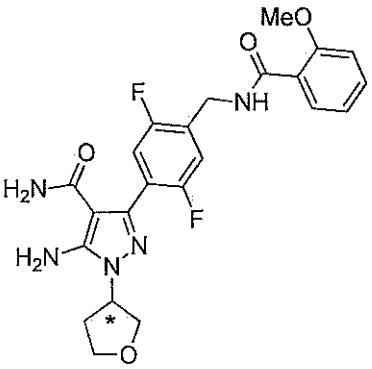


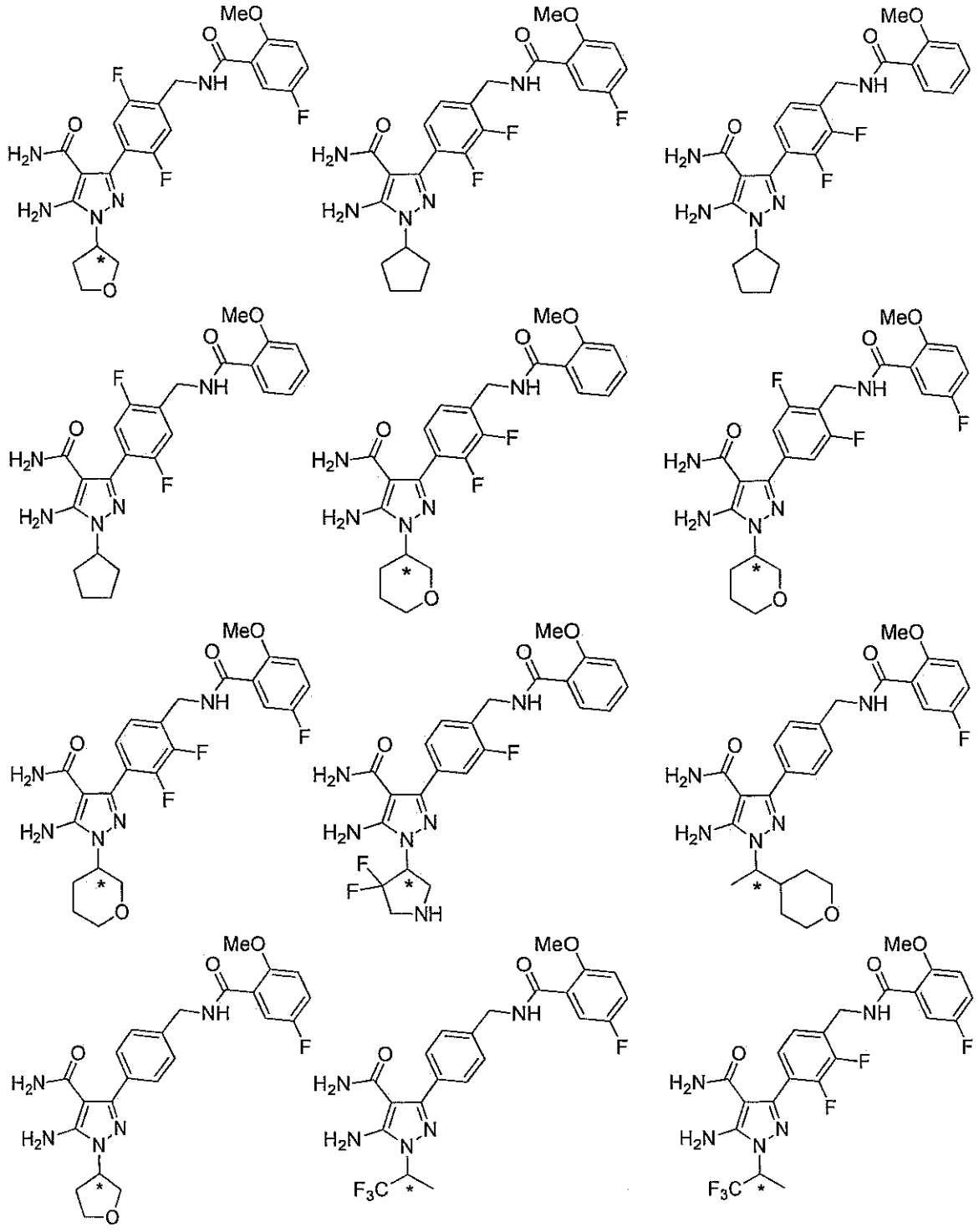












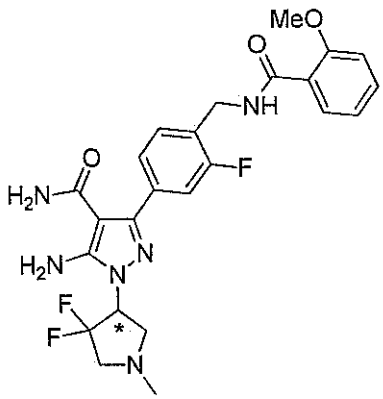
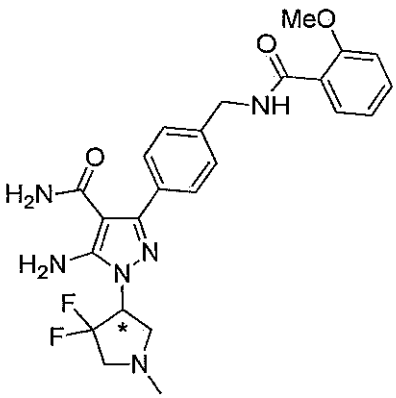
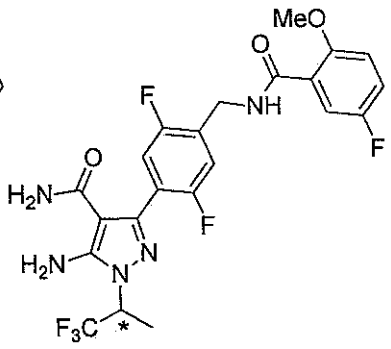
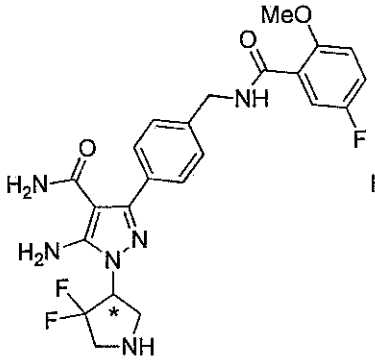
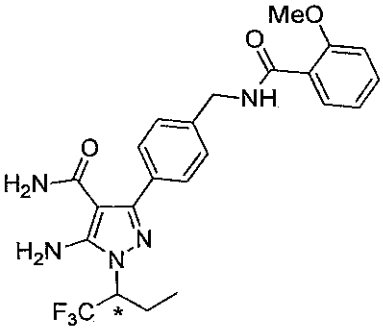
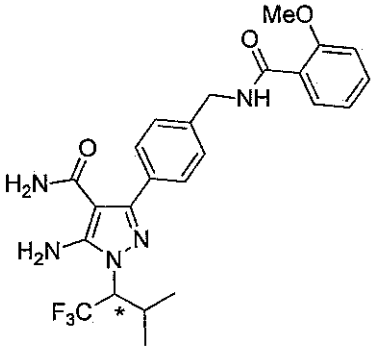
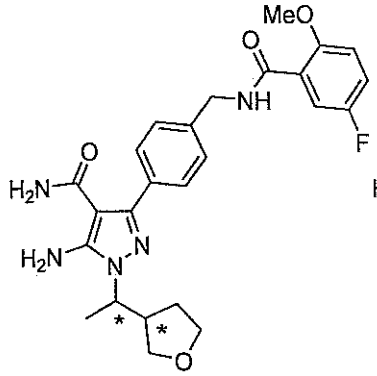
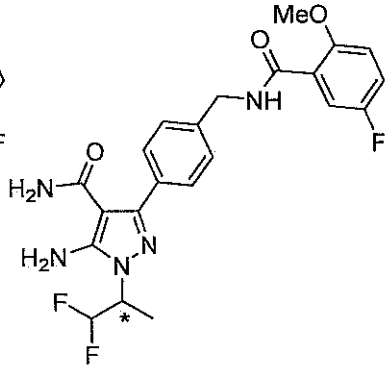
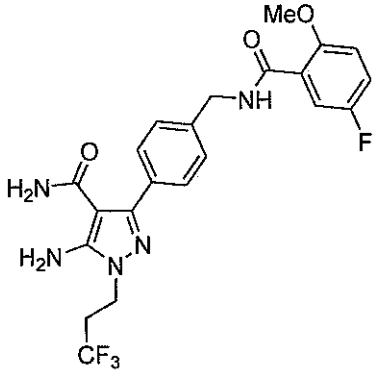
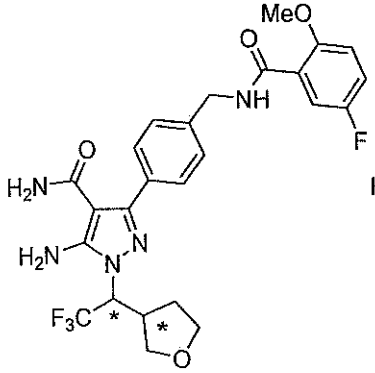
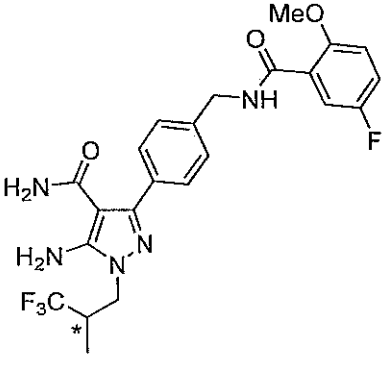
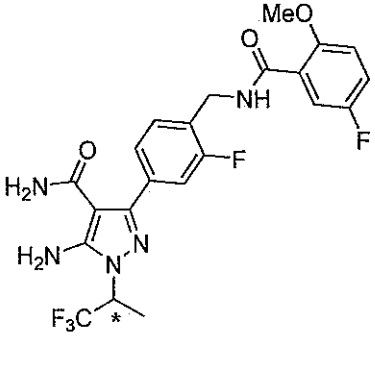











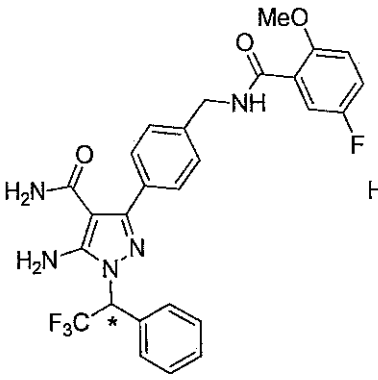
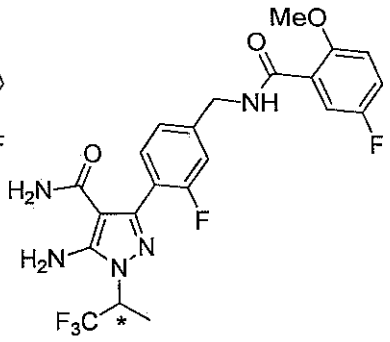
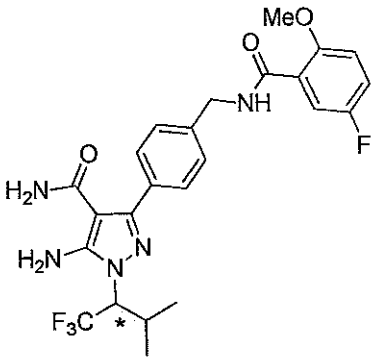
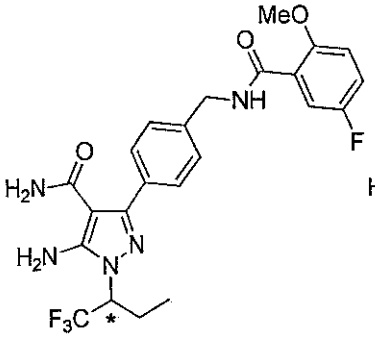
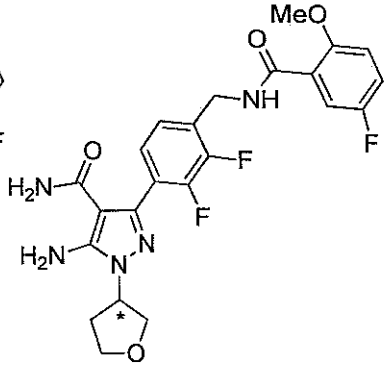
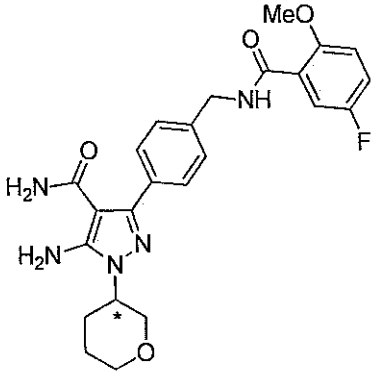
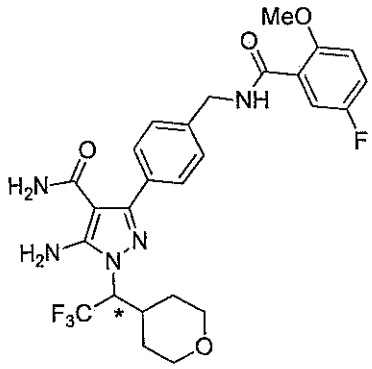
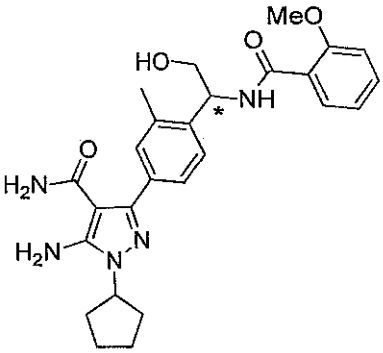
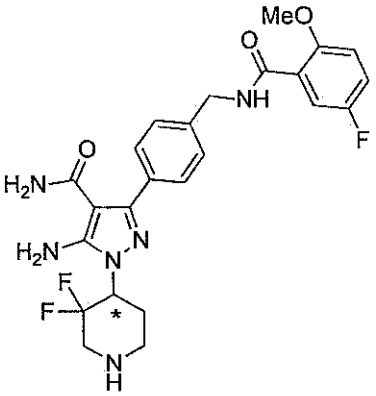
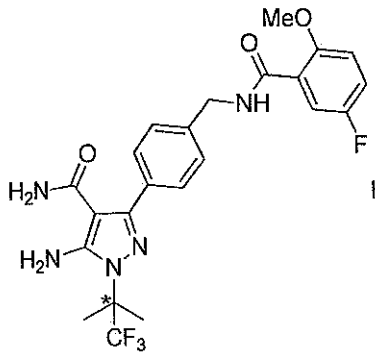
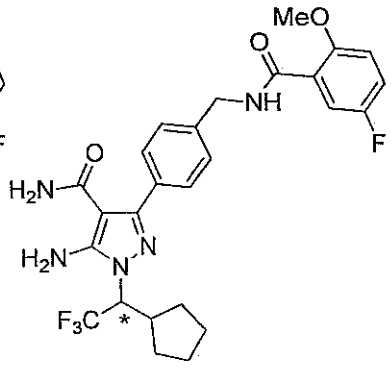
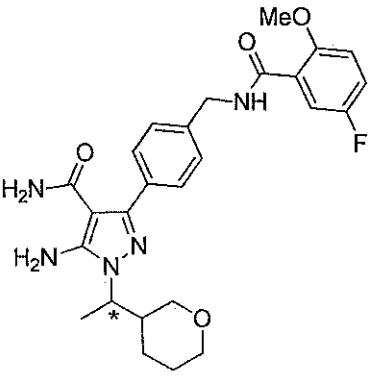













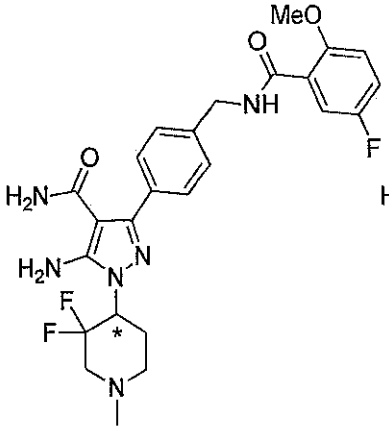
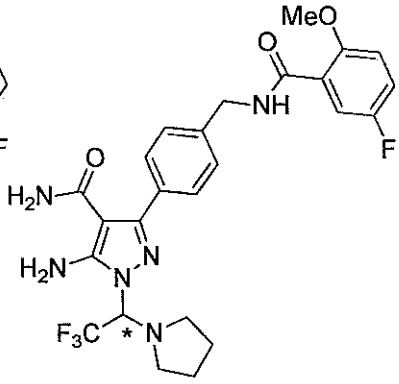
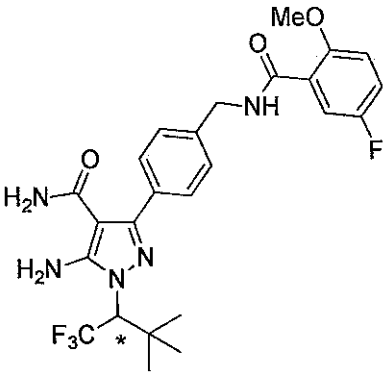
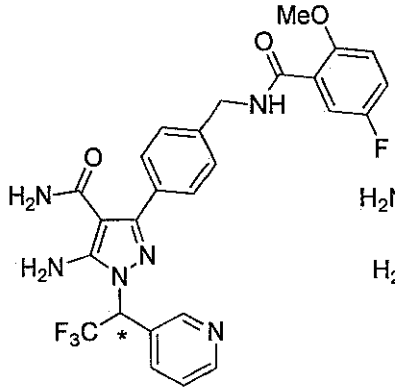
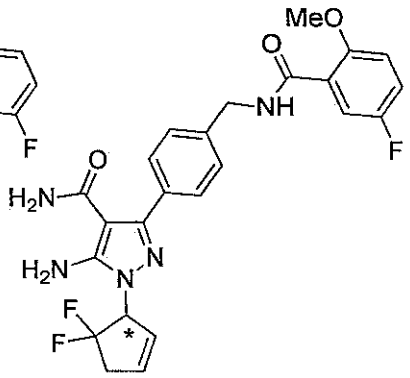
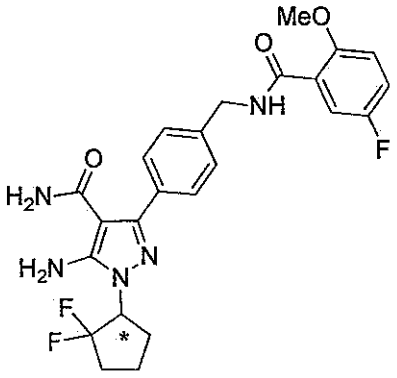
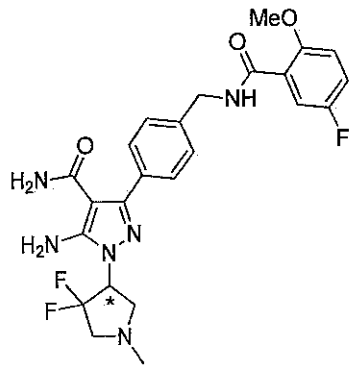
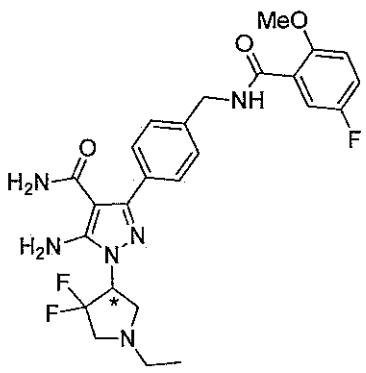
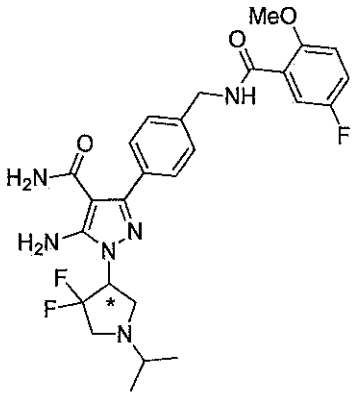
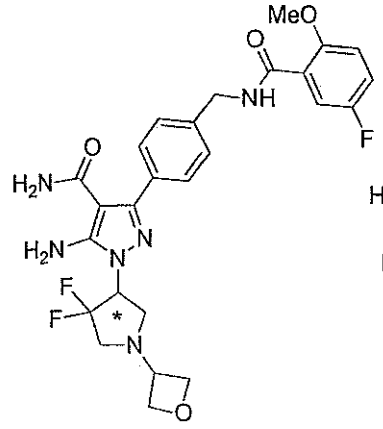
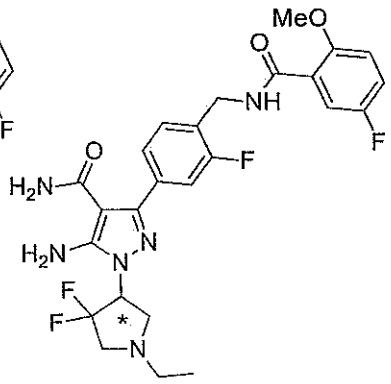
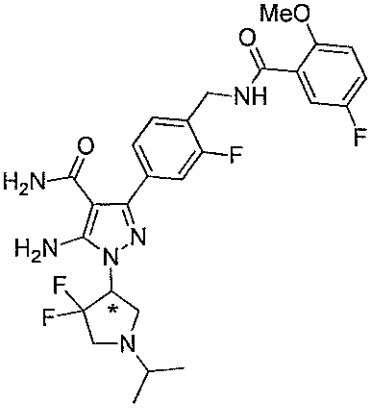













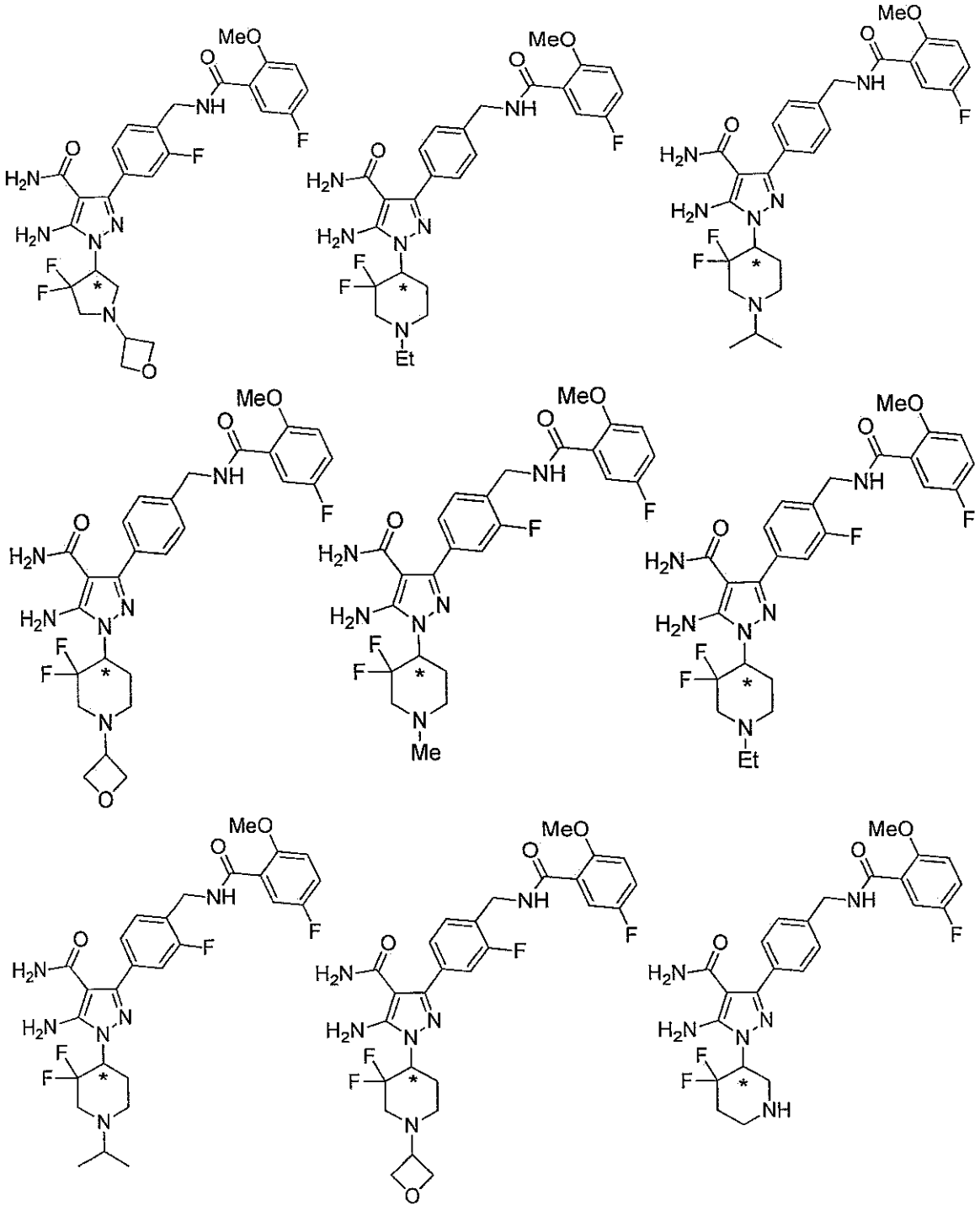













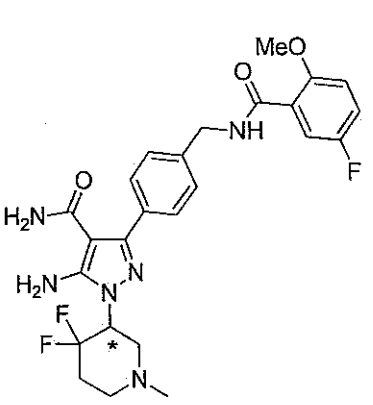
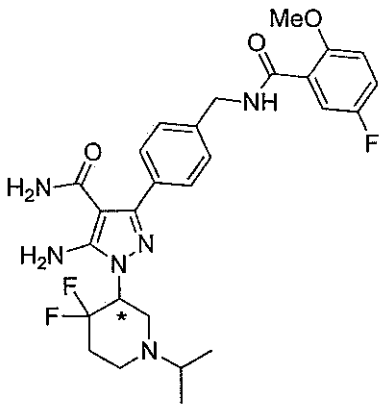
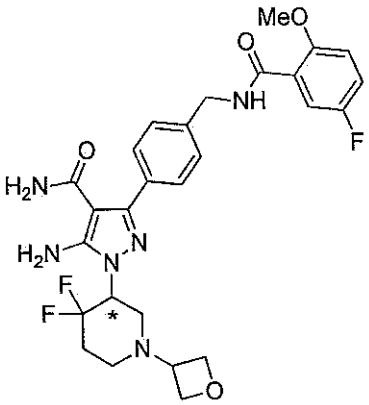
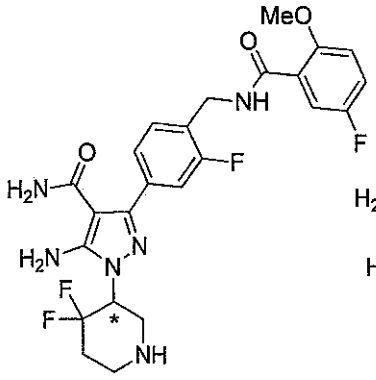
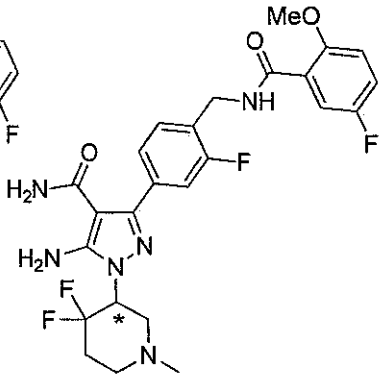
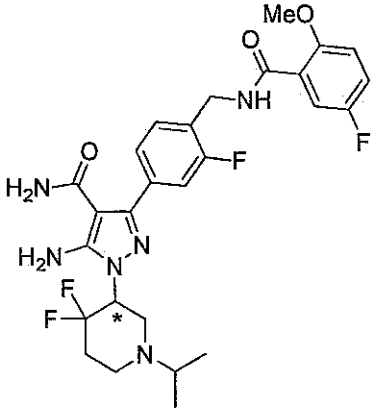
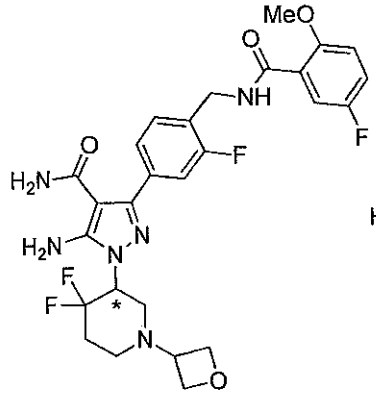
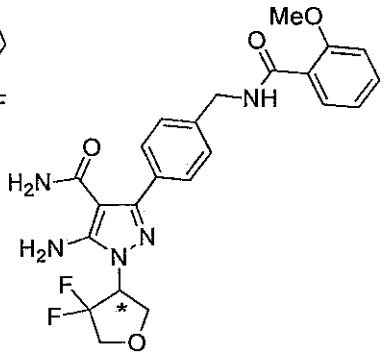
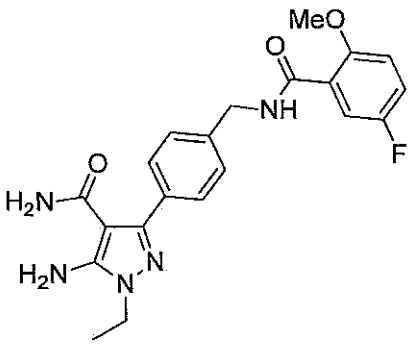
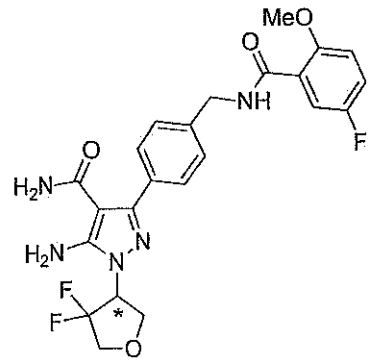
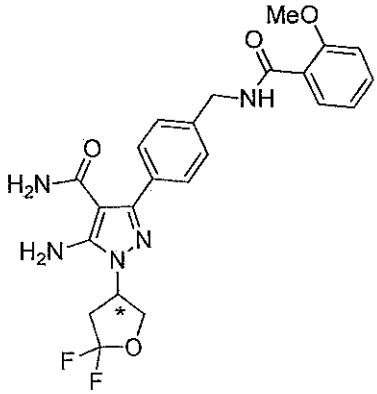
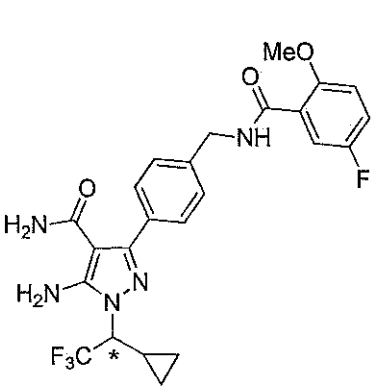


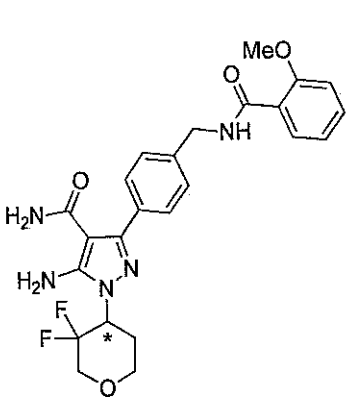
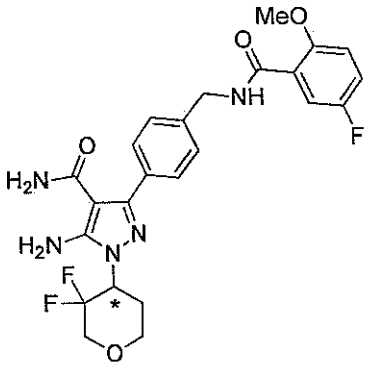
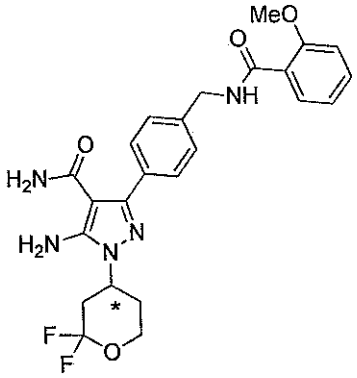
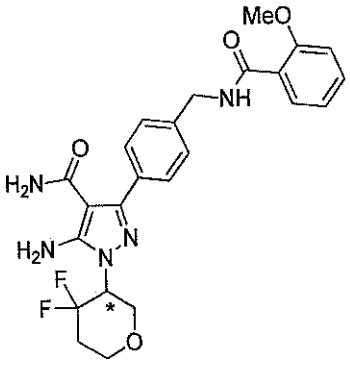
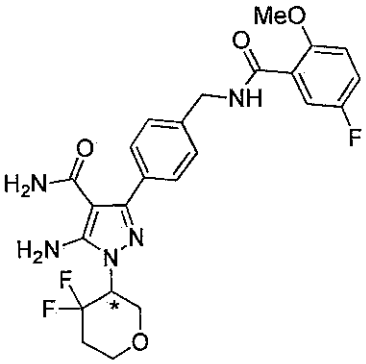
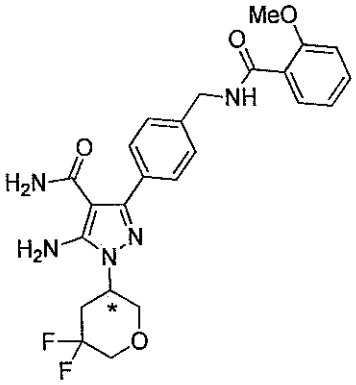
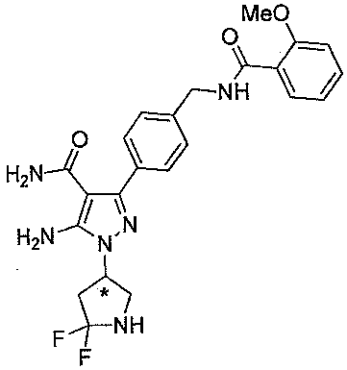
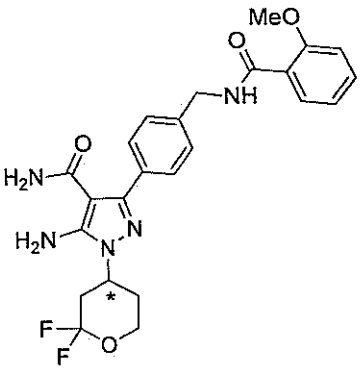
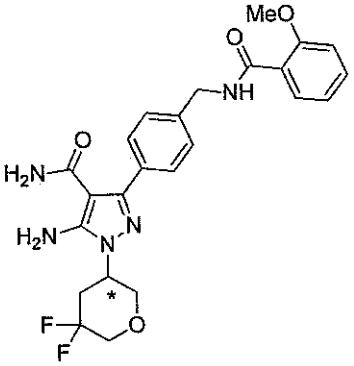
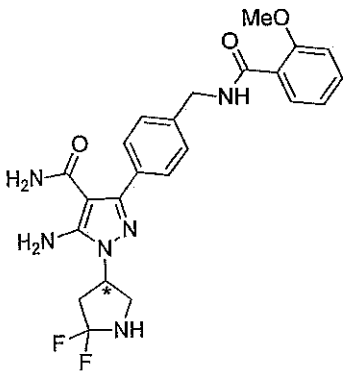
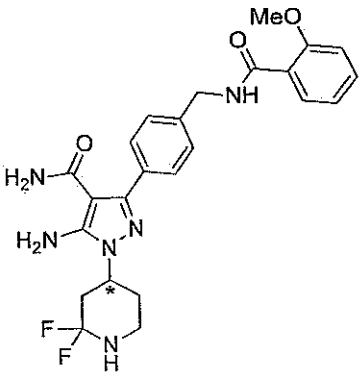
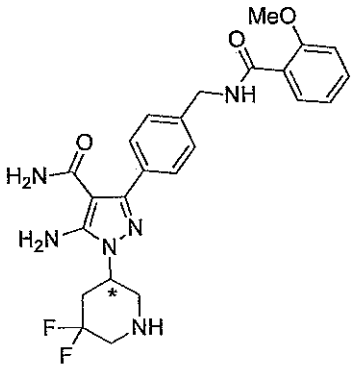













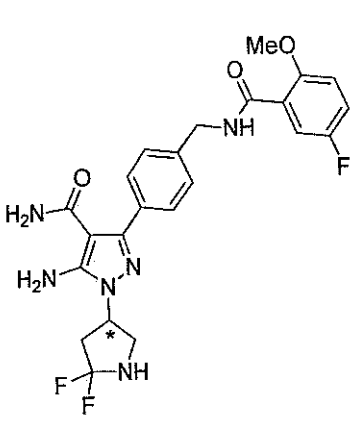
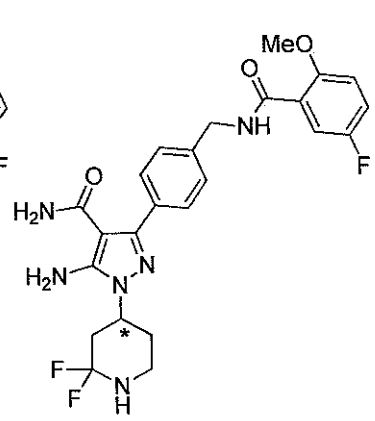
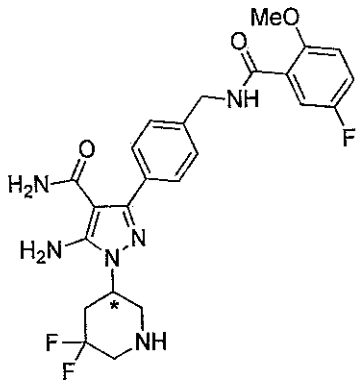
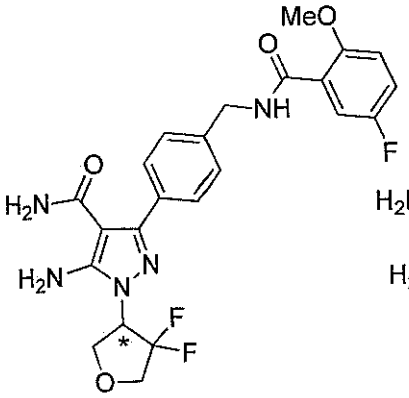
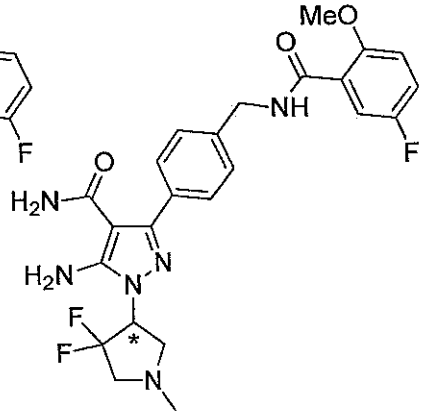
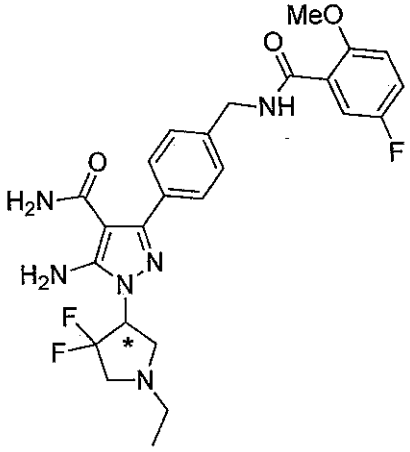
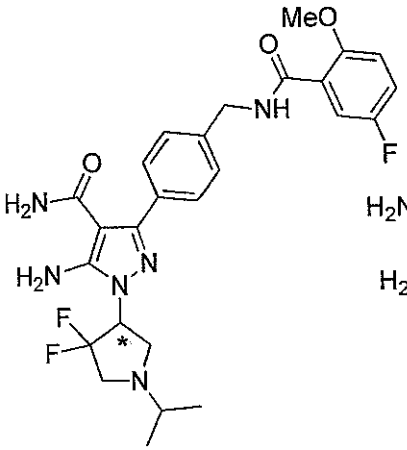
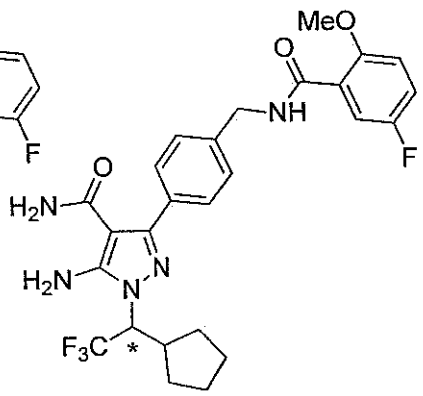
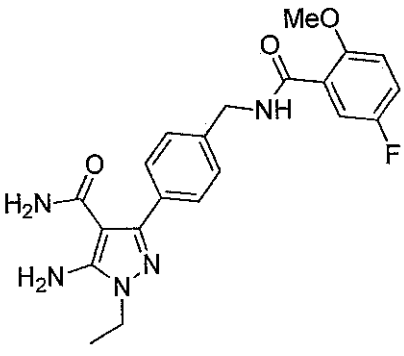













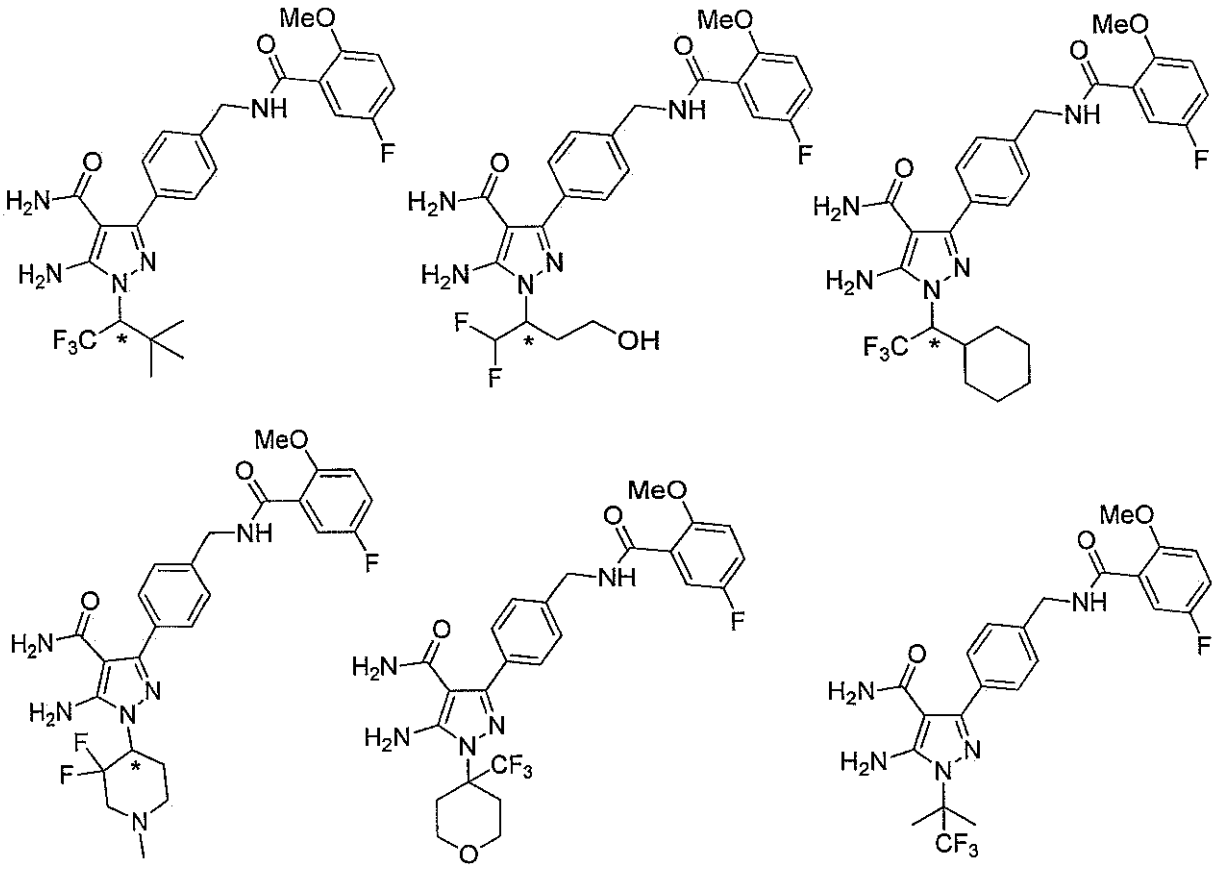















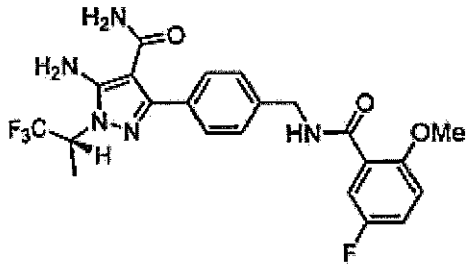















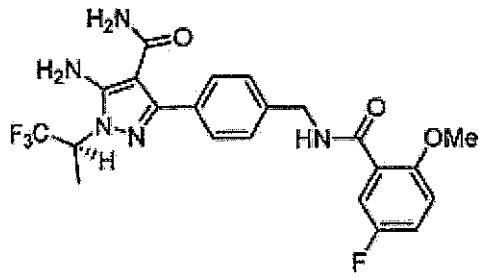
or a pharmaceutically acceptable salt thereof.

12. A compound of claim 1 wherein the compound is



, or a pharmaceutically acceptable salt thereof.

13. A compound of claim 1 wherein the compound is



, or a pharmaceutically acceptable salt thereof.

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

15. Use of a compound of any of claims 1 to 13 in the manufacture of a medicament for the treatment of a condition which is modulated by BTK, wherein the condition modulated by BTK is selected from the group consisting of:

cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

16. The use of claim 15, wherein the condition modulated by BTK is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B cell lymphoma, chronic lymphocyte leukemia, non-Hodgkin lymphoma preferably ABC-DLBCL, mantle cell lymphoma, follicular lymphoma, hairy cell leukemia B-cell non-Hodgi 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.

17. Use of a compound of any of claims 1 to 13 in the manufacture of a medicament for the treatment of: cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis.

18. Use of a compound of any of claims 1 to 13 in 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 preferably 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 (preferably, nonalcoholic steatohepatitis (NASH), cholestatic liver disease (preferably, primary biliary cirrhosis (PBC), cirrhosis, alcohol-induced liver fibrosis, biliary duct injury, biliary fibrosis, cholestasis or cholangiopathies, hepatic or liver fibrosis includes, but is not limited to, hepatic fibrosis associated with alcoholism, viral infection, preferably, hepatitis (preferably, hepatitis C, B or D), autoimmune hepatitis, nonalcoholic fatty liver disease (NAFLD), progressive massive fibrosis, exposure to toxins or irritants (preferably, alcohol, pharmaceutical drugs and environmental toxins), renal fibrosis (preferably, chronic kidney fibrosis), nephropathies associated with injury/fibrosis (preferably, chronic nephropathies associated with diabetes (preferably, 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.

19. Use of a compound of any of claims 1 to 13 in the manufacture of a medicament for the treatment of cancer, lymphoma, leukemia, autoimmune diseases, inflammatory disorders, heteroimmune conditions, or fibrosis, wherein medicament is formulated to be administered simultaneously, sequentially or separately with an additional anti-tumour agent.

20. A pharmaceutical composition, wherein the pharmaceutical composition comprises a compound of any of claims 1 to 13 and pharmaceutically acceptable excipients.

21. A pharmaceutical composition of claim 20 wherein the composition is a combination product and comprises an additional pharmaceutically active agent.