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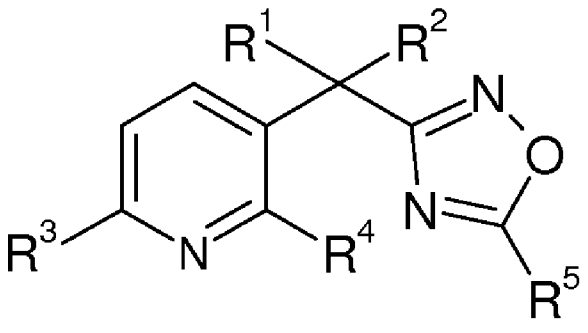
(54) Title: OXADIAZOLE INHIBITORS OF LEUKOTRIENE PRODUCTION



(I)

(57) Abstract: The present invention relates to compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein R^1-R^5 are as defined herein. The invention also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

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OXADIAZOLE INHIBITORS OF LEUKOTRIENE PRODUCTION

FIELD OF THE INVENTION

This invention relates to oxadiazoles that are useful as inhibitors of five lipoxygenase activating protein (FLAP) and are thus useful for treating a variety of diseases and disorders that are mediated or sustained through the activity of leukotrienes including asthma, allergy, rheumatoid arthritis, multiple sclerosis, inflammatory pain, acute chest syndrome and cardiovascular diseases including atherosclerosis, myocardial infarction and stroke. This invention also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

BACKGROUND OF THE INVENTION

Leukotrienes (LTs) and the biosynthetic pathway from arachidonic acid leading to their production have been the targets of drug discovery efforts for over twenty years. LTs are produced by several cell types including neutrophils, mast cells, eosinophils, basophils monocytes and macrophages. The first committed step in the intracellular synthesis of LTs involves oxidation of arachidonic acid by 5-lipoxygenase (5-LO) to LTA4, a process requiring the presence of the 18 kD integral membrane protein 5-lipoxygenase-activating protein (FLAP) (D.K. Miller et al., Nature, 1990, 343, 278-281; R.A.F. Dixon et al., Nature, 1990, 343, 282-284). Subsequent metabolism of LTA_4 leads to LTB_4, and the cysteinyl LTs- LTC_4, LTD_4 and LTE_4 (B. Samuelsson, Science, 1983, 220, 568-575). The cysteinyl LTs have potent smooth muscle constricting and bronchoconstricting effects and they stimulate mucous secretion and vascular leakage. LTB_4 is a potent chemotactic agent for leukocytes, and stimulates adhesion, aggregation and enzyme release.

Much of the early drug discovery effort in the LT area was directed towards the treatment of allergy, asthma and other inflammatory conditions. Research efforts have been directed towards numerous targets in the pathway including antagonists of LTB_4 and the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4, as well as inhibitors of 5-lipoxygenase (5-LO), LTA_4 hydrolase and inhibitors of 5-lipoxygenase activating protein (FLAP) (R.W. Friesen and D. Riendeau, Leukotriene Biosynthesis Inhibitors, Ann. Rep. Med. Chem., 2005, 40, 199-214). Years of effort in the above areas have yielded a few marketed products for the treatment of asthma including a 5-LO inhibitor, zileuton, and LT antagonists, montelukast, pranlukast and zafirlukast.

More recent work has implicated LTs in cardiovascular disease, including myocardial infarction, stroke and atherosclerosis (G. Riccioni et al., J. Leukoc. Biol., 2008, 1374-1378). FLAP and 5-LO were among the components of the 5-LO and LT cascade found in atherosclerotic lesions, suggesting their involvement in atherogenesis (R. Spanbroek et al., Proc. Natl. Acad. Sci. U.S.A., 2003, 100, 1238-1243). Pharmacological inhibition of FLAP has been reported to decrease atherosclerotic lesion size in animal models. In one study, oral dosing of the FLAP inhibitor MK-886 to apoE/LDL-R double knockout mice fed a high-fat diet from 2 months of age to 6 months led to a 56% decrease in plaque coverage in the aorta and a 43% decrease in the aortic root (J. Jawien et al., Eur. J. Clin. Invest., 2006, 36, 141-146). This plaque effect was coupled with a decrease in plaque-macrophage content and a concomitant increase in collagen and smooth muscle content which suggests a conversion to a more stable plaque phenotype. In another study, it was reported that administration of MK-886 via infusion to $ApoE^{-/-}$xCD4dnTβRII mice (apoE KO mice expressing a dominant-negative TGF-beta receptor which effectively removes all TGF-beta from the system) resulted in about a 40% decrease in plaque area in the aortic root (M. Back et al., Circ. Res., 2007, 100, 946-949). The mice were only treated for four weeks after plaque growth was already somewhat mature (12 weeks) thus raising the possibility of therapeutically treating atherosclerosis via this mechanism. In a study examining human atherosclerotic lesions, it was found that the expression of FLAP, 5-LO and LTA_4 hydrolase was significantly increased compared to healthy controls (H. Qiu et al., Proc. Natl. Acad. Sci. U.S.A., 103, 21, 8161-8166). Similar studies suggest

that inhibition of the LT pathway, for example by inhibition of FLAP, would be useful for the treatment of atherosclerosis (for reviews, see M. Back Curr. Athero. Reports, 2008 10, 244-251 and Curr. Pharm. Des., 2009, 15, 3116-3132).

In addition to the work cited above, many other studies have been directed towards understanding the biological actions of LTs and the role of LTs in disease. These studies have implicated LTs as having a possible role in numerous diseases or conditions (for a review, see M. Peters-Golden and W.R. Henderson, Jr., M.D., N. Engl. J. Med., 2007, 357, 1841-1854). In addition to the specific diseases cited above, LTs have been implicated as having a possible role in numerous allergic, pulmonary, fibrotic, inflammatory and cardiovascular diseases, as well as cancer. Inhibition of FLAP is also reported to be useful for treating renal diseases such as diabetes-induced proteinuria (see for example J. M. Valdivieso et al., Journal of Nephrology, 2003, 16, 85-94 and A Montero et al., Journal of Nephrology, 2003, 16, 682-690).

A number of FLAP inhibitors have been reported in the scientific literature (see for example J.F. Evans et al., Trends in Pharmacological Sciences, 2008, 72-78) and in U.S. patents. Some have been evaluated in clinical trials for asthma, including MK-886, MK-591, and BAY X1005, also known as DG-031. More recently, the FLAP inhibitor AM-103 (J.H. Hutchinson et al., J. Med. Chem. 52, 5803-5815) has been evaluated in clinical trials, based on its anti-inflammatory properties (D.S. Lorrain et al., J. Pharm. Exp. Ther., 2009, DOI:10.1124/jpet.109.158089). Subsequently, it was replaced by the back-up compound AM-803 (GSK-2190915) for the treatment of respiratory diseases. DG-031 has also been in clinical trials to evaluate its effect on biomarkers for myocardial infarction risk and showed a dose-dependent suppression of several biomarkers for the disease (H. Hakonarson et al., JAMA, 2005, 293, 2245-2256). MK-591 was shown in a clinical trial to reduce proteinuria in human glomerulonephritis (see for example A. Guash et al., Kidney International, 1999, 56, 291-267).

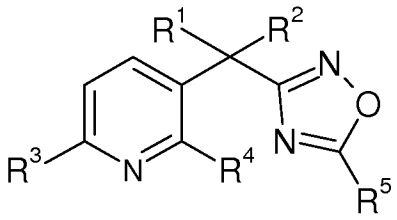
However, to date, no FLAP inhibitor has been approved as a marketed drug.

BRIEF SUMMARY OF THE INVENTION

The present invention provides novel compounds which inhibit 5-lipoxygenase activating protein (FLAP) and are thus useful for treating a variety of diseases and disorders that are mediated or sustained through the activity of leukotrienes, including allergic, pulmonary, fibrotic, inflammatory and cardiovascular diseases and cancer. This invention also relates to pharmaceutical compositions comprising these compounds, methods of using these compounds in the treatment of various diseases and disorders, processes for preparing these compounds and intermediates useful in these processes.

DETAILED DESCRIPTION OF THE INVENTION

In its first broadest embodiment, the present invention relates to a compound of formula I:



I

wherein:

R^1 and R^2 are each independently hydrogen, C_{1-7} alkyl or C_{3-10} carbocycle, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is a 5-11 membered heteroaryl ring containing one to three heteroatoms selected from nitrogen, oxygen and sulfur, wherein the heteroaryl ring is optionally independently substituted with one to three groups selected from C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-3} alkylhydroxy, amino, C_{1-3} alkylamino,C_{1-3} dialkylamino, oxo, -CN, halogen and 5-6 membered heteroaryl optionally substituted with one to three methyl groups;

R^4 is hydrogen, C_{1-3} alkyl, halogen or nitrile;

R^5 is C_{1-6} alkyl, C_{3-10} carbocycle, 5-11 membered heterocycle, aryl, 5-11 membered heteroaryl, -C(O)-R^6 or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

R^6 is C_{3-8} heterocycle or –NH-5-6 membered heterocycle, each optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11} ;

$R^7$and R^8 are each independently hydrogen or C_{1-6} alkyl, wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, -N(R^{12})(R^{13}) , 3-6 membered heterocycle, C_{1-6}alkoxy, halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, -C(O)N(R^{12})(R^{13}) or -$S(O)_n$$C_{1-6}$alkyl,

(g) C_{1-6}alkoxy,

(h) -N(R^{12})(R^{13}),

(i) -$S(O)_n$$C_{1-6}$alkyl,

(j) $–CO_2R^{12}$,

(k) -C(O)N(R^{12})(R^{13}),

(l) $–S(O)_2N(R^{12})(R^{13})$,

(m) a 3-10 membered heterocyclic group optionally substituted with one to three C_{1-6} alkyl groups or oxo,

(n') oxo,

(o) –C(O)-C_{1-3} alkyl;

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, –C_{1-6}alkyl, C(O)C_{1-6}alkyl C_{3-6} carbocycle and a 3-6 membered heterocyclic group, each of which is optionally independently substituted with one to three C_{1-6}alkyl groups, halogen, –OH, C_{1-6}alkoxy, -C(O)N(R^{14})(R^{15}), -S(O)$_n$$C_{1-6}$alkyl, CN, a 3-6 membered heterocyclic group, -OC_{1-6}alkyl, CF_3, or;

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and R^{15} are each independently selected from –H and –C_{1-6}alkyl;

n is 0, 1 or 2;
or a pharmaceutically acceptable salt thereof.

In a second embodiment, the present invention relates to a compound as described in the broadest embodiment above, wherein:

R^1 and R^2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cylohexyl, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, thienyl, furanyl or thiazolyl, wherein each heteroaryl ring is optionally independently substituted with one to three groups selected from C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylhydroxy, amino, C_{1-3} alkylamino and C_{1-3} dialkylamino, oxo, -CN, halogen and 5-6 membered heteroaryl optionally substituted with one to three methyl groups; or
R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;

R^4 is hydrogen, methyl or fluoro;

R^5 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, tetrahydropyranyl, pyrrolyl, thienyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, indolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, -C(O)-R^6 or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

R^6 is piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl or -NH-piperadinyl each optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen or C_{1-5} alkyl wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, $-N(R^{12})(R^{13})$, 3-6 membered heterocycle, C_{1-6}alkoxy , halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-C(O)N(R^{12})(R^{13})$ or $-S(O)_nC_{1-6}$alkyl,

(g) C_{1-6}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_nC_{1-6}$alkyl,

(j) $-CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $-S(O)_2N(R^{12})(R^{13})$,

(m) a 3-8 membered heterocyclic group optionally substituted with one to three C_{1-6} alkyl groups or oxo,

(n') oxo,

(o) $-C(O)-C_{1-3}$ alkyl,

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, $-C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, C_{3-6} carbocycle, and a 3-6 membered heterocyclic group, each of which is optionally independently substituted with one to three C_{1-6}alkyl groups, halogen, –OH, C_{1-6}alkoxy, $-C(O)N(R^{14})(R^{15})$, $-S(O)_nC_{1-6}$alkyl, CN, a 3-6 membered heterocyclic group, $-OC_{1-6}$alkyl, CF_3; or,

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached can form a heterocyclyl ring optionally substituted with one to three –OH, CN, $-OC_{1-6}$alkyl or oxo;

R^{14} and R^{15} are each independently selected from –H and $-C_{1-4}$alkyl;

n is 1 or 2;
or a pharmaceutically acceptable salt thereof.

In a third embodiment, the present invention relates to a compound as described in any of the preceding embodiments above, wherein:

R^1 and R^2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl or cyclobutyl, with the proviso that both R^1 and R^2 are not hydrogen;
or a pharmaceutically acceptable salt thereof.

In a fourth embodiment there is provided a compound of formula (I) as described in any of the preceding embodiments above, wherein:

R^3 is pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl, wherein each heteroaryl ring is optionally independently substituted with one to two groups selected from C_{1-3} alkyl, C_1-C_3 alkoxy, C_{1-2} alkylhydroxy, dimethylpyrrole, oxo, -CN, halogen, C_{1-3} alkylamino and amino;or
R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;
or a pharmaceutically acceptable salt thereof.

In a fifth embodiment there is provided a compound as described in any of the preceding embodiments above, wherein:

R^5 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, -C(O)-piperizinyl, -C(O)-piperidinyl, -C(O)-NH-piperidinyl or $-NR^7R^8$, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen or C_1-C_5 alkyl wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,
(b) -OH,
(c) halogen,
(d) -CN,
(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-N(R^{12})(R^{13})$, morpholinyl, piperazinyl, C_{1-6}alkoxy, $-SO_2C_{1-3}$alkyl or $-C(O)N(R^{12})(R^{13})$,

(g) C_{1-3}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_2C_{1-6}$alkyl,

(j) $–CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $–S(O)_2N(R^{12})(R^{13})$,

(m) morpholinyl, piperazinyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, dioxotetrahydrothienyl or oxetanyl each optionally substituted with a methyl group,

(n') oxo,

(o) $–C(O)-CH_3$,

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, C_{3-6} carbocycle, 3-6 membered heterocycle and $–C_{1-6}$alkyl, wherein the alkyl group is optionally substituted with one to three halogen, –OH, C_{1-6}alkoxy, 5-6 membered heterocyclic group, $-C(O)N(R^{14})(R^{15})$ or $-S(O)_2C_{1-6}$alkyl; or

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring selected from pyrrolidinyl, piperidinyl and morpholinyl, wherein each heterocyclic ring is optionally substituted with one to three –OH, CN, $-OC_{1-6}$alkyl or oxo;

R^{14} and $R^{15}$are each independently selected from –H and $–C_{1-4}$alkyl;

or a pharmaceutically acceptable salt thereof.

In a sixth embodiment there is provided a compound of formula (I) as described in the first or second embodiment above, wherein:

R^1 and R^2 are each independently hydrogen, methyl, isopropyl, or cyclopropyl, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl, wherein each heteroaryl ring is optionally independently substituted with one to two groups selected from C_{1-3} alkyl, methoxy,-CH_2OH, amino, -NH-CH_3, oxo, -CN, fluoro and 2,5- dimethylpyrrole; or
R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;
R^4 is hydrogen;

R^5 is pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, pyrazolopyrimidinyl, phenyl or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen, methyl or ethyl optionally substituted with hydroxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,
(b) -OH,
(c) halogen,
(d) -CN,
(e) -CF_3,
(f) C_{1-6}alkyl optionally substituted with one to three –OH, -N(R^{12})(R^{13}) , morpholinyl, piperazinyl, C_{1-3}alkoxy, halogen, CN, –CO_2R^{12}, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, -SO_2CH_3 or -C(O)N(R^{12})(R^{13}),
(g) C_{1-3}alkoxy,
(h) -N(R^{12})(R^{13}),
(i) -$S(O)_2C_{1-2}$alkyl,
(j) –CO_2R^{12},
(k) -C(O)N(R^{12})(R^{13}),
(l) –$S(O)_2$N(R^{12})(R^{13}),

(m) morpholinyl, piperazinyl, tetrahydropyranyl, dioxotetrahydrothienyl or oxetanyl each optionally substituted with a methyl group,

(n') oxo,

(o) –C(O)-CH_3,

(p) C_{1-4}alkenyl substituted optionally substituted with a –OH;

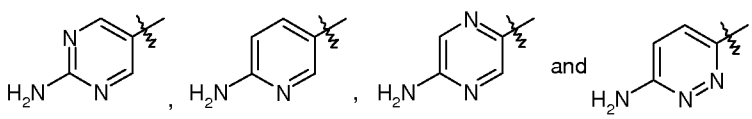
R^{12} and R^{13} are each independently selected from –H, cyclopropyl, tetrahydrofuranyl, tetrahydropyranyl and –C_{1-6}alkyl, wherein the alkyl group is optionally independently substituted with one to three halogen, –OH, C_{1-6}alkoxy, tetrahydrofuranyl, tetrahydropyranyl, -C(O)N(R^{14})(R^{15}), or -$S(O)_2C_{1-6}$alkyl; or

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring selected from pyrrolidinyl, piperidinyl and morpholinyl, wherein each heterocyclic ring is optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and $R^{15}$are each independently selected from –H and –C_{1-4}alkyl;
or a pharmaceutically acceptable salt thereof.

In a seventh embodiment there is provided a compound as described in the sixth embodiment above, wherein:
R^1 is methyl,
R^2 is selected from methyl, isopropyl and cyclopropyl;
or a pharmaceutically acceptable salt thereof.

In an eighth embodiment there is provided a compound as described in the sixth embodiment above, wherein:
R^3 is selected from



or a pharmaceutically acceptable salt thereof.

In a ninth embodiment there is provided a compound as described in the sixth embodiment above, wherein:

R^5 is pyrazolyl optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11} ;

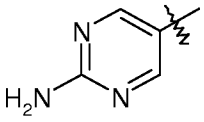
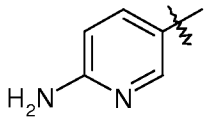
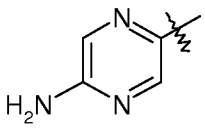
or a pharmaceutically acceptable salt thereof.

In a tenth embodiment there is provided a compound as described in the sixth embodiment above, wherein:

R^1 is methyl,

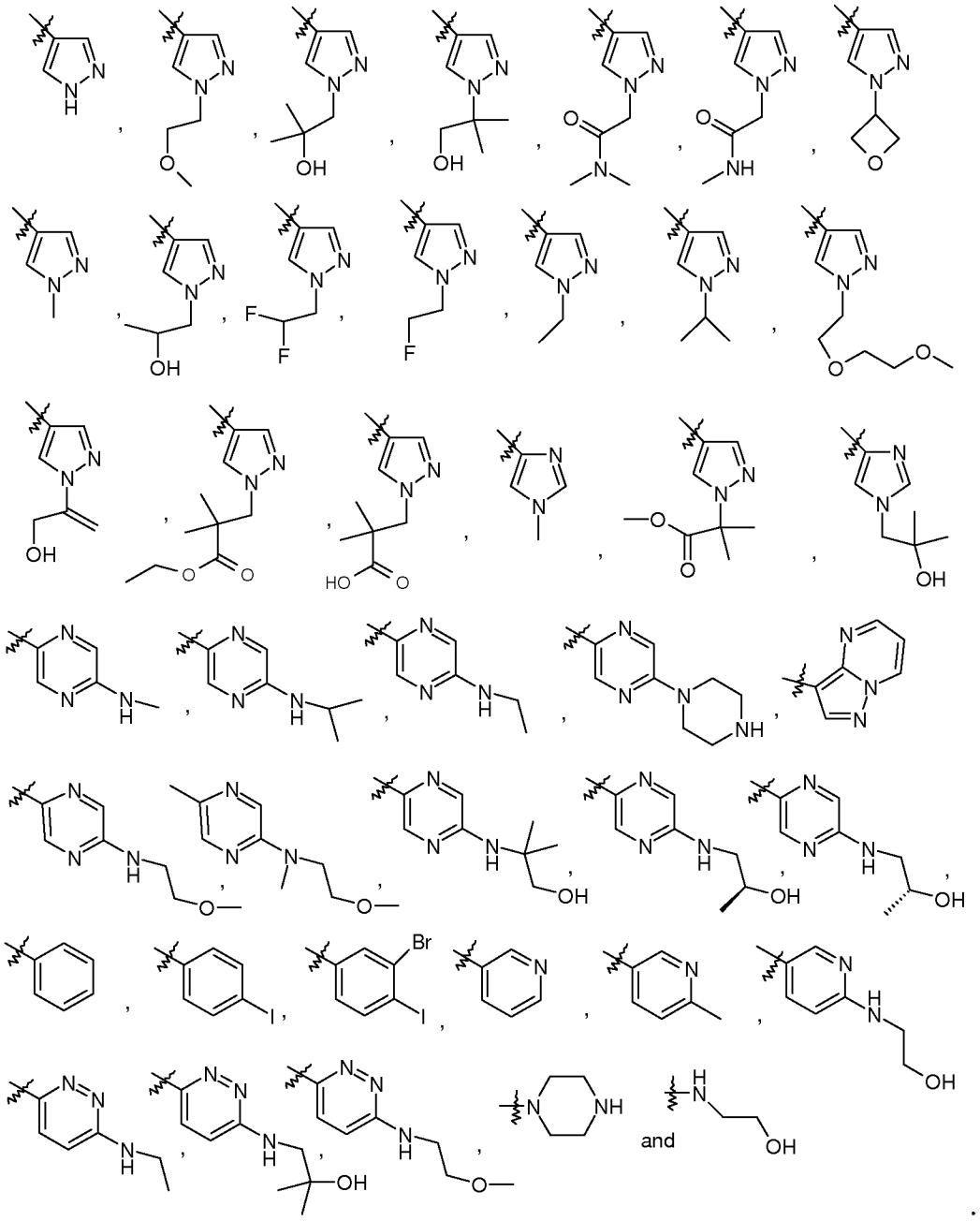
R^2 is selected from methyl, isopropyl and cyclopropyl;

R^3 is selected from


, 
, and 
;

R^4 is hydrogen,

R^5 is selected from



;

or pharmaceutically acceptable salts thereof.

In an eleventh embodiment there is provided a compound as described in the tenth embodiment above, wherein:

R^2 is cyclopropyl;

or a pharmaceutically acceptable salt thereof.

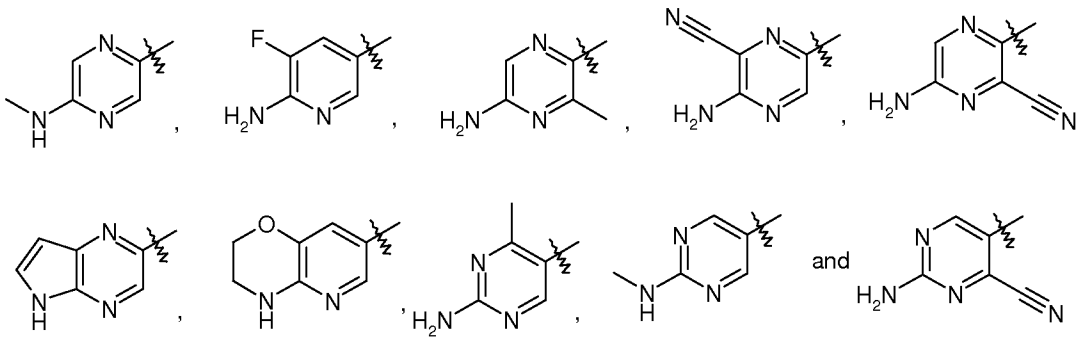
In a twelfth embodiment there is provided a compound as described in the tenth embodiment above, wherein:

R^2 is selected from methyl and isopropyl;

or a pharmaceutically acceptable salt thereof.

In a thirteenth embodiment there is provided a compound as described in the sixth embodiment above, wherein:

R^3 is selected from



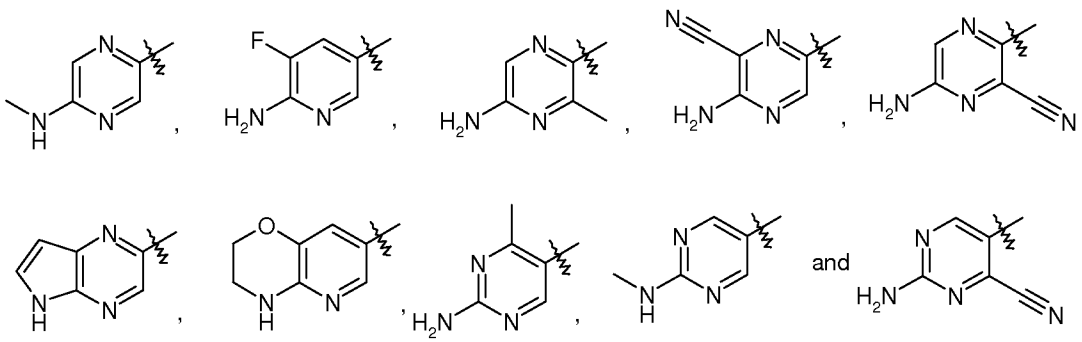
or a pharmaceutically acceptable salt thereof.

In a fourteenth embodiment there is provided a compound as described in the sixth embodiment above, wherein:

R^1 is methyl,

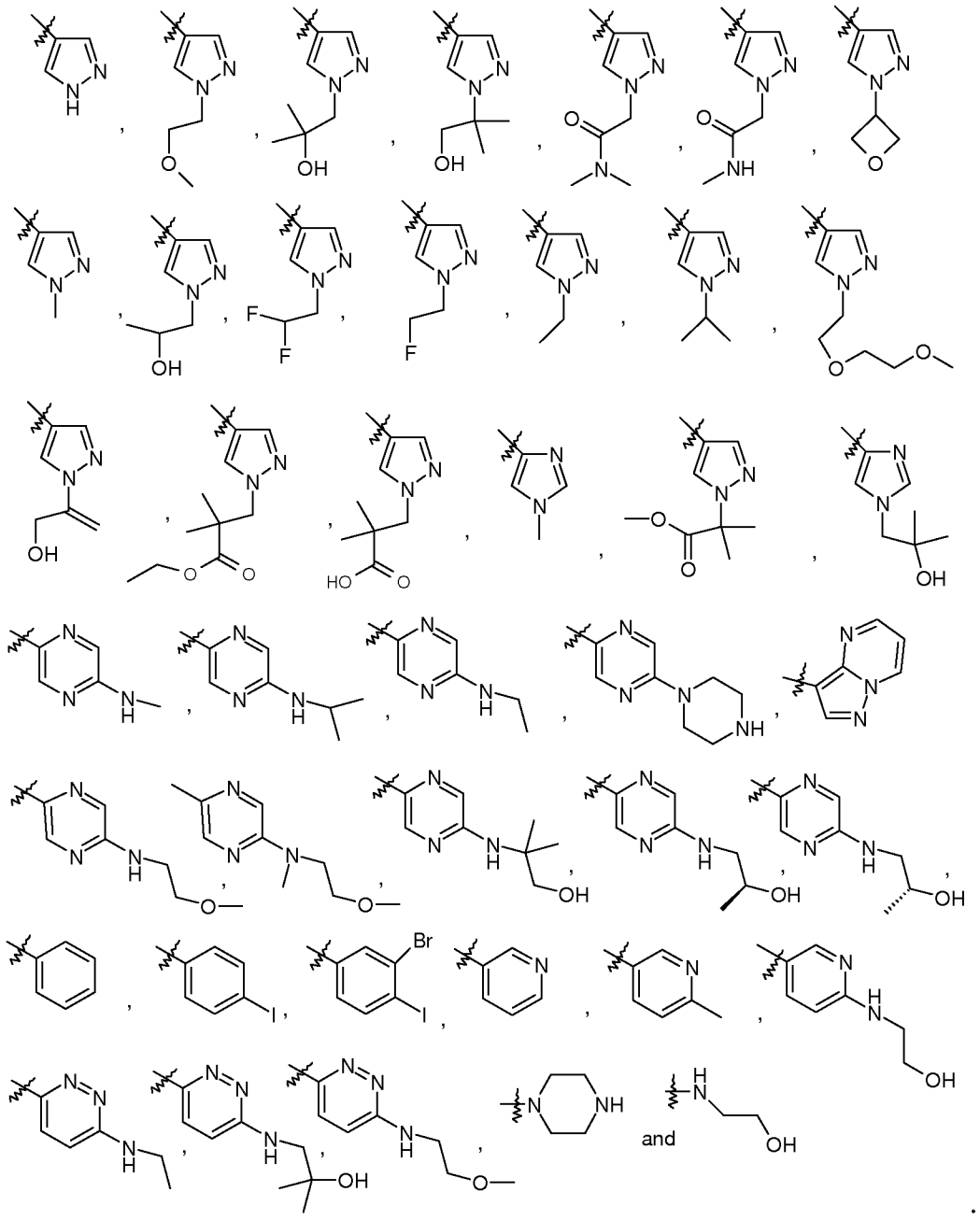
R^2 is selected from methyl, isopropyl and cyclopropyl;

R^3 is selected from



R^4 is hydrogen,

R^5 is selected from

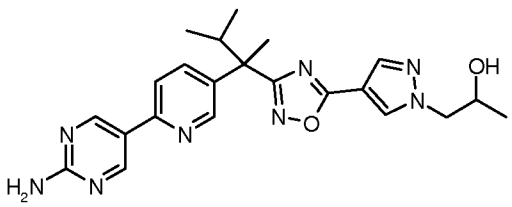
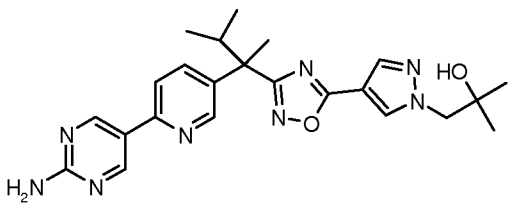
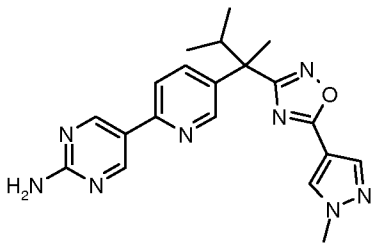
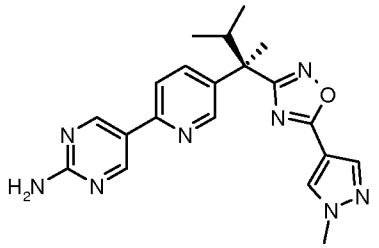


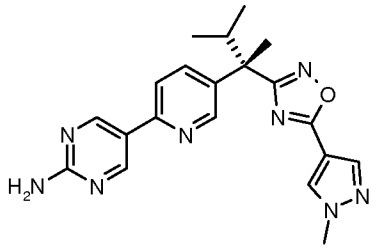
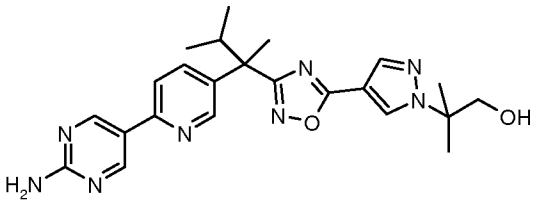
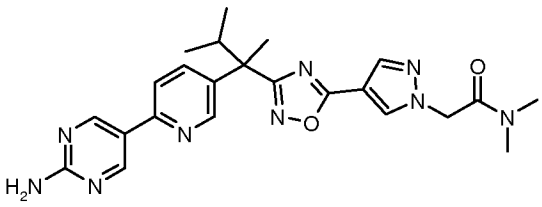
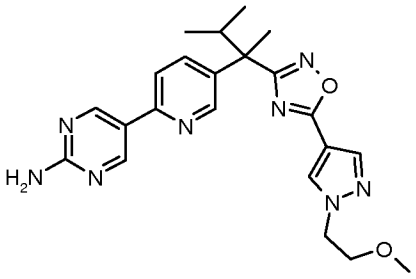
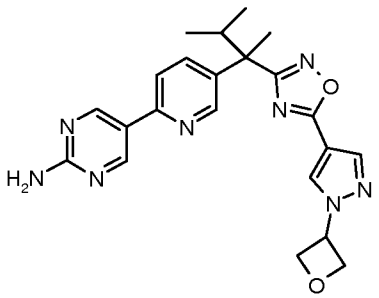
;

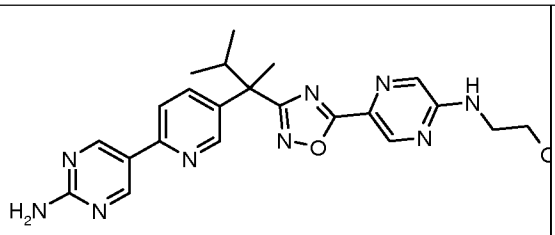
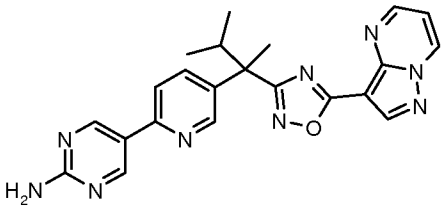
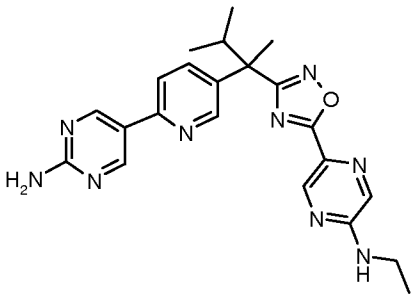
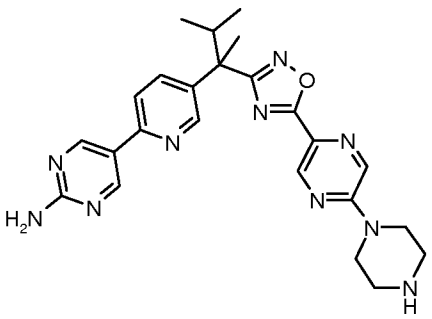
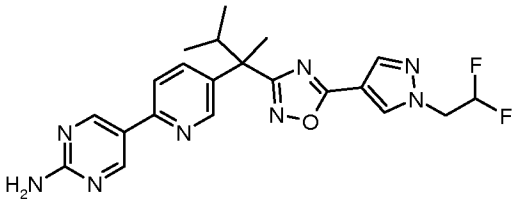
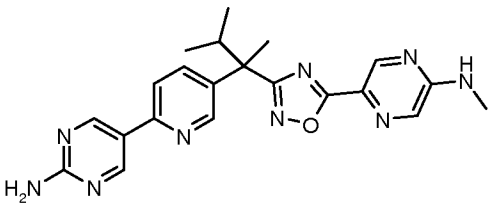
or pharmaceutically acceptable salts thereof.

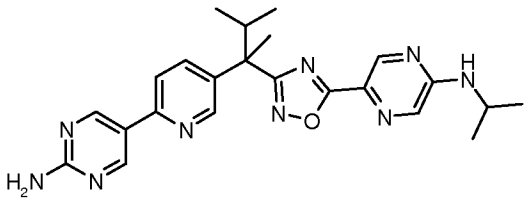
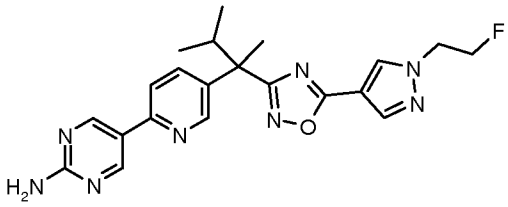
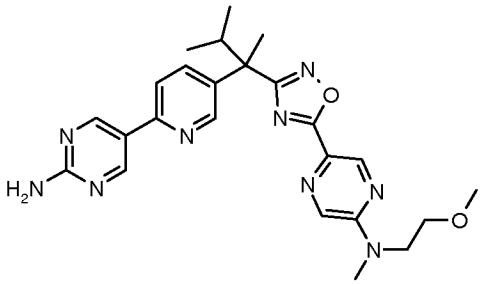
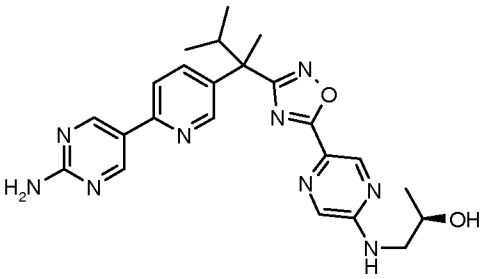
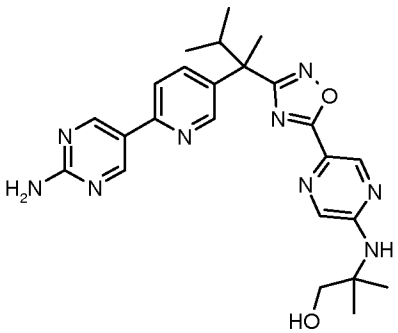
The following are representative compounds of the invention which can be made by the general synthetic schemes, the examples, and known methods in the art.

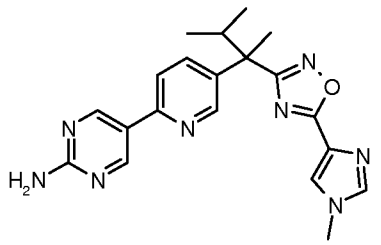
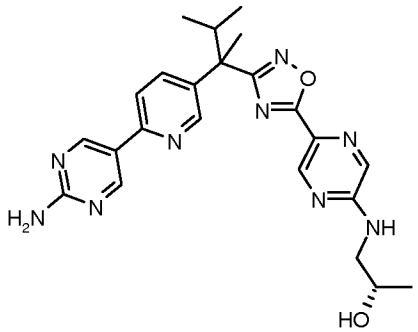
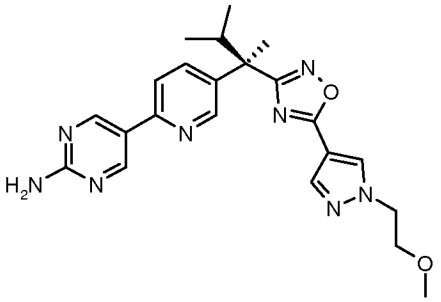
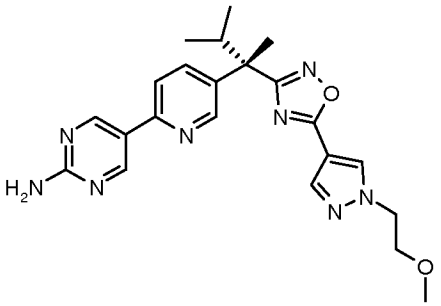
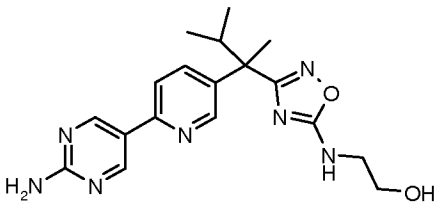
Table I

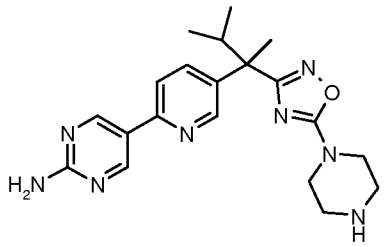
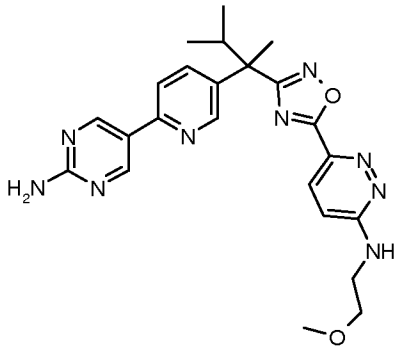
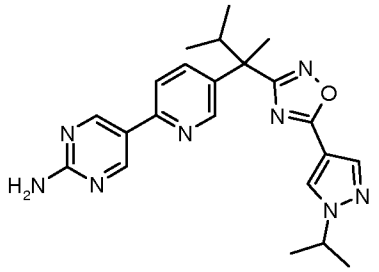
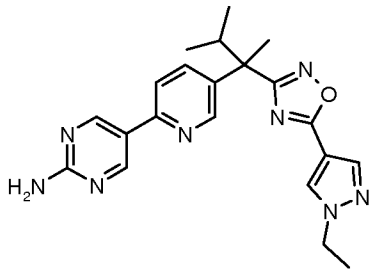
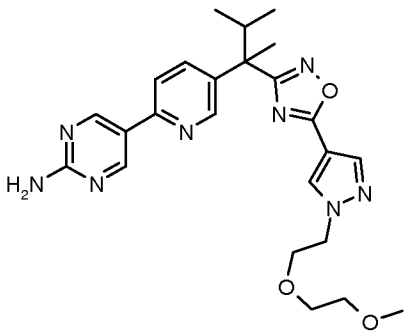
Example	Structure	Name
1		1-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]propan-2-ol
2		1-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
3		5-(5-{3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
4		5-(5-{(2R)-3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine

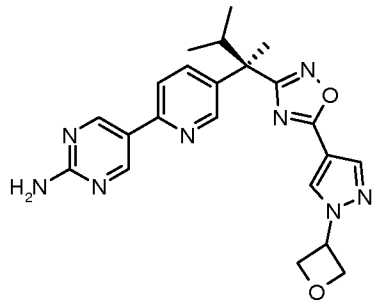
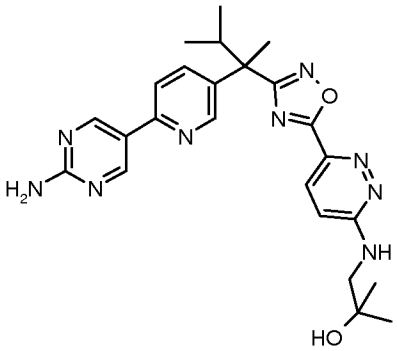
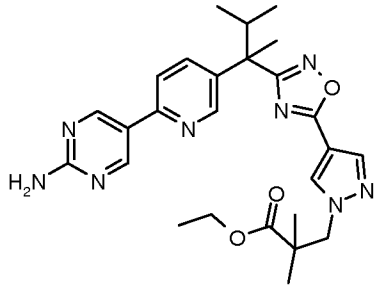
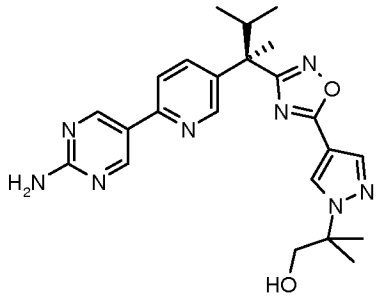
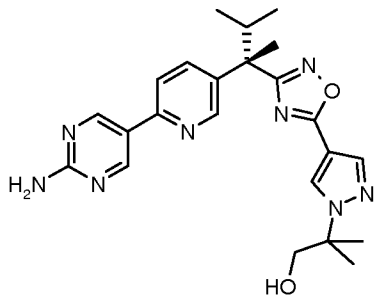
5		5-(5-{(2S)-3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
6		2-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-1-ol
7		2-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide
8		5-[5-(2-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl)pyridin-2-yl]pyrimidin-2-amine
9		5-[5-(3-methyl-2-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-amine

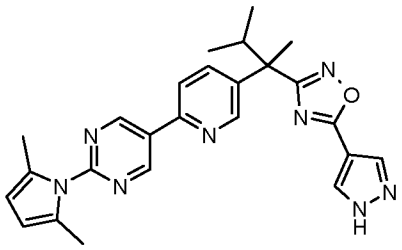
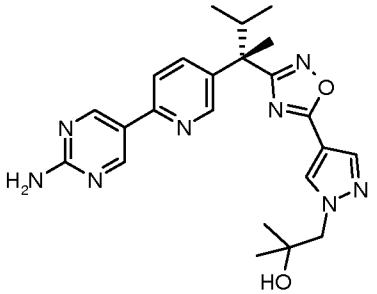
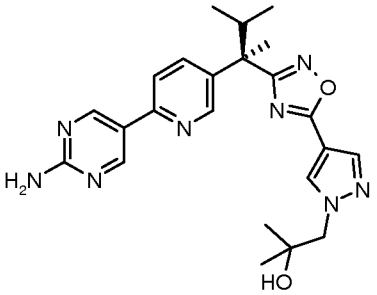
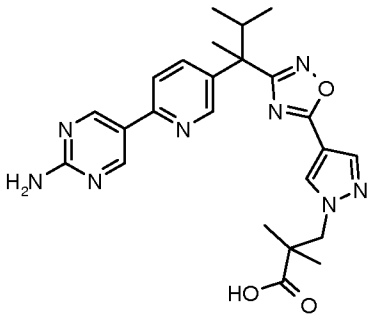
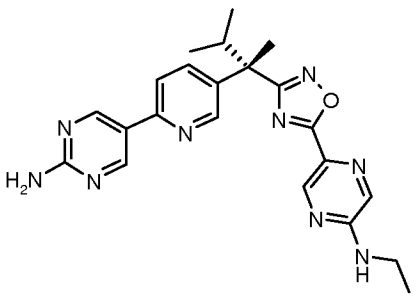
10		5-{5-[2-(5-{5-[(2-methoxyethyl)amino]pyrazin-2-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
11		5-(5-{3-methyl-2-[5-(pyrazolo[1,5-a]pyrimidin-3-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
12		5-[5-(2-{5-[5-(ethylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl)pyridin-2-yl]pyrimidin-2-amine
13		5-[5-(3-methyl-2-{5-[5-(piperazin-1-yl)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-amine
14		5-[5-(2-{5-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl)pyridin-2-yl]pyrimidin-2-amine
15		5-[5-(3-methyl-2-{5-[5-(methylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-

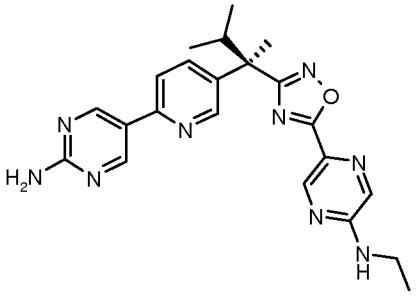
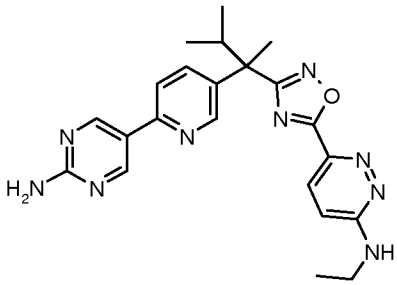
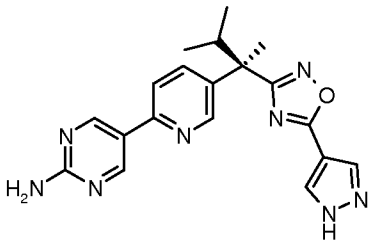
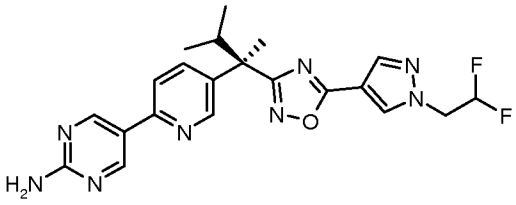
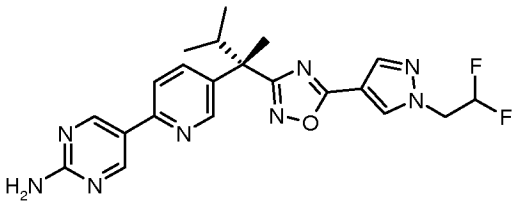
		amine
16		5-[5-(3-methyl-2-{5-[5-(propan-2-ylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-amine
17		5-[5-(2-{5-[1-(2-fluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl)pyridin-2-yl]pyrimidin-2-amine
18		5-{5-[2-(5-{5-[(2-methoxyethyl)(methyl)amino]pyrazin-2-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
19		(2R)-1-{[5-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyrazin-2-yl]amino}propan-2-ol
20		2-{[5-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyrazin-2-yl]amino}-2-methylpropan-1-ol

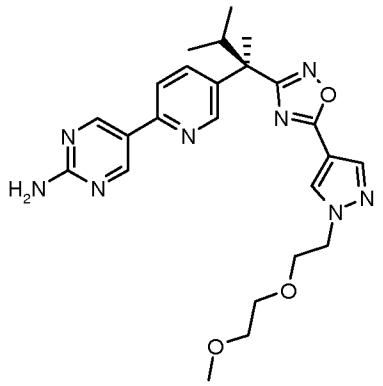
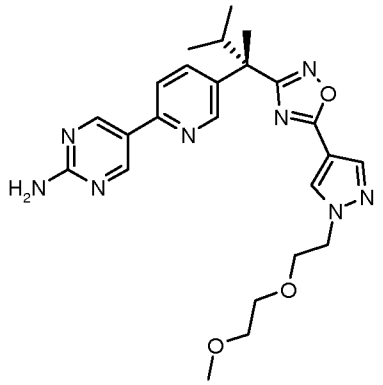
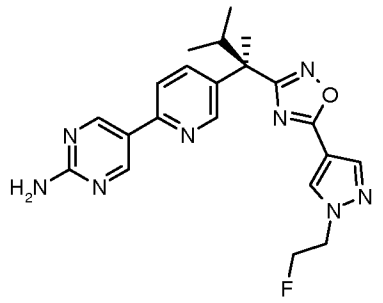
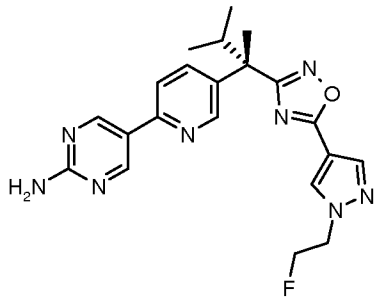
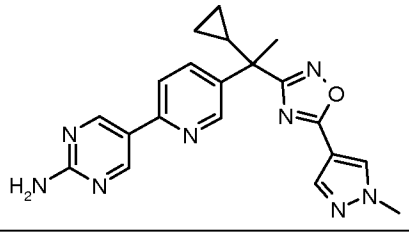
21		5-(5-{3-methyl-2-[5-(1-methyl-1H-imidazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
22		(2S)-1-{[5-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyrazin-2-yl]amino}propan-2-ol
23		5-{5-[(2R)-2-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
24		5-{5-[(2S)-2-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
25		2-[(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)amino]ethanol

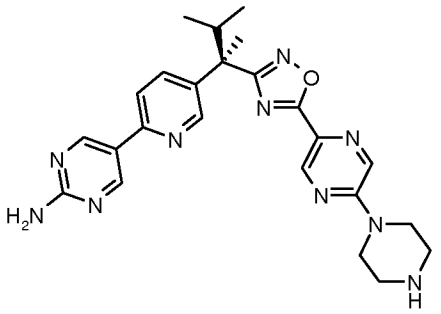
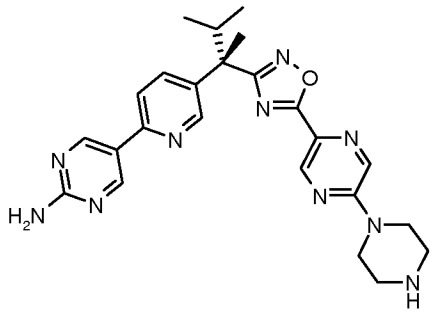
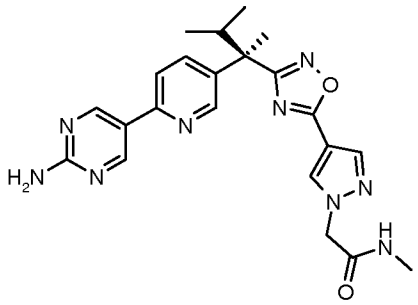
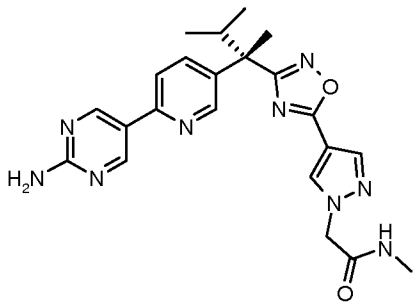
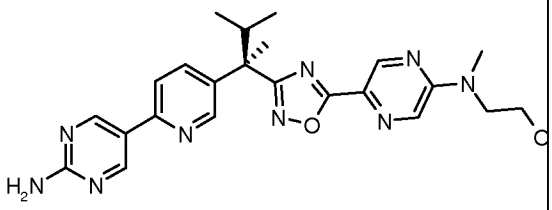
26		5-(5-{3-methyl-2-[5-(piperazin-1-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
27		6-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-N-(2-methoxyethyl)pyridazin-3-amine
28		5-[5-(3-methyl-2-{5-[1-(propan-2-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-amine
29		5-(5-{2-[5-(1-ethyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]-3-methylbutan-2-yl}pyridin-2-yl)pyrimidin-2-amine
30		5-{5-[2-(5-{1-[2-(2-methoxyethoxy)ethyl]-1H-pyrazol-4-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine

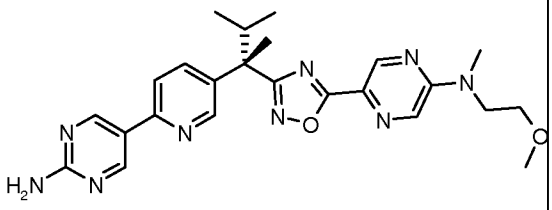
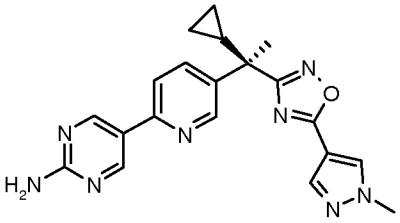
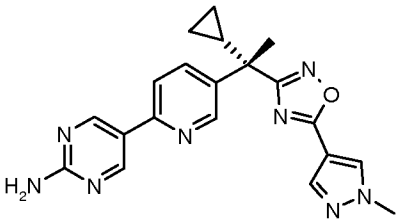
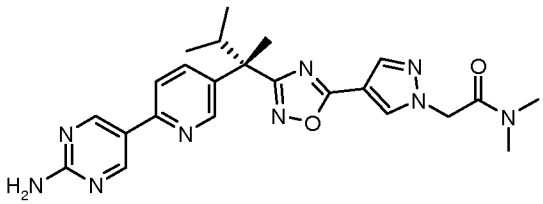
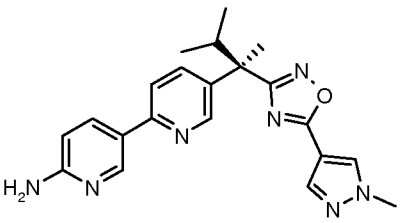
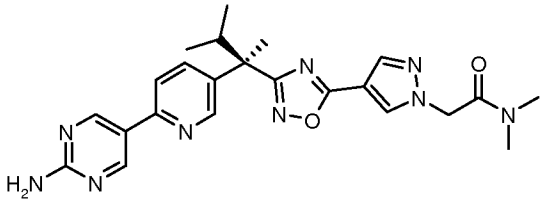
31		5-{5-[(2R)-3-methyl-2-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl]pyridin-2-yl}pyrimidin-2-amine
32		1-{[6-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyridazin-3-yl]amino}-2-methylpropan-2-ol
33		ethyl 3-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropanoate
34		2-[4-(3-{(2R)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-1-ol
35		2-[4-(3-{(2S)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-1-ol

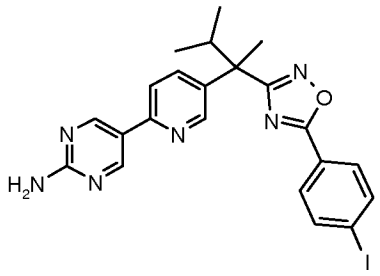
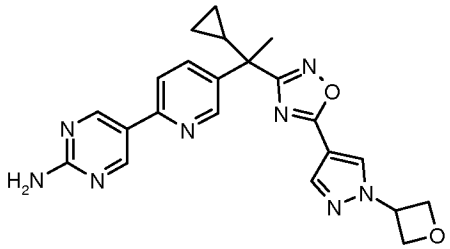
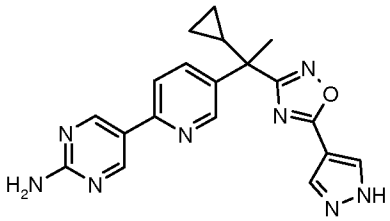
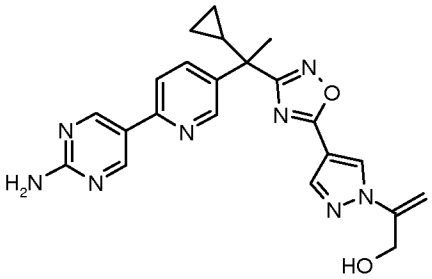
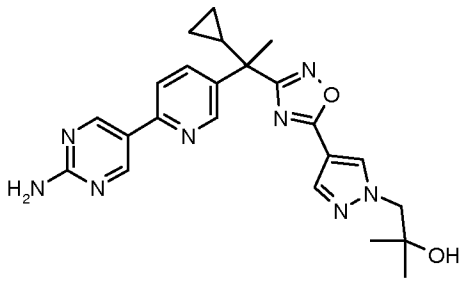
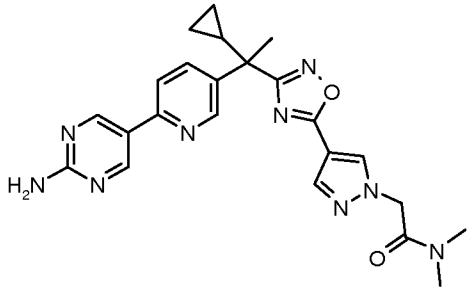
36		2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-(5-{3-methyl-2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidine
37		1-[4-(3-{(2S)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
38		1-[4-(3-{(2R)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
39		3-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropanoic acid
40		5-{5-[(2S)-2-{5-[5-(ethylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine

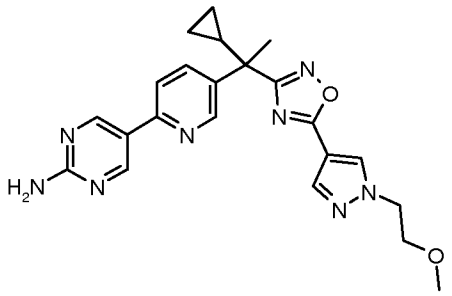
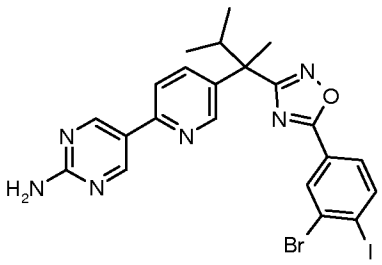
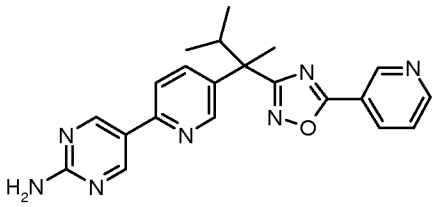
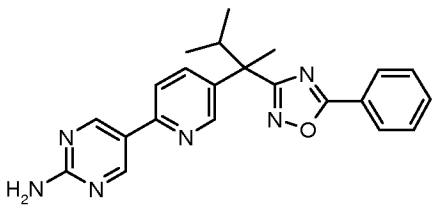
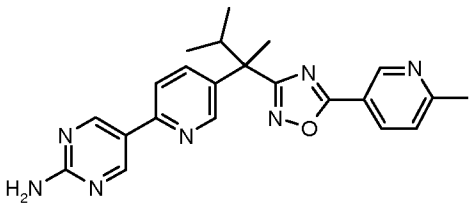
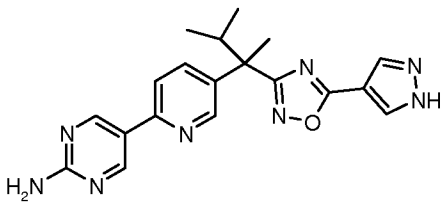
41		5-{5-[(2R)-2-{5-[5-(ethylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
42		6-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-N-ethylpyridazin-3-amine
43		5-(5-{(2R)-3-methyl-2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
44		5-{5-[(2R)-2-{5-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
45		5-{5-[(2S)-2-{5-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine

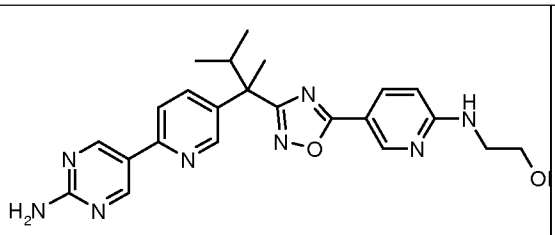
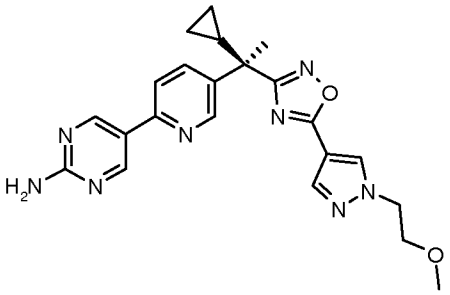
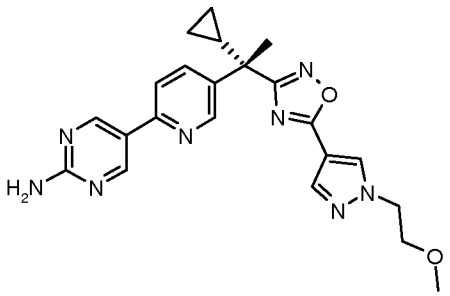
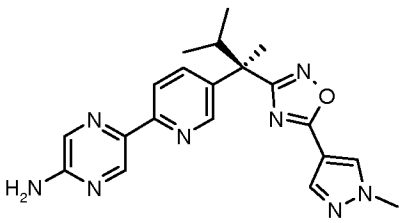
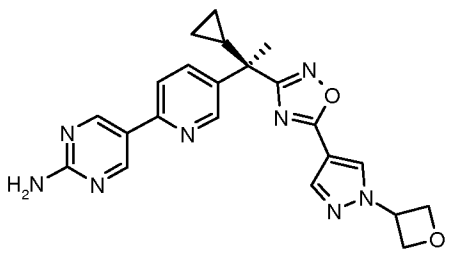
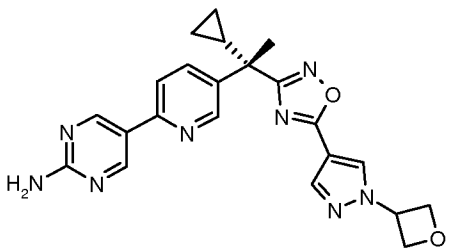
46		5-{5-[(2R)-2-(5-{1-[2-(2-methoxyethoxy)ethyl]-1H-pyrazol-4-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
47		5-{5-[(2S)-2-(5-{1-[2-(2-methoxyethoxy)ethyl]-1H-pyrazol-4-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
48		5-{5-[(2R)-2-{5-[1-(2-fluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
49		5-{5-[(2S)-2-{5-[1-(2-fluoroethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
50		5-(5-{1-cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]ethyl}pyridin-2-yl)pyrimidin-2-amine

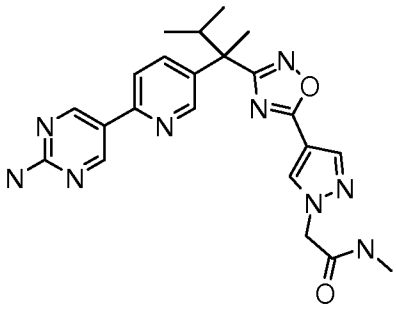
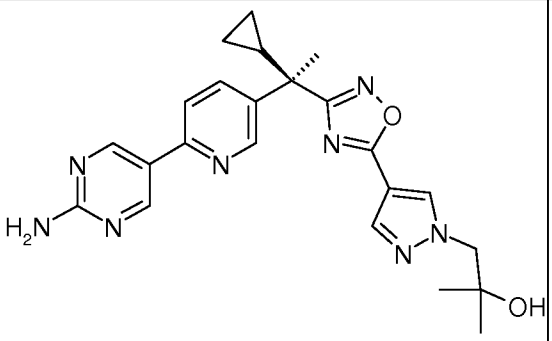
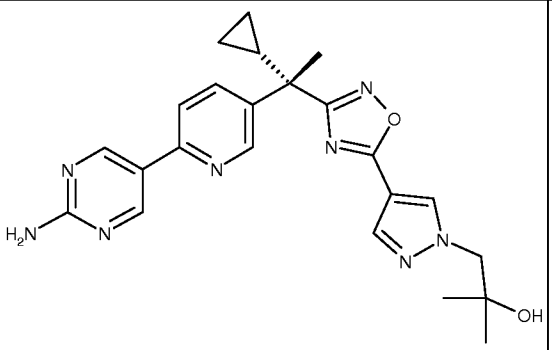
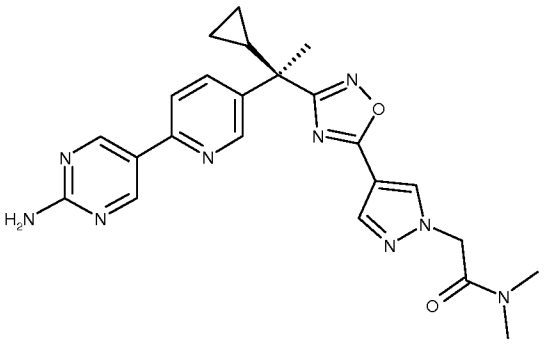
51		5-{5-[(2R)-3-methyl-2-{5-[5-(piperazin-1-yl)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl]pyridin-2-yl}pyrimidin-2-amine
52		5-{5-[(2S)-3-methyl-2-{5-[5-(piperazin-1-yl)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl]pyridin-2-yl}pyrimidin-2-amine
53		2-[4-(3-{(2R)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N-methylacetamide
54		2-[4-(3-{(2S)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N-methylacetamide
55		5-{5-[(2R)-2-(5-{5-[(2-methoxyethyl)(methyl)amino]pyrazin-2-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine

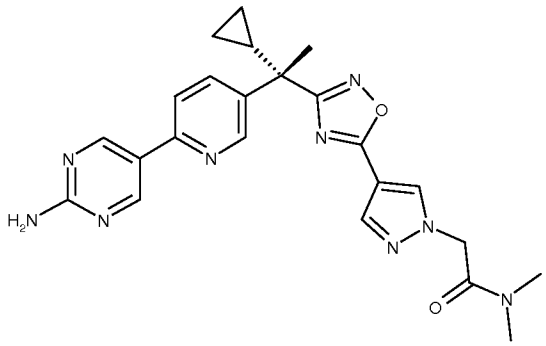
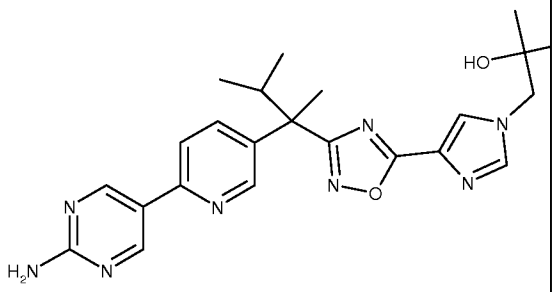
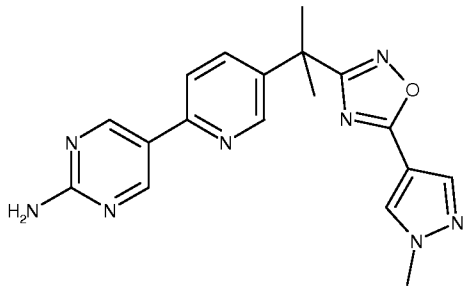
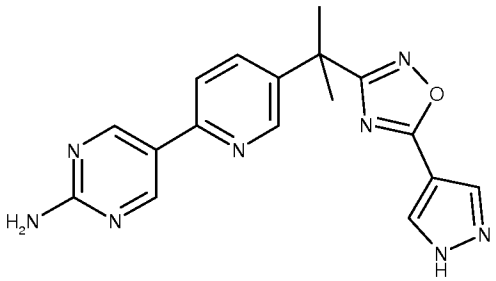
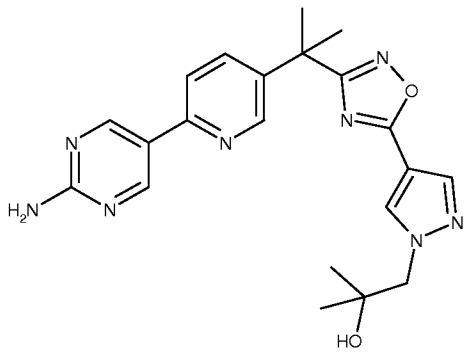
56		5-{5-[(2S)-2-(5-{5-[(2-methoxyethyl)(methyl)amino]pyrazin-2-yl}-1,2,4-oxadiazol-3-yl)-3-methylbutan-2-yl]pyridin-2-yl}pyrimidin-2-amine
57		5-(5-{(1R)-1-cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]ethyl}pyridin-2-yl)pyrimidin-2-amine
58		5-(5-{(1S)-1-cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]ethyl}pyridin-2-yl)pyrimidin-2-amine
59		2-[4-(3-{(2S)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide
60		5-{(2R)-3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}-2,3'-bipyridin-6'-amine
61		2-[4-(3-{(2R)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide

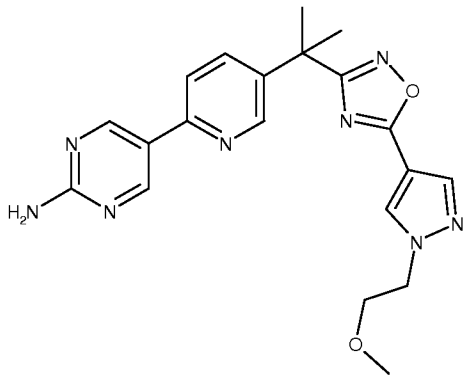
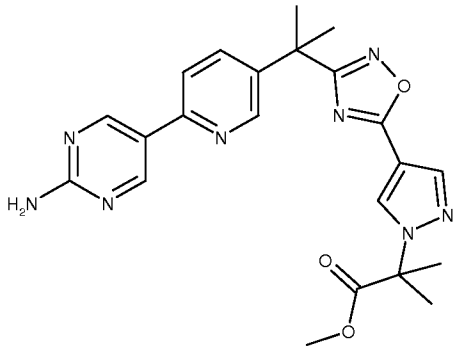
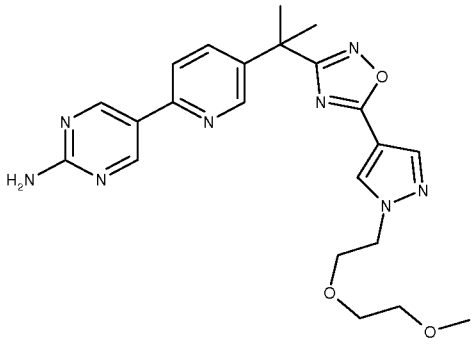
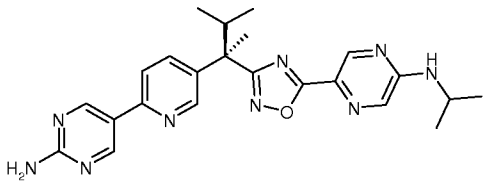
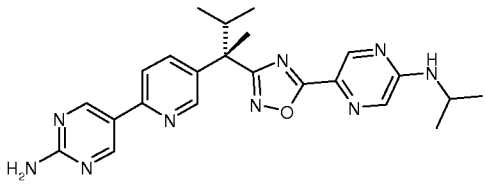
62		5-(5-{2-[5-(4-iodophenyl)-1,2,4-oxadiazol-3-yl]-3-methylbutan-2-yl}pyridin-2-yl)pyrimidin-2-amine
63		5-[5-(1-cyclopropyl-1-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl)pyridin-2-yl]pyrimidin-2-amine
64		5-(5-{1-cyclopropyl-1-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]ethyl}pyridin-2-yl)pyrimidin-2-amine
65		2-[4-(3-{1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]prop-2-en-1-ol
66		1-[4-(3-{1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
67		2-[4-(3-{1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide

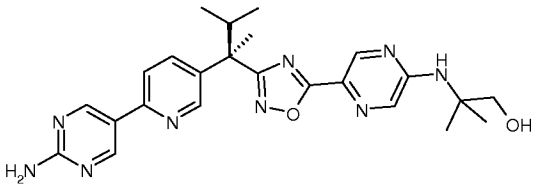
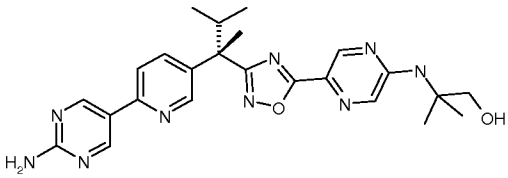
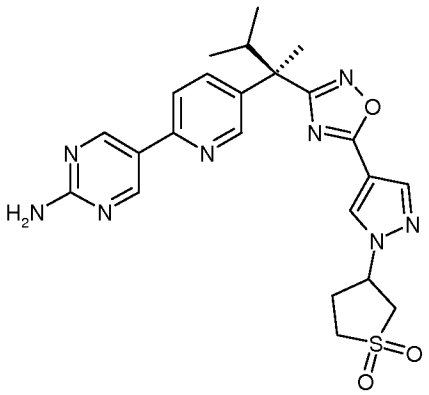
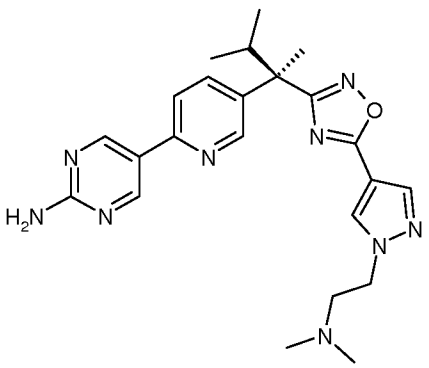
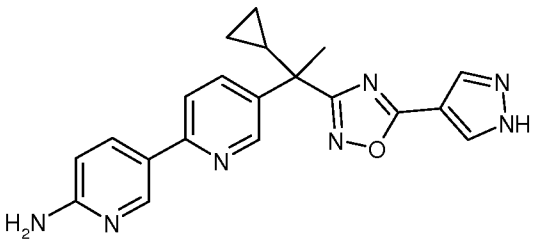
68		5-[5-(1-cyclopropyl-1-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl)pyridin-2-yl]pyrimidin-2-amine
69		5-(5-{2-[5-(3-bromo-4-iodophenyl)-1,2,4-oxadiazol-3-yl]-3-methylbutan-2-yl}pyridin-2-yl)pyrimidin-2-amine
70		5-(5-{3-methyl-2-[5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
71		5-{5-[3-methyl-2-(5-phenyl-1,2,4-oxadiazol-3-yl)butan-2-yl]pyridin-2-yl}pyrimidin-2-amine
72		5-(5-{3-methyl-2-[5-(6-methylpyridin-3-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine
73		5-(5-{3-methyl-2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine

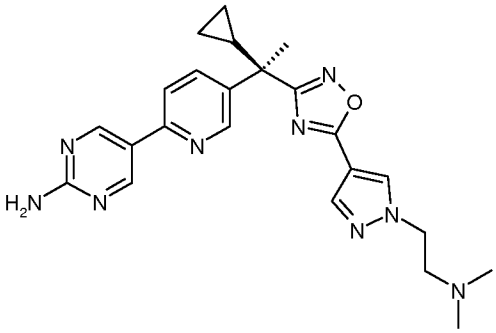
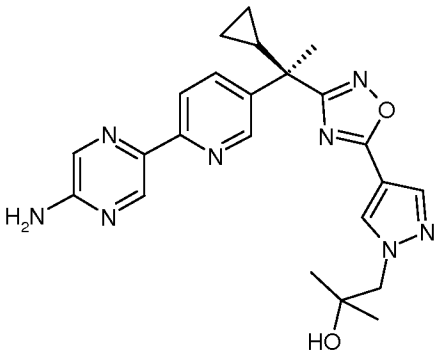
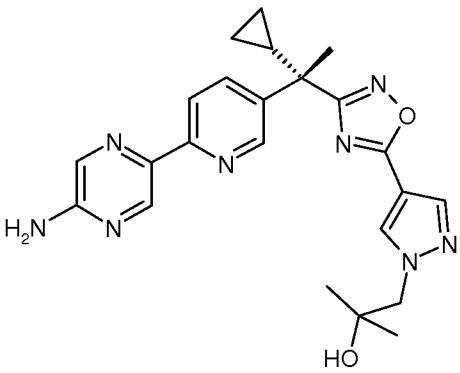
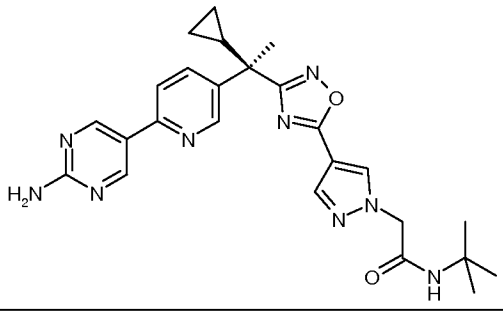
74		2-{[5-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyridin-2-yl]amino}ethanol
75		5-{5-[(1R)-1-cyclopropyl-1-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl]pyridin-2-yl}pyrimidin-2-amine
76		5-{5-[(1S)-1-cyclopropyl-1-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl]pyridin-2-yl}pyrimidin-2-amine
77		5-(5-{(2R)-3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrazin-2-amine
78		5-{5-[(1R)-1-cyclopropyl-1-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl]pyridin-2-yl}pyrimidin-2-amine
79		5-{5-[(1S)-1-cyclopropyl-1-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl]pyridin-2-yl}pyrimidin-2-amine

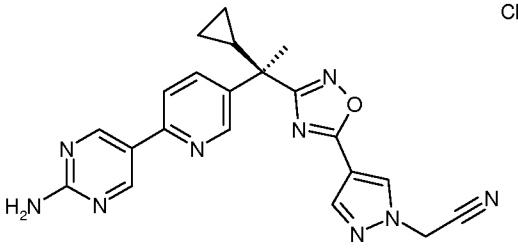
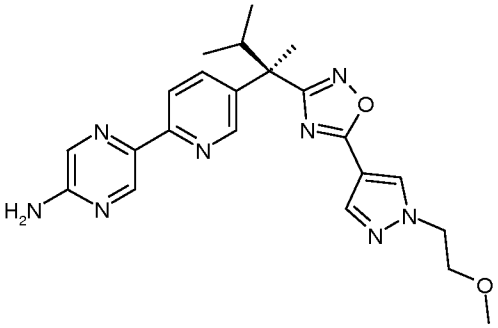
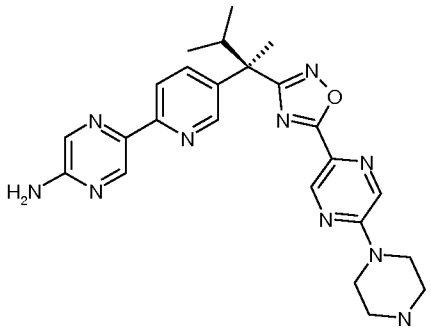
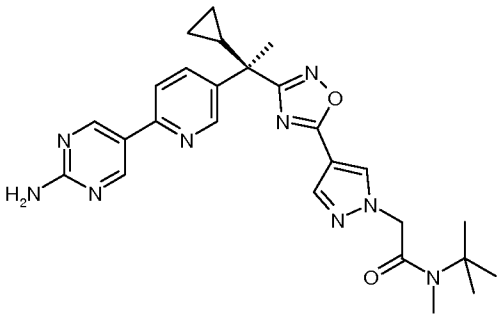
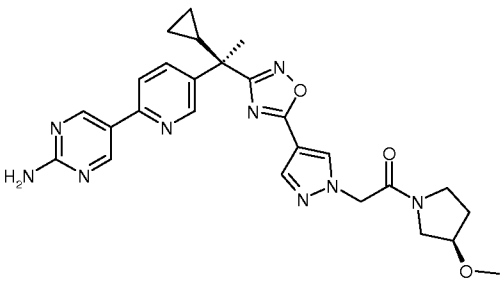
80		2-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N-methylacetamide
81		1-[4-(3-{(1R)-1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
82		1-[4-(3-{(1S)-1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol
83		2-[4-(3-{(1R)-1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide

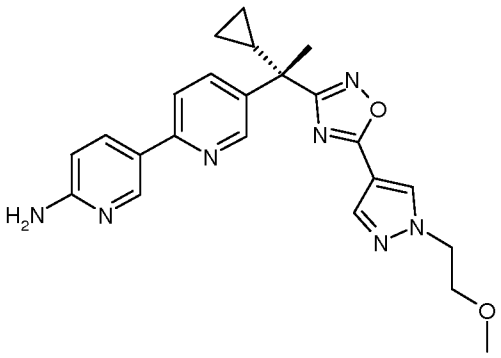
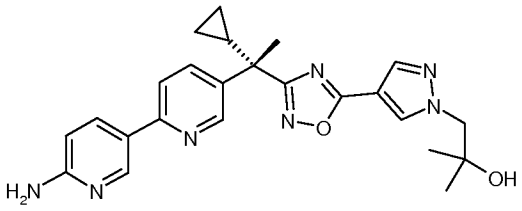
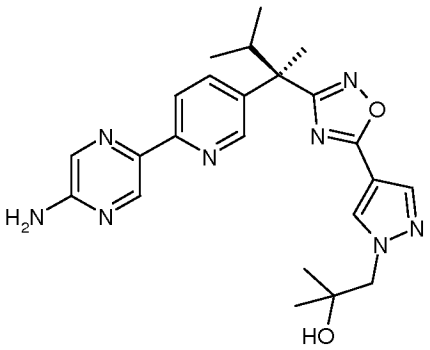
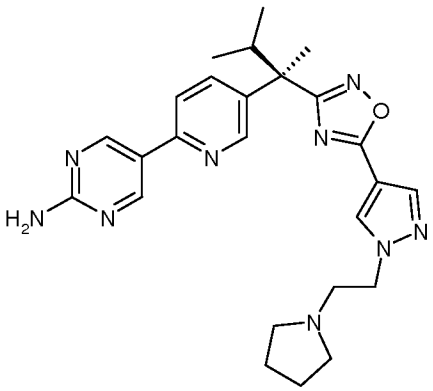
84		2-[4-(3-{(1S)-1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-N,N-dimethylacetamide
85		1-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-imidazol-1-yl]-2-methylpropan-2-ol
86		5-(5-{2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}pyridin-2-yl)pyrimidin-2-amine
87		5-(5-{2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}pyridin-2-yl)pyrimidin-2-amine
88		1-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]propan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol

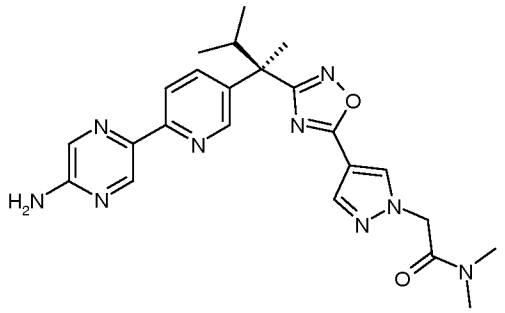
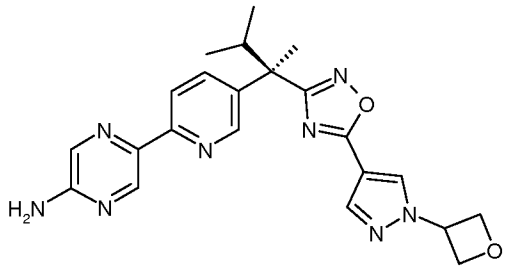
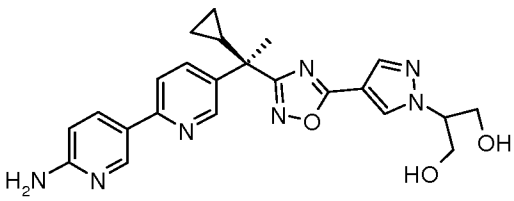
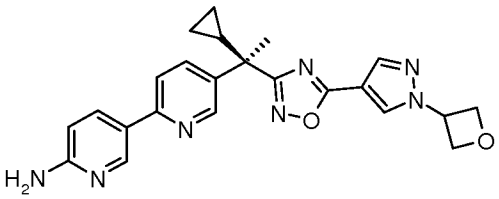
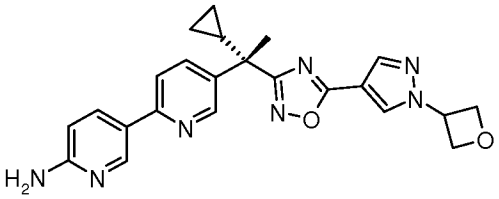
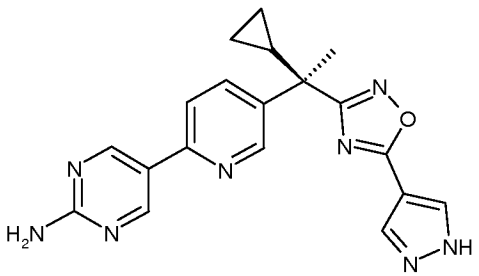
89		5-[5-(2-{5-[1-(2-methoxyethyl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}propan-2-yl)pyridin-2-yl]pyrimidin-2-amine
90		methyl 2-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]propan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropanoate
91		5-{5-[2-(5-{1-[2-(2-methoxyethoxy)ethyl]-1H-pyrazol-4-yl}-1,2,4-oxadiazol-3-yl)propan-2-yl]pyridin-2-yl}pyrimidin-2-amine
92		5-(5-{(R)-1-[5-(5-Isopropylamino-pyrazin-2-yl)-[1,2,4]oxadiazol-3-yl]-1,2-dimethyl-propyl}-pyridin-2-yl)-pyrimidin-2-ylamine
93		5-(5-{(S)-1-[5-(5-Isopropylamino-pyrazin-2-yl)-[1,2,4]oxadiazol-3-yl]-1,2-dimethyl-propyl}-pyridin-2-yl)-pyrimidin-2-ylamine

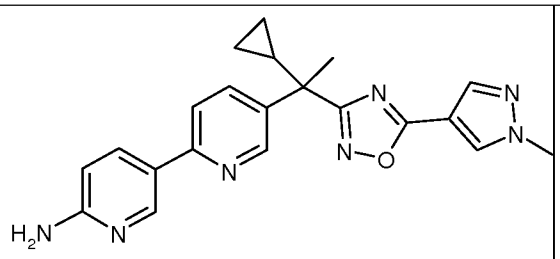
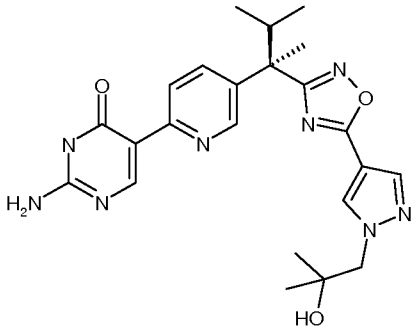
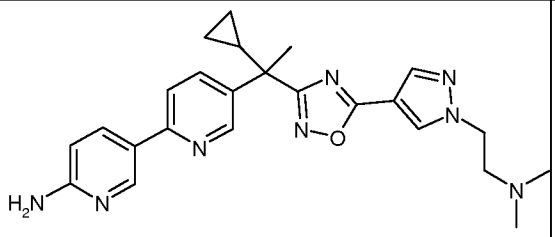
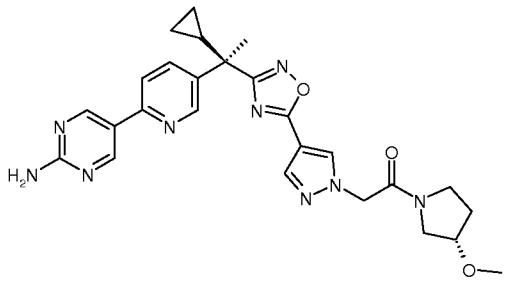
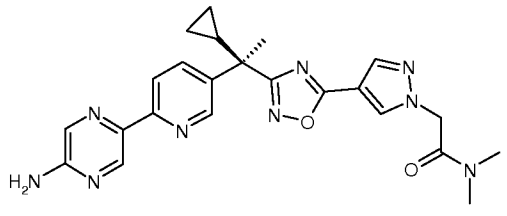
94		2-[5-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol
95		2-[5-(3-{(S)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazin-2-ylamino]-2-methyl-propan-1-ol
96		5-[5-((R)-1-{5-[1-(1,1-Dioxo-tetrahydro-1l6-thiophen-3-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-pyrimidin-2-ylamine
97		5-[5-((R)-1-{5-[1-(2-Dimethylamino-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-pyrimidin-2-ylamine
98		5-{1-Cyclopropyl-1-[5-(1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine

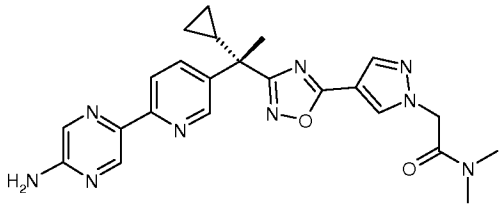
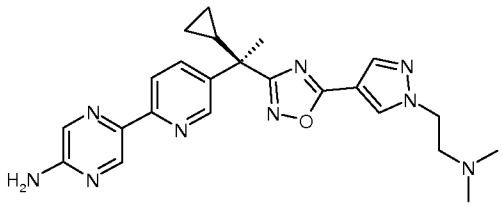
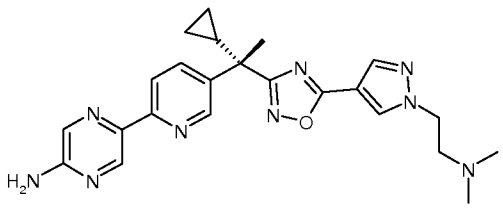
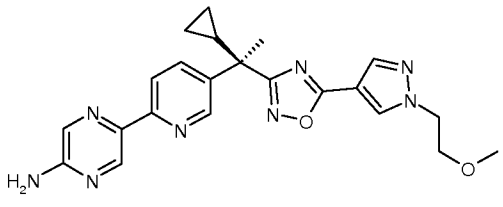
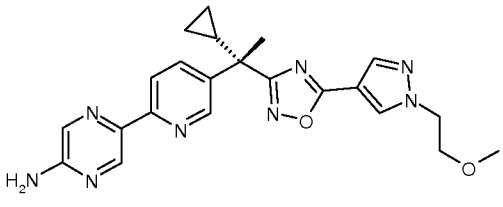
99	 Chira	5-[5-((R)-1-Cyclopropyl-1-{5-[1-(2-dimethylamino-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrimidin-2-ylamine
100		1-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
101		1-[4-(3-{(S)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
102		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N-tert-butyl-acetamide

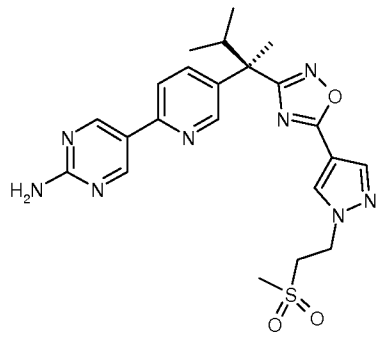
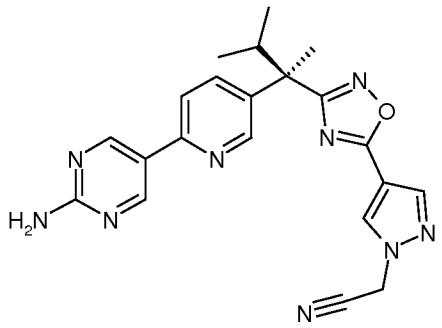
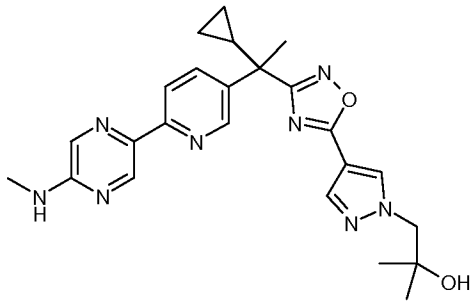
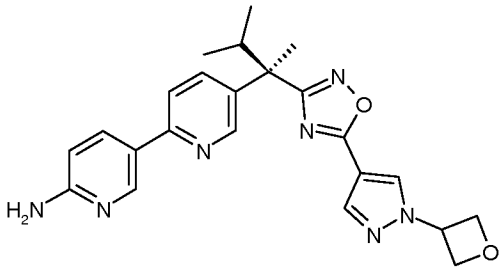
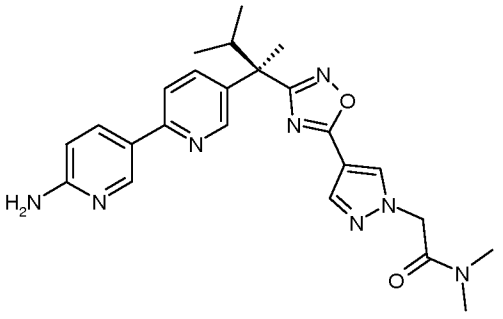
103	 Chira	[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-acetonitrile
104		5-[5-((R)-1-{5-[1-(2-Methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-pyrazin-2-ylamine
105		5-(5-{(R)-1,2-Dimethyl-1-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl)-[1,2,4]oxadiazol-3-yl]-propyl}-pyridin-2-yl)-pyrazin-2-ylamine
106		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N-tert-butyl-N-methyl-acetamide
107		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-1-((R)-3-methoxy-pyrrolidin-1-yl)-ethanone

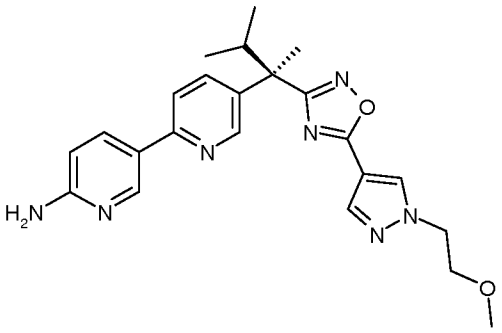
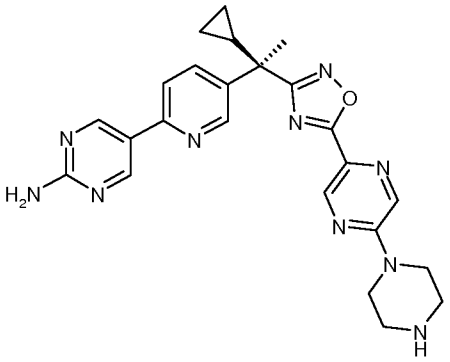
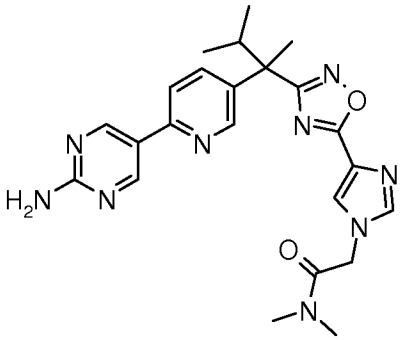
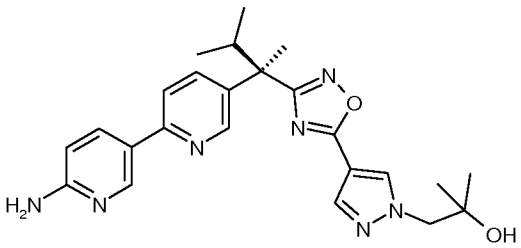
108		5-((S)-1-Cyclopropyl-1-{5-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-[2,3']bipyridinyl-6'-ylamine
109		1-(4-{3-[(S)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol
110		1-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
111		5-[5-((R)-1,2-Dimethyl-1-{5-[1-(2-pyrrolidin-1-yl-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-propyl)-pyridin-2-yl]-pyrimidin-2-ylamine

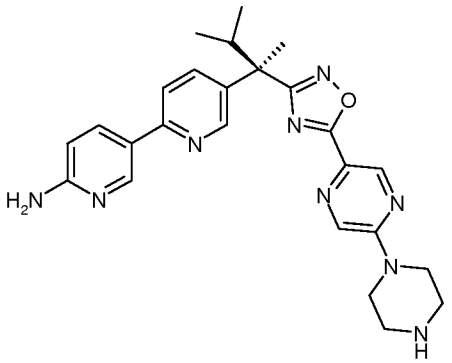
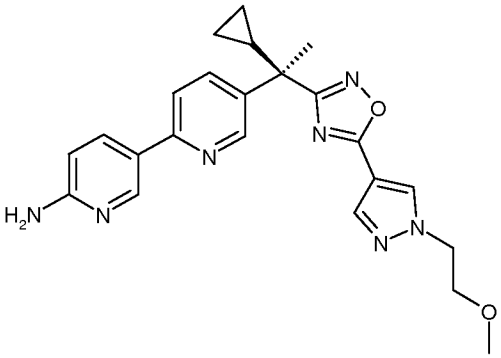
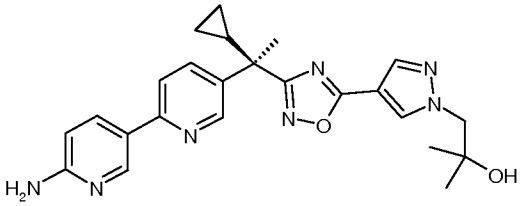
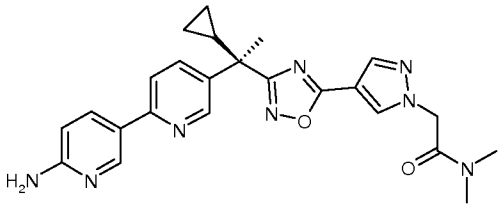
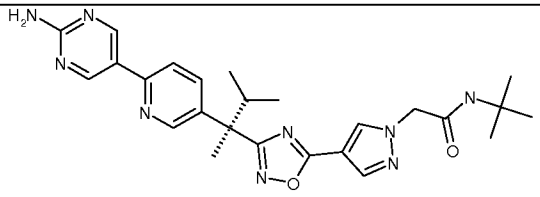
112		2-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N,N-dimethyl-acetamide
113		5-(5-{(R)-1,2-Dimethyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-propyl}-pyridin-2-yl)-pyrazin-2-ylamine
114		2-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-propane-1,3-diol
115		5-{(R)-1-Cyclopropyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine
116		5-{(S)-1-Cyclopropyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine
117		5-(5-{(R)-1-Cyclopropyl-1-[5-(1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrimidin-2-ylamine

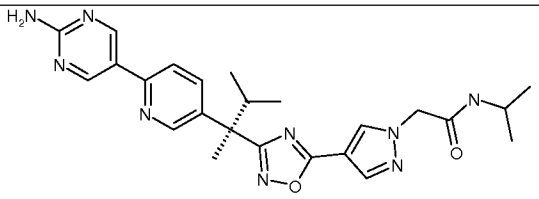
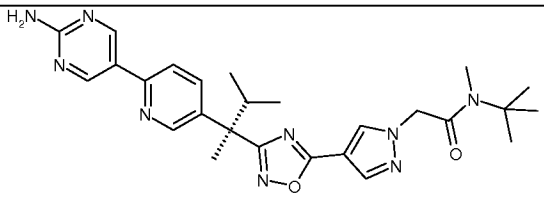
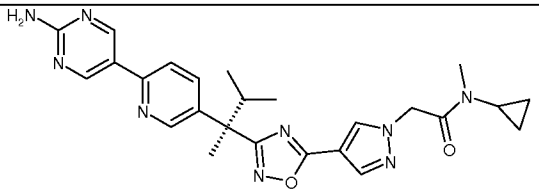
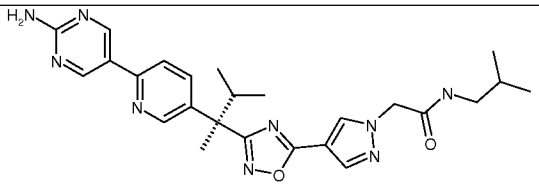
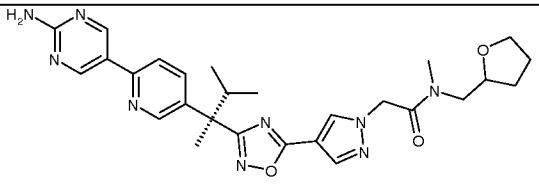
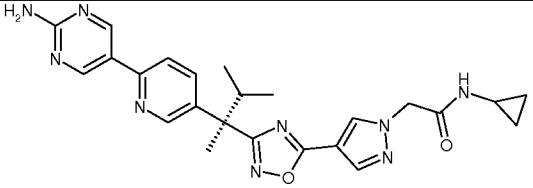
118		5-{1-Cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine
119		2-Amino-5-[5-((R)-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-3H-pyrimidin-4-one
120		5-(1-Cyclopropyl-1-{5-[1-(2-dimethylamino-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-[2,3']bipyridinyl-6'-ylamine
121		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-1-((S)-3-methoxy-pyrrolidin-1-yl)-ethanone
122		2-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N,N-dimethyl-acetamide

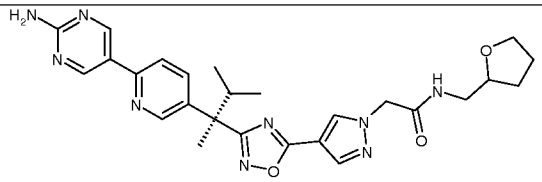
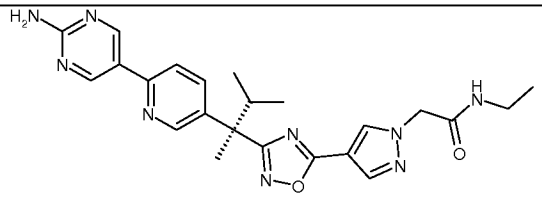
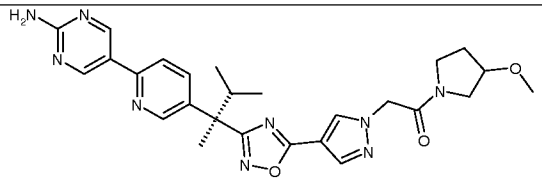
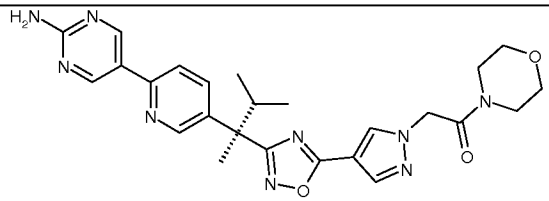
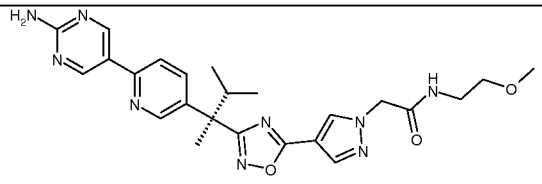
123		2-[4-(3-{(S)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N,N-dimethyl-acetamide
124		5-[5-((R)-1-Cyclopropyl-1-{5-[1-(2-dimethylamino-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-ylamine
125		5-[5-((S)-1-Cyclopropyl-1-{5-[1-(2-dimethylamino-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-ylamine
126		5-[5-((R)-1-Cyclopropyl-1-{5-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-ylamine
127		5-[5-((S)-1-Cyclopropyl-1-{5-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-ylamine

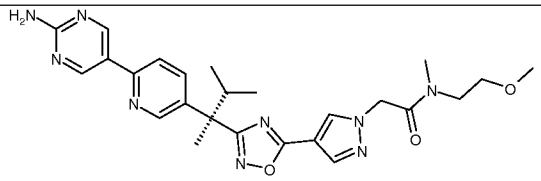
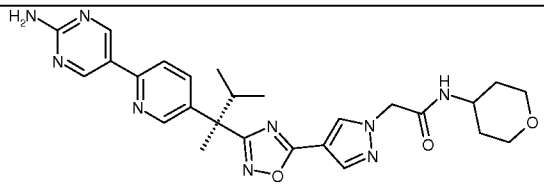
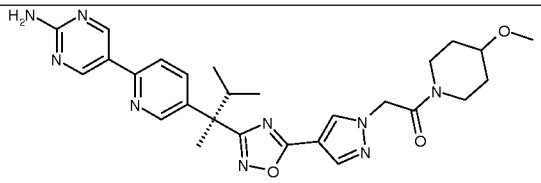
128		5-[5-((R)-1-{5-[1-(2-Methanesulfonyl-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-pyrimidin-2-ylamine
129		[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-acetonitrile
130		1-[4-(3-{1-Cyclopropyl-1-[6-(5-methylamino-pyrazin-2-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
131		5-{(R)-1,2-Dimethyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-propyl}-[2,3']bipyridinyl-6'-ylamine
132		2-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1,2-dimethyl-propyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-N,N-dimethyl-acetamide

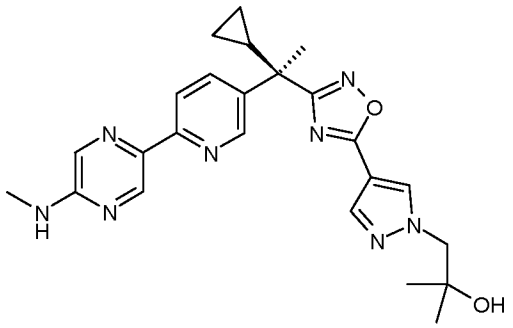
133		5-((R)-1-{5-[1-(2-Methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-[2,3']bipyridinyl-6'-ylamine
134		5-(5-{(R)-1-Cyclopropyl-1-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrimidin-2-ylamine
135		2-[4-(3-{1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-imidazol-1-yl]-N,N-dimethyl-acetamide
136		1-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1,2-dimethyl-propyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol

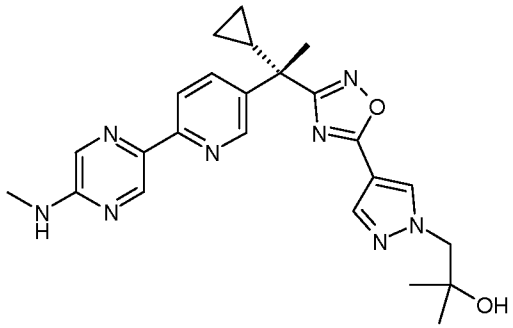
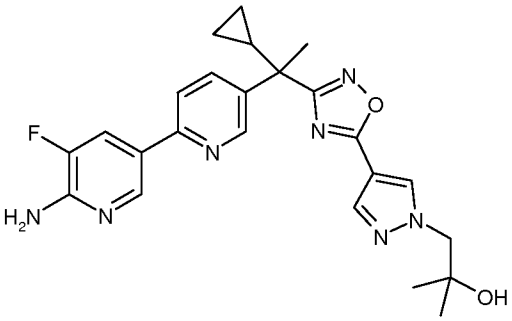
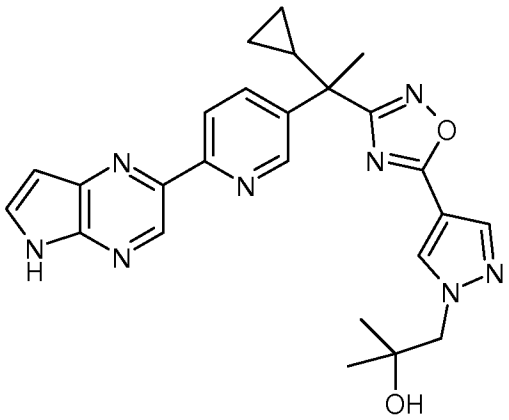
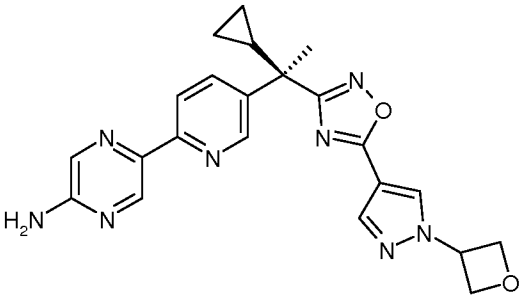
137		5-{(R)-1,2-Dimethyl-1-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl)-[1,2,4]oxadiazol-3-yl]-propyl}-[2,3']bipyridinyl-6'-ylamine
138		5-((R)-1-Cyclopropyl-1-{5-[1-(2-methoxy-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-[2,3']bipyridinyl-6'-ylamine
139		1-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol
140		2-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-N,N-dimethyl-acetamide
141		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-tert-butyl-acetamide

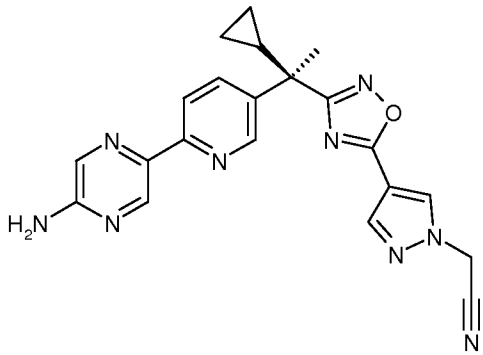
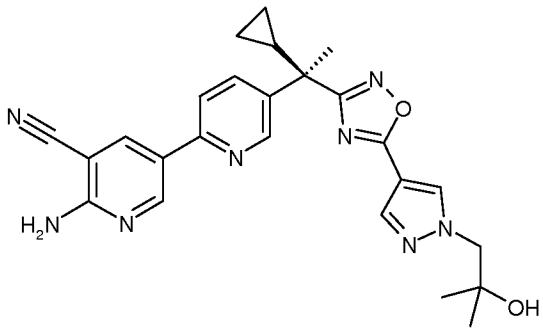
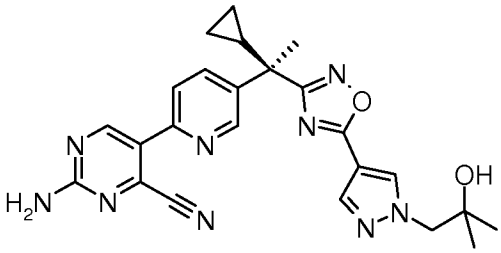
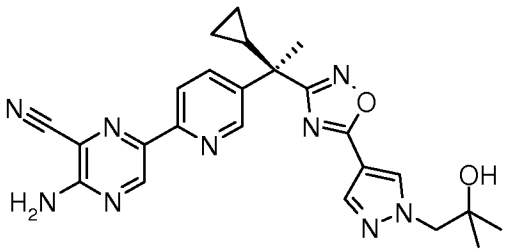
142		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-isopropyl-acetamide
143		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-tert-butyl-N-methyl-acetamide
144		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-cyclopropyl-N-methyl-acetamide
145		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-isobutyl-acetamide
146		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-methyl-N-(tetrahydro-furan-2-ylmethyl)-acetamide
147		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-

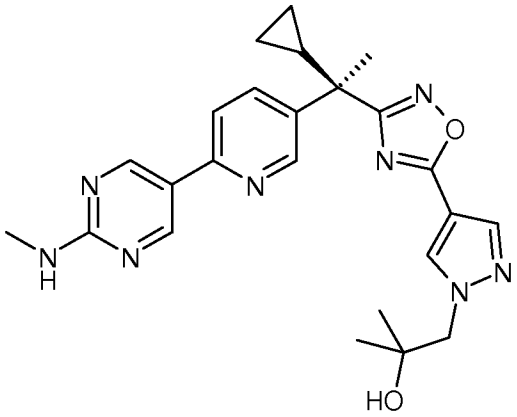
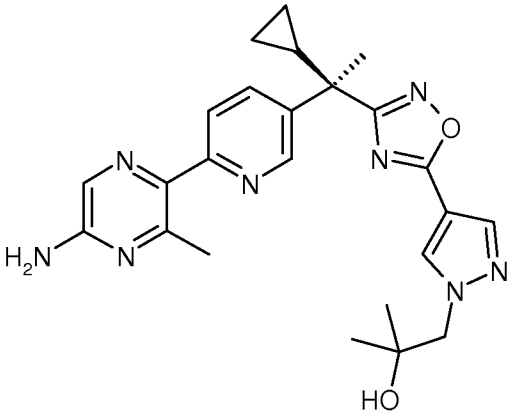
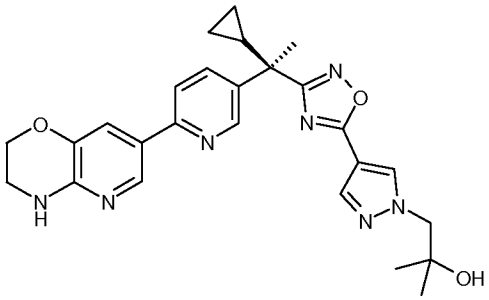
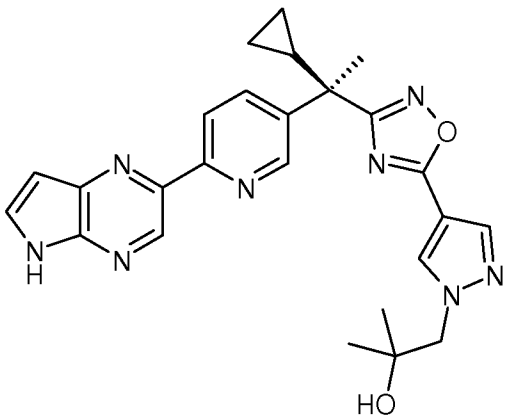
		cyclopropyl-acetamide
148		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-(tetrahydro-furan-2-ylmethyl)-acetamide
149		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-ethyl-acetamide
150		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-1-(3-methoxy-pyrrolidin-1-yl)-ethanone
151		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-1-morpholin-4-yl-ethanone
152		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-(2-methoxy-ethyl)-acetamide

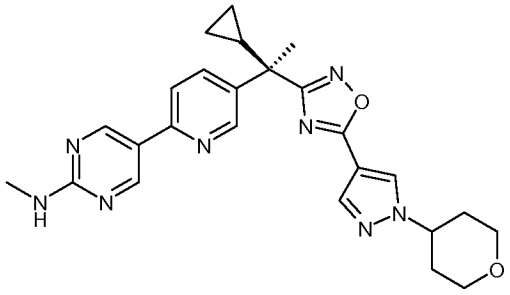
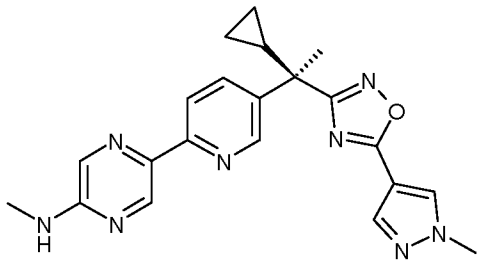
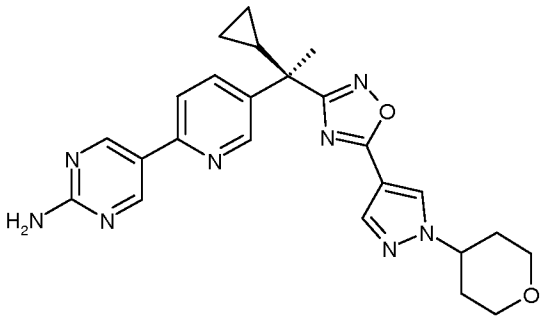
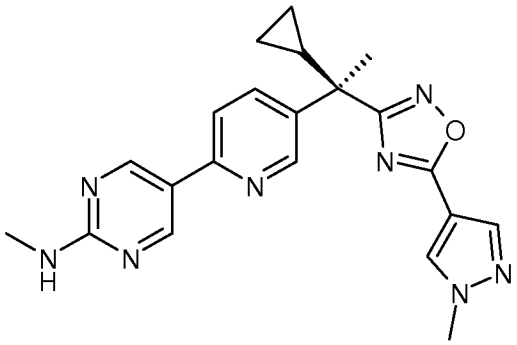
153		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-(2-methoxy-ethyl)-N-methyl-acetamide
154		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-N-(tetrahydro-pyran-4-yl)-acetamide
155		2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-1-(4-methoxy-piperidin-1-yl)-ethanone

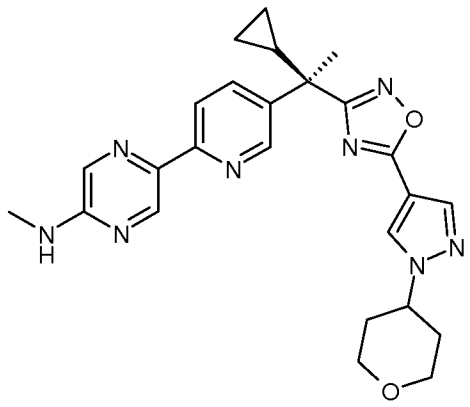
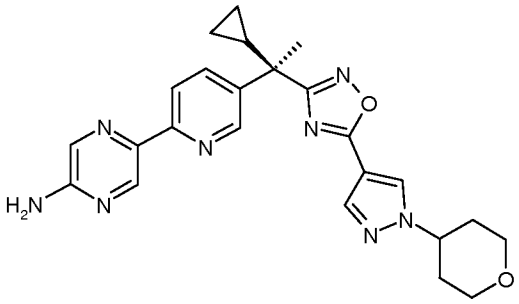
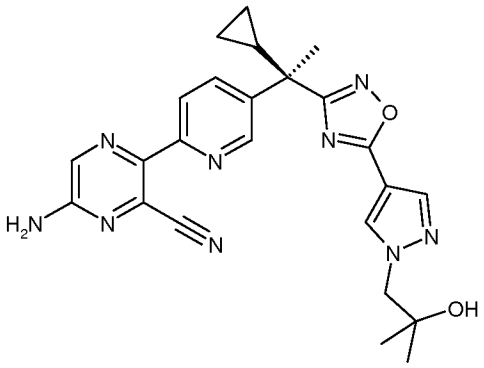
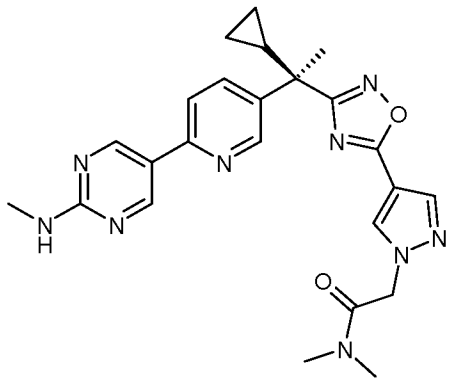
156		1-[4-(3-{(R)-1-Cyclopropyl-1-[6-(5-methylamino-pyrazin-2-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol

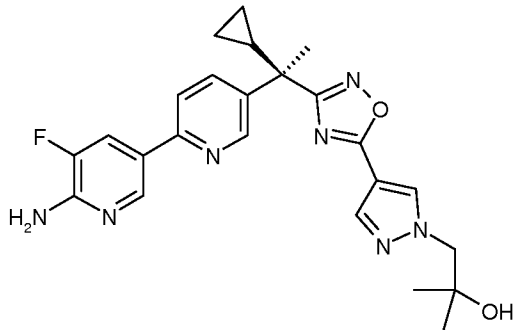
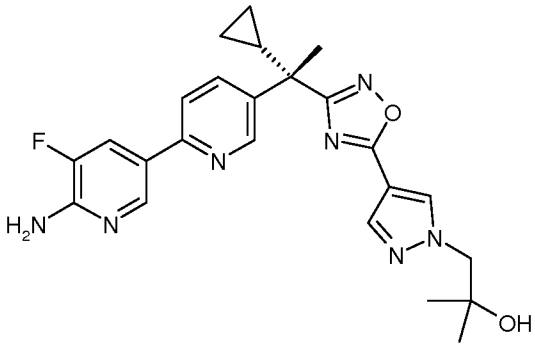
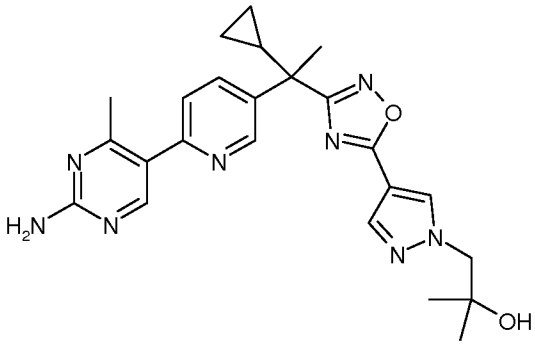
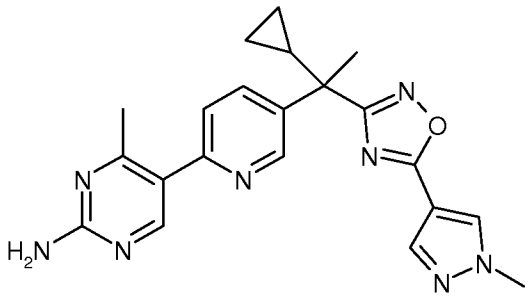
157		1-[4-(3-{(S)-1-Cyclopropyl-1-[6-(5-methylamino-pyrazin-2-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
158		1-(4-{3-[1-(6'-Amino-5'-fluoro-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol
159		1-[4-(3-{1-Cyclopropyl-1-[6-(5H-pyrrolo[2,3-b]pyrazin-2-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
160		5-(5-{(R)-1-Cyclopropyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrazin-2-ylamine

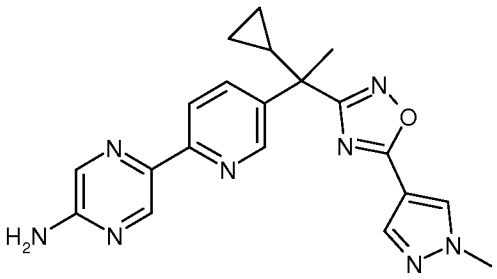
161		[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-acetonitrile
162		6'-Amino-5-((R)-1-cyclopropyl-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-[2,3']bipyridinyl-5'-carbonitrile
163		2-Amino-5-[5-((R)-1-cyclopropyl-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrimidine-4-carbonitrile
164		3-Amino-6-[5-((R)-1-cyclopropyl-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazine-2-carbonitrile

165		1-[4-(3-{(R)-1-Cyclopropyl-1-[6-(2-methylamino-pyrimidin-5-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
166		1-[4-(3-{(R)-1-[6-(5-Amino-3-methyl-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
167		1-[4-(3-{(R)-1-Cyclopropyl-1-[6-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
168		1-[4-(3-{(R)-1-Cyclopropyl-1-[6-(5H-pyrrolo[2,3-b]pyrazin-2-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol

169		{5-[5-((R)-1-Cyclopropyl-1-{5-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrimidin-2-yl}-methyl-amine
170		[5-(5-{(R)-1-Cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrazin-2-yl]-methyl-amine
171		5-[5-((R)-1-Cyclopropyl-1-{5-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrimidin-2-ylamine
172		[5-(5-{(R)-1-Cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrimidin-2-yl]-methyl-amine

173		{5-[5-((R)-1-Cyclopropyl-1-{5-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-yl}-methyl-amine
174		5-[5-((R)-1-Cyclopropyl-1-{5-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazin-2-ylamine
175		6-Amino-3-[5-((R)-1-cyclopropyl-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrazine-2-carbonitrile
176		2-[4-(3-{(R)-1-Cyclopropyl-1-[6-(2-methylamino-pyrimidin-5-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N,N-dimethyl-acetamide

177		1-(4-{3-[(R)-1-(6'-Amino-5'-fluoro-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol
178		1-(4-{3-[(S)-1-(6'-Amino-5'-fluoro-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-2-methyl-propan-2-ol
179		1-[4-(3-{1-[6-(2-Amino-4-methyl-pyrimidin-5-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol
180		5-(5-{1-Cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-4-methyl-pyrimidin-2-ylamine

181		5-(5-{1-Cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrazin-2-ylamine

In one embodiment, the invention relates to any of the compounds depicted in Table I above and the pharmaceutically acceptable salt thereof.

Representative compounds of the invention show activity in the FLAP binding assay and in the human whole blood LTB_4 production inhibition assay, described in the assessment of biological properties section, as shown in Table II.

Table II

Example	FLAP SPA IC_{50} (nM)	hWB LTB_4 IC_{50} (nM)
1	8.3	54
2	10.0	74
3	4.7	68
4	3.0	20
5	76.2	750
6	8.6	220
7	14.4	180
8	6.3	68
9	5.9	25
10	4.9	60
11	2.9	40
12	3.6	55
13	10.9	490
14	6.5	45
15	2.3	75
16	2.3	65
17	4.5	53
18	2.7	83
19	4.8	140
20	4.0	140

21	51.2	570
22	3.6	140
23	3.9	39
24	170	990
25	520	>5000
26	400	3900
27	7.5	71
28	3.8	72
29	4.0	40
30	12.0	160
31	1.4	12
32	17.3	860
33	5.2	210
34	6.6	94
35	210	3200
36	30% inhibition at 1uM	>5000
37	167.8	>5000
38	6.4	33
39	20.4	>5000
40	7.9	100
41	1.8	34
42	8.3	210
43	1.2	32
44	0.9	24
45	140.7	1400
46	5.0	98
47	180	2000
48	2.6	20
49	80.9	1100
50	9.5	110
51	3.0	160
52	14.0	270
53	12.7	230
54	70.7	750
55	2.5	46
56	11.8	230
57	16.0	33
58	230	980
59	450	1800
60	3.4	17
61	3.0	48

62	19.4	420
63	8.7	29
64	6.3	80
65	1.6	28
66	19.7	52
67	110	290
68	24	80
69	64.8	840
70	12.4	240
71	8.1	840
72	26.4	440
73	3.9	110
74	3.1	220
75	32.0	52
76	190	2000
77	0.14	15
78	8.0	29
79	140	650
80	5.6	230
81	16	41
82	340	1200
83	76	200
84	45% inhibition at 1uM	2900
85	350	1900
86	140	790
87	670	>5000
88	370	1500
89	230	880
90	140	950
91	300	1500
92	15	92
93	21	28
94	26	74
95	92	210
96	9.9	240
97	7.9	30
98	26	500
99	32	150
100	53	210
101	280	990
102	13	89
103	6.3	32
104	5.7	17

105	7.8	450
106	10	30
107	72	220
108	360	2300
109	350	1100
110	5.9	31
111	13	30
112	4.8	71
113	4	12
114	52	850
115	24	110
116	360	2000
117	8.7	86
118	47	210
119	3.4	2200
120	42	300
121	67	220
122	34	450
123	300	3300
124	18	60
125	120	370
126	8.8	25
127	220	410
128	10	270
129	8.1	19
130	15	94
131	5.6	39
132	12	130
133	7.5	30
134	7.2	310
135	700	>5000
136	9.9	61
137	11	590
138	22	100
139	33	68
140	44	150
141	8.3	68
142	16	85
143	9.2	51
144	13	68
145	14	110
146	9.4	53
147	8.6	170
148	22	290
149	15	140

150	42	180
151	32	190
152	24	190
153	16	150
154	21	550
155	19	110
156	27	54
157	420	969
158	230	502
159	27	167
160	15	23
161	21	32
162		319
163	290	348
164	40	97
165	56	82
166	41	57
167		171
168		63
169		105
170		112
171		119
172		104
173		221
174		53
175		144
176		267
177	65	256
178	2000	2349
179	450	483
180	190	309
181	34	65

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of the invention, or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent

have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Isomers shall be defined as being enantiomers and diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of the invention can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C_{1-6} alkoxy" is a C_{1-6} alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy. All alkyl, alkenyl, and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "alkyl" refers to both branched and unbranched alkyl groups. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy",

"alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O).

In all alkyl groups or carbon chains, one or more carbon atoms can be optionally replaced by heteroatoms such as O, S or N. It shall be understood that if N is not substituted then it is NH. It shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo to result in definitions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.
As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. For example, for a -S-C_{1-6} alkyl radical, unless otherwise specified, shall be understood to include -S(O)-C_{1-6} alkyl and -$S(O)_2$-C_{1-6} alkyl.

The term C_{1-3} hydroxy also means C_{1-3}alkylhydroxy or C_{1-3}alkyl-OH.

The term "C_{3-10} carbocycle" or C_{3-10} cycloalkyl refers to a nonaromatic 3 to 10-membered (but preferably, 3 to 6-membered) monocyclic carbocyclic radical or a nonaromatic 6 to 10-membered fused bicyclic, bridged bicyclic, or spirocyclic carbocyclic radical. The C_{3-10} carbocycle may be either saturated or partially unsaturated, and the carbocycle may be attached by any atom of the cycle which results in the creation of a stable structure. Non-limiting examples of 3 to 10-membered monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, and cyclohexanone. Non-limiting examples of 6 to 10-membered fused bicyclic carbocyclic radicals include bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, and bicyclo[4.4.0]decanyl (decahydronaphthalenyl). Non-limiting examples of 6 to 10-membered bridged bicyclic carbocyclic radicals include bicyclo [2.2.2]heptanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.2.1]octanyl. Non-limiting examples of 6 to 10-membered spirocyclic carbocyclic radicals include but are not limited to spiro[3,3]heptanyl, spiro[3,4]octanyl and spiro[4,4]heptanyl.

The term "C_{6-10} aryl" or "aryl" refers to aromatic hydrocarbon rings containing from six to ten carbon ring atoms. The term C_{6-10} aryl includes monocyclic rings and bicyclic rings where at least one of the rings is aromatic. Non-limiting examples of C_{6-10} aryls include phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, benzocycloheptanyl and benzocycloheptenyl.

The term "5 to 11-membered heterocycle" refers to a stable nonaromatic 4-8 membered monocyclic heterocyclic radical or a stable nonaromatic 6 to 11-membered fused bicyclic, bridged bicyclic or spirocyclic heterocyclic radical. The 5 to 11-membered heterocycle consists of carbon atoms and one or more, preferably from one to four heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be either saturated or partially unsaturated. Non-limiting examples of nonaromatic 4-8 membered monocyclic heterocyclic radicals include tetrahydrofuranyl, tetrahydropyranyl, oxetanyl, azetidinyl, pyrrolidinyl, pyranyl, tetrahydropyranyl, dioxanyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, piperidinyl, piperazinyl, and azepinyl. Non-limiting examples of nonaromatic 6 to 11-membered fused bicyclic radicals include octahydroindolyl, octahydrobenzofuranyl, and octahydrobenzothiophenyl. Non-limiting examples of nonaromatic 6 to 11-membered bridged bicyclic radicals include 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, and 3-azabicyclo[3.2.1]octanyl. Non-limiting examples of nonaromatic 6 to 11-membered spirocyclic heterocyclic radicals include 7-aza-spiro[3,3]heptanyl, 7-spiro[3,4]octanyl, and 7-aza-spiro[3,4]octanyl.

The term "5 to 11-membered heteroaryl" shall be understood to mean an aromatic 5 to 6-membered monocyclic heteroaryl or an aromatic 7 to 11-membered heteroaryl bicyclic ring where at least one of the rings is aromatic, wherein the heteroaryl ring contains 1-4 heteroatoms such as N, O and S. Non-limiting examples of 5 to 6-membered monocyclic heteroaryl rings include furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, tetrazolyl, triazolyl, thienyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, and purinyl. Non-limiting examples of 7 to 11-membered heteroaryl bicyclic heteroaryl rings include benzimidazolyl, quinolinyl,

dihydro-2*H*-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, pyrrolopyrimidinyl, pyrazolopyridinyl, pyrrolopyridazinyl, pyrrolopyrazinyl, pyrido-oxazinyl, pyrazolopyrimidinyl indolyl, isoindolyl, benzofuranyl, benzopyranyl, benzodioxolyl, benzoxazolyl and benzothiazolyl.

It will be understood that one to three carbon ring moieties in the each of the C_{3-10} carbocyclic rings, the 5 to 11-membered heterocyclic rings, the nonaromatic portion of the bicyclic aryl rings, and the nonaromatic portion of the bicyclic heteroaryl rings can independently be replaced with a carbonyl, thiocarbonyl, or iminyl moiety, i.e., -C(=O)-, -C(=S)- and -C(=NR^8)-, respectively, where R^8 is as defined above.
The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, and S.

The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine. The definitions "halogenated", "partially or fully halogenated"; partially or fully fluorinated; "substituted by one or more halogen atoms", includes for example, mono, di or tri halo derivatives on one or more carbon atoms. For alkyl, a non-limiting example would be -CH_2CHF_2, -CF_3 etc.

Each alkyl, carbocycle, heterocycle or heteroaryl, or the analogs thereof, described herein shall be understood to be optionally partially or fully halogenated.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the inventive methods disclosed herein.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a

pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the invention.

Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C_1-C_4 alkyl)$_4^+$ salts.

In addition, within the scope of the invention is use of prodrugs of compounds of the invention. Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

The compounds of formula I may be made using the general synthetic methods described below, which also constitute part of the invention.

GENERAL SYNTHETIC METHODS

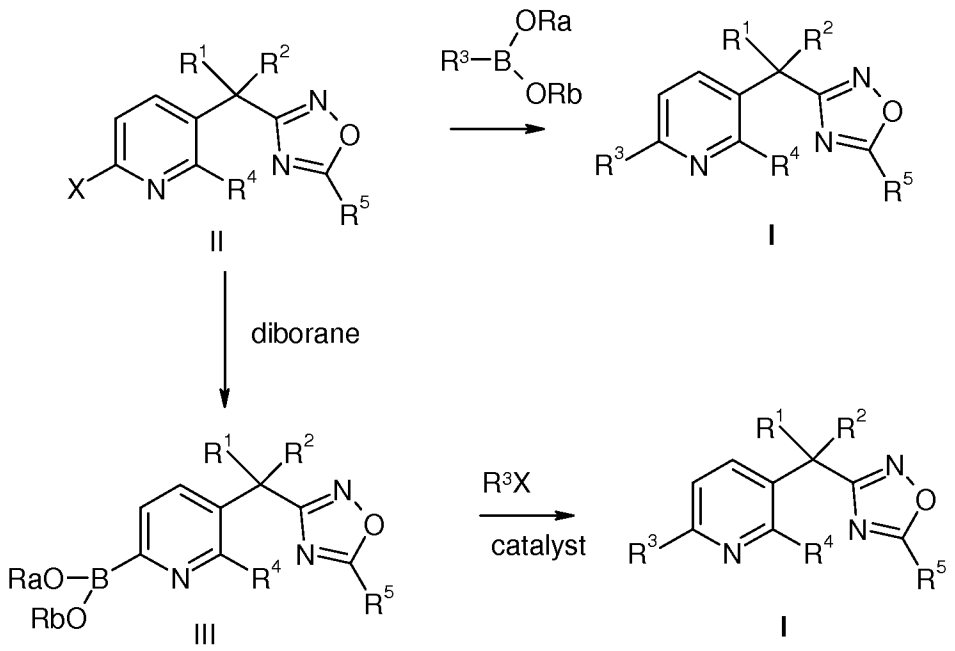
The invention also provides processes for making compounds of Formula (I). In all Schemes, unless specified otherwise, R^1, R^2, R^3, R^4 and R^5 in the Formulas below shall

have the meaning of R^1, R^2, R^3, R^4 and R^5 in Formula (I) of the invention described herein above.

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC) or LC-MS, if desired, and intermediates and products may be purified by chromatography on silica gel, recrystallization and/or preparative HPLC.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the Schemes below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

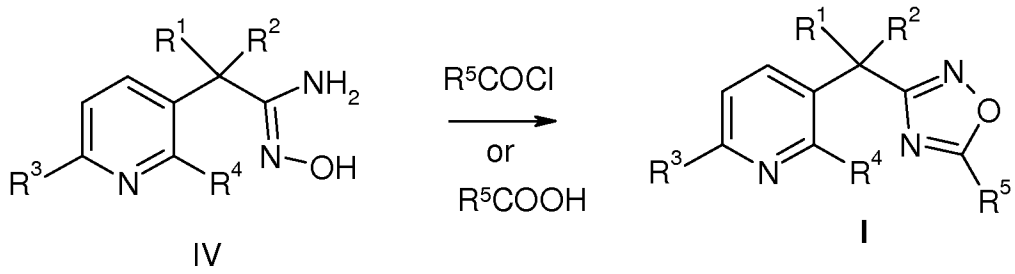
The compounds of Formula (I) may be synthesized according to Scheme 1:



Scheme 1

As illustrated in scheme 1, reaction of a compound of formula II with a boronic acid or the corresponding boronic acid ester shown in the above scheme, in a suitable solvent, in the presence of a suitable catalyst, provides a compound of formula (I). Ra and Rb are hydrogen or Ra and Rb together with the oxygen atoms to which they are attached form a 5-6 membered ring optionally substituted with 2-4 methyl groups.
Alternatively, reaction of a compound of formula II with a diborane, under standard reaction conditions, provides a compound of formula III. Coupling the intermediate of formula III with a halide or triflate R^3X, in a suitable solvent, in the presence of a suitable catalyst, provides a compound of formula (I). X is chloro,bromo, triflate, or iodo.

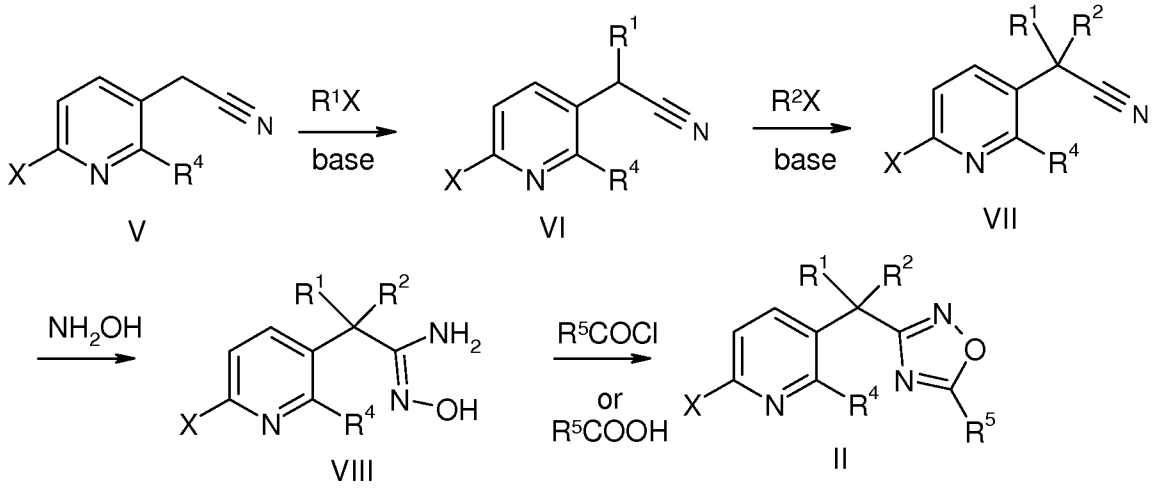
The compounds of Formula (I) may be prepared according to Scheme 2:



Scheme 2

As illustrated in scheme 2, reaction of a compound of formula IV with an acid chloride R^5COCl, in a suitable solvent, in the presence of a suitable base, provides a compound of formula (I).
Alternatively, reaction of a compound of formula IV with an acid R^5COOH, in a suitable solvent, in the presence of carbonyl diimidazole, or other suitable amide coupling reagent, provides a compound of formula (I).
Reaction of a compound of formula IV with trichloroacetic anhydride, under standard conditions, provides a compound of formula (I) wherein R^5 is trichloromethyl. The trichloromethyl group may be converted to another R^5 group by reactions known to one of skilled in the art.

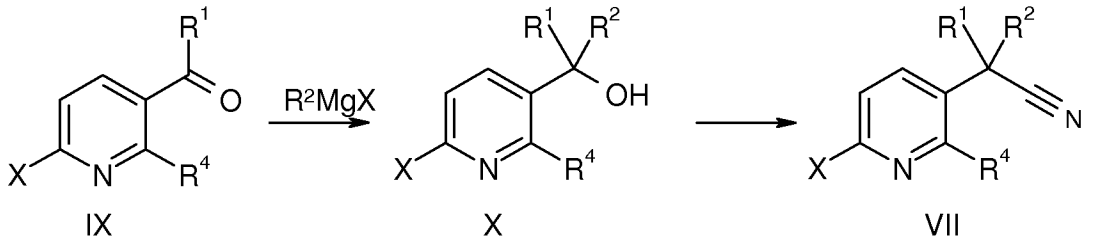
The intermediate of formula II may be synthesized as outlined in Scheme 3:



Scheme 3

As illustrated in scheme 3, reaction of a nitrile of formula V with a halide R^1X, in a suitable solvent, in the presence of a suitable base such as sodium hydride, provides a substituted nitrile of formula VI. Further reaction of the intermediate of formula VI with a halide R^2X, in a suitable solvent, in the presence of a suitable base, provides the corresponding disubstituted nitrile of formula VII. X is chloro, bromo, or iodo. Reaction of the compound of formula VII with hydroxylamine, under standard reaction conditions, provides a compound of formula VIII. Reaction of the compound of formula VIII with an acid chloride R^5COCl, in a suitable solvent, in the presence of a suitable base, provides a compound of formula II. Alternatively, reaction of a compound of formula VIII with an acid R^5COOH, in a suitable solvent, in the presence of carbonyl diimidazole, or other suitable amide coupling reagent, provides a compound of formula II.
Alternatively, reaction of a compound of formula VIII with a reagent such as carbonyldiimidazole provides a compound of formula II wherein R^5 is -OH. Further tranformation of this –OH may be carried out by procedures known in the art, to provide additional compounds of formula II.

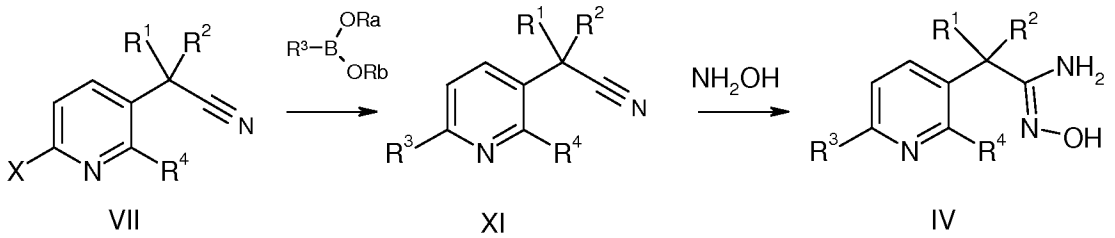
The intermediate of formula II may also be synthesized as shown in Scheme 4:



Scheme 4

As shown in scheme 4, reaction of a carbonyl compound of formula IX with a grignard reagent R^2MgX, in a suitable solvent, provides a hydroxy compound of formula X. Conversion of the hydroxyl group in compound of formula X to a cyano group, using standard procedures, provides a compound of formula VII. The compound of formula VII is converted to the intermediate of formula II by the reactions shown in scheme 3. X in R^2MgX is chloro, bromo or iodo.

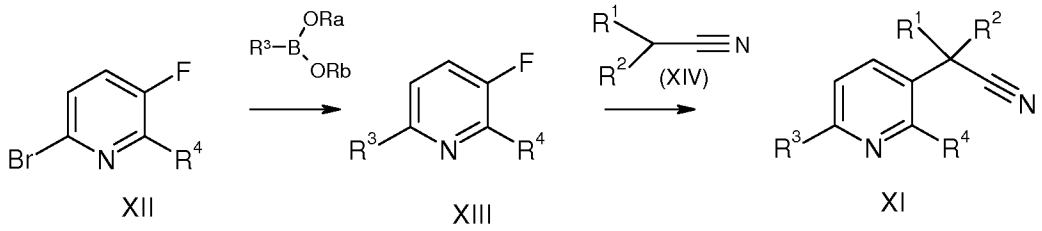
The intermediate of formula IV may be synthesized according to Scheme 5:



Scheme 5

As illustrated above in scheme 5, reaction of a nitrile of formula VII with a boronic acid or the corresponding boronic acid ester shown in the above scheme, in a suitable solvent, in the presence of a suitable catalyst, provides a compound of formula XI. Ra and Rb are hydrogen or Ra and Rb together with the oxygen atoms to which they are attached form a 5-6 membered ring optionally substituted with 2-4 methyl groups. Reaction of a compound of formula XI with hydroxylamine, under standard reaction conditions, provides a compound of formula IV.

The intermediate of formula XI may be synthesized according to Scheme 6:



Scheme 6

As illustrated above in scheme 6, reaction of a dihalide of formula XII with a boronic acid or the corresponding boronic acid ester shown in the above scheme, in a suitable solvent, in the presence of a suitable catalyst, provides a compound of formula XIII. Ra and Rb are hydrogen or Ra and Rb together with the oxygen atoms to which they are attached form a 5-6 membered ring optionally substituted with 2-4 methyl groups. Reaction of a compound of formula XIII with a nitrile of formula XIV, under standard reaction conditions, in the prence of a suitable base, provides a compound of formula XI.

Compounds of formula I as well as intermediates prepared by the above methods may be further converted to additional intermediates or compounds of formula I by methods known in the art and exemplified in the Synthetic Examples section below.

SYNTHETIC EXAMPLES

The following are representative compounds of the invention which can be made by the general synthetic schemes, the examples, and known methods in the art.
LCMS retention time and observed *m/z* data for the compounds below are obtained by one of the following methods:

LC-MS Method A

Column	Waters Atlantis dC18 100 x 2.1mm, 3µm column 40 °C
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%

Flow rate	0.6 ml/min	
Injection volume	3µl	
Detector	215nm (nominal)	
Gradient	Time (mins)	% B
	0	5
	5	100
	5.4	100
	5.42	5

LC-MS Method B

Column	Atlantis dC18 2.1 x 50mm, 3µm column	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	1 ml/min	
Injection volume	3µl	
Detector	215nm (nominal)	
Gradient	Time (mins)	% B
	0	5
	2.5	100
	2.7	100
	2.71	5
	3	5

LC-MS Method C

Column	Agilent SB-C18 1.8µm, 3x50mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	1.5 ml/min	
Injection volume	3µl	
Detector	220nm and 254nm	
Gradient	Time (mins)	% B
	0	5
	3.8	90
	4.5	100

LC-MS Method D

Column	Agilent SB-C18 1.8µm, 3x50mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	1.5 ml/min	
Injection volume	3µl	
Detector	220nm and 254nm	
Gradient	Time (mins)	% B
	0	12
	0.25	30
	0.3	40
	1.19	95
	1.75	100

LC-MS Method E

Column	Agilent Zorbax Eclipse XDB-C8 5µm, 4.6x150mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	1.5 ml/min	
Injection volume	7µl	
Detector	210nm-400nm	
Gradient	Time (mins)	% B
	0	5
	7	95
	9	95
	9.3	5
	10	5

LC-MS Method F

Column	Waters BEH C18 1.7µm , 2.1x50mm column Ambient temperature
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile)

	0.1%	
Flow rate	0.8 ml/min	
Injection volume	7µl	
Detector	210nm-400nm	
Gradient	Time (mins)	% B
	0	10
	4.5	95
	4.58	95

LC-MS Method G

Column	Agilent SB-AQ 1.8µm, 3x50mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	1.5 ml/min	
Injection volume	1µl	
Detector	210nm-400nm	
Gradient	Time (mins)	% B
	0	5
	0.25	50
	0.3	70
	1.3	90
	1.7	100

LC-MS Method H

Column	Agilent Zorbax C18 SB 3.5µm, 4.6x30mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.1% B = Formic acid (acetonitrile) 0.1%	
Flow rate	2.5 ml/min	
Injection volume	7µl	
Detector	210nm-400nm	
Gradient	Time (mins)	% B
	0	5
	1.7	95
	2	95

	2.1	5
	2.3	5

LC-MS Method I

Column	Waters BEH C18 1.7µm , 2.1x50mm column Ambient temperature	
Mobile phase	A = Formic acid (aq) 0.05% B = Formic acid (acetonitrile) 0.05%	
Flow rate	0.8 ml/min	
Injection volume	1µl	
Detector	210nm-400nm	
Gradient	Time (mins)	% B
	0	10
	1.19	100
	1.7	100

HPLC purification methods used anywhere from 0-100% acetonitrile in water and may contain 0.1% formic acid, 0.1% TFA or 0.2% ammonium hydroxide and used one of the following columns:

a) Waters Sunfire OBD C18 5 µm 30x150 mm column

b) Waters XBridge OBD C18 5 µm 30x150 mm column

c) Waters ODB C8 5 µm 19x150 mm column

d) Waters Atlantis ODB C18 5 µm 19x50 mm column

e) Waters Atlantis T3 OBD 5 µM 30x100 mm column

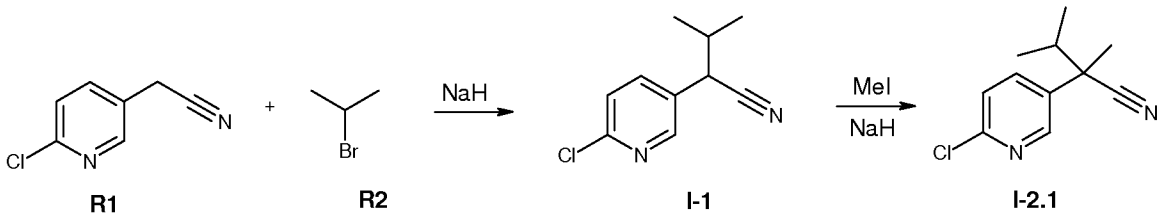
f) Phenomenex Gemini Axia C18 5 µm 30x100 mm column

g) Waters SunFire C18 Prep OBD 5µm 19 x 100 mm column

h) Waters XBridge Prep C18 5 µm 19 x 100 mm column

Starting materials and reagents are either commercially available or may be prepared by one skilled in the art using methods described in the chemical literature.

Method A: Synthesis of Intermediate I-2.1.



Step 1: Synthesis of I-1.

To a solution of compound **R1** (30.0 g, 0.20 mol) in DMF (500 mL) at 0 °C is slowly added NaH (60% in oil suspension, 8.26g, 0.21 mol). The mixture is stirred for a further 15 minutes and **R2** (18.5 mL, 0.20 mol) is added. The reaction mixture is allowed to warm up to room temperature and stirring continued for 2 hours. The reaction mixture is concentrated *in vacuo*. The residue is partitioned between DCM and brine. The combined organics are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel column chromatography (0-15% EtOAc in heptane) to yield **I-1** (26.9g); *m/z* 195 [M+H].

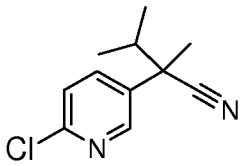
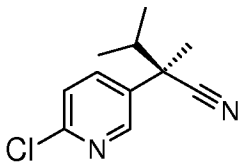
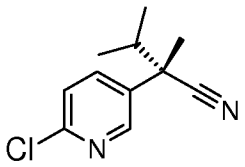
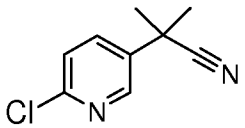
Step 2: Synthesis of Intermediate I-2.1.

To a solution of **I-1** (10.3 g, 52.81 mmol) in THF (100 mL) at 0°C is added MeI (3.8 mL, 60.91 mmol) followed by the addition of NaH (60% in oil suspension, 2.4 g, 59.98 mmol) portionwise. The reaction mixture is allowed to warm up to room temperature and stirring is continued for 18 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc and washed with water then brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel column chromatography (0-40% EtOAc in heptane) to yield **I-2.1** (10.5g).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 1

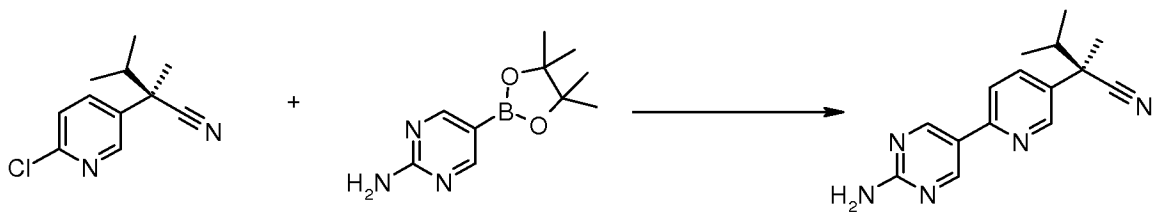
Intermediate	Structure	*m/z* [M+H]

I-2.1		209
I-2.2[a]		209
I-2.3[a]		209
I-2.4		NA[b]

a) Intermediates I-2.2 and I-2.3 were obtained by SFC chiral separation on ChiralPak AD-H, 250×50mm I.D., CO_2: MeOH 85:15, flow:160mL/min, racemic mixture loaded in MeOH.

b) ^{1}H-NMR(CDCl3, 400 MHz) 8.49 (1H, d, J = 2.8 Hz), 7.76 (1H, q, J = 3.6, 2.8 Hz), 7.35 (1H, d, J = 8 Hz), 1.74 (6H, s).

Method B: Intermediate I-3.1: Synthesis of 2-[6-(2-amino-pyrimidin-5-yl)-pyridin-3-yl]-2,3-dimethyl-butyronitrile



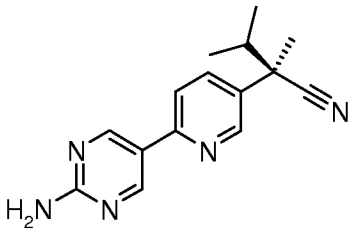
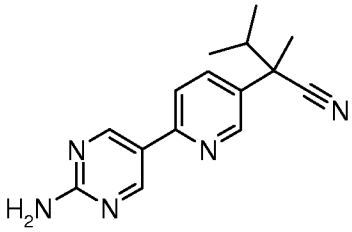
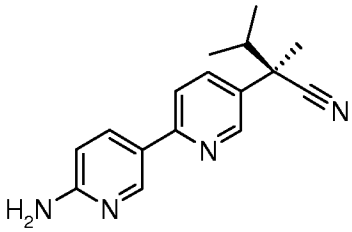
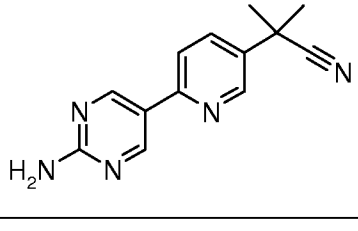
I-2.2 **R3** **I-3.1**

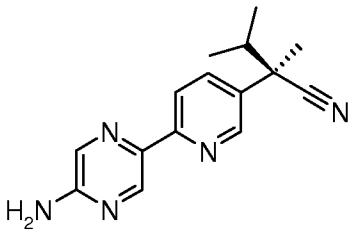
In a pressure tube, $Pd(PPh_3)_4$ (2.77 g, 2.40 mmol) and 2M Na_2CO_3 aqueous solution (40.0 mL, 80.0 mmol) are added to a suspension of **I-2.2** (10.0 g, 47.92 mmol) and **R3** (12.2 g,

55.1 mmol) in THF (100 mL). The mixture is heated at 90 °C for 3 hours, cooled to room temperature and filtered. The solid is washed with water and cold EtOAc, additional solid is formed in the filtrate and it is filtered. The combined cakes are then diluted with EtOAc and washed with water and brine. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure to afford the crude product that is purified via silica gel column chromatography to afford **I-3.1** (11.0g).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 2

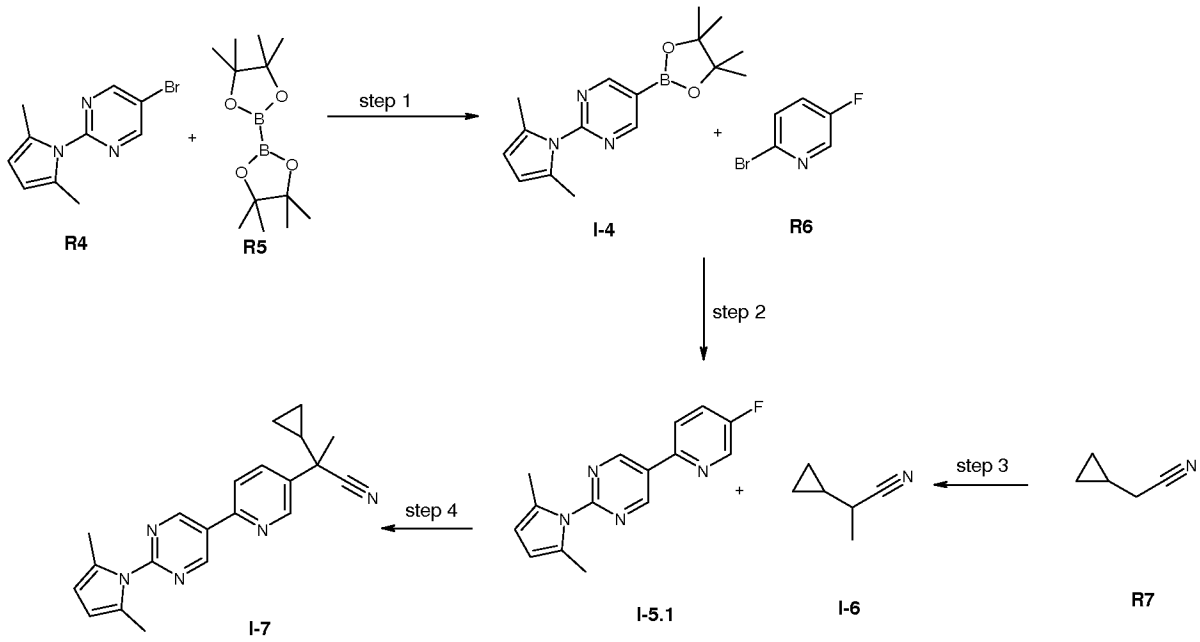
Intermediate	Structure	*m/z* [M+H]
I-3.1		268
I-3.2[a]		268
I-3.3		267
I-3.4[b]		252

I-3.5		268

a) The reaction is run in DMF, using $PdCl_2(PPh_3)_2$ as catalyst, heating at 80°C overnight.

b) The reaction is run at reflux overnight.

Method C: Synthesis of Intermediate I-7.



Step 1: Synthesis of Intermediate I-4.

To a sealed flask is added **R4** (8.83 g, 35.02 mmol), **R5** (17.78 g, 70.00 mmol), dppf (0.97 g, 1.75 mmol), $PdCl_2(dppf)CH_2Cl_2$ (1.43 g, 1.75 mmol) and KOAc (13.74 g, 140.0 mmol) in 1,4-Dioxane (100 mL). The reaction mixture is stirred at 110 °C for 16 hours.

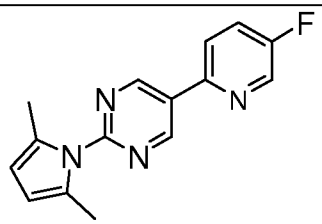
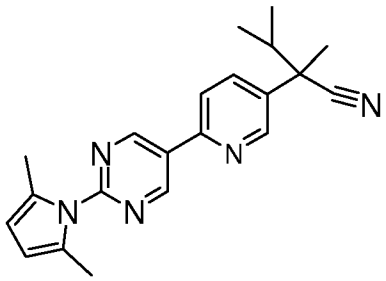
After this time, the reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc and washed with saturated $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel column chromatography (0-20% EtOAc in heptane) then triturated in cold hexane to yield **I-4** (9.0 g); *m/z* 300 [M+H].

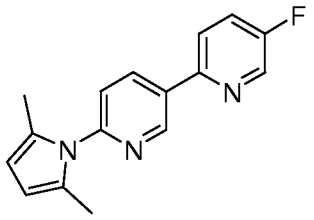
Step 2: Synthesis of Intermediate I-5.1.

To a suspension of **R6** (15.0 g, 85.23 mmol), **I-4** (28.05 g, 93.76 mmol) and $Pd(PPh_3)_4$ (1.97 g, 1.71 mmol) in DMF (250 mL) is added 2M Na_2CO_3 aqueous solution (85.23 mL, 170.47 mmol) and the reaction mixture is stirred at 90 °C for 4 hours. After cooling, the reaction mixture is diluted with water (1.5 L) and EtOAc (1 L). The layers are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is recrystallized from EtOAc/heptane to yield **I-5.1** (19.3 g).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 3

Intermediate	Structure	*m/z* [M+H]
I-5.1		269
I-5.2[a]		346

I-5.3		268

a) Intermediate I-5.2 is synthesized using I-2.1.

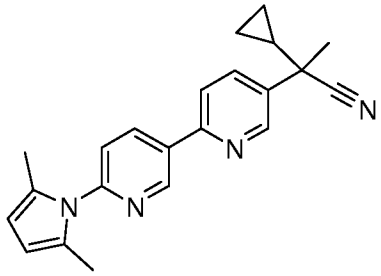
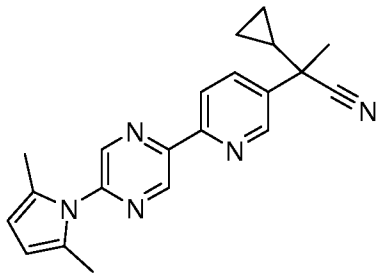
Step 3: Synthesis of Intermediate I-6.

LDA (2M in heptane/THF/ethylbenzene, 74 mL, 148.00 mmol) is added slowly into the cooled solution of **R7** (10 g, 123.28 mmol) in THF (170 mL) at -78 °C under N_2. After the addition, the reaction mixture is stirred at – 78 °C for 2 hours. MeI (21 g, 147.95 mmol) is then added and the reaction mixture is allowed to warm up to room temperature and stirred for 2 hours. After this time, the reaction mixture is quenched with saturated NH_4Cl solution and extracted with ether. The layers are separated and the organic layer is washed with water then brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified through distillation to afford **I-6** (10.7 g); (400 MHz, *DMSO-d*) δ ppm 2.41- 2.48 (1 H, m), 1.26 – 1.3 (3 H, d, *J*=7.1 Hz), 0.98 – 1.05 (1 H, m), 0.51 – 0.55 (2 H, m), 0.23 – 0.37 (2 H, m),

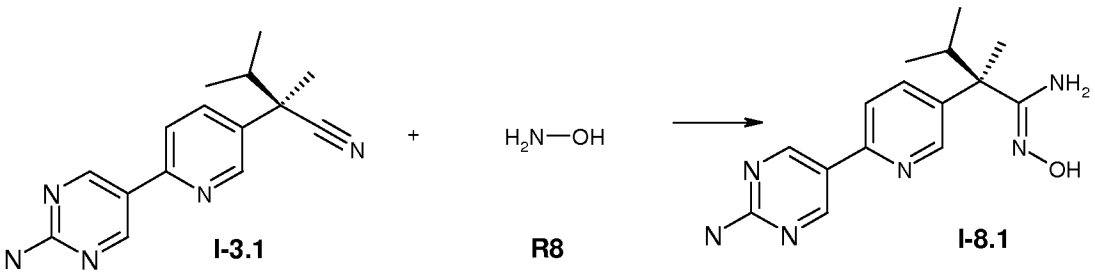
Step 4: Synthesis of Intermediate I-7.

To a solution of **I-5.1** (500.00 mg, 1.86 mmol) in toluene (1.0 mL) is added **I-6** (1.00 g, 10.51 mol) and KHMDS (0.5 M in toluene, 6.0 mL, 3.00 mmol). The reaction mixture is heated at 100°C for 18 hours. After cooling, the reaction mixture is diluted with EtOAc and washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel column chromatography (0-20% EtOAc in heptane) to yield **I-7** (350.0 mg); *m/z* 344 [M+H].

Intermediate	Structure	*m/z* [M+H]

I-7.1		343
I-7.2		344

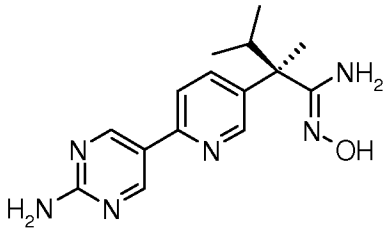
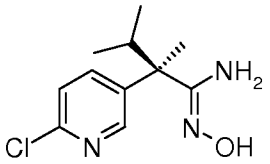
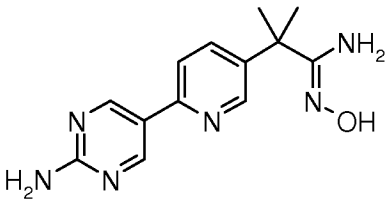
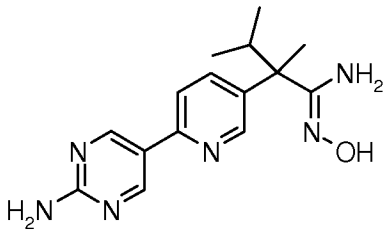
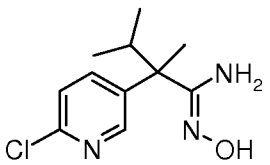
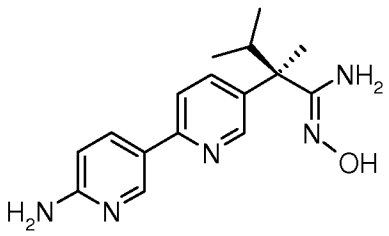
Method D: Synthesis of Intermediate I-8.1.

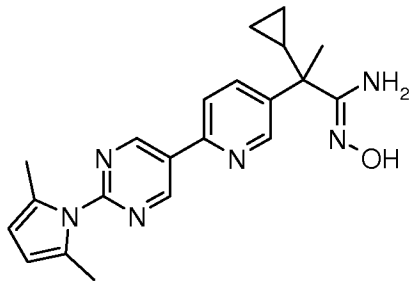
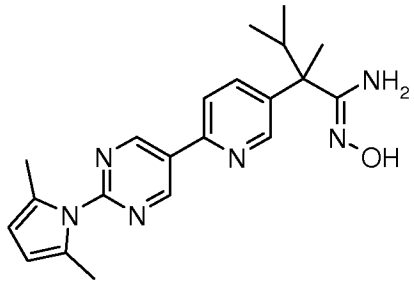
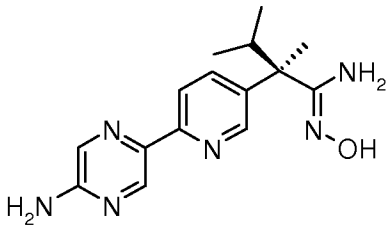
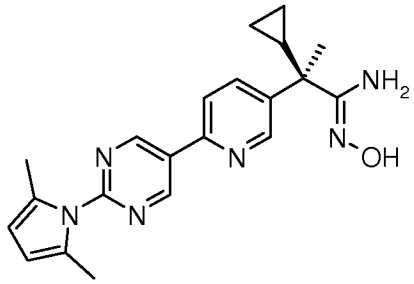
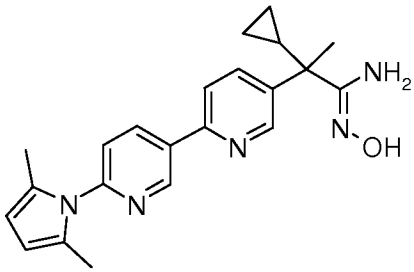


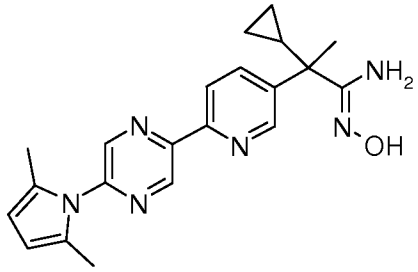
In a pressure tube, **R8** (50% aqueous solution, 90.0 mL) is added to a solution of **I-3.1** (12.1 g, 45.19 mmol) in ethanol (120 mL). The reaction mixture is stirred at 90°C for 18 hours. After allowing the reaction mixture to cool to room temperature, the solvent is removed under reduced pressure, the crude is diluted with EtOAc and washed with water and brine. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure and the obtained material is triturated with CH_3CN. The solid is filtered and washed with CH_3CN to afford **I-8.1** (11.3 g).

The following intermediates were synthesized in a similar fashion from the appropriate reagents. In some cases hydroxylamine hydrochloride in EtOH has been used instead of the aqueous solution of hydroxylamine in EtOH.

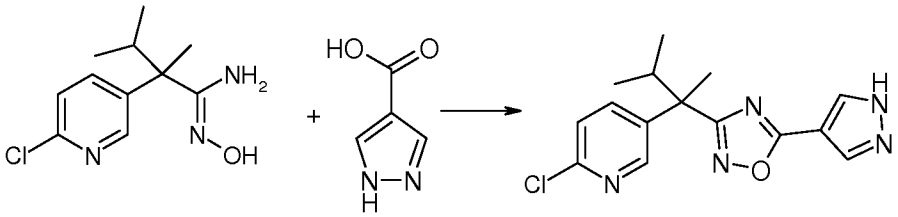
Table 4

Intermediate	Structure	*m/z* [M+H]
I-8.1		301
I-8.2		242
I-8.3		273
I-8.4		301
I-8.5		242
I-8.6		300

I-8.7		377
I-8.8		379
I-8.9		301
I-8.10		378
I-8.11		376

I-8.12		377

Method E: Synthesis of Intermediate I-9.1.

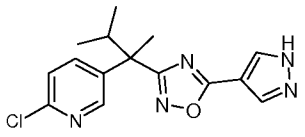


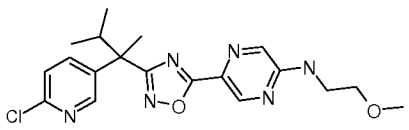
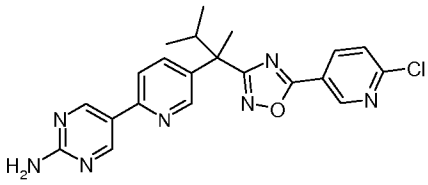
I-8.5 **R9** **I-9.1**

A solution of **I-8.5** (3.00 g, 12.4 mmol), **R9** (1.4g, 12.4 mmol), triethylamine (1.7 mL, 12.4 mmol) and HATU (4.7 g, 12.4 mmol) in DMF (20.0 mL) is stirred at room temperature overnight and then at 110°C until completion. The solvent is removed under reduced pressure, the crude diluted in DCM and washed with saturated $NaHCO_3$ solution. After drying the organic phase over anhydrous Na_2SO_4 and filtering, the solvent is removed under vacuum and the crude is purified via silica gel column chromatography (DCM/MeOH) to afford **I-9.1** (4.2g).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

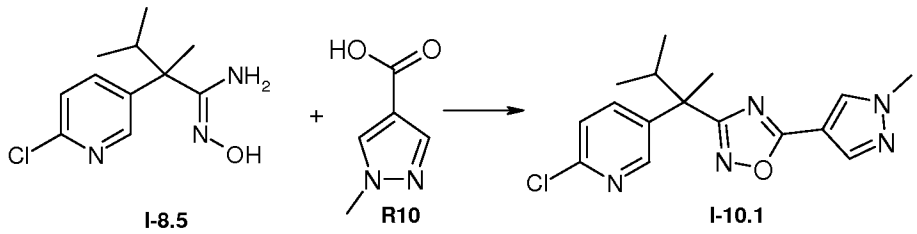
Table 5

Intermediate	Structure	*m/z* [M+H]
I-9.1		348

I-9.2[a]		403
I-9.3		422

a) Prepared from I-18.2.

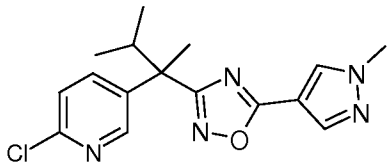
Method F: Synthesis of Intermediate I-10.1.

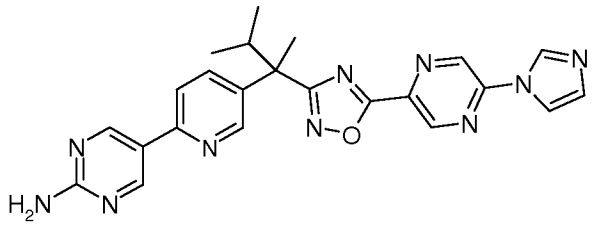
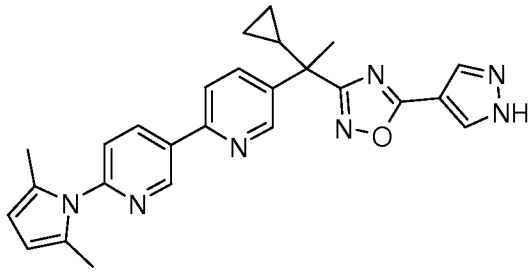
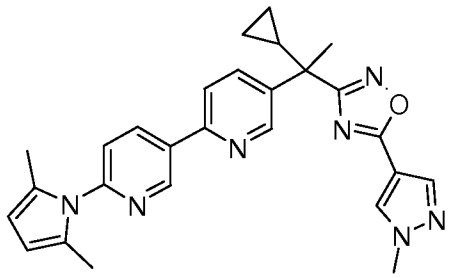
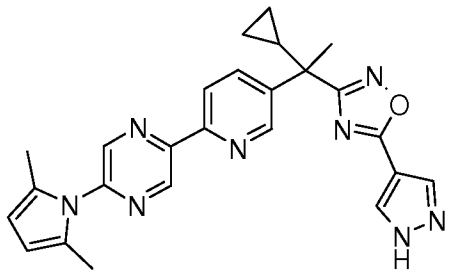


A suspension of **R10** (187.7 mg, 1.46 mmol) and 1,1'-carbonyldiimidazole. (237.5 mg, 1.46 mmol) in THF (2.0 mL) is heated at 50°C for 20 minutes. **I-8.5** (322.0 mg, 1.33 mmol) is added and the solution is heated at 55°C for one hour in an oil bath and at 150°C in the microwave for 40 minutes. The solvent is removed under reduced pressure and the crude is purified by silica gel column chromatography (DCM/MeOH) to afford **I-10.1** (416 mg).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

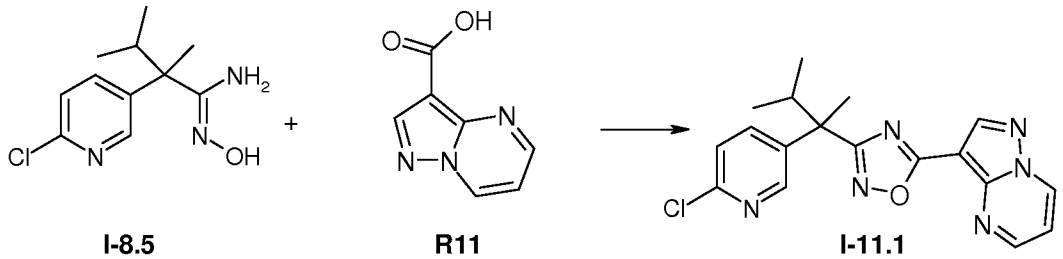
Table 6

Intermediate	Structure	*m/z* [M+H]
I-10.1		332

I-10.2[a]		455
I-10.3		452
I-10.4		466
I-10.5		453

a) The reaction is run in DMF using 5-chloro-pyrazine-2-carboxylic acid and after the addition of **I-8.4** it is heated at 110°C for 2 hours in an oil bath.

MethodG: Synthesis of Intermediate I-11.1.

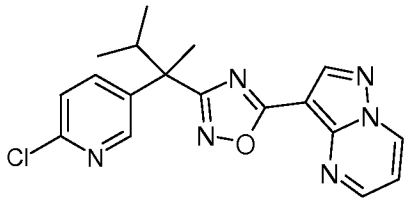
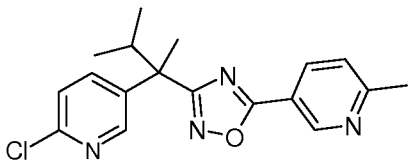
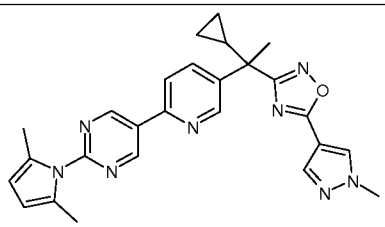


I-8.5 **R11** **I-11.1**

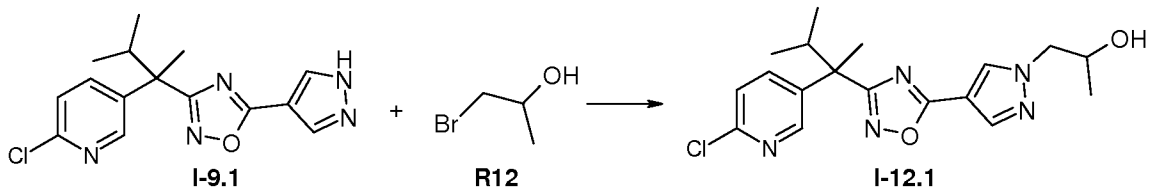
Thionyl chloride (72.4 uL, 0.99 mmol) is added to a solution of **R11** (141.8mg, 0.87mmol) in pyridine (4.0 mL) and the reaction mixture is stirred at room temperature for 30 minutes. **I-8.5** is added and the reaction mixture is stirred at room temperature for 15 minutes and heated overnight at 110°C. The solvent is removed under reduced pressure and the crude diluted in DCM and washed with
saturated $NaHCO_3$ solution. The organic phase is dried over anhydrous Na_2SO_4 to afford **I-11.1**(142 mg).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 7

Intermediate	Structure	*m/z* [M+H]
I-11.1		369
I-11.2		343/345 [M/M+2H]
I-11.3		467

Method H: Synthesis of Intermediate I-12.1.

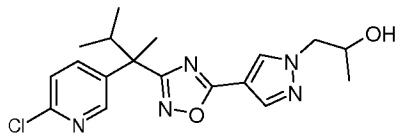
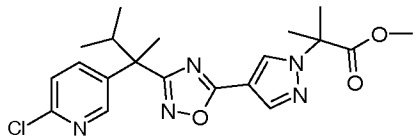
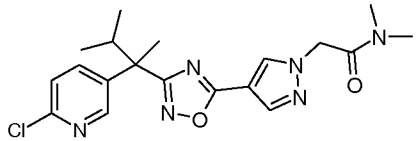
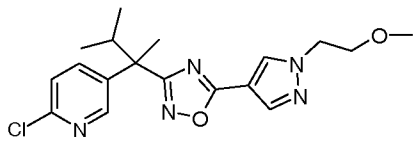
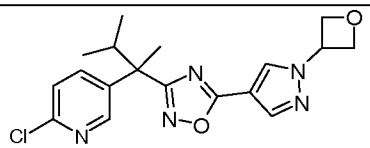
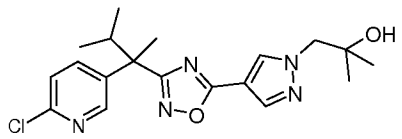
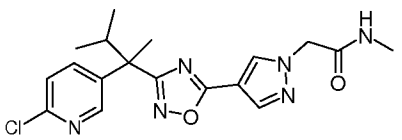


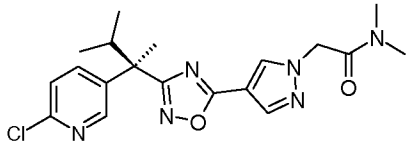
I-9.1 **R12** **I-12.1**

A solution of **I-9.1** (200.0 mg, 0.63 mmol), **R12** (91.8 mg, 0.66 mmol) and K_2CO_3 (104.4 mg, 0.75 mmol) in DMF (3.0 mL) is heated at 80°C overnight. The solvent is removed under reduced pressure, the crude diluted in DCM and washed with saturated NaH_4Cl solution. After drying the organic phase over anhydrous Na_2SO_4 and filtering, the solvent is removed under vacuum to afford **I-12.1** (181.0 mg).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 8

Intermediate	Structure	*m/z* [M+H]
I-12.1		376
I-12.2		418
I-12.3[a]		403
I-12.4		376
I-12.5[b]		374
I-12.6[c]		390
I-12.7		389

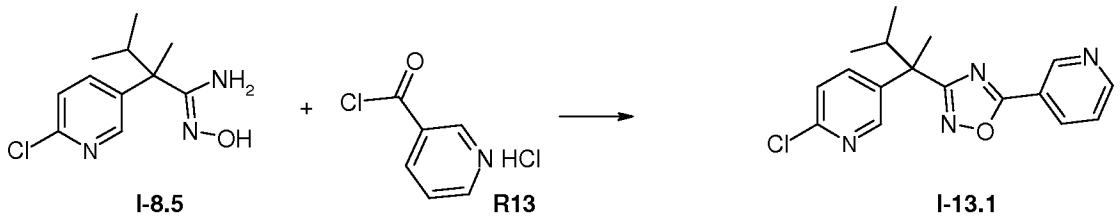
I-12.8[a]		403

a) The reaction is run using the corresponding chloride and in the presence of 0.1eq NaI.

b) The reaction is run using the corresponding iodide.

c) The reaction is run at room temperature using the corresponding chloride and 1.1 eq of NaH in DMF.

Method I: Synthesis of Intermediate 13.1.

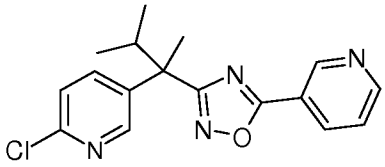


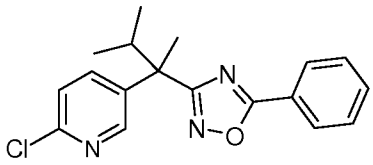
I-8.5 R13 I-13.1

A solution of **I-8.5** (260.0 mg, 1.07 mmol) and **R13** (382 mg, 2.15 mmol) in pyridine (1.5 mL) is heated in a pressure tube at 110°C for 2 hours. The solvent is removed under reduced pressure, the crude is diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure, the crude is purified via silica gel column chromatography to afford **I-13.1** (282.0 mg).

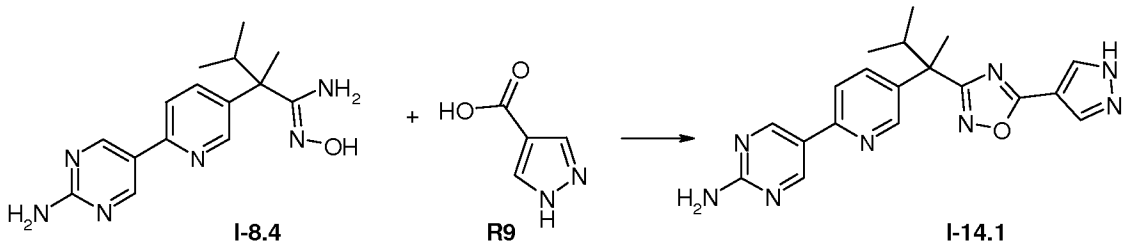
The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 9

Intermediate	Structure	*m/z* [M+H]
I-13.1		329

I-13.2		328

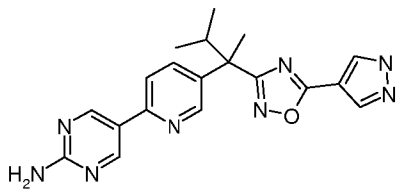
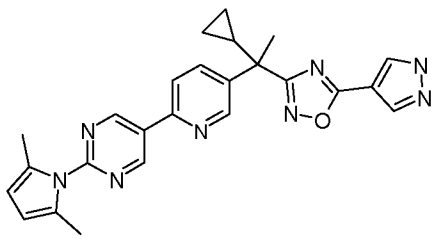
Method J: Synthesis of Intermediate I-14.1.

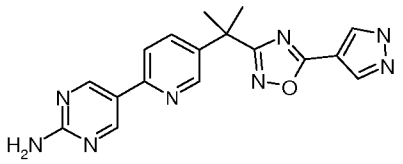
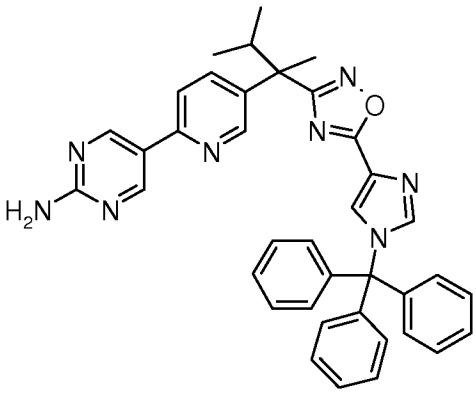


A suspension of **R9** (0.3 g, 4.58 mmol) and 1,1'-carbonyldiimidazole. (0.74 g, 4.58 mmol) in NMP (4.0 mL) is heated at 50°C for 20 min. **I-8.4** is added (1.25 g, 4.16 mmol) and the solution is heated at 130°C for 2 hours. The reaction mixture is cooled to room temperature, water is added and it is stirred overnight. A gooey residue is formed, the liquid is decanted and the crude is purified via silica gel column chromatography (DCM/MeOH) affords **I-14.1** (1.41 g).

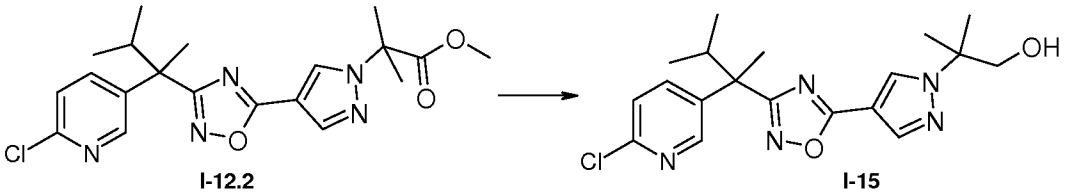
The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 10

Intermediate	Structure	*m/z* [M+H]
I-14.1		377
I-14.2		453

I-14.3		349
I-14.4		377 [M+H]-trityl

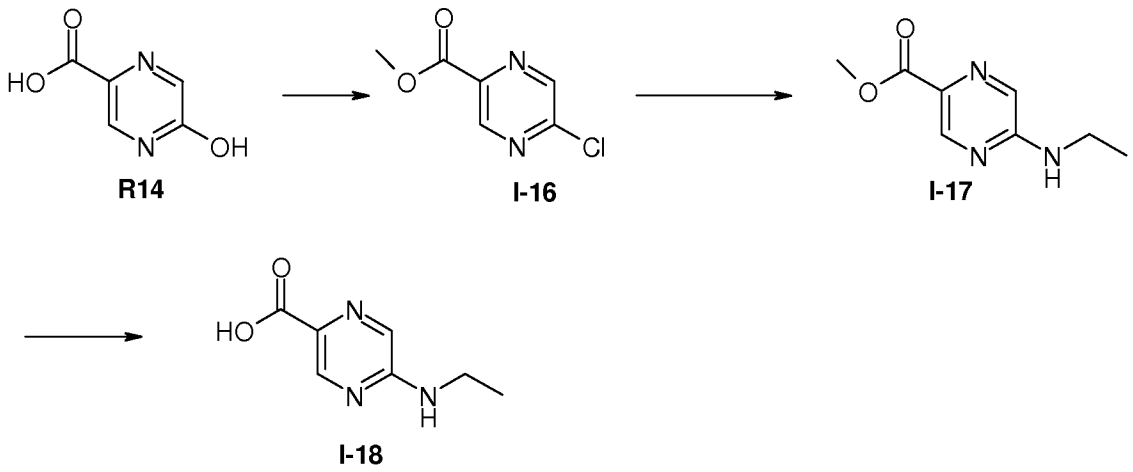
Method K: Synthesis of Intermediate I-15.



I-12.2 I-15

Lithium borohydride (104.1 mg, 4.78 mmol) is added to a solution of **I-12.2** (679.0 mg, 1.62 mmol) in THF (20.0 mL) at 0°C. The reaction mixture is allowed to warm to room temperature and then stirred for 2 hours. The solvent is removed under reduced pressure, the crude diluted in EtOAc and washed with saturated $NaHCO_3$ solution. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure to afford **I-15** (650mg, 83% pure); *m/z* 390 [M+H].

Method L: Synthesis of Intermediate I-18.



Step1: Synthesis of I-16.

A solution of **R14** (2.0 g, 14.3mmol) and thionyl chloride (10.0 mL) with a catalytic amount of DMF is refluxed for 4 hours. The solvent is removed under reduced pressure, MeOH (10.0 mL) and pyridine (1.4 mL, 17.1 mmol) are slowly added and the mixture is stirred overnight at room temperature. The solvent is removed under reduced pressure, the crude is purified via silica gel column chromatography to afford **I-16** (1.12 g); *m/z* 173 [M+H].

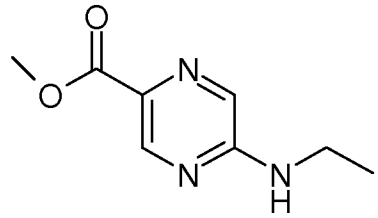
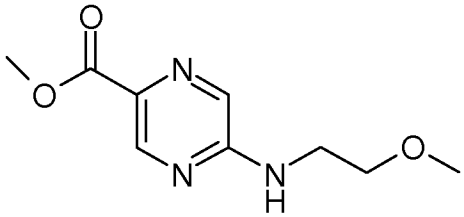
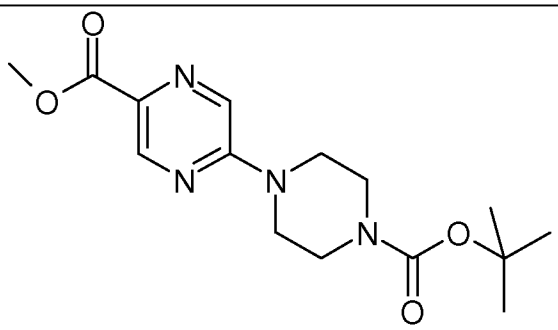
Step2: Synthesis of I-17.1.

Ethylamine (1.7 mL, 3.48 mmol) is added to a solution of **I-16** (500.0 mg, 2.90 mmol) in DMSO (4.0 mL) and the mixture is heated at 80°C overnight. The reaction mixture is cooled to room temperature, water (5.0 mL) is added and the solution is acidified to pH~2.0 with 2N HCl. The mixture is extracted with EtOAc, the organic layers are combined, dried over anhydrous Na_2SO_4 and filtered. The solvent is removed to afford **I-17.1** (451.0 mg).

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 11

Intermediate	Structure	*m/z* [M+H]

I-17.1		182
I-17.2		212
I-17.3		323

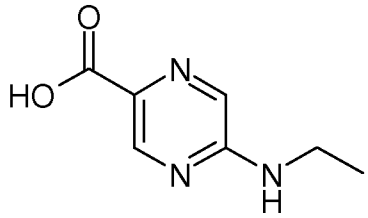
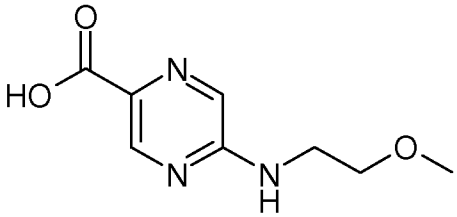
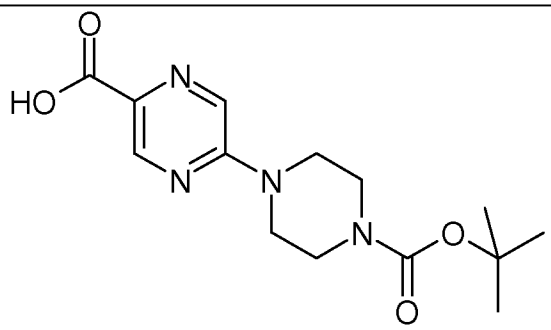
Step 3: Synthesis of Intermediate I-18.1.

Lithium hydroxide (87.4 mg, 3.65 mmol) is added to a solution of **I-17.1** (441.0 mg, 2.43 mmol)in THF/water (6.0 mL/ 6.0 mL). The solution is stirred at room temperature for 2 days, acidified to pH~3.0 with 2N HCl and extracted with EtOAc. The organic layers are combined, dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under vacuum to afford **I-18.1** (367.0 mg).

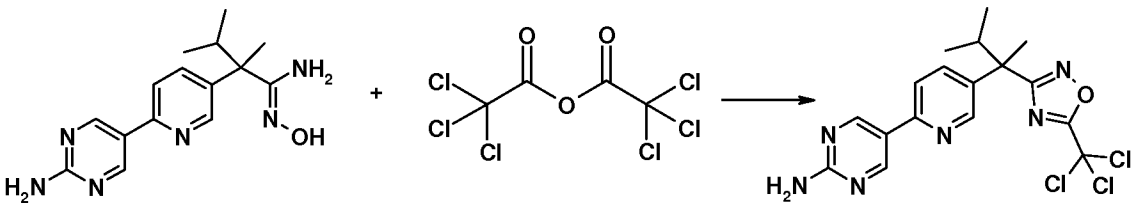
The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 12

Intermediate	Structure	*m/z* [M+H]

I-18.1		168
I-18.2		196 [M-H]
I-18.3		309

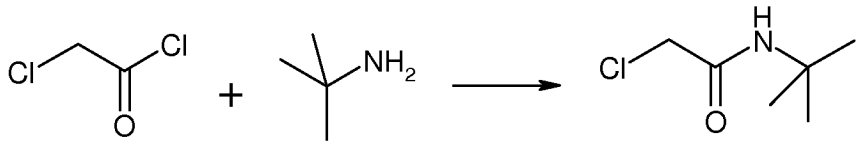
Method M: Synthesis of Intermediate I-19.



I-8.4 R15 I-19

To a mixture of **I-8.4** (1.3 g, 1.328 mmol) in toluene (50 mL) is added **R15** (0.949 mL, 5.194 mmol). The reaction mixture is heated to reflux for 3.5 hours. After allowing the reaction mixture to cool to room temperature, the precipitate formed is collected through filtration. The solid is washed with EtOAc to give the title intermediate **I-19** (1.89 g); *m/z* 427 [M+H].

Method N: Synthesis of Intermediate I-24

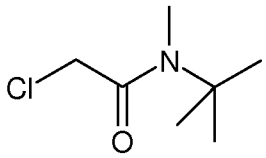
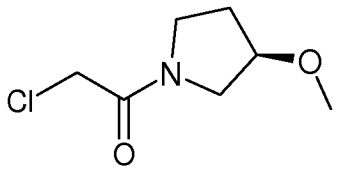
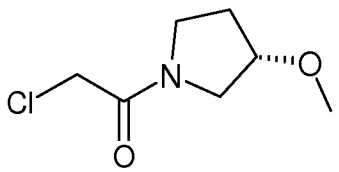


I-24

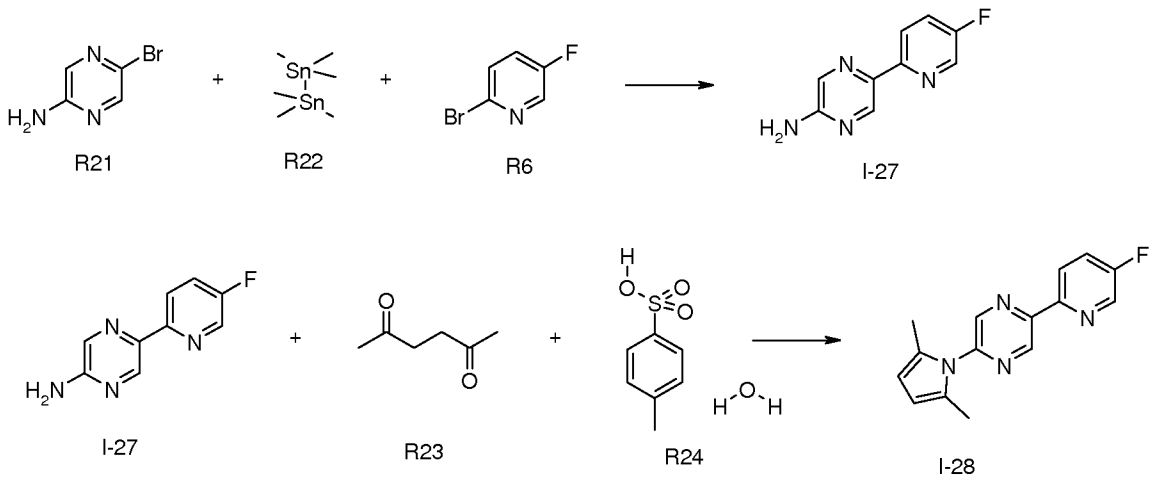
To a vial was added chloroacetyl chloride (500 mg, 4.43 mmol) in THF (6 ml), followed by the addition of tert-butylamine (485 mg, 6.63 mmol) and triethylamine (672 mg, 6.64 mmol) slowly. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was disolved in EtOAc, washed with water, brine, dried under anhy. Na_2SO_4, filtered and concentrated to afford title compound (500 mg), *m/z*: 150 [M+H]

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 13

Intermediate	Structure	*m/z* [M+H]
I-24.1		164
I-24.2		178
I-24.3		178

Method O: Synthesis of Intermediate I-28



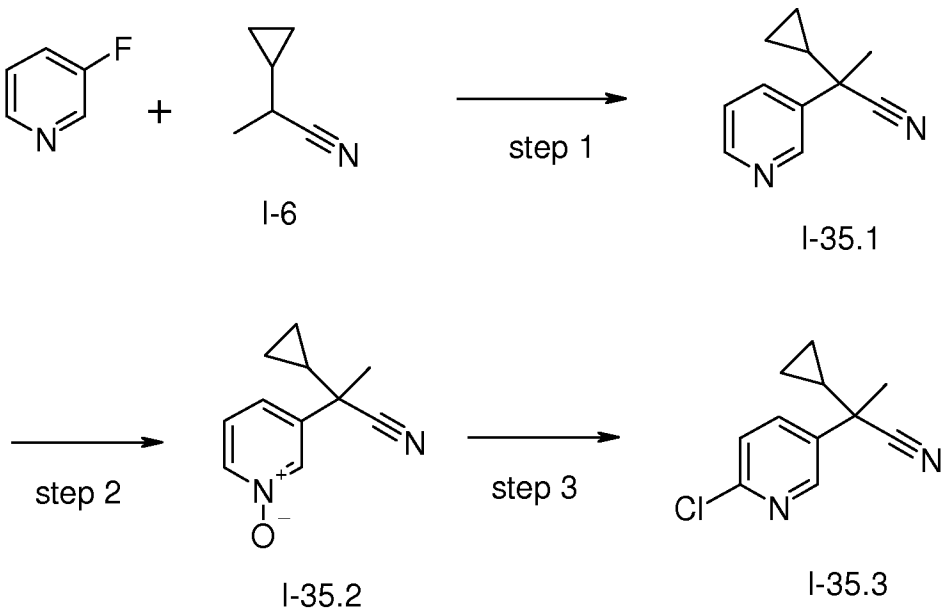
Step 1: Synthesis of Intermediate I-27

R21 (1.00 g, 5.75 mmol) in a pressure flask is treated with degassed toluene (16 mL), $Pd(Ph_3P)_4$ (398 mg, 0.345 mmol), and R22 (1.25 mL, 6.04 mmol) and the resulting mixture is heated at 115 °C for 1 hour. The mixture is then cooled to room temperature and R6 (1.42 g, 8.05 mmol) is added followed by $Pd(Ph_3P)_4$ (332 mg, 0.287 mmol) and the resulting mixture is heated at 115 °C for 1 hour. The resulting mixture is cooled to room temperature and is concentrated. The residue is purified by silica gel column chromatography (0-10% methanol in CH_2Cl_2) to yield **I-27** (432 mg); *m/z*: 191 [M+H].

Step 2: Synthesis of Intermediate I-28

I-27 (432 mg, 2.27 mmol) is treated with R23 (374 mL, 3.18 mmol), R24 (8.6 mg, 0.045 mmol), and toluene (15 mL) and refluxed with a Dean-Stark trap for 24 hours. The reaction is then concentrated and the residue is purified by silica gel column chromatography (0-20% EtOAc in heptanes) to yield **I-28** (414 mg); *m/z*: 269 [M+H].

Method P: Synthesis of Intermediate I-35.3



Step 1: Synthesis of Intermediate I-35.1

To a pressure reactor is added 3-fluoropyridine (2 g, 20.6 mmol), followed by the addition of I-6 (5.39 g, 56.7 mmol) and potassium bis(trimethylsilyl)amide (0.5M in toluene) (61.8 ml, 30.9 mmol). The reaction mixture is stirred at 100 °C for 10 hours. The reaction mixture is diluted with EtOAc, is washed with water, brine, is dried under anhy. Na_2SO_4, and is filtered and is concentrated. The residue is purified by flash chromatography (SiO_2, 0-3% MeOH/CH_2Cl_2) to afford I-35.1 (3.18 g); *m/z* 172.4 [M+1]

Step 2: Synthesis of Intermediate I-35.2

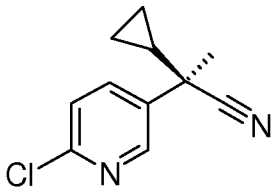
To a round bottom flask is added I-29.1 (3.18 g, 18.5 mmol) in CH_2Cl_2 (70 ml), follows by the addition of 3-chloroperoxybenzoic acid (4.4 g, 25.5 mmol). The reaction mixture is stirred at room temperature for 3 hours. The reaction mixture is queched with sat. sodium thiosulfate solution and is stirred for 1 hour. The organic phase is separated, is washed with water, brine, is dried under anhy. Na_2SO_4, is filtered and is concentrated. The residue is purified by flash chromatography (SiO_2, 0-5% MeOH/CH_2Cl_2) to afford I-35.2 (3.31 g); *m/z* 189.4 [M+1]

Step 3: Synthesis of Intermediate I-35.3

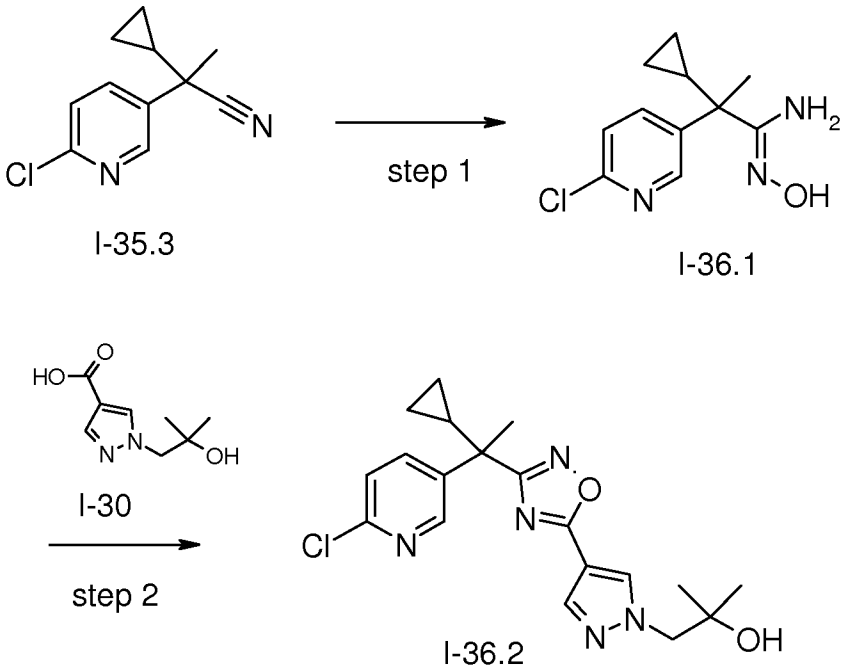
A solution of $POCl_3$ (3.3 ml, 35.4 mmol)) in CH_2Cl_2 (10 ml) is added dropwise at 0 °C to a stirred solution of I-29.2 (3.31 mg, 17.6 mmol)) and Et_3N (4.9 ml, 35.2 mmol)) in CH_2Cl_2 (50 ml). The reaction mixture is stirred at room temperature for 1 hour, then at 40 °C for 3 hours. The reaction mixture is queched with sat. $NaHCO_3$. The organic layer is separated, is washed with brine, is dried under anhy. Na_2SO_4, is filtered and is concentrated. The residue is purified by flash chromatography (SiO_2, 0-25% EtOAc/heptane) to afford I-35.3 (1.34 g); *m/z* 207.1 [M+1]

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 15

Intermediate	Structure	*m/z* [M+H]
I-35.4		207

Method Q: Synthesis of Intermediate of I-36.2



Step 1: Synthesis of Intermediate I-36.1

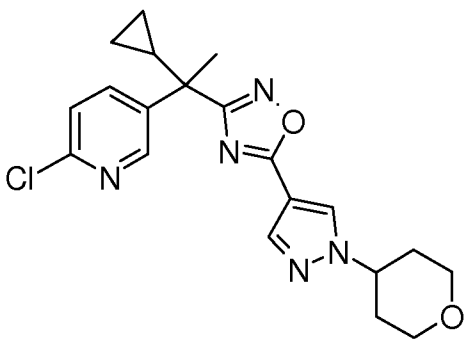
To a pressure reactor is added I-35.3 (500 mg, 2.42 mmol) in EtOH (3 ml), follows by the addition of hydroxylamine (3 ml, 49 mmol). The reaction mixture is stirred at 90 °C for 3 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc, is washed with water, brine, is dried under anhy. Na_2SO_4, is filtered and is concentrated. The residue is purified by flash chromatography (SiO_2, 0-5% MeOH/CH_2Cl_2) to afford I-36.1 (567 mg); *m/z* 240.1 [M+1]

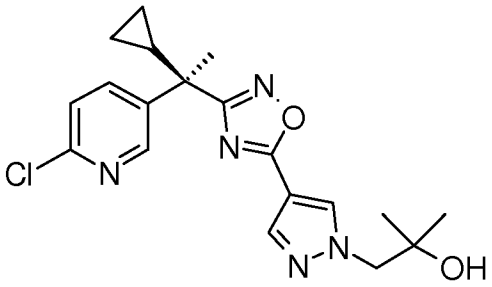
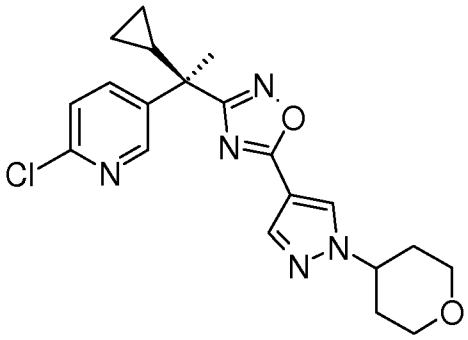
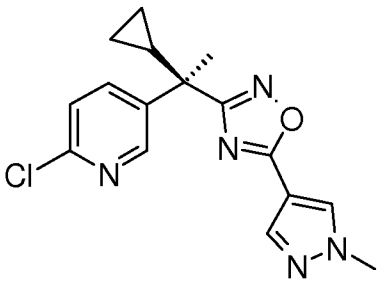
Step 2: Synthesis of Intermediate I-36.2

To a pressure tube is added I-36.1 (250 mg, 1.04 mmol) in 1,4-dioxane (5 ml), follows by the addition of 1,1'-carbonyldiimidazole (186 mg, 1.15 mmol). The reaction mixture is stirred at 55 °C for 60 minutes, followed by the addition of I-30 (211 mg, 1.15 mmol). The reaction mixture is stirred at 110 °C for 16 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc, is washed with water, brine, is dried under anhy. Na_2SO_4, is filtered and is concentrated. The residues is purified by flash chromatography (SiO_2, 0-5% MeOH/CH_2Cl_2) to afford I-36.2 (352 mg); *m/z* 388.2 [M+1]

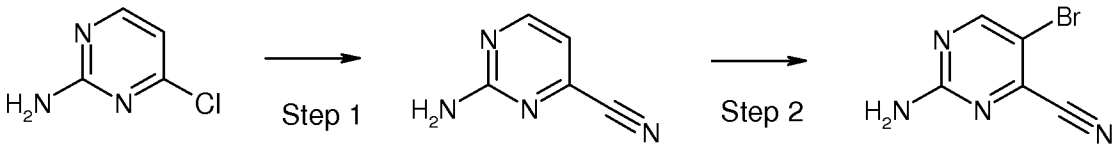
The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 16

Intermediate	Structure	*m/z* [M+H]
I-36.3		400

I-36.4		390
I-36.5		402
I-36.6		332

Method R: Synthesis of intermediate I-37.2



R-31 I-37.1 I-37.2

Step 1: Synthesis of I-37.1

To a solution of R-31 (200 mg, 1.5 mmol) in DMF (10 mL) are added $ZnCN_2$ (217 mg, 1.8 mmol) and $Pd(PPh_3)_4$ (178 mg ,0.15 mmol) at room temperature. The solution is heated at 120 °C in a microwave reactor for 2 hours. The solution is cooled down and water (10 mL) is added. The solution is extracted with EtOAc (30 mL) and the combined

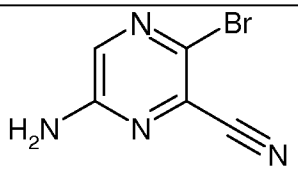
organic layer is dried with $MgSO_4$ and is filtered. The filtrate is concentrated and the residue (I-37.1: *m/z*: 120 [M^+]) is used in the next step of the synthesis without further purification.

Step 2: Synthesis of I-37.2

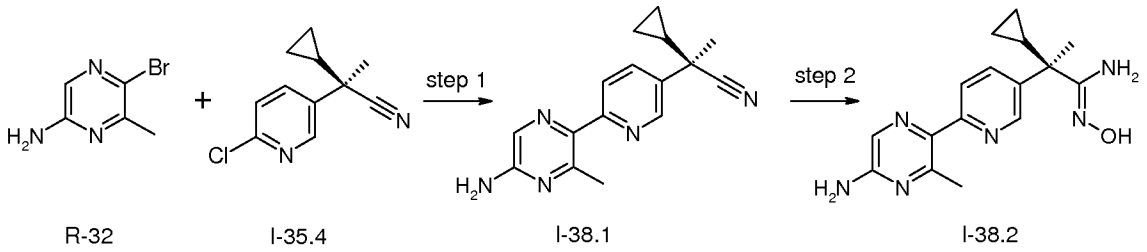
To a solution of I-37.1 (100 mg, 0.83 mmol) in CH_3CN (10 mL) is added NBS (222 mg, 1.2 mmol) at room temperature. The solution is stirred at the same temperature for 12 hours. The solution is concentrated and the residue is purified by silica gel flash column chromatography with 10% MeOH in CH_2Cl_2 as the eluent to afford I-37.2 (100 mg); *m/z*: 200 [M^++1]

The following intermediates were synthesized in a similar fashion from the appropriate reagents:

Table 17

Intermediate	Structure	*m/z* [M+H]
I-37.3		200

Method S: Synthesis of Intermediate I-38.2



R-32 I-35.4 I-38.1 I-38.2

Step 1: Synthesis of I-38.1

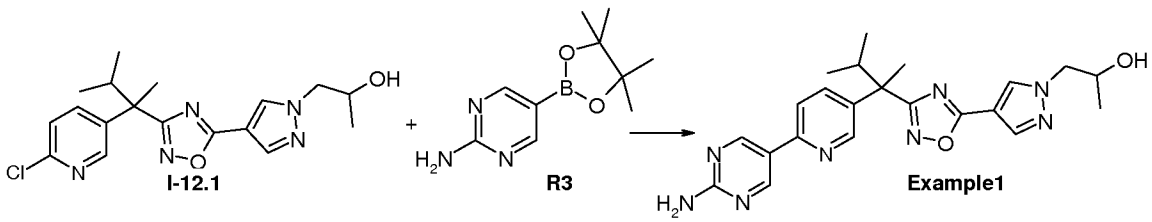
To a solution of I-35.4 (495 mg, 2.39 mmol) in THF (5ml) in a microwave vial is added hexamethyldistannane (0.55 ml, 2.64 mmol) followed by bis(triphenylphosphine)palladium(II) chloride (168 mg, 0.239 mmol). The reaction mixture is degassed with argon, capped, and stirred at 85 °C for 16 hrs. R-32 (450 mg,

2.39 mmol) is added followed by tetrakis(triphenylphosphine)palladium (0) (276 mg, 0.239 mmol). The reaction vessel is degassed with argon, then capped and heated at 85 °C for 16 hours. The reaction mixture is passed through a plug of Celite and rinsed with DCM. The filtrate is concentrated *in vacuo* and purified by flash chromatography (SiO_2, 0-5% MeOH/DCM) to afford the title intermdiate (160 mg); *m/z* 281.3 [M+1]

Step 2: Synthesis of I-38.2

To a solution of I-38.1 (160 mg, 0.57 mmol) in 4 ml of EtOH stirring in a roundbottom flask with a condenser is added hydroxylamine (50% solution in water) (2.5ml, 81.6 mmol) and stirred at 90 °C for 3 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc, is washed with water, brine, is dried under anhy. Na_2SO_4, is filtered and is concentrated to afford title intermediate (169 mg); *m/z* 313.2 [M+1]

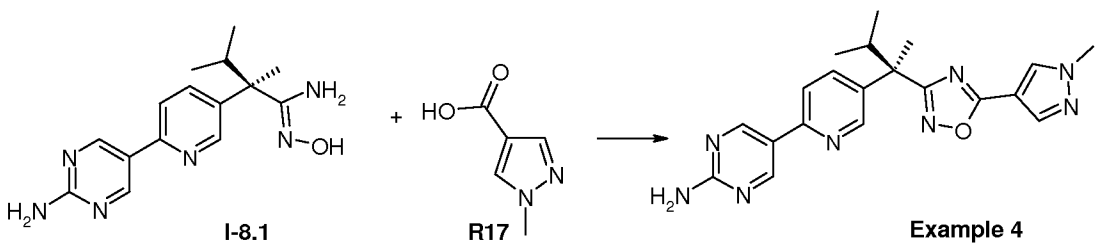
Method 1: Synthesis of 1-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]propan-2-ol (Example 1).



A solution of **I-12.1** (181.0 mg, 0.48 mmol), **R3** (319.5 mg, 1.45 mmol), bis(triphenylphosphine)palladium(II)chloride (67.6mg, 0.096mmol) and 2M Na_2CO_3 solution (0.48 mL) in DMF (3.0 mL) is heated at 80°C until completion. The reaction mixture is cooled to room temperature, filtered, the solvent is removed under vacuum, the crude diluted in DCM and washed with saturated $NaHCO_3$ solution. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under vacuum and the crude is purified via preparative HPLC to afford **Example 1** (26.5 mg).

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of some that were purified via silica gel column chromatography; Example 3 for which tetrakis(triphenylphosphine)palladium(0) in THF is used; Example 5 that derived from chiral resolution of Example 3 via a Chiracel AD column in 80% (EtOH+0.1% diethylamine) in Heptane @ 75 mL/min; Example 23 and Example 24 derived from chiral resolution of Example 8 via a Chiracel AD column in 95% (EtOH+0.4% diethylamine) in Heptane @ 55 mL/min; Example 34 and Example 35 derived from chiral resolution of Example 6 via a chiral column AD-H in 95% (EtOH+0.4% diethylamine) in Heptane @ 55 mL/min; Example 53 and Example 54 derived from chiral resolution of Example 80 on 4.6 x 100mm Regis Pack from Regis Technologies, CO_2 cosolvent EtOH:IPA + 0.1% isopropilamine, 65% cosolvent at 4mL/min, P=100 bar, T=25°C; Example 59 and Example 61 derived from chiral resolution of Example 7 on 4.6 x 100mm Chiral Pack AD from Chiral Technologies, CO_2 cosolvent IPA:MeOH 7:3 + 0.1% isopropilamine, 50% cosolvent at 4mL/min, P=125 bar, T=25°C; Example 70, Example 71 and Example 72 for which 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium and catalytic amount of 1,1'-bis(diphenylphosphino)ferrocene are used.

Method 2: Synthesis of 5-(5-{(2R)-3-methyl-2-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine (Example 4).

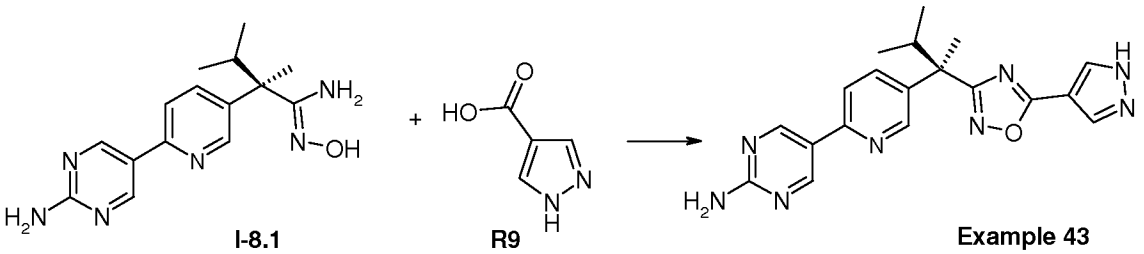


This method is performed in accordance to the procedure reported for Method G, using 1.1 eq of acid and CDI.

Examples listed in Table 13 have been synthesized in a similar manner, in some cases compounds were purified via prep HPLC, in some others via silica gel column

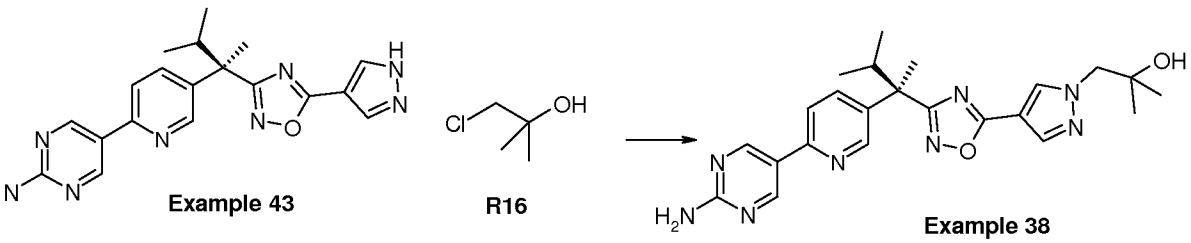
chromatography. For Example 21 the reaction is carried out in DMF and heating at 110°C for 7 hours after the addition of **I-8.4**.

Method 3: Synthesis of 5-(5-{(2R)-3-methyl-2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]butan-2-yl}pyridin-2-yl)pyrimidin-2-amine (Example 43).



In a sealed tube **R9** (4.4 g, 37.9 mmol) is added in 1,4-dioxane (100.0 mL), followed by the addition of 1,1'-carbonyldiimidazole (6.1 g, 37.9 mmol). The reaction mixture is stirred at 55 °C for 30 minutes. The reaction mixture first becomes a clear solution, then cloudy. A solution of **I-8.1** (10.8 g, 32.1 mmol) in 1,4-dioxane (10.0 mL) is added. The reaction mixture is stirred at 120 °C for 8 hours. The solvent is removed under reduced pressure, the crude is purified by silica gel column chromatography (DCM/MeOH) to afford **Example 43** (11.9 g).

Method 4: Synthesis of 1-[4-(3-{(2R)-2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol (Example 38).



A solution of **Example 43** (2.0 g, 5.14 mmol), K_2CO_3 (1.06 g, 7.71 mmol) and **R16** (1.05 mL, 10.28 mmol) in DMF (10.0 mL) is stirred at 80°C for 3 days. K_2CO_3 (355 mg, 2.57 mmol) is added and the reaction mixture is heated for additional 2 hours. The reaction mixture is diluted with EtOAc and washed with water. The water layer is extracted with

EtOAc. The organic phase is dried over anhydrous Na_2SO_4 and filtered; the solvent removed under vacuum and the crude purified via silica gel column chromatography (DCM/MeOH) to afford **Example 38** (1.99 g).

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of Example 14 for which 1.0 eq of base and 1.0 eq of iodide are used; for Example 17 the corresponding iodide is used; for Example 28 1.5 eq of the corresponding bromide are used and the reaction is run at room temperature overnight; for Example 29 1.5 eq of the corresponding iodide are used and the reaction is run at room temperature overnight; for Example 30 1.2 eq of the corresponding bromide are used and the reaction is heated at 100°C over three days; for Example 31 1.5eq of the corresponding iodide in DMF at room temperature for 12 hours; Example 33 1.1.eq of the corresponding chloride is used and the reaction is run at 100°C over three days in the presence of a catalytic amount of TBAI; Example 37 derived from chiral resolution of Example 2 via a chiral column AD-H in 95% (EtOH+0.4% diethylamine) in Heptane @ 8 mL/min; Example 44 and Example 45 derived from chiral resolution of Example 14 on 4.6 x 100mm Regis Pack from Regis Technologies, CO_2 cosolvent + 0.1% isopropilamine in isopropanol, 30% cosolvent at 4mL/min, P=100 bar, T=25°C; Example 46 and Example 47 derived from chiral resolution of Example 30 via a chiral column AD-H in 95% (EtOH+0.4% diethylamine) in Heptane at 55mL/min; Example 48 and Example 49 derived from chiral resolution of Example 17 via a chiral column AD-H in 95% (EtOH+0.4% diethylamine) in Heptane 55mL/min; Example 88 the reaction is run in the presence of catalytic amount of TBAI and it is heated at 100°C for three days; for Example 89 the corresponding bromide is used the reaction is run at 100°C for three days; for Example 90 the corresponding bromide is used the reaction is run at 100°C for three days.

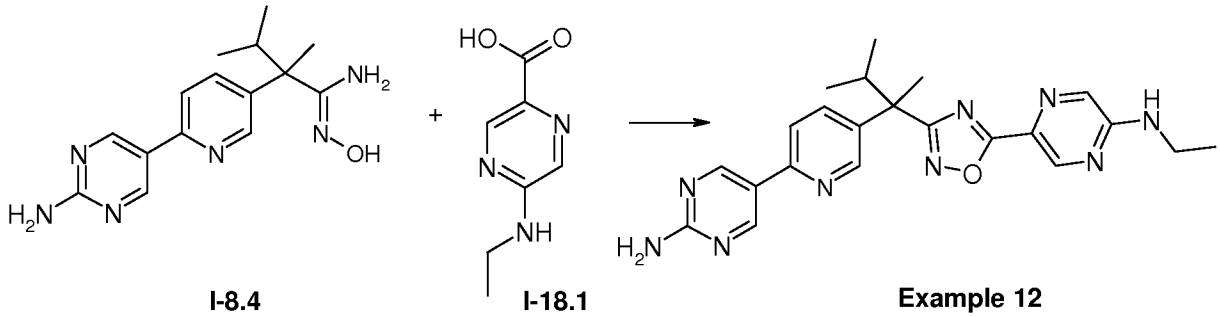
The following compounds are made in a similar manner to method 4:

Example 96 uses the corresponding bromide, Cs_2CO_3 in place of K_2CO_3, and is carried out at 70 °C for 3 hours followed by a second addition of bromide and base and heating for another 1 hour at 70 °C.

Examples 97 and 129 use Cs_2CO_3 in place of K_2CO_3, and are carried out at 60 °C for 1 hour with purification by reverse-phase preparative HPLC.

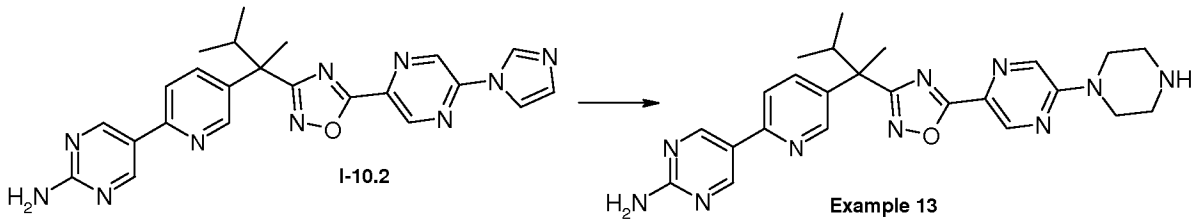
Example 111 uses Cs_2CO_3 in place of K_2CO_3, and is carried out at 50 °C for 2 hours then room temperature overnight with purification by reverse-phase preparative HPLC.
Example 140 uses Cs_2CO_3 in place of K_2CO_3, and is carried out at 50 °C for 2 hours with purification by reverse-phase preparative HPLC.

Method 5: Synthesis of 5-[5-(2-{5-[5-(ethylamino)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}-3-methylbutan-2-yl)pyridin-2-yl]pyrimidin-2-amine (Example 12).



This method is performed in accordance to the procedure reported for Method F.
Examples listed in Table 13 have been synthesized in a similar manner with the exception of Example 40 and Example 41 that derived from chiral separation of Example 12 on a 4.6x100mm ChiralPak OD-H column from Chiral Technologies, isopropanol/35% CO_2 + 0.1% isopropylamine at 4mL/min, P=100 bar, T=25°C, sample dissolved in MeOH.

Method 6: Synthesis of 5-[5-(3-methyl-2-{5-[5-(piperazin-1-yl)pyrazin-2-yl]-1,2,4-oxadiazol-3-yl}butan-2-yl)pyridin-2-yl]pyrimidin-2-amine (Example 13).

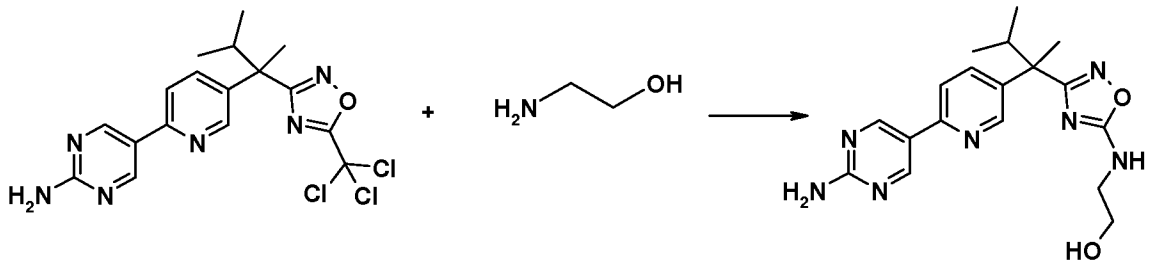


Piperazine (175.1 mg, 2.03 mmol) is added to a solution of **I-10.2** (700 mg, 88% pure, 1.35 mmol) in DMSO (3.0 mL) and the reaction mixture is heated at 80°C for 2 hours. The mixture is cooled to room temperature, diluted with water and the pH is adjusted to ~12 with 1N NaOH. The mixture is extracted with EtOAc, the combined extracts are

washed with brine. The organic phase is dried over anhydrous Na_2SO_4 and filtered. The solvent removed under vacuum to afford the crude product that is purifed by silica gel column chromatography (DCM/MeOH) to afford **Example 13** (183.0 mg).

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of the following compounds for which the second step is carried out with the indicated modifications: Example 15 in 2M Methylamine in THF at 80°C in sealed tube for 18 hours; Example 16 in NMP (4.2 eq.) employing 15 eq of the corresponding amine; Example 18 in NMP (4.6 eq.) with 20.0 eq. of the corresponding amine; Example 19 in NMP (4.6 eq.) with 12.3 eq. of the corresponding amine; Example 20 in NMP (4.2 eq.) with 5.0 eq. of the corresponding amine; Example 22 in NMP (4.6 eq.) with 20.0 eq of the corresponding amine; Example 27 in THF with 13.0 eq of corresponding amine at 50°C over three days; Example 32 in THF/NMP 1/1 with 9.0 eq of corresponding amine at 50°C over three days; Example 42 in THF and 3.0 eq of the corresponding amine (2.0M solution in THF) at room temperature over three days; Example 51 and Example 52 are derived from chiral resolution of Example 13 on 4.6 x 100mm Regis Pack column from Regis Technologies, CO_2 cosolvent + 0.1% isopropilamine in isopropanol, 40% cosolvent at 4mL/min, P=100 bar, T=25°C; Example 55 and Example 56 derived from chiral resolution of Example 18 on 4.6 x 100mm Chiral Pack AD column from Chiral Technologies, CO_2 cosolvent IPA/MeOH 7/3 + 0.1% isopropilamine, 50% cosolvent at 4mL/min, P=125 bar, T=40°C; some of the compounds were purified via prep HPLC; Example 92 and 93 are derived from chiral resolution of Example 16 on 4.6 x 100mm Chiral Pack OD-H column from Chiral Technologies, T=40 °C; CO_2 cosolvent (Solvent B) 0.1% isopropylamine in isopropanol isocratic method: 30% co-solvent at 4mL/min; system pressure 125 bar; column temperature: 25°C; sample diluent: methanol; Example 94 and 95 are derived from resoluiton on Example 20 on 4.6x100mm ChiralPak AD-H from Chiral Technologies, CO_2 cosolvent (Solvent B) 0.1% isopropylamine in isopropanol; isocratic method: 15% co-solvent at 80mL/min; system pressure 100 bar; column temperature: 25°C; sample diluent: methanol.

Method 7: Synthesis of 2-[(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)amino]ethanol (Example 25).

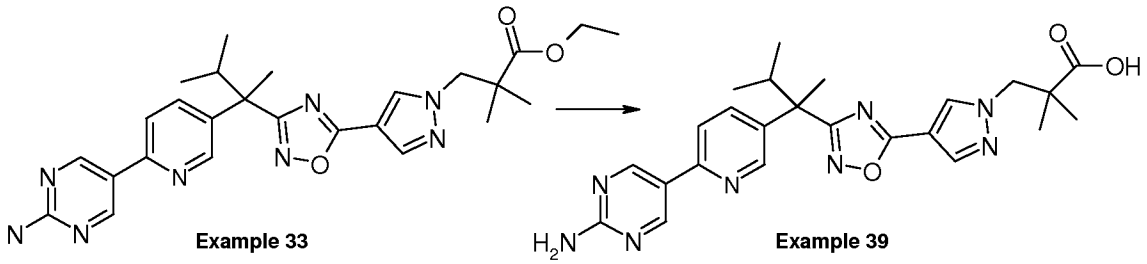


I-19 R17 Example 25

To a stirred solution of **R17** (0.021 mL, 0.351 mmol) and KOH (23.17 mg, 0.351 mmol) in DMSO (1 mL) is added **I-19** (100 mg, 0.234 mmol). The reaction mixture is stirred at room temperature for 1.5 hours. After this time, the reaction mixture is quenched with water and extracted with EtOAc twice. The organcis are combined and washed with water then brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel column chromatography (1-10% MeOH in DCM) to yield **Example 25** (38.0 mg).

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of Example 26 for which KOH and piperazine (7.0 eq) are employed in DMF and the compound is purified via silica gel column chromatography (10 % MeOH/DCM with 3% 2N NH_3 in MeOH)

Method 8: Synthesis of 3-[4-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2,2-dimethylpropanoic acid (Example 39).

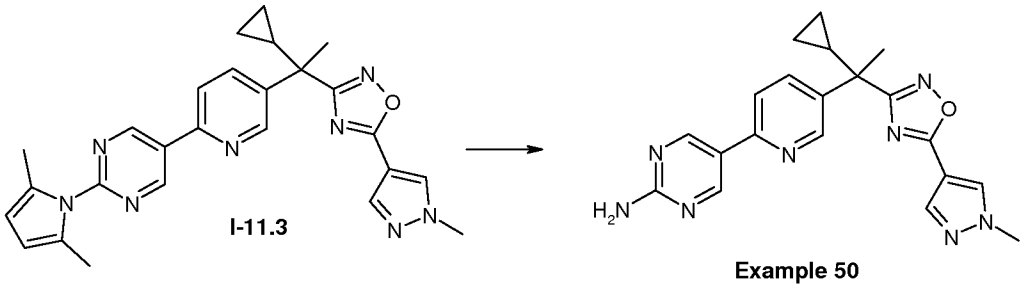


Example 33 Example 39

A solution of **Example 33** (45.0 mg, 0.089mmol) in THF (3.0 mL), LiOH (4.0 mg, 0.178 mmol) and water (1.0 mL) is stirred at room temperature until complete disappearance of the starting material. The solvent is removed under reduced pressure, the crude is diluted with EtOAc, washed with water. The water phase is brought to pH=2-3 and extracted

with EtOAc. The organic layers are combined, dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the crude is purified via prep HPLC to afford **Example 39** (15.0 mg).

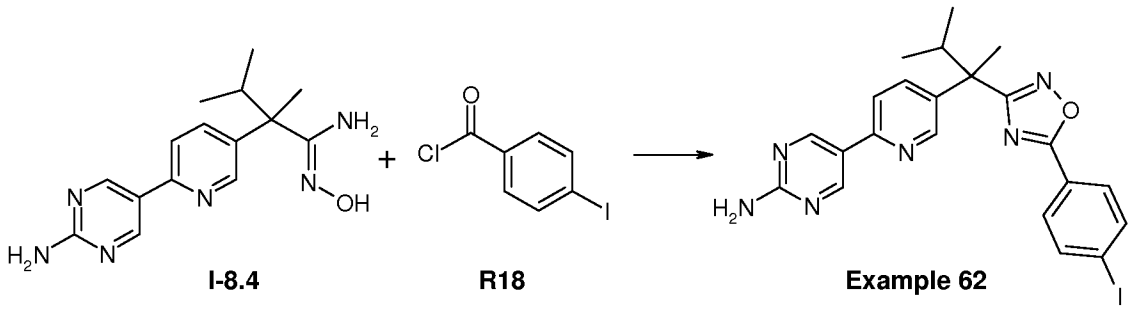
Method 9: Synthesis of 5-(5-{1-cyclopropyl-1-[5-(1-methyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]ethyl}pyridin-2-yl)pyrimidin-2-amine (Example 50).



A solution of **I-11.3** (86.0 mg, 0.18 mmol) and hydroxylamine hydrochloride (128 mg, 1.84 mmol) in EtOH (1.5 mL), water (0.7mL) and TEA (19 mg, 0.19 mmol) is stirred at 90 °C for 18 hours. The reaction mixture is diluted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude is purified via silica gel column chormatography (DCM/MeOH) to afford **Example 50** (48.0 mg).

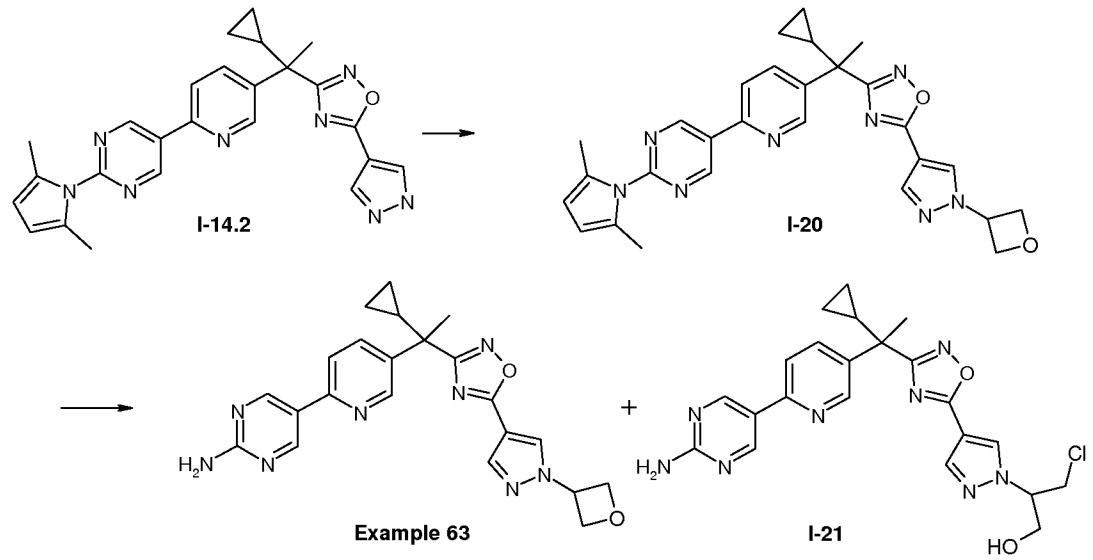
Examples listed in Table 13 have been synthesized in a similar manner, with the exception of Example 57 and Example 58 that are derived from chiral resolution of Example 50 AD-H column (4.6x250mm) and 95% (EtOH+0.1%diethylamine):heptane at 0.4 ml/min and 40°C, or more recently a 2.1x250mm column at 0.5 ml/min.

Method 10: Synthesis of 5-(5-{2-[5-(4-iodophenyl)-1,2,4-oxadiazol-3-yl]-3-methylbutan-2-yl}pyridin-2-yl)pyrimidin-2-amine (Example 62).



I-8.4 (150.0 mg, 0.499 mmol) is dissolved in DMF (2.0 ml) and treated with DIEA (0.59 mL, 3.20 mmol) and **R18** (160.0 mg, 0.599 mmol). The resulting mixture is heated at 110°C. After 1h no product is detected by LC-MS check (it is possible that the acyl chloride is hydrolyzed to the corresponding acid), the reaction mixture is cooled to room temperature and HATU (0.25 g) is added. The reaction mixture is warmed to 80°C and stirred over night. After this time, the reaction appeared to be ~50% complete (checked by LC-MS). The reaction mixture is cooled to room temperature, poured into water and extracted twice with EtOAc. The combined organics are washed with brine, dried over anhydrous Na_2SO_4 and concentrated after filtration. The crude is purified via silica gel column chromatography (DCM/MeOH) to afford **Example 62** (256.0 mg).

Method 11: Synthesis of 5-[5-(1-cyclopropyl-1-{5-[1-(oxetan-3-yl)-1H-pyrazol-4-yl]-1,2,4-oxadiazol-3-yl}ethyl)pyridin-2-yl]pyrimidin-2-amine (Example 63).



Step 1: Synthesis of Intermediate I-20.

Performed according to Method 4. I-20, *m/z*: 509 [M+H]

Step2:Synthesis of Example 63.

Performed according to Method 9, I-21,*m/z*: 467 [M+H]is formed as a byproduct.

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of Example 78 and Example 79 that are derived from chiral resolution of Example 63 on 4.6 x 100mm ChiralPak AD-H from Chiral Technologies, CO_2 cosolvent + 0.1% isopropilamine in methanol:isopropanol 3:1, 55% cosolvent at 4mL/min, P=125 bar, T=25°C.

The following compounds are made in a similar manner to method 11:

Examples 108 and 138 are derived from chiral resolution on an AD-H column (20x250mm) and 70% (EtOH+0.1%diethylamine):heptane at 8.5 ml/min and 45 °C.

Examples 122 and 123 are derived from chiral resolution on a AD-H column (20x250mm) and 95% (EtOH+0.1%diethylamine):heptane at 7.0 ml/min and 40°C.

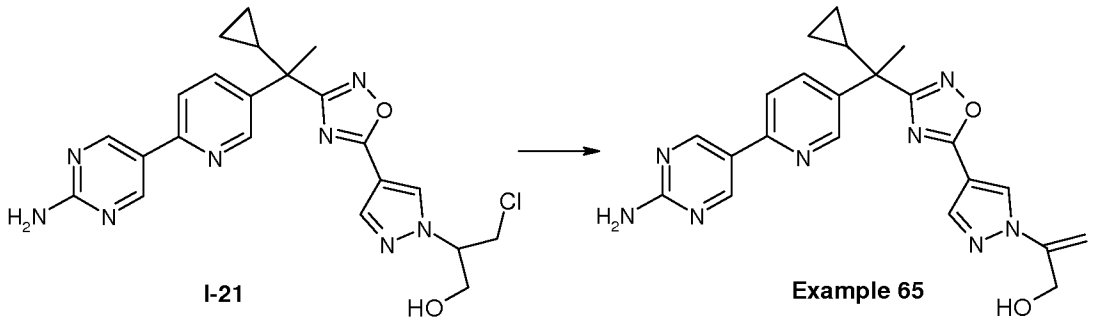
Examples 109 and 139 use Cs_2CO_3 in place of K_2CO_3, are carried out at 60 °C for step 1, and are derived from chiral resolution AD-H column (20x250mm) and 74% (EtOH+0.1%diethylamine):heptane at 9.0 ml/min and 45 °C.

Example 120 uses Cs_2CO_3 in place of K_2CO_3 and is carried out at 60 °C for step 1

Examples 124 and 125 use Cs_2CO_3 in place of K_2CO_3, are carried out at 60 °C for step 1, and are derived from chiral resolution on a AD-H column (20x250mm) and 95% (EtOH+0.1%diethylamine):heptane at 6.5 ml/min and 45 °C.

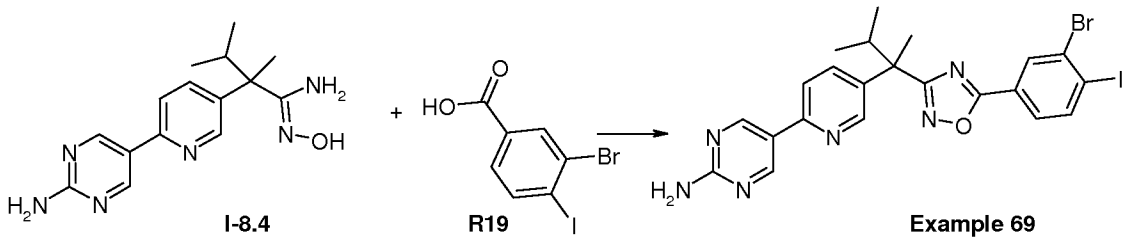
Examples 126 and 127 use Cs_2CO_3 in place of K_2CO_3, are carried out at 60 °C for step 1, and are derived from chiral resolution on a AD-H column (20x250mm) and 95% (EtOH+0.1%diethylamine):heptane at 6.5 ml/min and 45°C.

Method 12: Synthesis of 2-[4-(3-{1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]prop-2-en-1-ol (Example 65).



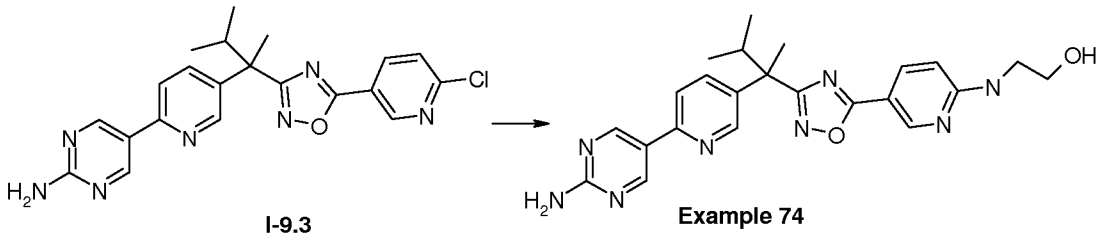
A solution of **I-21** (102.0 mg, 0.22 mmol) and KOH (14.4 mg, 0.22 mmol) in EtOH (1.0 mL) is refluxed for 30 minutes. The solution is cooled to room temperature, the solvent is removed under reduced pressure and the crude is purified via silica gel column chromatography to afford **Example 65** (70.0 mg).

Method 13: Synthesis of 5-(5-{2-[5-(3-bromo-4-iodophenyl)-1,2,4-oxadiazol-3-yl]-3-methylbutan-2-yl}pyridin-2-yl)pyrimidin-2-amine (Example 69).



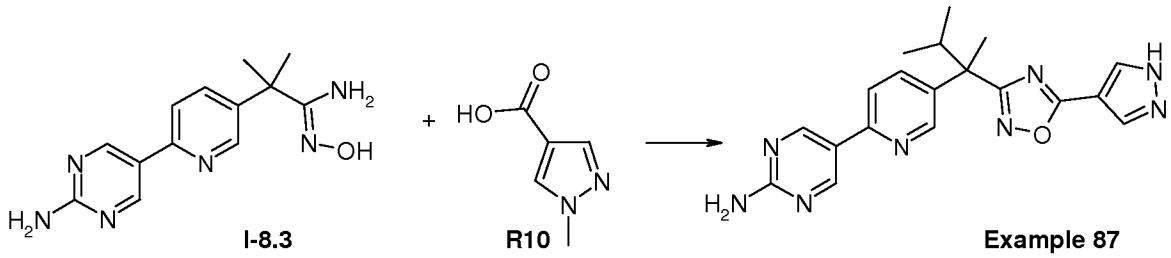
A suspension of **R19** (163.3 mg, 0.50 mmol) and 1,1'-carbonyldiimidazole (81.0 mg, 0.50 mmol) in THF (2.0 mL) is heated at 50°C for 30 min. **I-8.4** (100.0 mg, 0.33 mmol) is added and the solution is heated under reflux for 3 hours. The mixture is cooled to room temperature and AcOH (0.2 mL) is added. The reaction mixture is stirred at 80°C overnight. After cooling to room temperature, the mixture is poured into water and extracted with EtOAc. The organic layers are combined, dried over anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure. Purification via silica gel column chromatography affords **Example 69** (67.0 mg).

Method 14: Synthesis of 2-{[5-(3-{2-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-3-methylbutan-2-yl}-1,2,4-oxadiazol-5-yl)pyridin-2-yl]amino}ethanol (Example 74).



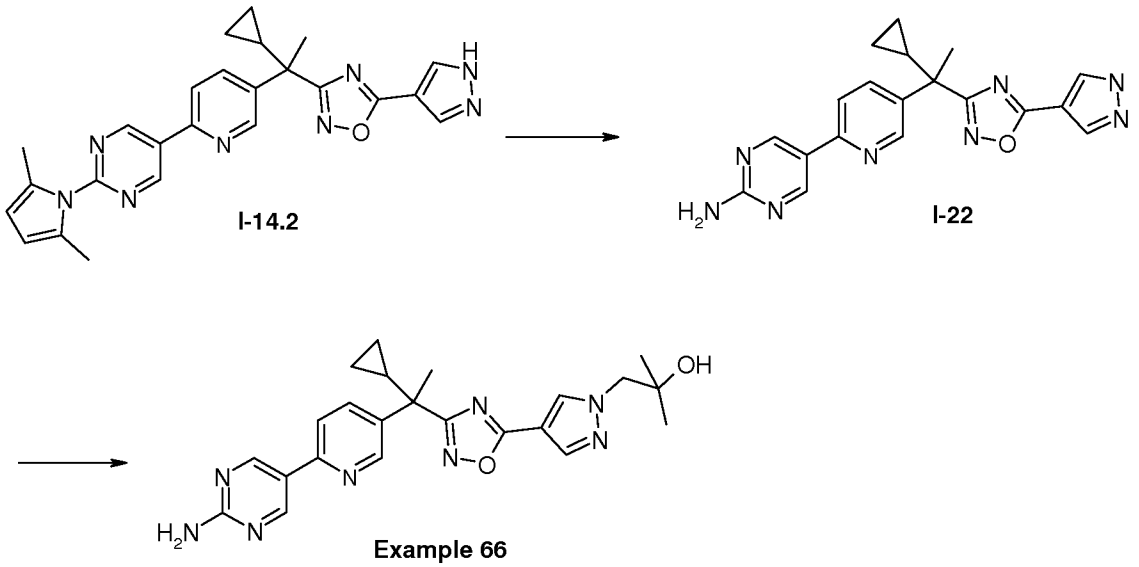
A mixture of **I-9.3** (200.0 mg, 0.38 mmol) and ethanolamine (1.0 mL) is stirred at 80°C for 1 hour. The solvent is removed under reduced pressure, the crude purified via preparative HPLC to afford **Example 74** (120.0 mg).

Method 15: Synthesis of 5-(5-{2-[5-(1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl]propan-2-yl}pyridin-2-yl)pyrimidin-2-amine (Example 87).



This method is performed in accordance to the procedure reported for Method J. Examples listed in Table 13 have been synthesized in a similar manner.

Method 16: Synthesis of 1-[4-(3-{1-[6-(2-aminopyrimidin-5-yl)pyridin-3-yl]-1-cyclopropylethyl}-1,2,4-oxadiazol-5-yl)-1H-pyrazol-1-yl]-2-methylpropan-2-ol (Example 66)



Step 1: Synthesis of Intermediate I-22.

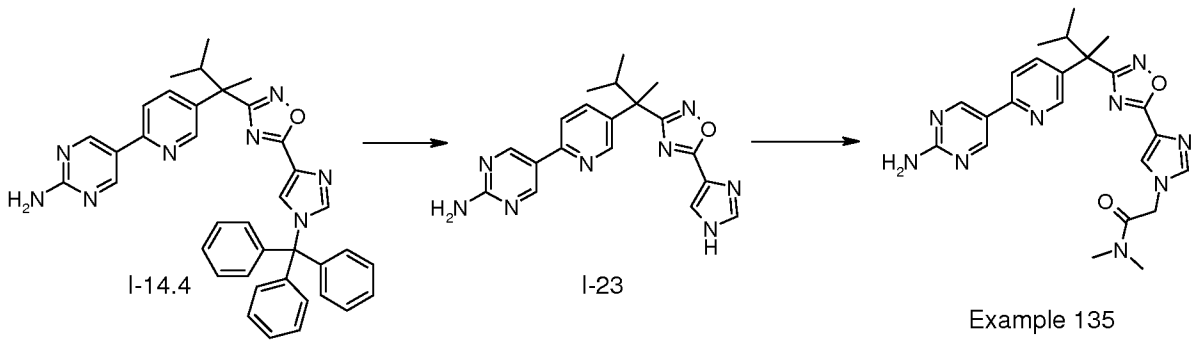
Performed according to Method 9. I-22, *m/z*: 375 [M+H]

Step2:Synthesis of Example 66.

Performed according to Method 4.

Examples listed in Table 13 have been synthesized in a similar manner, with the exception of Example 67 for which 2.0eq of the corresponsing chloride and potassium carbonate are employed and the reaction mixture is stirred at room temperature for two hours; for Example 68 the corresponding bromide is employed and the reaction mixture is heated at 80 °C for 18 hours; Example 75 and Example 76 are obtained from chiral resolution of Example 68 via a chiral column AD-H in 95% (EtOH+0.01% diethylamine) in Heptane at 8 mL/min; Example 81 and Example 82 are derived from chiral resolution of Example 66 via a chiral column AD-H column(4.6x250mm) and 95%(EtOH+0.1%diethylamine):heptane at 0.4 ml/min and 40°C, or more recently a 2.1x250mm column at 0.5ml/min; Example 83 and Example 84 are obtained from chiral resolution of Example 67 on 4.6 x 100mm ChiralPak AD-H from Chiral Technologies, CO_2 cosolvent + 0.1% isopropilamine in methanol:isopropanol 9:1, 45% cosolvent at 4mL/min, P=125 bar, T=25°C.

Method 17: Synthesis of 2-[4-(3-{1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-imidazol-1-yl]-N,N-dimethyl-acetamide (Example 135)



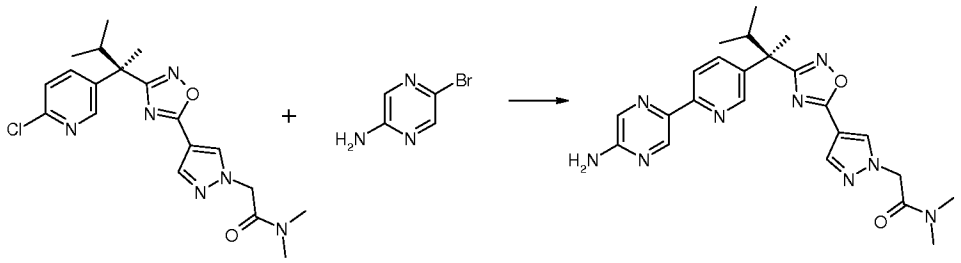
Step 1: Synthesis of I-23:

To a solution of I-14.4 (360 mg, 0.6mmol) in CH_2Cl_2 is added TFA (0.13 mL, 1.7 mmol) at room temperature. The solution is stirred at the same temperature for 24 hours. The solution is concentrated under vaccuum and the residue I-23 (180 mg) *m/z*: 377 [M+H] is used in the next step of the synthesis without further purification.

Step 2: Synthesis of example 135.

To a solution of I-23 (200 mg, 0.53 mmol) in DMF (15 mL) are added 2-chloro-N,N-dimethylacetamide (0.08 mL, 0.8 mmol) and K_2CO_3 (220 mg, 1.6 mmol) at room temperature. The mixture is stirred at room temperature for 48 hours. The solution is concentrated and the residue is purified by silica gel flash column chromatography to afford a mixture of regioisomer products. Further purification with preparative HPLC afford title compound (144 mg).

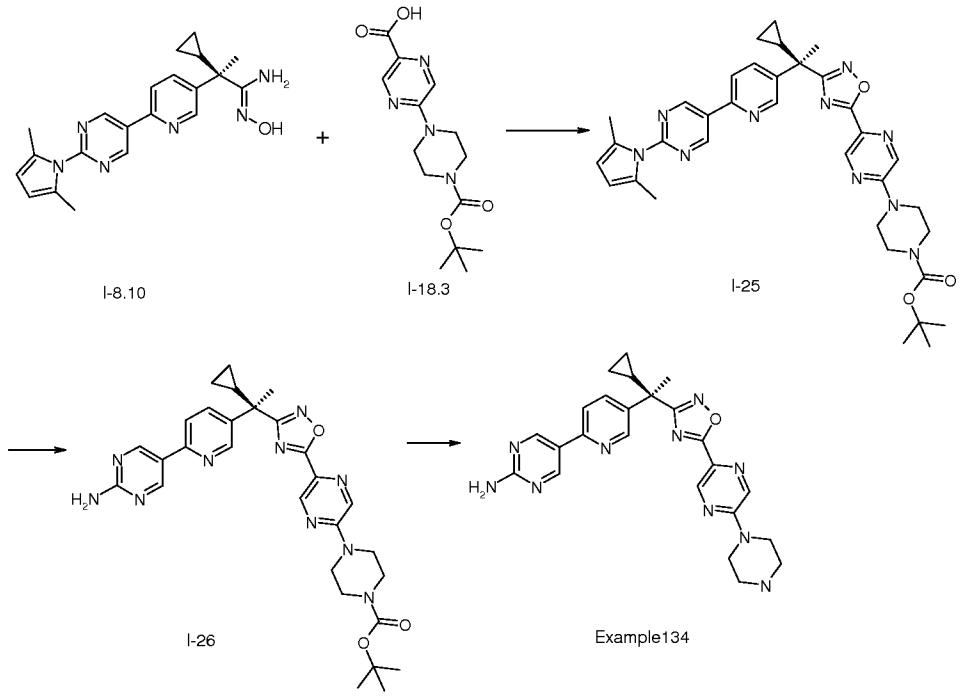
Method 18: Synthesis of 2-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-N,N-dimethyl-acetamide (Example 112)



I- 12.8 R-20 Example 112

In a 20 ml microwave vial is dissolved R-20 (100 mg, 0.575 mmol) in toluene (2.5ml) and is added hexamethylditin (0.132 ml, 0.635 mmol) and is degassed with argon for 5 minutes. $Pd(Ph_3P)_4$ (33.2 mg, 0.050 mmol) is then added and the vial is capped and heated to 115 °C for 1 hour, then the reaction is cooled to room temperature. I-12.8 (277 mg, 0.690 mmol) is dissolved in toluene (2.5ml) and is added to the reaction mixture follows by $Pd(Ph_3P)_4$.(33.2 mg, 0.05 mmol) The reaction vial is capped and stirred at 115 °C for 8 hours. The reaction mixture is concentrated in vacuo, and is purified by flash chromatography (SiO_2, 0-10% MeOH/DCM). The product is further purified by prep HPLC to yield the title compound (43 mg).

Method 19: Synthesis of 5-(5-{(R)-1-Cyclopropyl-1-[5-(3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-pyridin-2-yl)-pyrimidin-2-ylamine (Example 134)



Step 1: Synthesis of I-25

A suspension of I-18.3 (209 mg, 0.657 mmol) and CDI (102 mgs, 06328 mmol) in 1,4-dioxane (3 mL) in a sealed tube is stirred at 55 °C for one hour. A solution of I-8.10 (225 mg, 0.598 mmol) in dioxane (3ml) is added and the reaction mixture is stirred at 120 °C for 18 hours. After cooling to room temperature, the reaction mixture is poured into brine and extracted with EtOAc (4x20ml). The combined organic fractions are dried with sodium sulfate, filtered, and is concentrated in vacuo. The resdiue is purified by flash chromatography (SiO_2, Biotage SNAP 100g, 0-5%MeOH/DCM) to yield I-25 (298 mg), *m/z*: 649 [M+H]

Step 2: Synthesis of I-26

I-26 is prepared in a manner similar to Method 9.

m/z: 571.4 [M+1]

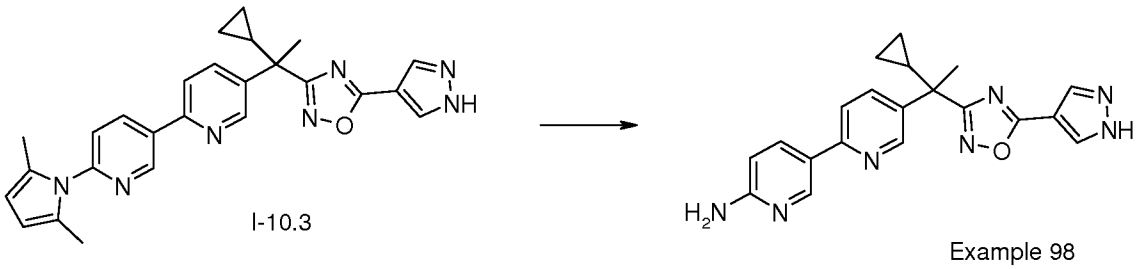
Step 3: Synthesis of example 134

4M HCl in dioxane (5 mL) is added to a solution of I-26 (55 mg, 0.096 mmol) in MeOH (3 mL) at 70 °C. The reaction mixture is stirred at room temperature for 72 hours. The

pH of the mixture is adjusted to 7 with 7N aq. NaOH and it is then concentrated in vacuo. The crude mixture is purified by flash chromatography (SiO_2, 0-25% MeOH/DCM) to afford the title compound (21 mg)

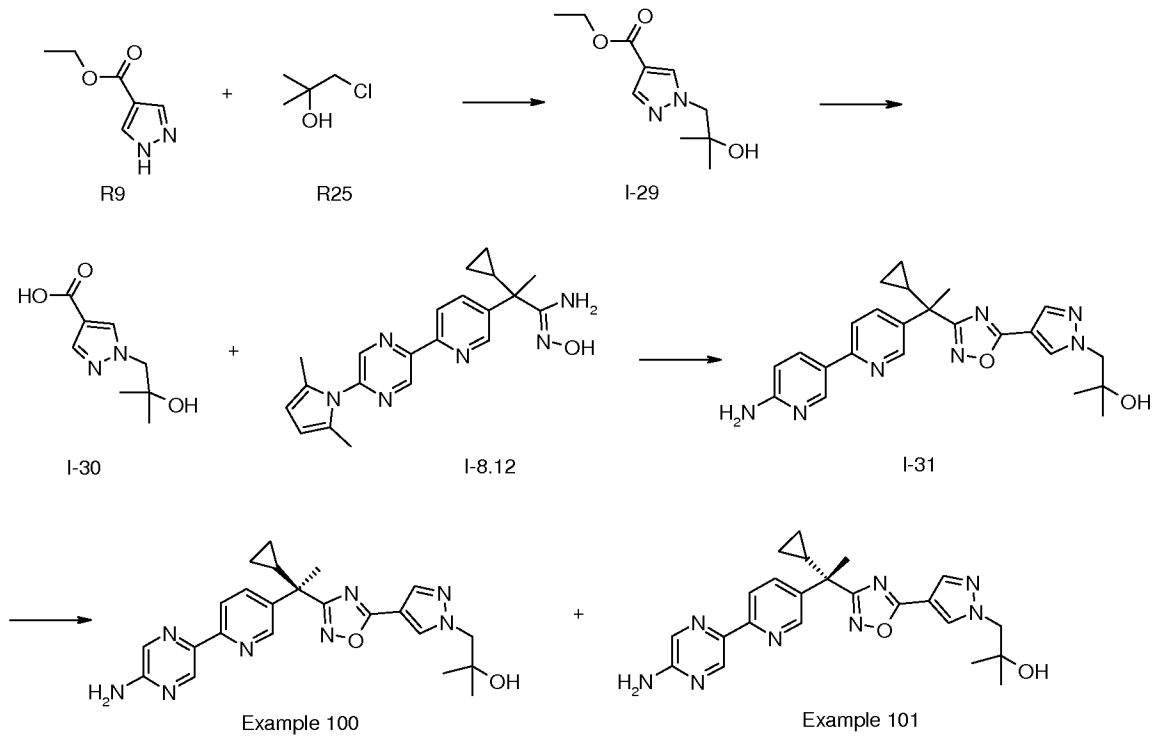
Example 137 is prepared with a similar procedure as the last step of method 19 (hydrolysis). The intermediate for that is prepared according to procedures described in Method 1.

Method 20: Synthesis of 5-{1-Cyclopropyl-1-[5-(1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine (Example 98)



Performed according to Method 9 with purification by preparative HPLC to afford the title compound.

Method 21: Synthesis of 1-[4-(3-{(R)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol (Example 100) and 1-[4-(3-{(S)-1-[6-(5-Amino-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol (Example 101)



Step 1: Synthesis of I-29

R9 (2.00 g, 14.3 mmol) is treated with R25 (3.10 g, 28.5 mmol), K_2CO_3 (2.96 g, 21.4 mmol), and DMF (10 mL) and the reaction is stirred at 80 °C for 48 hours. The resulting mixture is diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue is purified by silica gel column chromatography (0-5% methanol in CH_2Cl_2) to yield **I-29** (2.55 g); *m/z* 213 [M+H].

Step 2: Synthesis of I-30

I-29 (3.69 g, 17.4 mmol) is treated with THF (15 mL), NaOH (0.90 g, 22.5 mmol), water (7.0 mL), and methanol (5.0 mL) and the resulting mixture is stirred for 18 hours. The resulting mixture is then concentrated *in vacuo* and the residue partitioned between water and EtOAc. The layers are separated and the organics are washed with brine, collected, dried over Na_2SO_4, filtered , and concentrated *in vacuo* to yield **I-30** (3.20 g); *m/z* 185 [M+H].

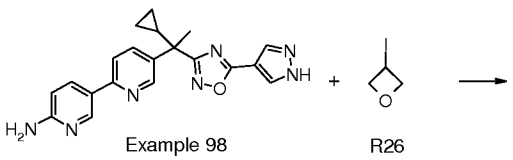
Step 3: Synthesis of I-31

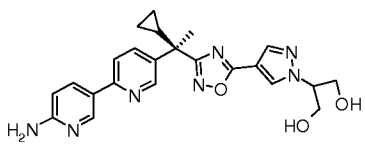
This method is performed in accordance to the procedure reported for Method J; I-31, *m/z*: 525 [M+H].

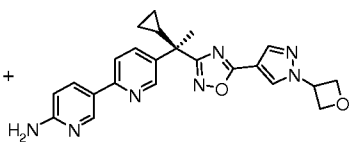
Step 4: Synthesis of Examples 100 and 101.

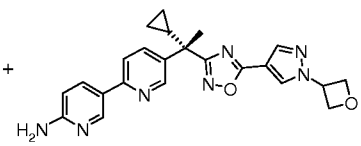
This method is performed according to the procedure reported for Method 9. **Examples 100** and **101** are then obtained from chiral resolution on an AD-H column (20x250mm) and 60% (EtOH+0.1%diethylamine):heptane at 4.5 ml/min and 40 °C.

Method 22: Synthesis of 2-(4-{3-[(R)-1-(6'-Amino-[2,3']bipyridinyl-5-yl)-1-cyclopropyl-ethyl]-[1,2,4]oxadiazol-5-yl}-pyrazol-1-yl)-propane-1,3-diol (Example 114), 5-{(R)-1-Cyclopropyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine (Example 115), and 5-{(S)-1-Cyclopropyl-1-[5-(1-oxetan-3-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]-ethyl}-[2,3']bipyridinyl-6'-ylamine (Example 116)





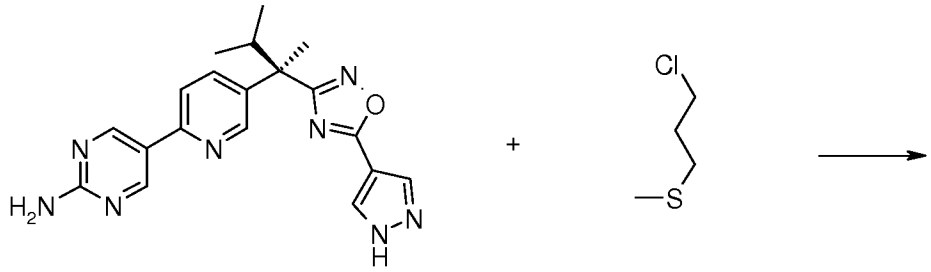




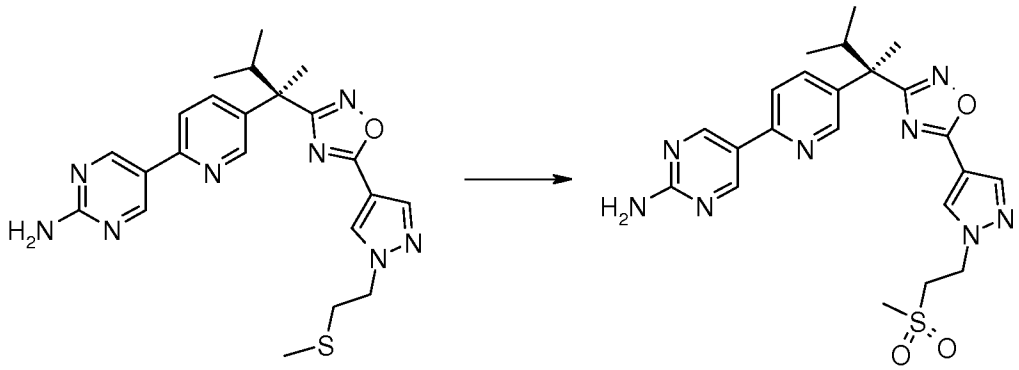
Example 98 (120 mg, 0.321 mmol) is treated with R26 (88.7 mg, 0.482 mmol), Cs_2CO_3 (157 mg, 0.482 mmol), and DMF (1.50 mL) and the resulting mixture is stirred at 50 °C for 2 hours, then 80 °C for 4 hours. The resulting mixture is purified by reverse-phase preparative HPLC. **Examples 115** (11 mg) and **116** (8 mg) are obtained from chiral resolution on an AD-H

column (20x250mm) and 80% (EtOH+0.1%diethylamine):heptane at 8 ml/min and 40 °C, with **Example 114** (6 mg) being obtained as a by-product from the chiral separation.

Method 23: Synthesis of 5-[5-((R)-1-{5-[1-(2-Methanesulfonyl-ethyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-pyrimidin-2-ylamine (Example 128)



Example 43 R27



I-32 Example 128

Step 1: Synthesis of I-32

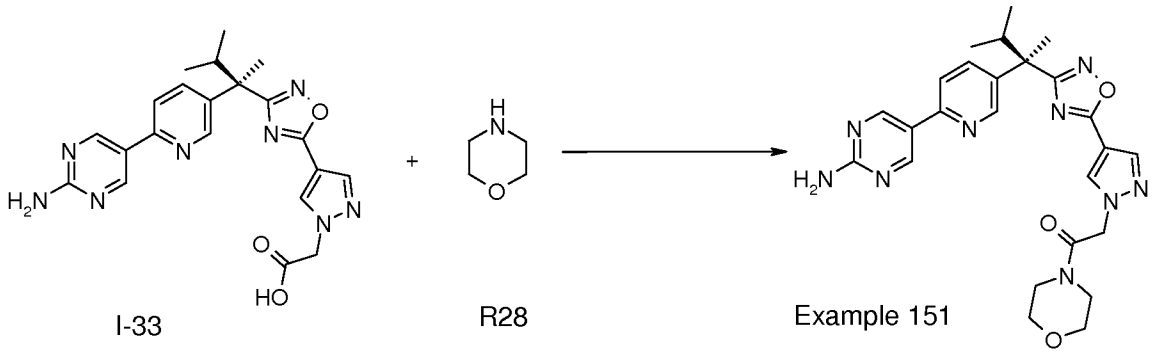
Prepared according to method 4 with Cs_2CO_3 in place of K_2CO_3, and is carried out at 60 °C for 1.5 hours with purification by reverse-phase preparative HPLC. The product is used as is without further purification.

Step 2: Synthesis of example 128

I-32 (60.0 mg, 0.106 mmol) is treated with THF (3.0 mL), water (1.0 mL), and oxone (130 mg, 0.212 mmol) and the resulting mixture is stirred for 1 hour. Another charge of oxone (33.0 mg, 0.053 mmol) is added and the reaction is stirred for 2 hours. The

resulting mixture is concentrated and the residue purified by reverse phase preparative HPLC to give **Example 128** (11.0 mg).

Method 24: Synthesis of 2-[4-(3-{(R)-1-[6-(2-Amino-pyrimidin-5-yl)-pyridin-3-yl]-1,2-dimethyl-propyl}-1,2,4-oxadiazol-5-yl)-pyrazol-1-yl]-1-morpholin-4-yl-ethanone. (Example 151)



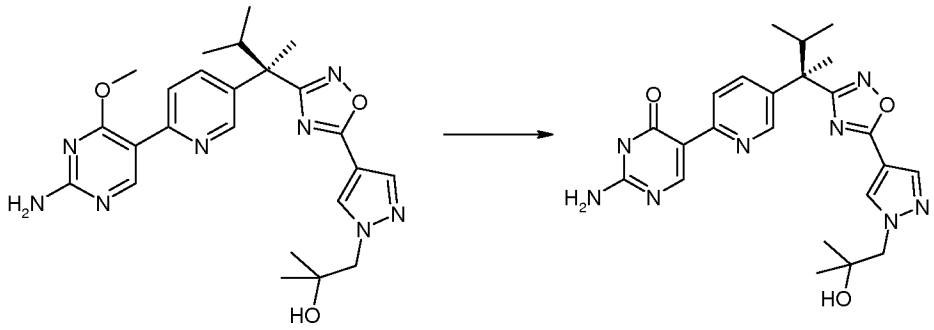
Step 1: Synthesis of Intermedate I-33:

Prepared according to method 8. I-33 *m/z*: 435 [M+H]

Step 2: Synthesis of Example 151:

I-33 (43.4 mg, 0.10 mmol) is treated with R28 (13.1 mg, 0.15 mmol), HATU (68.4 mg, 0.18 mmol), DIEA (105 μL, 0.60 mmol), and DMA (1.80 mL) and the resulting mixture is heated at 60 °C for 16 hours. The reaction is purified directly by reverse phase preparative HPLC to give the title compound (20.9 mg).

Method 25: Synthesis of 2-Amino-5-[5-((R)-1-{5-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-1,2-dimethyl-propyl)-pyridin-2-yl]-3H-pyrimidin-4-one (Example 119)



I-34 Example 119

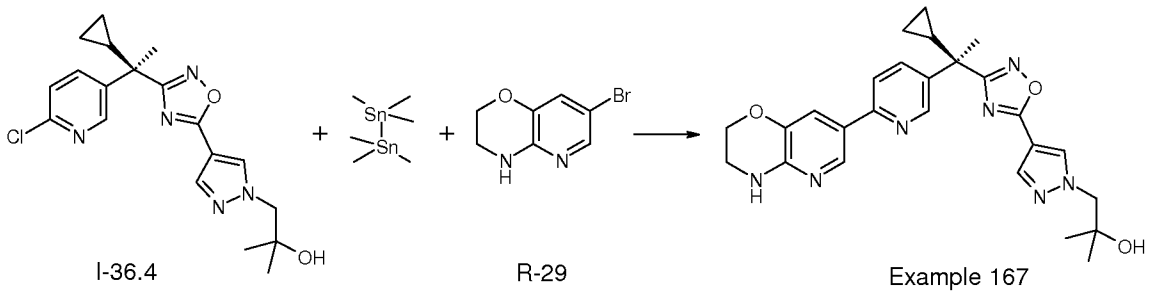
Step 1: Synthesis of I-34:

Prepared according to method 18. I-34, *m/z*: 479 [M+H]

Step 2: Synthesis of Example 119:

To a solution of I-34 (8 mg, 0.02 mmol) in THF (0.5 mL) is added 48% HBr (0.15 mL). The mixture is heated to 70 °C for 24 hours. The solution is concentrated and the residue is purified by preparative HPLC to afford the title compound (4 mg).

Method 26: Synthesis of 1-[4-(3-{(R)-1-Cyclopropyl-1-[6-(3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-pyridin-3-yl]-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol (Example 167)

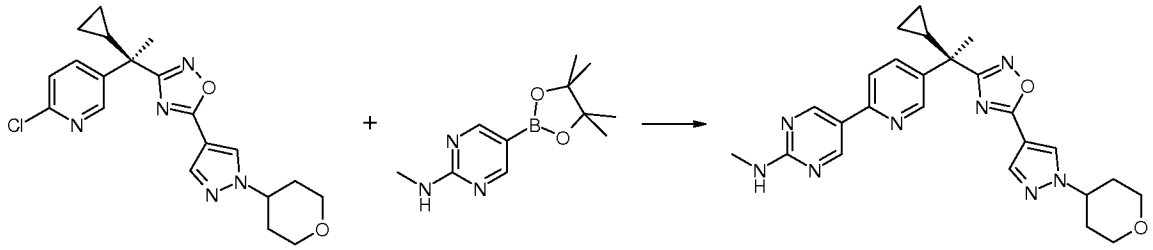


I-36.4 R-29 Example 167

In a pressure tube is added I-36.4 (100 mg, 0.26 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.016 mmol), dichlorobis(triphenylphosphine)palladium(II) (15 mg, 0.021 mmol) and hexamethyldistannane (0.064 ml, 0.31 mmol) in 1,4-dioxane (3 ml). The reaction mixture is degassed with argon. The reaction mixture is stirred at 115 °C for 16 hours. The

reaction mixture is cooled down to room temperature, followed by the addition of R-29 (67 mg, 0.312 mmol) and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol). The reaction mixture is degassed with argone and is capped, and is stirred at 115 °C for 16 hours. The reaction mixture is concentrated *in vacuo*. The residue is purified by flash chromatography (SiO_2, 0-5% MeOH/CH_2Cl_2) to afford title compound (30 mg); *m/z* 488.4 [M+1]

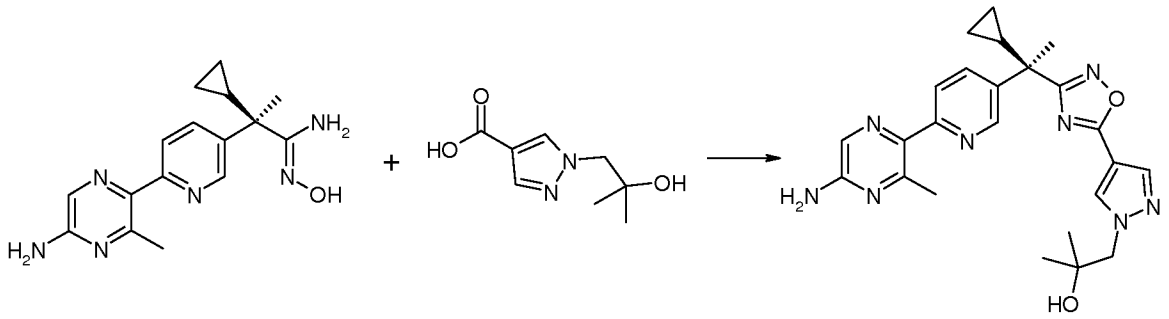
Method 27: Synthesis of {5-[5-((R)-1-Cyclopropyl-1-{5-[1-(tetrahydro-pyran-4-yl)-1H-pyrazol-4-yl]-[1,2,4]oxadiazol-3-yl}-ethyl)-pyridin-2-yl]-pyrimidin-2-yl}-methyl-amine (Example 169)



I-36.5 R-30 Example 169

To a pressure tube is added I-36.5 (213 mg, 0.53 mmol), R-30 (150 mg, 0.64 mmol), Tetrakis(triphenylphosphine)palladium (0) (61 mg, 0.053 mmol) and 2M aq. Na_2CO_3 (1 ml, 2 mmol) in THF (8 ml). The reaction mixture is stirred at 90 °C for 16 hours. The reaction mixture is conecntrated *in vacuo*. The residue is diluted with EtOAc, is washed with water, brine, is dried under anhy. Na_2SO_4, and is filtered and concentrated. The residue is purified by flash chromatography (SiO_2, 0-5% MeOH/CH_2Cl_2) to afford the title compound (131 mg); *m/z* 473.4 [M+1]

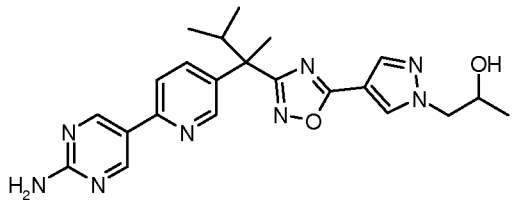
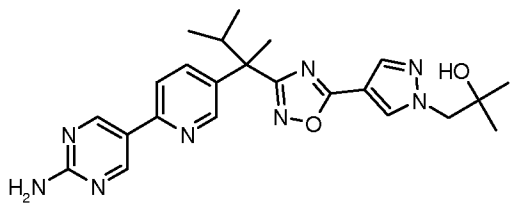
Method 28: Synthesis of 1-[4-(3-{(R)-1-[6-(5-Amino-3-methyl-pyrazin-2-yl)-pyridin-3-yl]-1-cyclopropyl-ethyl}-[1,2,4]oxadiazol-5-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol (Example 166)

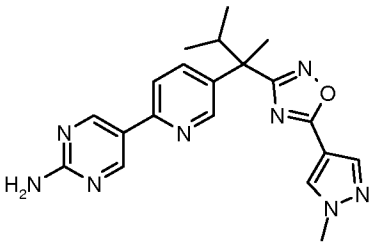
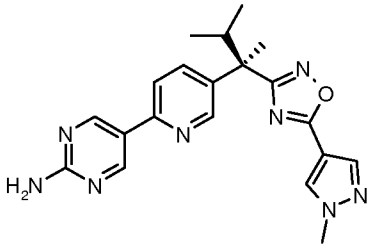
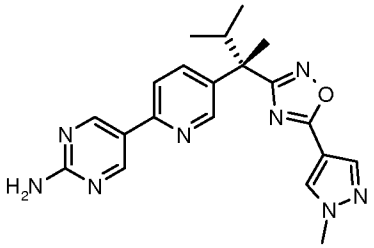
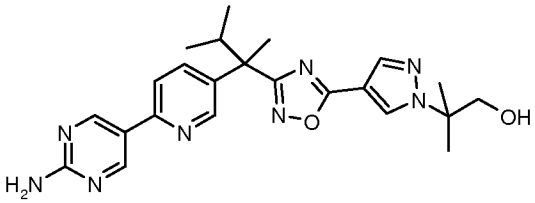
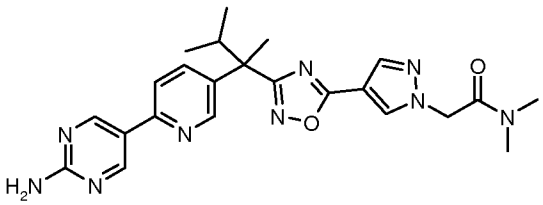
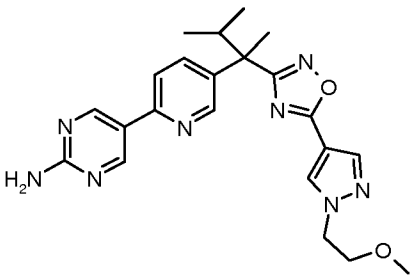


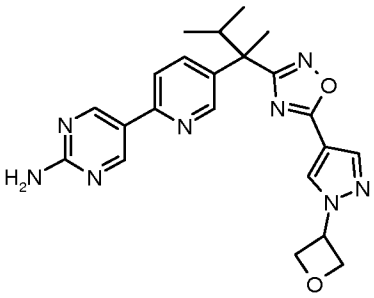
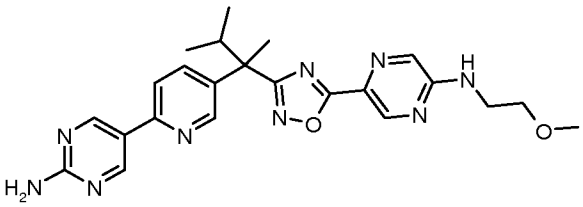
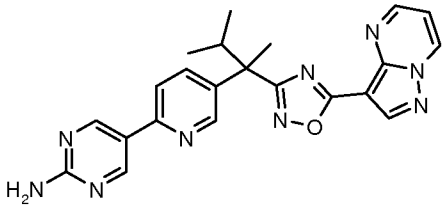
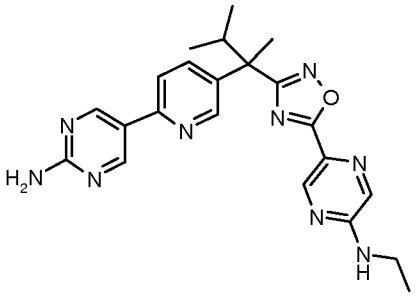
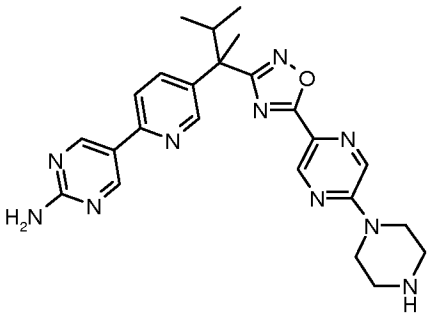
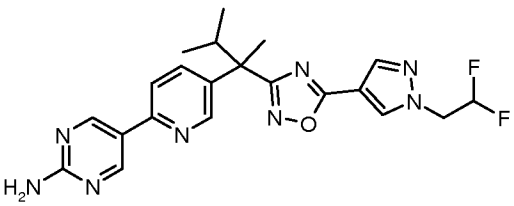
I-38.2 I-30 Example 166

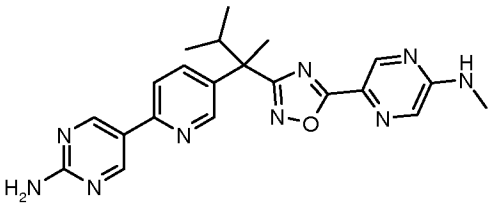
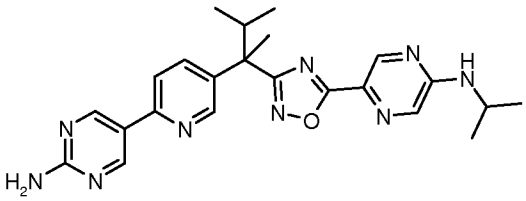
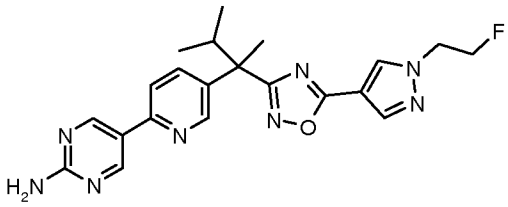
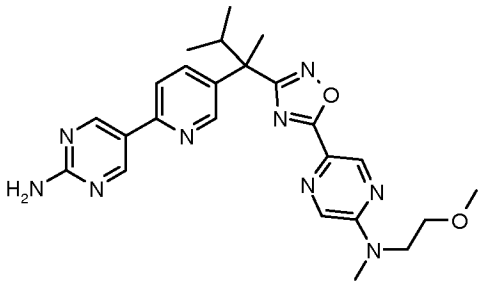
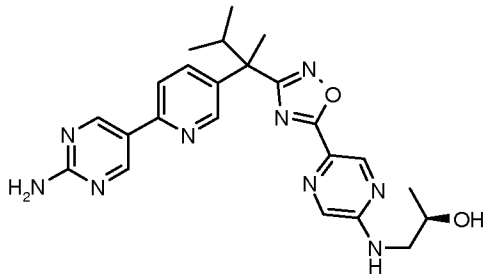
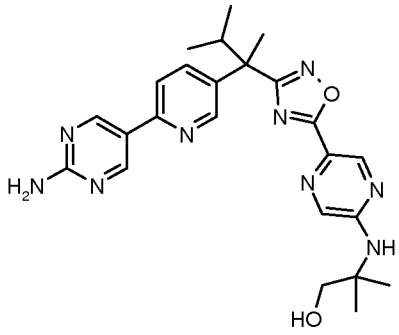
To a scintillation vial is added I-30 (143 mg, 0.79 mmol) in 5 ml of 1,4-dioxane, followed by the addition of 1,1'-carbonyldiimidazole (120 mg, 0.74 mmol). The reaction mixture is stirred at 55 °C for 60 minutes. I-38.3 (165 mg, 0.53 mmol) is added to the reaction mixture, and is stirred at 120 °C for 6 hours. The reaction mixture is concentrated *in vacuo*. The residue is diluted with EtOAc, is washed with water, brine, dried under anhy. Na_2SO_4, and is filtered and concentrated. The residue is purified by HPLC (20-90% MeCN/water with 0.1% TFA), basified with sat. $NaHCO_3$, extracted with DCM, and concentrated *in vacuo* to afford the title compound (75 mg); *m/z* 461.1 [M+1]

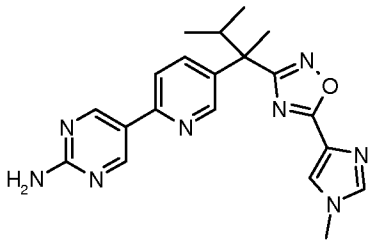
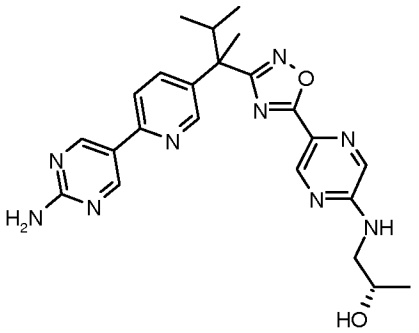
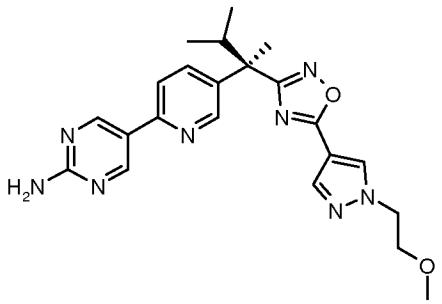
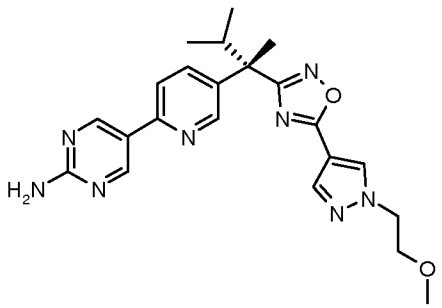
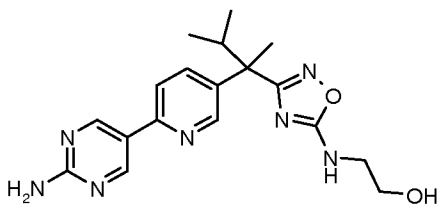
Table 14

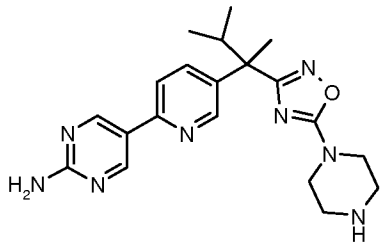
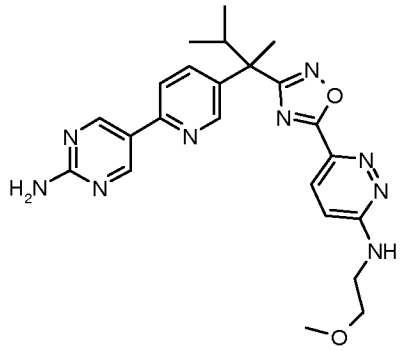
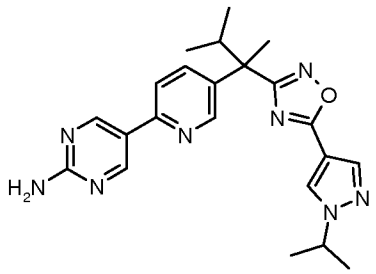
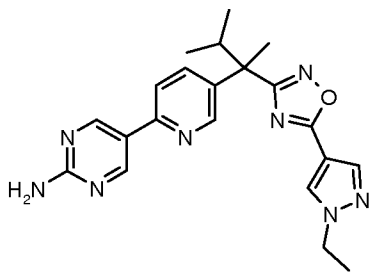
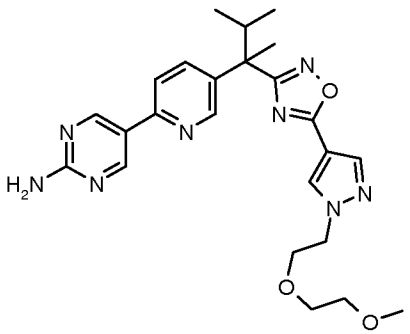
Example #	Structure	Method	LC-MS Method	Retention Time	*m/z* [M+H]
1		1	A	3.46	435.3
2		4	A	3.59	449.3

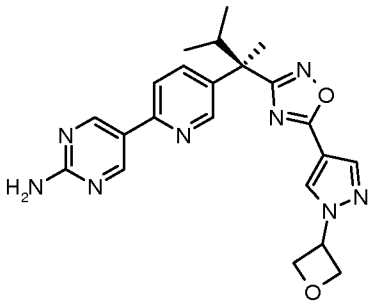
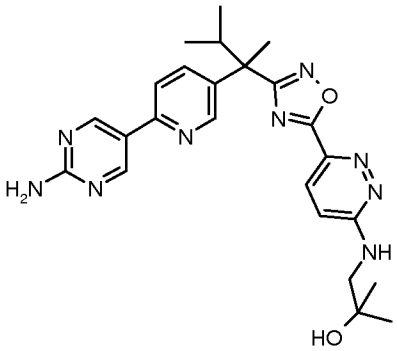
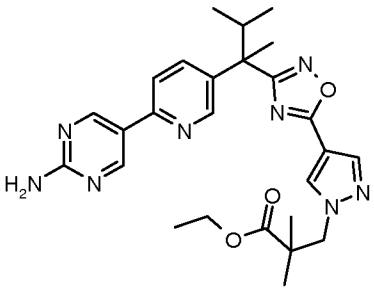
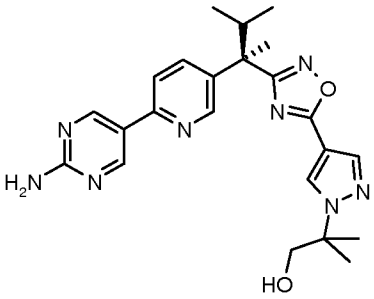
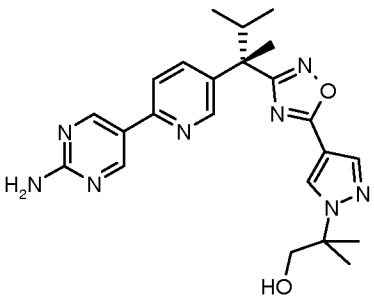
3		1	E	4.97	391.6
4		2	E	4.98	391.3
5		1	E	4.98	391.3
6		1	A	3.76	449.3
7		1	A	3.36	462.2
8		1	A	3.78	435.3

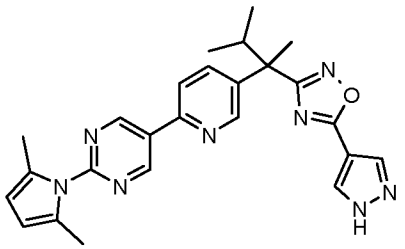
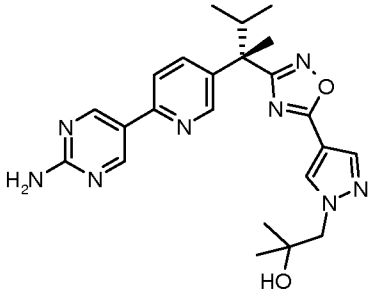
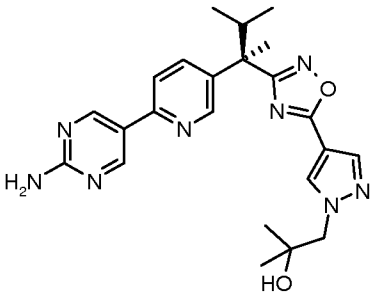
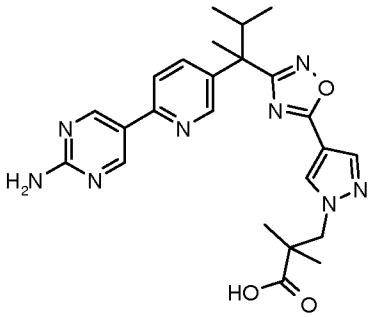
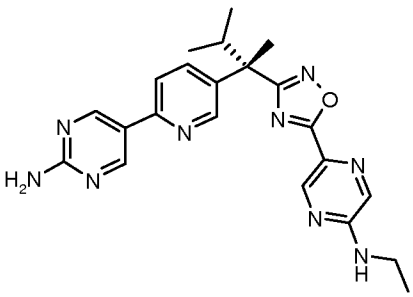
9		1	B	3.6	433.3
10		1	A	3.61	462.3
11		1	A	3.48	428.26
12		5	A	3.75	432.2
13		6	B	1.47	473.24
14		4	A	3.78	441.2

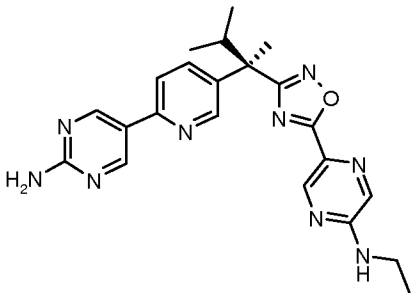
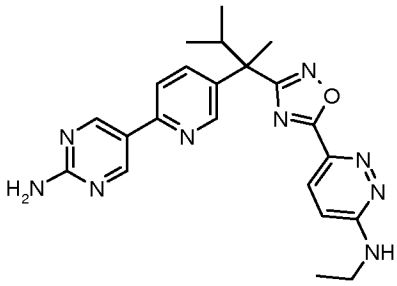
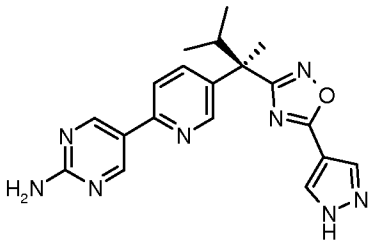
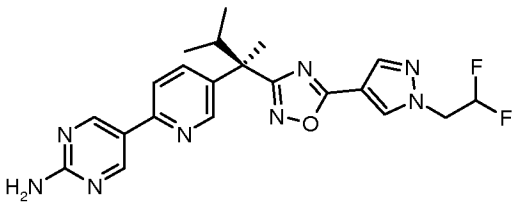
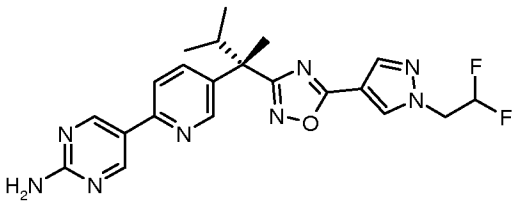
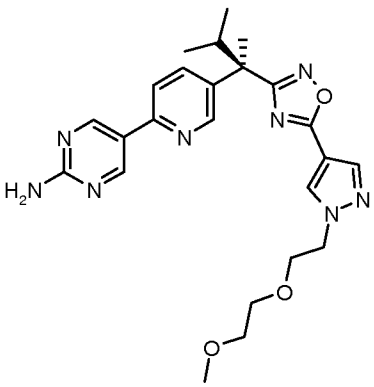
15		6	A	3.55	418.2
16		6	A	4.01	446.2
17		4	A	3.68	423.2
18		6	A	3.95	476.3
19		6	B	3.39	462.2
20		6	A	3.72	476.2

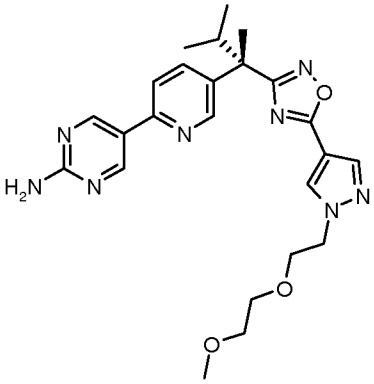
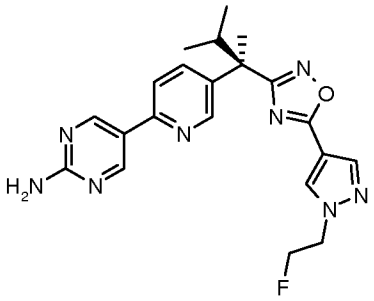
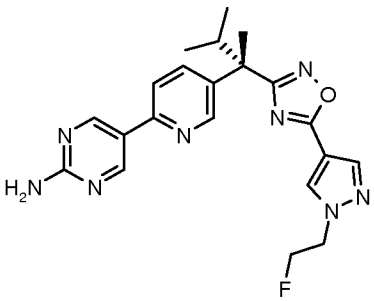
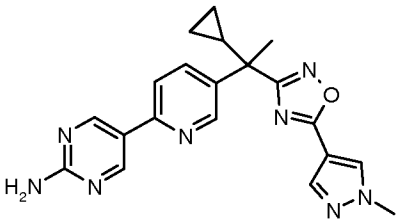
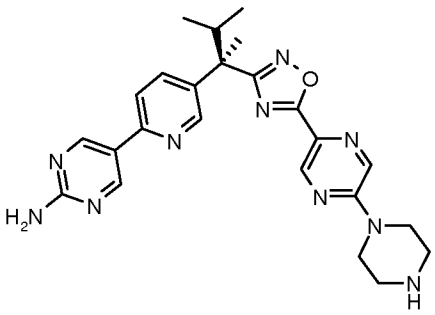
21		2	B	1.63	391.4
22		6	B	1.7	462.2
23		1	E	5.16	435.3
24		1	E	5.16	435.3
25		7	G	1.13	370.4

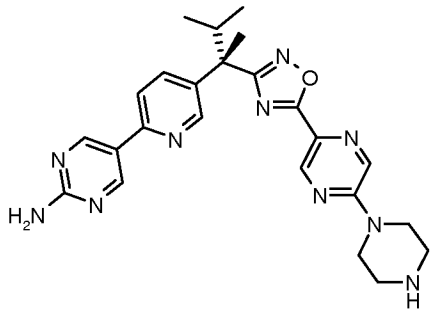
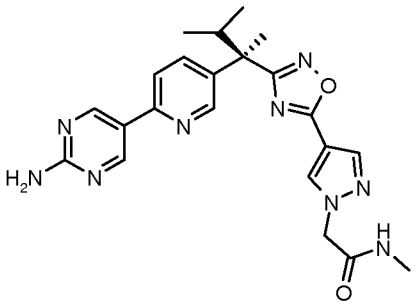
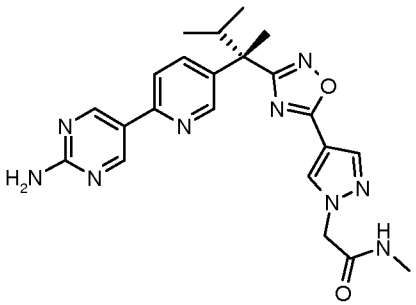
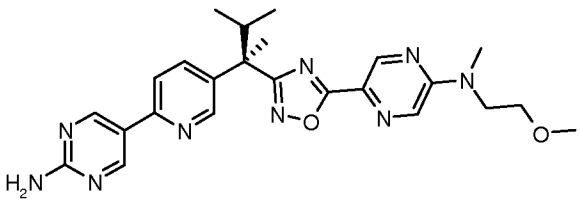
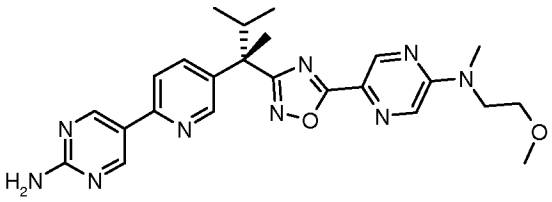
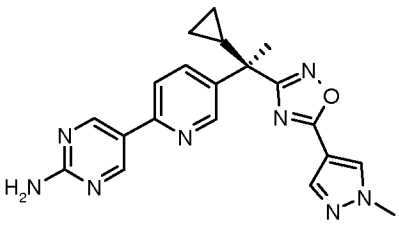
26		7	G	1.02	395.4
27		6	C	2	462.4
28		4	C	2.5	419.4
29		4	D	1.25	405.4
30		4	D	1.41	479.6

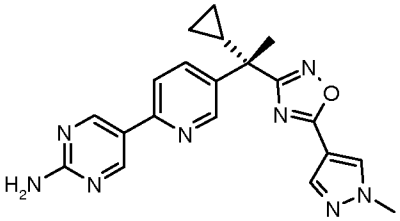
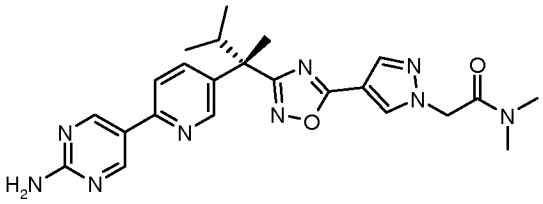
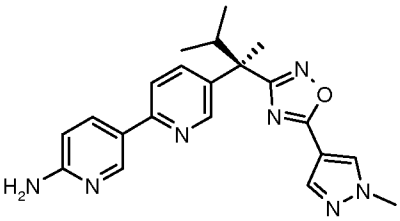
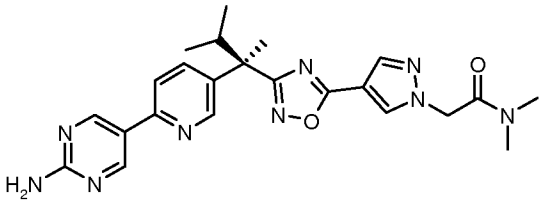
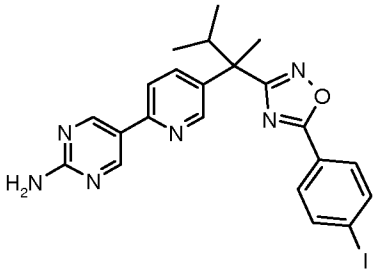
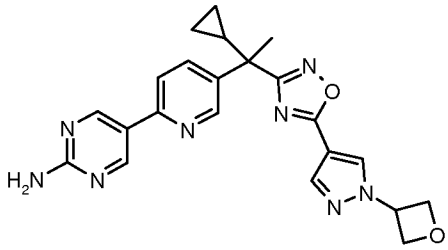
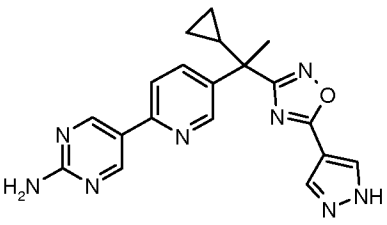
31		4	C	2.05	433.4
32		6	C	1.95	476.4
33		4	D	1.42	505.4
34		1	D	1.2	449.4
35		1	D	1.21	449.4

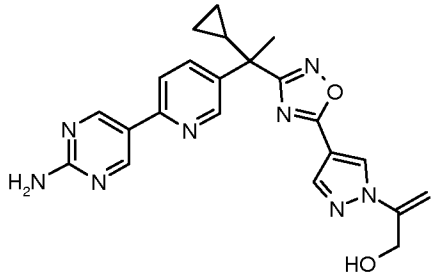
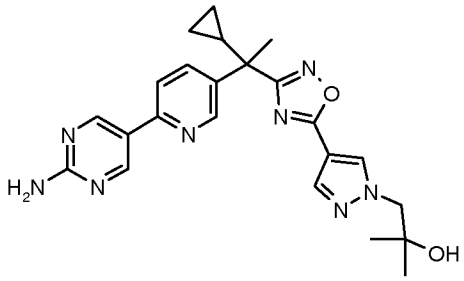
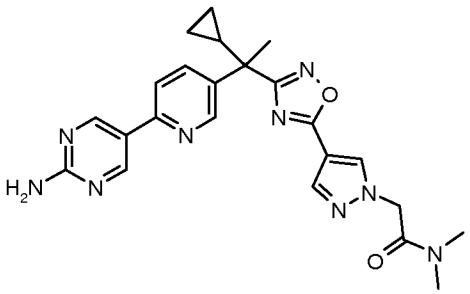
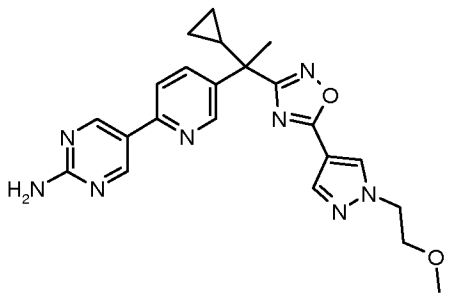
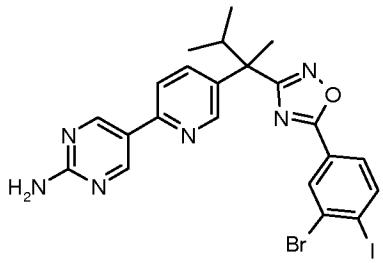
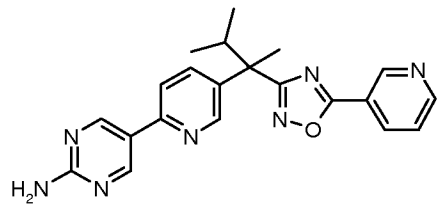
36		2	H	1.94	455.5
37		4	D	1.19	449.37
38		4	D	1.18	449.37
39		8	D	1.2	477.4
40		5	D	1.25	432.4

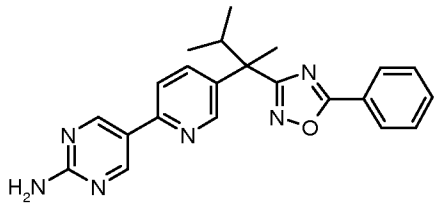
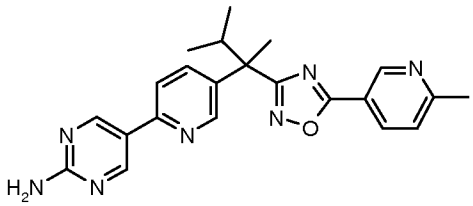
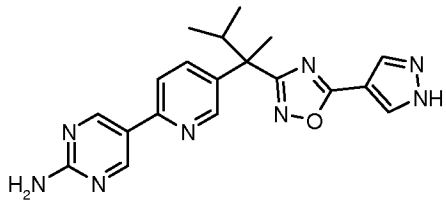
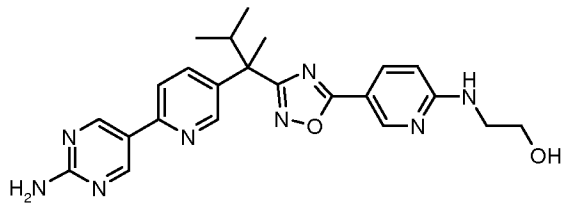
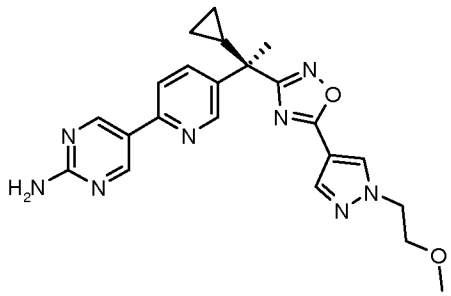
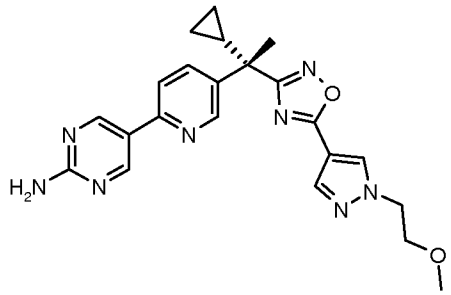
41		5	D	1.24	432.4
42		6	C	2.04	432.4
43		3	C	1.86	377.4
44		4	D	1.24	441.4
45		4	D	1.24	441.4
46		4	D	1.23	479.4

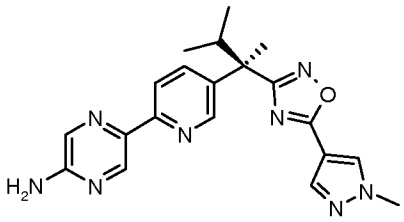
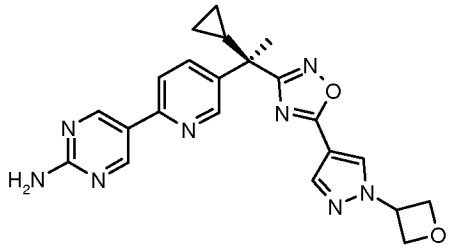
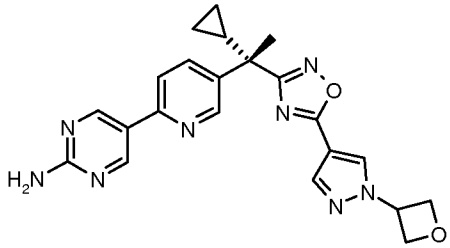
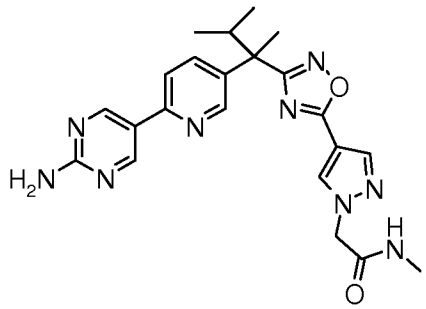
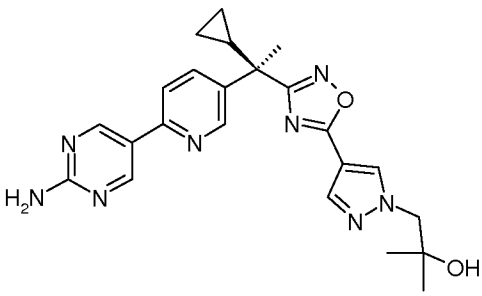
47		4	D	1.22	479.4
48		4	D	1.21	423.4
49		4	D	1.21	423.4
50		9	H	1.33	389.3
51		6	D	0.92	473.4

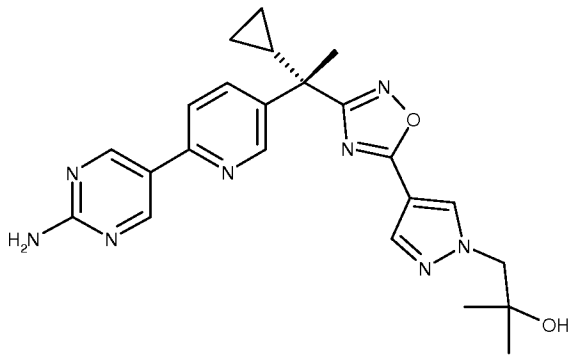
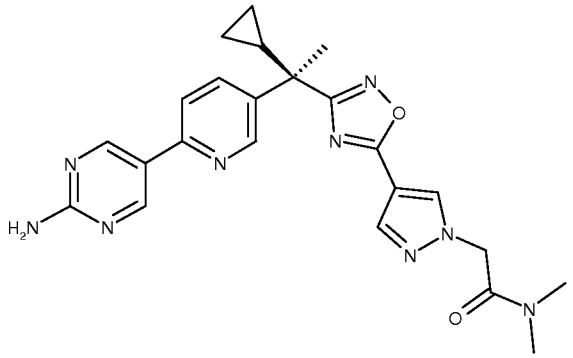
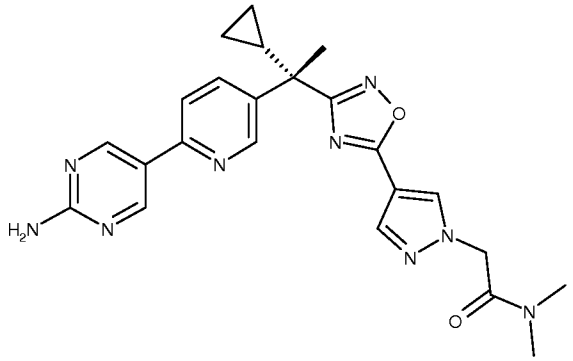
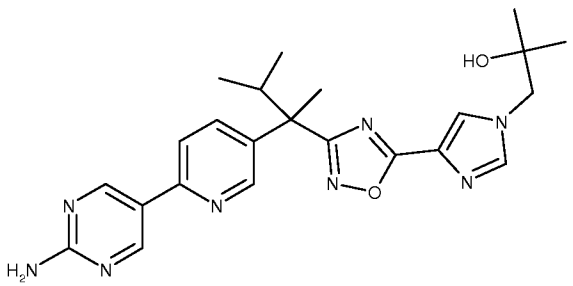
52		6	D	0.92	473.4
53		1	F	1.26	448.4
54		1	F	1.26	448.4
55		6	F	2.17	476.2
56		6	F	2.23	476.2
57		9	H	1.33	389.3

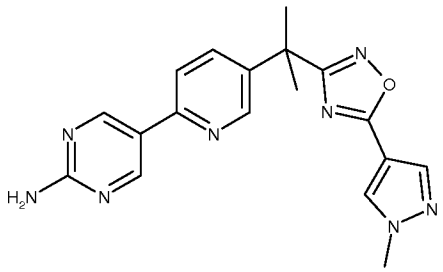
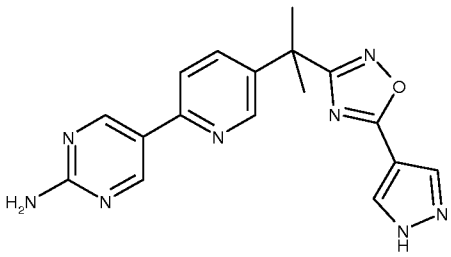
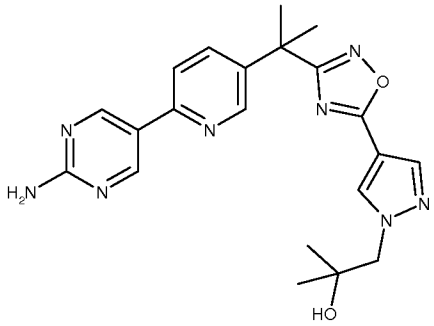
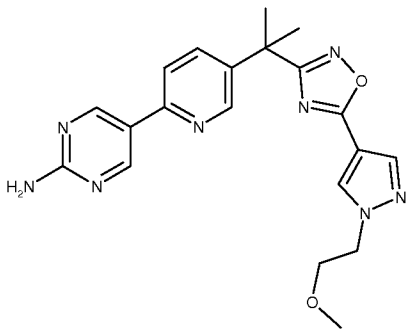
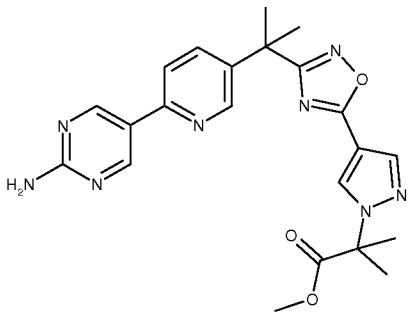
58		9	H	1.33	389.3
59		1	F	1.39	461.7
60		2	H	1.49	390.4
61		1	F	1.38	461.7
62		10	D	1.61	513.2
63		11	G	1.28	431.4
64		9	H	1.24	375.3

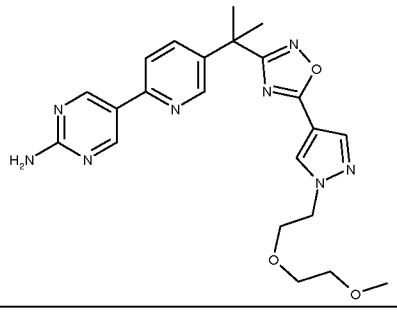
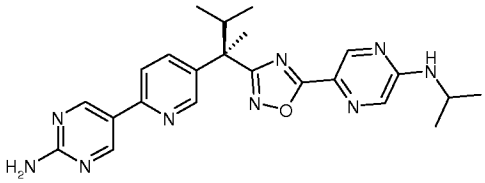
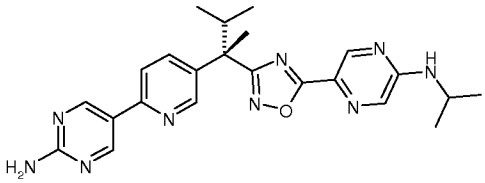
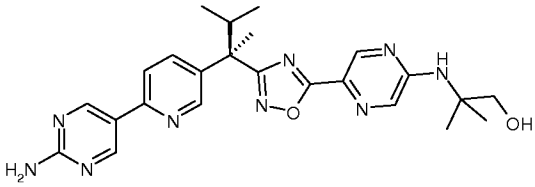
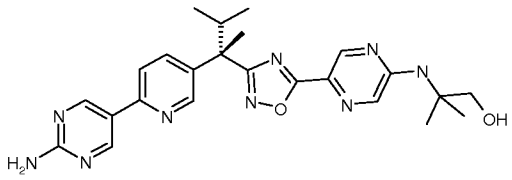
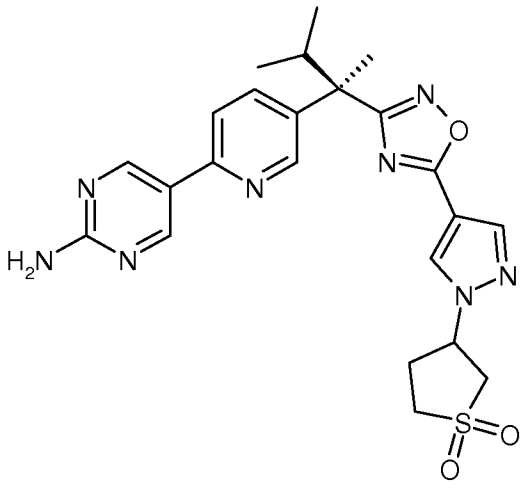
65		12	G	1.27	431.4
66		16	E	4.65	447.4
67		16	H	1.19	460.4
68		16	H	1.32	433.3
69		13	D	1.7	591593 M/M+2
70		1	A	3.77	388.1

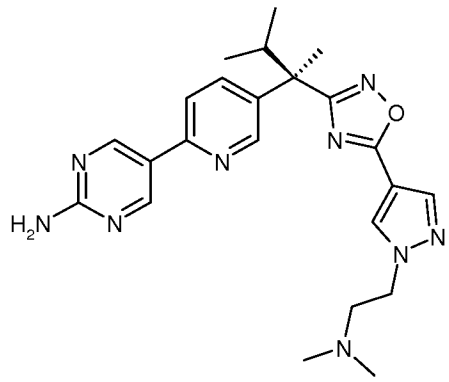
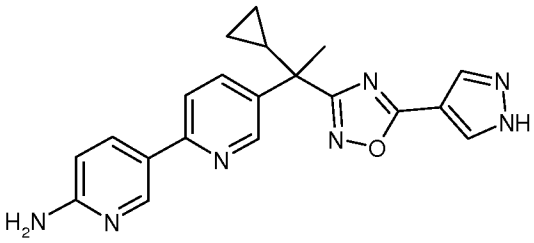
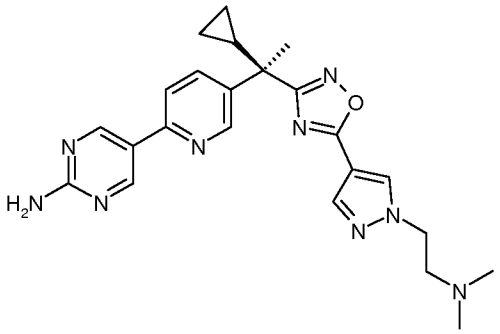
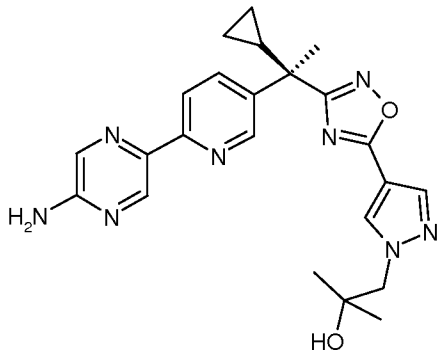
71		1	A	4.52	387.1
72		1	A	3.9	402.1
73		1	B	1.61	377
74		14	A	3.38	447.3
75		4	E	4.87	433.3
76		4	E	4.86	433.3

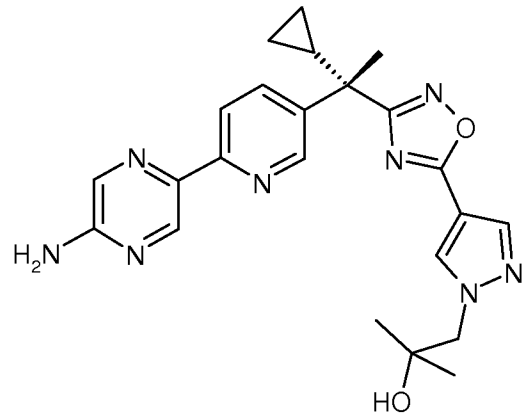
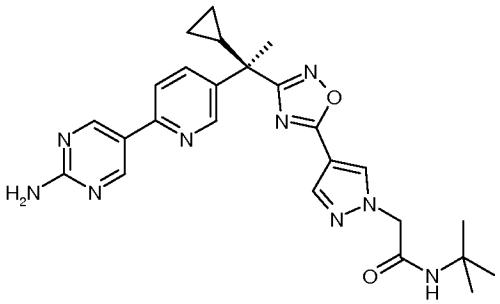
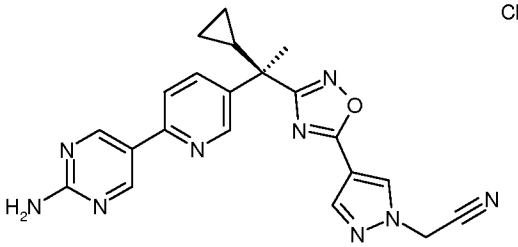
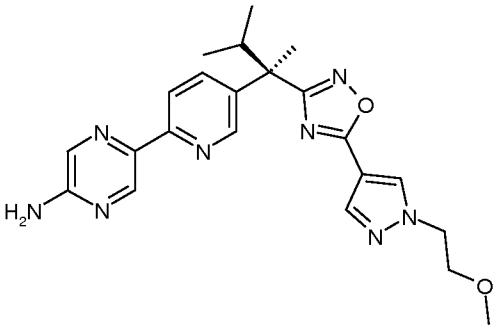
77		2	E	4.53	391.3
78		11	G	1.28	431.4
79		11	G	1.28	431.4
80		1	A	3.27	448.3
81		16	F	1.42	447.3

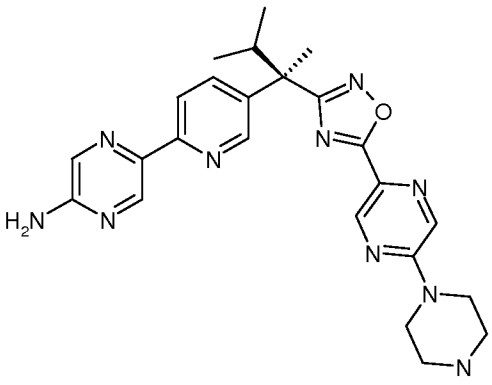
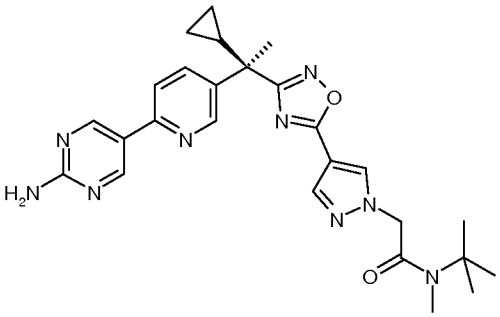
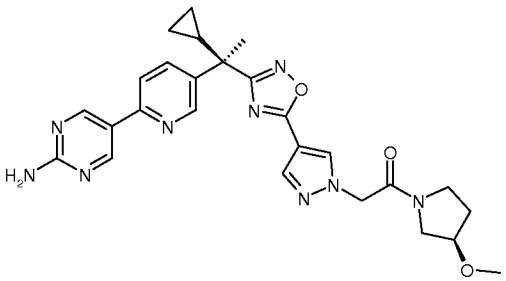
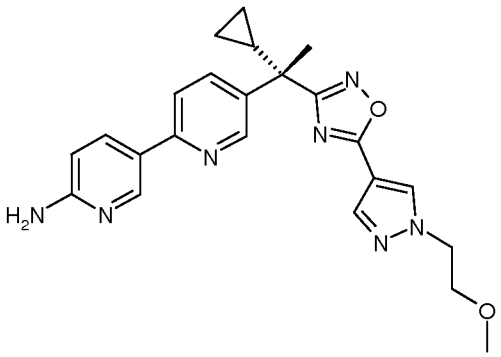
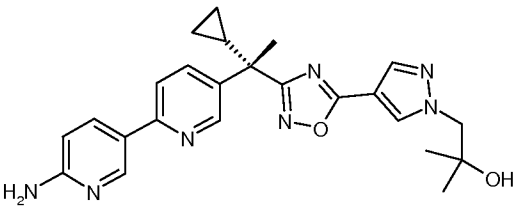
82		16	F	1.42	447.3
83		16	G	1.23	460.4
84		16	G	1.24	460.4
85		1	A	3.24	449.2

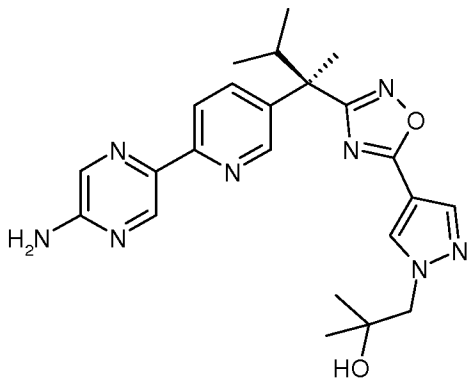
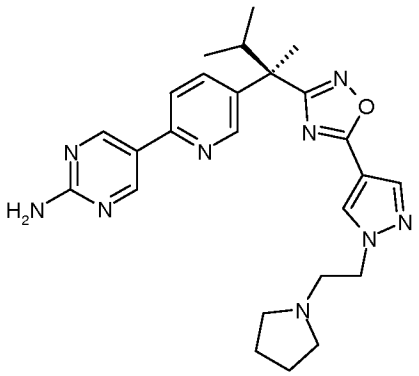
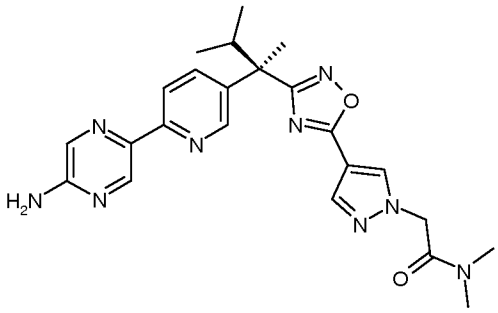
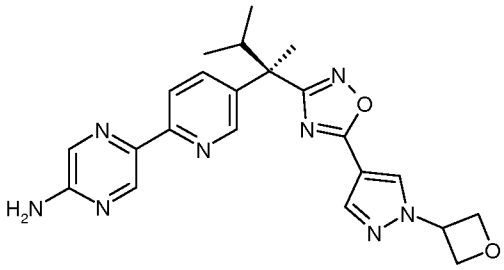
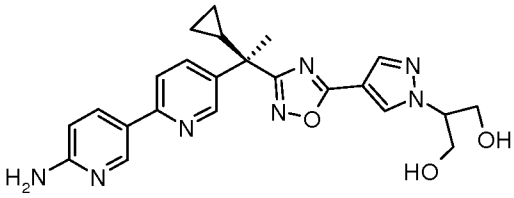
86		15	D	1.07	363.4
87		15	D	0.99	349.4
88		4	D	1.09	421.4
89		4	D	1.11	407.4
90		4	D	1.22	449.4

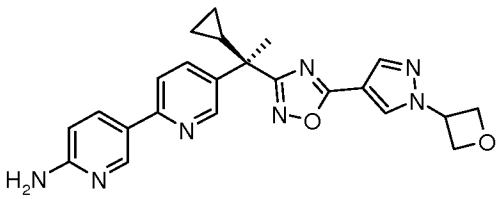
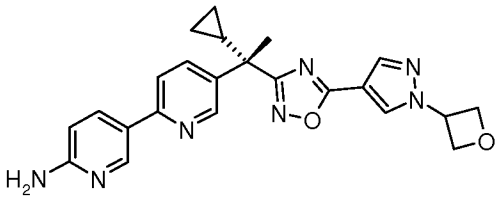
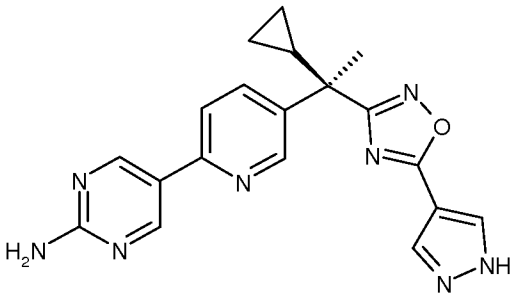
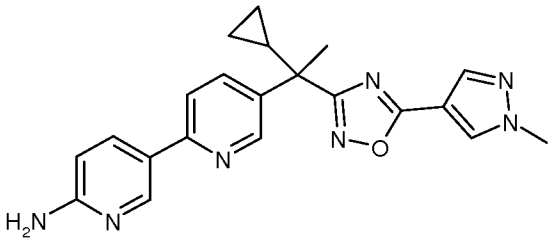
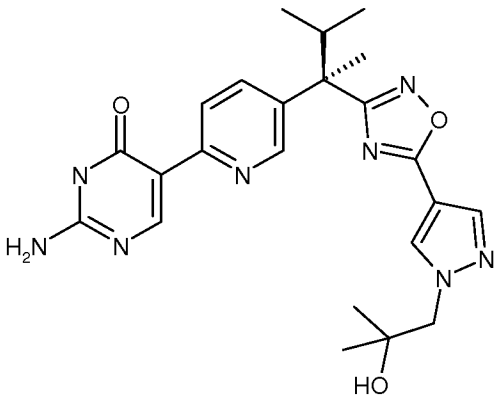
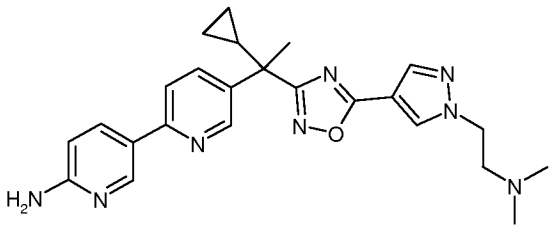
91		4	D	1.12	451.4
92		6	F	2.12	446
93		6	F	2.12	446
94		6	F	1.92	476
95		6	F	1.92	476
96		4	D	1.15	495.4

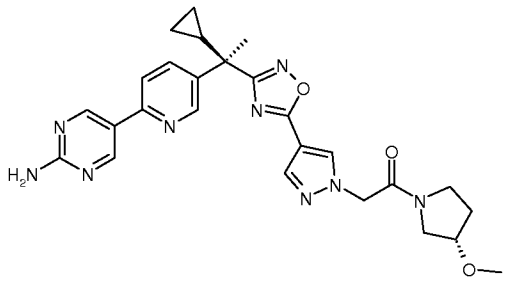
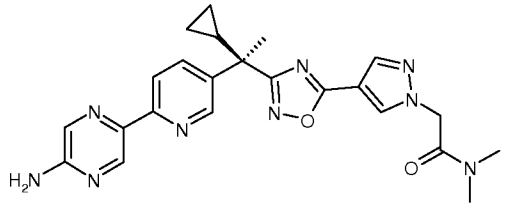
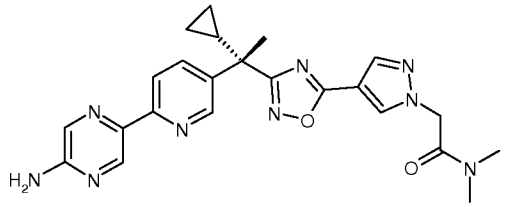
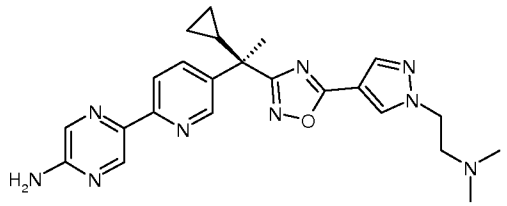
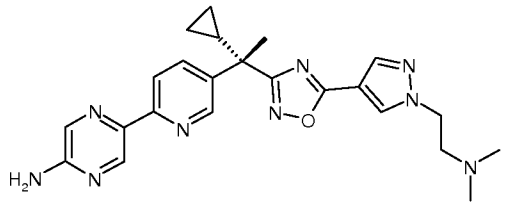
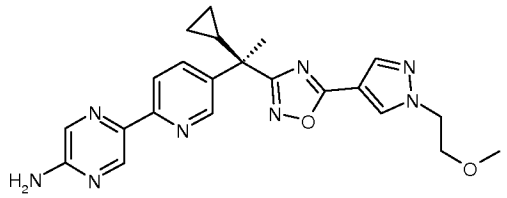
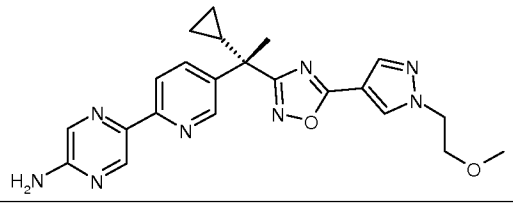
97		4	D	0.97	448.4
98		20	I	0.56	374.2
99	Chiral 	4	I	0.47	446.3
100		21	I	0.71	447.3

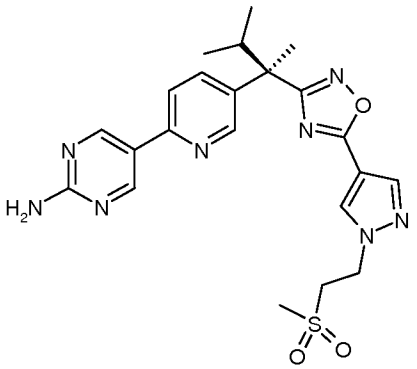
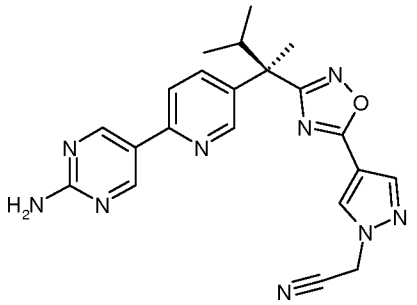
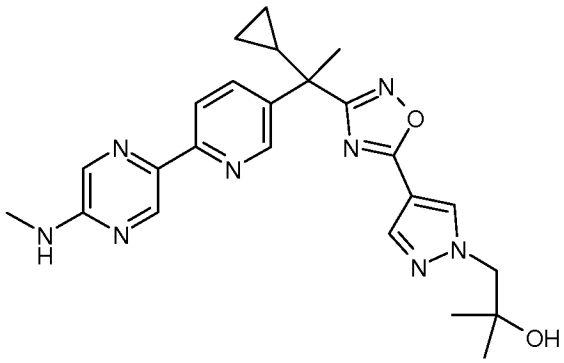
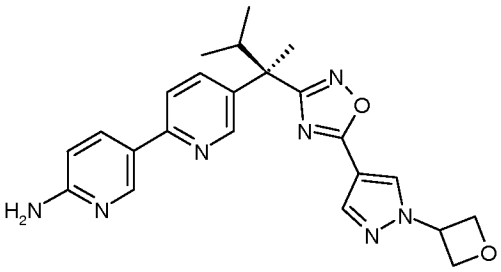
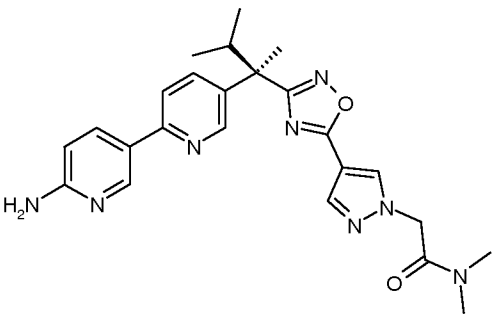
101		21	I	0.71	447.3
102		4	I	0.72	488.3
103	Chiral 	4	I	0.75	414.3
104		18	F	1.6	435.3

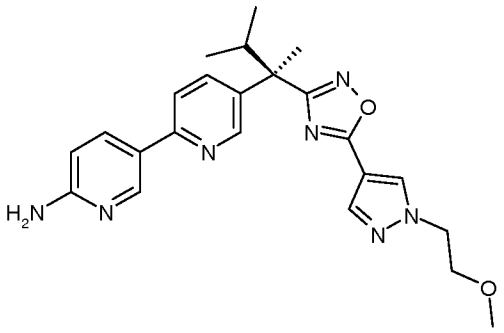
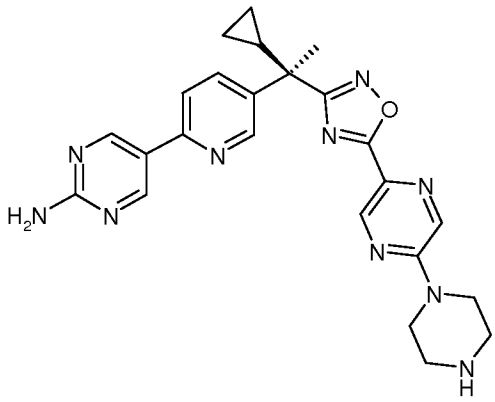
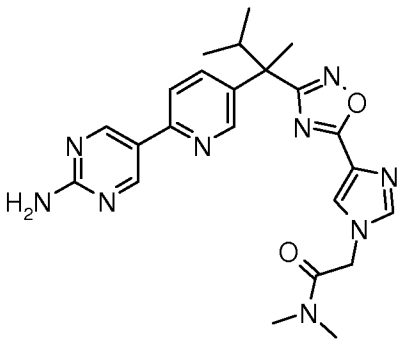
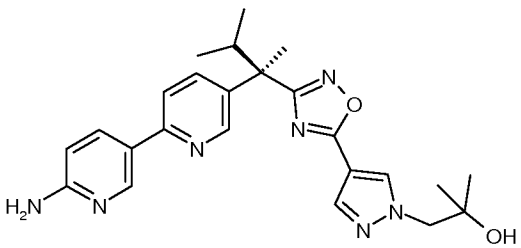
105		18	D	0.94	473.4
106		4	I	0.82	502.3
107		4	I	0.68	516.3
108		20	I	0.66	432.3
109		11	I	0.64	446.3

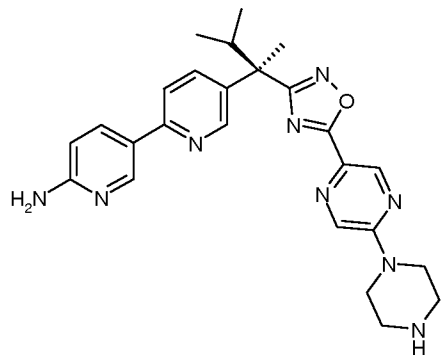
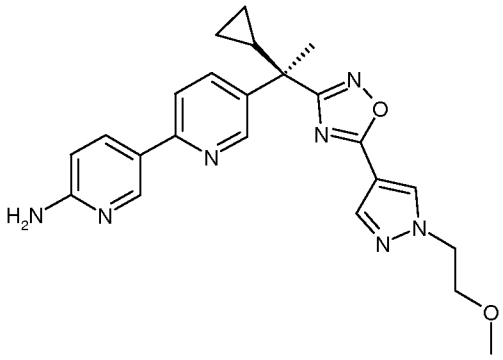
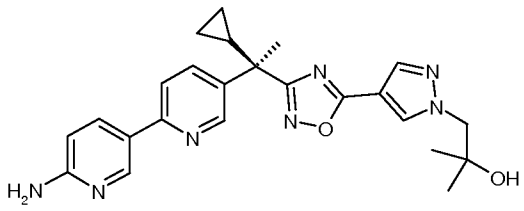
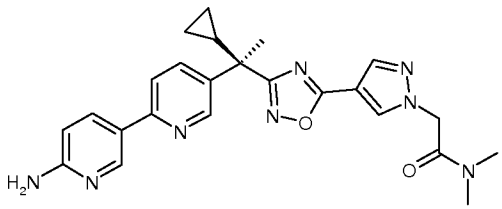
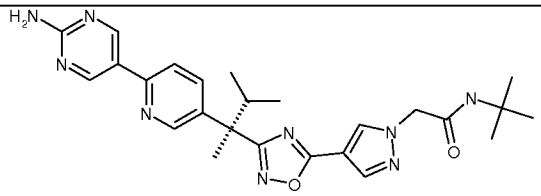
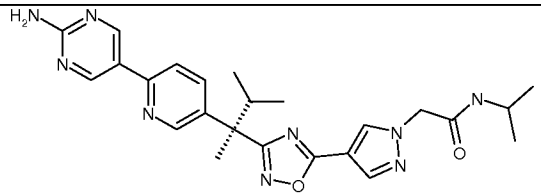
110		18	I	0.73	449.3
111		4	I	0.64	474.4
112		18	F	1.39	462.5
113		18	F	1.55	433.3
114		22	I	0.91	448.4

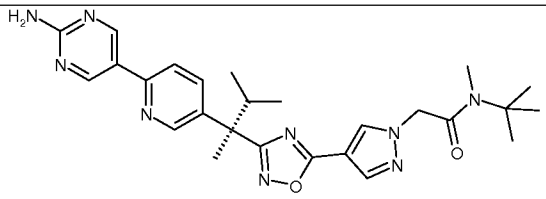
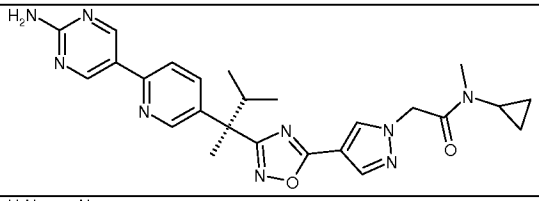
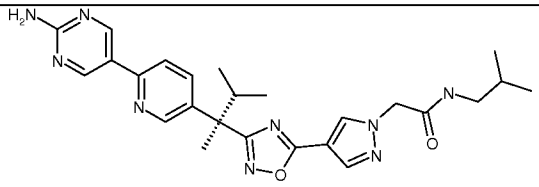
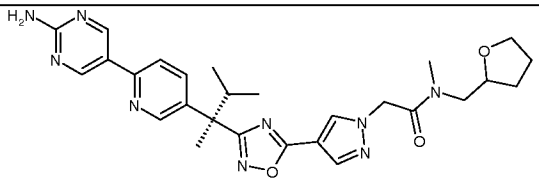
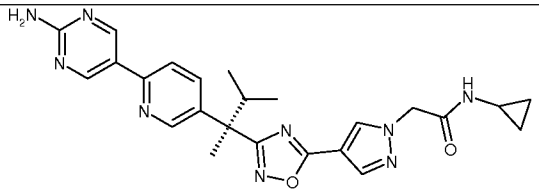
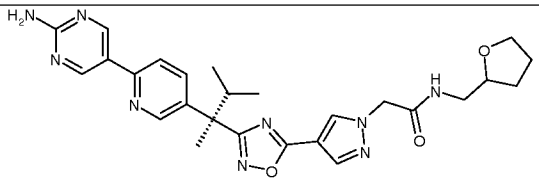
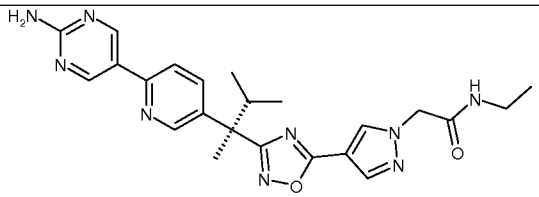
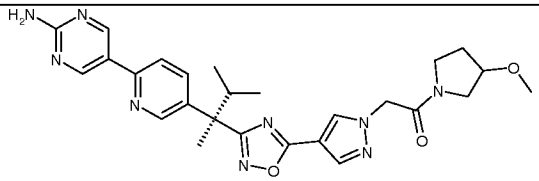
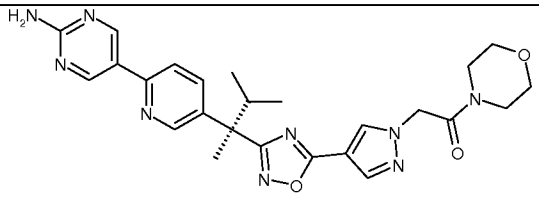
115		22	I	0.99	430.4
116		22	I	0.99	430.4
117		9	I	0.68	375.2
118		20	D	0.99	388.4
119		25	I	0.61	465.3
120		11	D	0.79	445.4

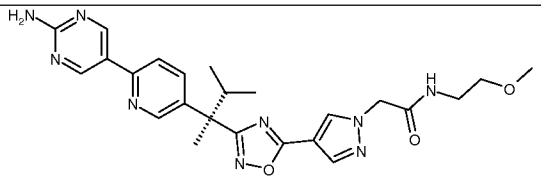
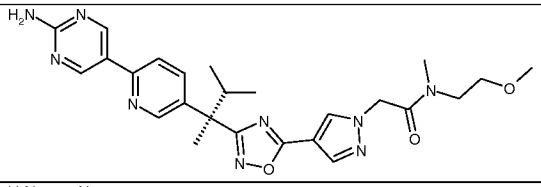
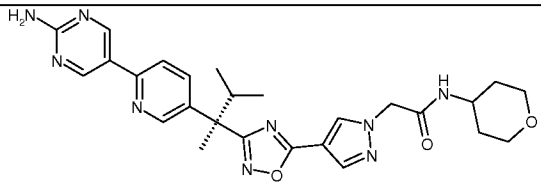
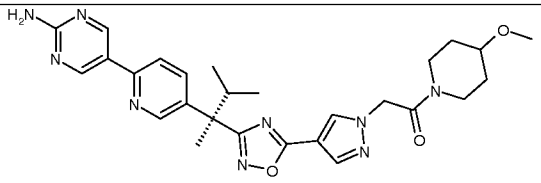
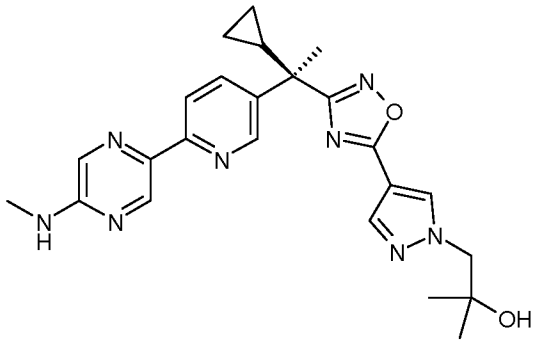
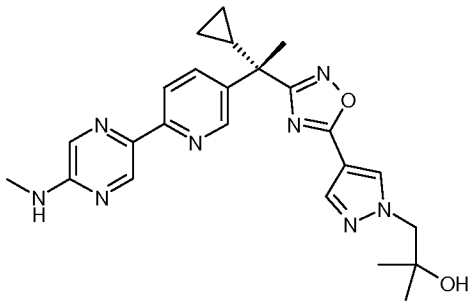
121		4	I	0.65	516.3
122		11	I	0.56	460.3
123		11	I	0.56	460.3
124		11	D	0.89	446.4
125		11	I	0.52	446.3
126		11	I	0.75	433.3
127		11	I	0.75	433.3

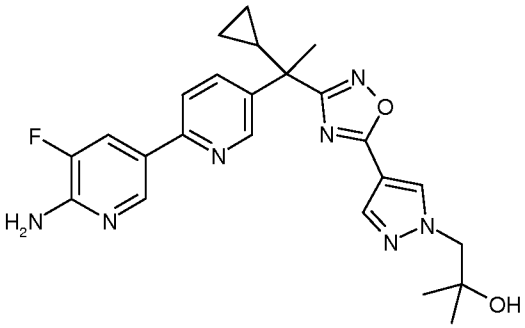
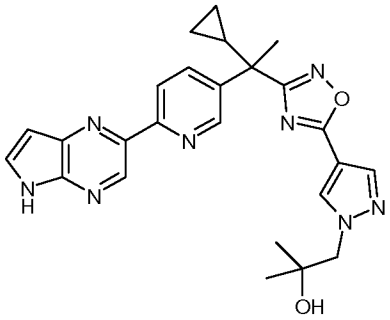
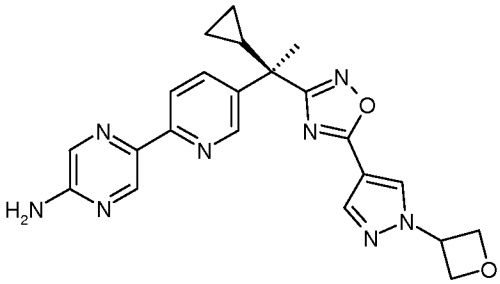
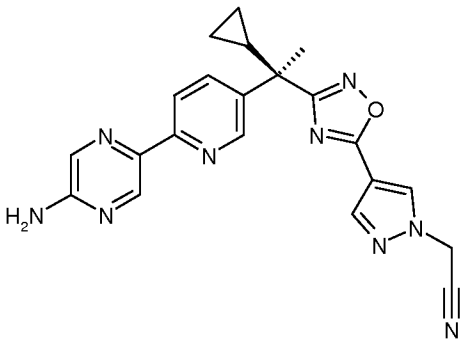
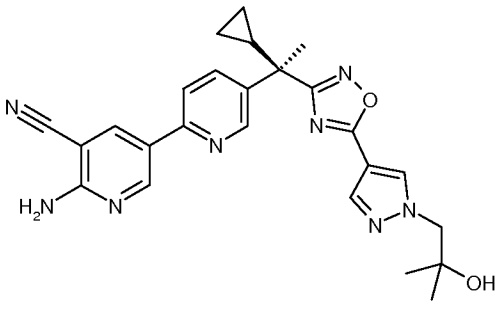
128		23	D	1.1	483.4
129		4	D	1.16	416.4
130		21	I	0.74	461.4
131		1	I	0.66	432.3
132		1	I	0.62	461.4

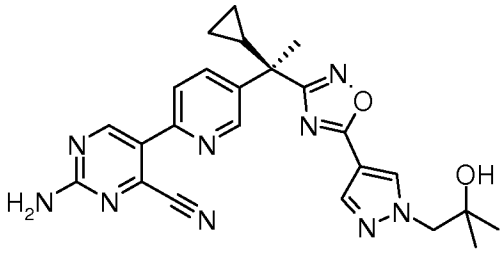
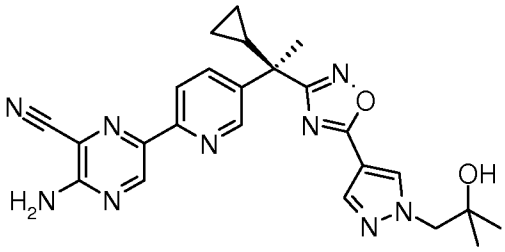
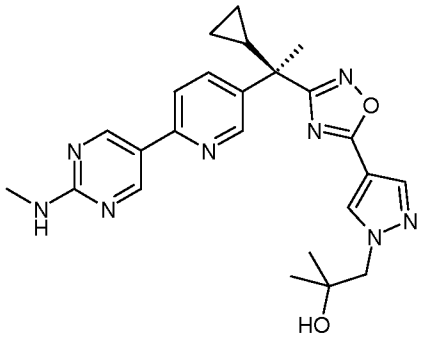
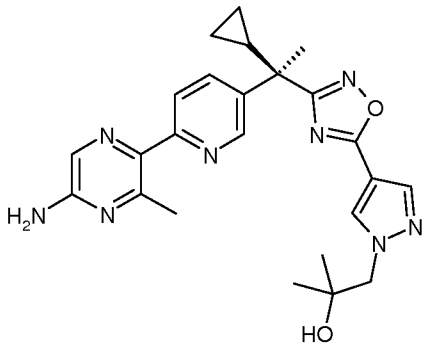
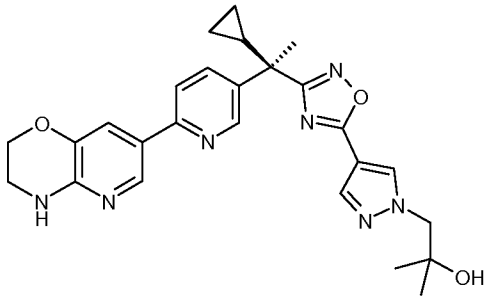
133		1	F	1.3	434.3
134		19	I	0.53	471.3
135		17	I	0.58	462.31
136		1	I	0.68	448.4

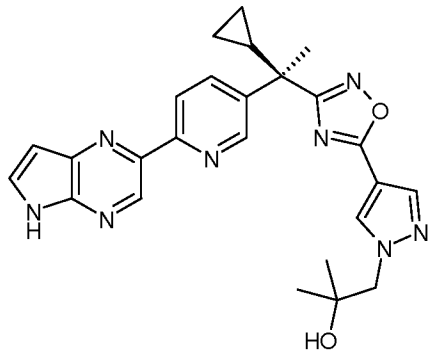
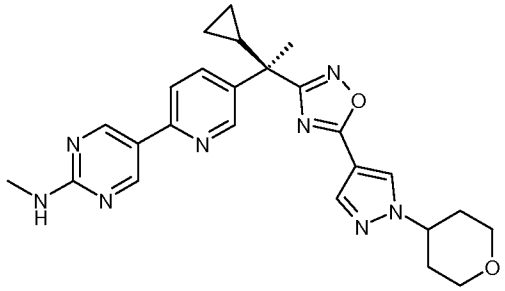
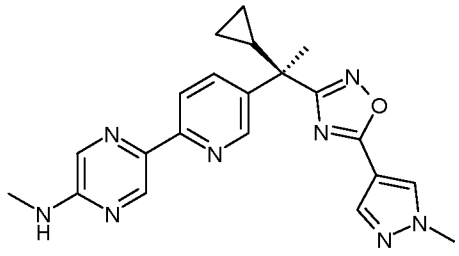
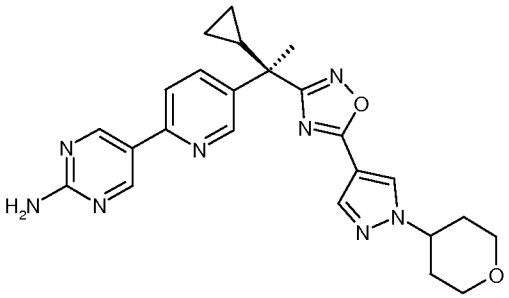
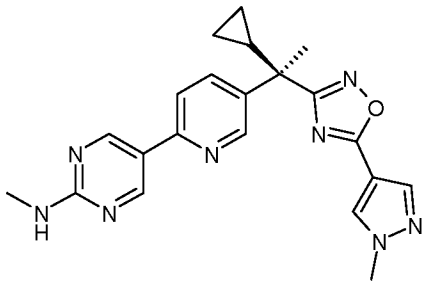
137		19	I	0.49	472.4
138		11	I	0.66	432.3
139		11	I	0.64	446.3
140		4	I	0.54	459.2
141		24	I	0.98	490.4
142		24	I	0.91	476.3

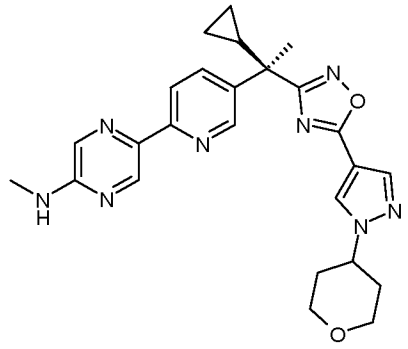
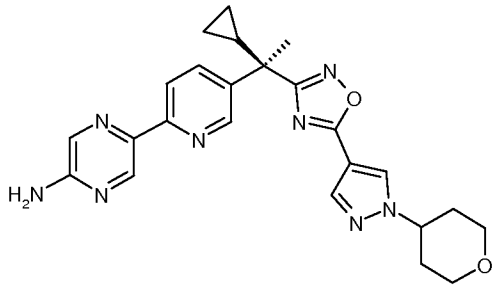
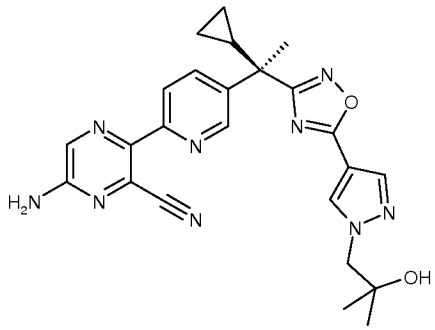
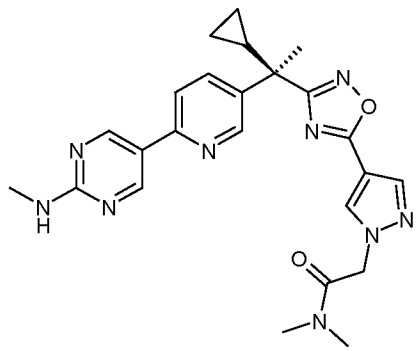
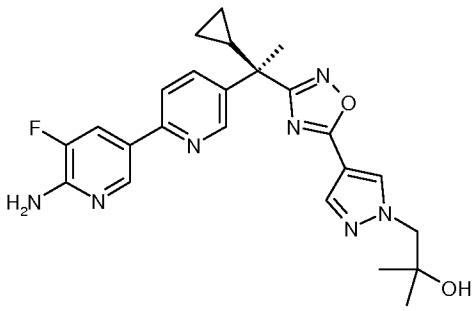
143		24	I	1.02	504.4
144		24	I	0.93	488.3
145		24	I	0.96	490.3
146		24	I	0.91	532.4
147		24	I	0.79	474.3
148		24	I	0.8	518.4
149		24	I	0.78	462.3
150		24	I	0.79	518.4
151		24	I	0.77	504.3

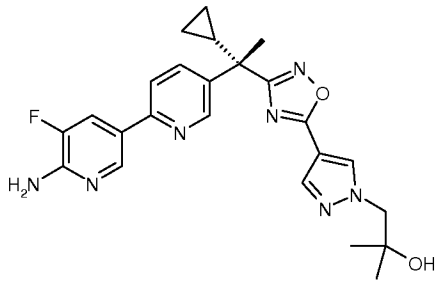
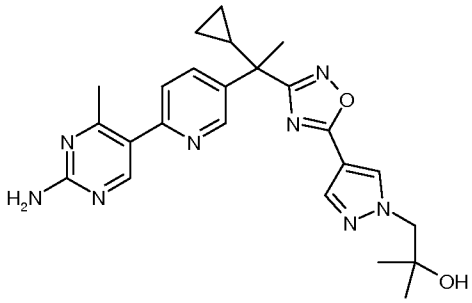
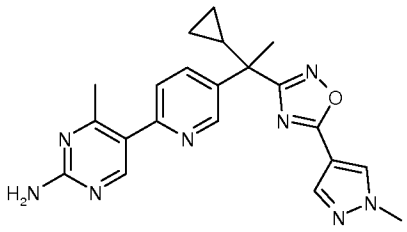
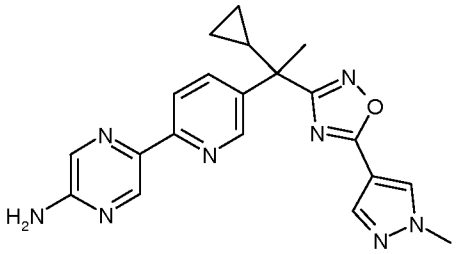
152		24	I	0.78	492.4
153		24	I	0.82	506.4
154		24	I	0.79	518.4
155		24	I	0.83	532.3
156		21	I	0.75	461.3
157		21	I	0.75	461.3

158		18	I	0.8	464.3
159		2	F	2	471.4
160		16	I	0.67	M-H=429.3
161		16	I	0.69	M-H=412.3
162		18	I	0.8	471.4

163		26	I	0.79	472.3
164		18	I	0.86	472.3
165		1	F	1.57	461.2
166		28	F	1.22	461.1
167		26	I	0.64	488.4

168		18	F	1.64	471.3
169		27	I	0.82	473.4
170		18	I	0.68	403.7
171		23	I	0.75	459.4
172		1	F	1.53	403

173		18	F	1.5	473.1
174		16	I	0.7	459.1
175		26	I	0.8	472.3
176		1	F	1.25	474.3
177		21	I	0.92	464.3

178		21	I	0.92	464.3
179		27	I	0.88	461.3
180		27	I	0.62	403.2
181		18	I	0.6	389.2

Assessment of Biological Properties

1. Binding Assay

Compounds are assessed for the ability to bind to FLAP in a binding assay that measures compound-specific displacement of an iodinated (^{125}I) FLAP inhibitor via a Scintillation Proximity Assay format (adapted from S. Charleson et al., Mol. Pharmacol., 1992, 41, 873-879).

Cell pellets produced from sf9 insect cells expressing recombinant human FLAP protein are resuspended in buffer A [15 mM Tris-HCl (pH 7.5), 2 mM $MgCl_2$, 0.3 mM EDTA, 1 mM PMSF]. The cells are lysed with a Dounce homogenizer and the material is centrifuged at 10,000 x g for 10 minutes. The supernatant is then collected and centrifuged at 100,000 x g for 60 minutes. To prepare membrane protein for an assay, an aliquot of the 100,000 x g pellet is resuspended in 1 ml of buffer A, Dounce homogenized, and finally subjected to polytron mixing (30 seconds). Membrane protein (25 µl, 5 µg) is mixed with WGA SPA beads (Amersham) and stirred for 1h. To an assay plate (Perkin Elmer FlexiPlate) is added 25 µl of test compound prepared in Binding buffer [100 mM Tris (pH 7.5), 140 mM NaCl, 5% glycerol, 2 mM EDTA, 0.5 mM TCEP, 0.05% Tween 20], 25 µl of [^{125}I]L-691,831 (an iodinated analog of MK-591, *Charleson et al. Mol. Pharmacol., 41, 873-879, 1992*) and finally 50 µl of the bead/protein mixture. (final concentrations: beads, 200 µg/well; protein, 5µg/well; [^{125}I] probe, 0 08 nM/well(17 nCi/well). The plates are shaken for 2h before reading on a Microbeta plate reader. Non-specific binding is determined by the addition of 10 µM cold L-691,831 compound.

In general, the preferred potency range (IC_{50}) of compounds in the above assay is between 0.1 nM to 10 µM, the more preferred potency range is 0.1 nM to 1 µM, and the most preferred potency range is 0.1 nM to 100 nM.

2. Whole Blood Assay

Compounds are additionally tested in a human whole blood assay to determine their ability to inhibit the synthesis of LTB_4 in a cellular system. Compounds are combined with heparinized human whole blood and incubated for 15 minutes at 37°C. Calcimycin (20µM final, prepared in phosphate-buffered saline, pH 7.4) is then added and the mixture is incubated for another 30 minutes at 37°C. The samples are centrifuged for 5 min at low speed (1500 x g) and the plasma layer is removed. Plasma LTB_4 concentrations are then measured using an antibody-based homogenous time-resolved fluorescence method (CisBio, Bedford, MA).

In general, the preferred potency range (IC_{50}) of compounds in the above assay is between 10 nM to 10 μM, the more preferred potency range is 10 nM to 1 μM, and the most preferred potency range is 10 nM to 100 nM.

METHOD OF USE

The compounds of the invention are effective inhibitors of 5-lipoxygenase activating protein (FLAP) and thus inhibit leukotriene production. Therefore, in one embodiment of the invention, there is provided methods of treating leukotriene-mediated disorders using compounds of the invention. In another embodiment, there is provided methods of treating cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer using compounds of the invention.

Without wishing to be bound by theory, by inhibiting the activity of FLAP, the compounds of the invention block the production of LTs resulting from the oxidation of arachidonic acid by 5-LO and subsequent metabolism. Thus, the inhibition of FLAP activity is an attractive means for preventing and treating a variety of diseases mediated by LTs. These include:

Cardiovascular diseases including atherosclerosis, myocardial infarction, stroke, aortic aneurysm, sickle cell crisis, ischemia-reperfusion injury, pulmonary arterial hypertension and sepsis;

Allergic diseases including asthma, allergic rhinitis, rhinosinusitis, atopic dermatitis and urticaria;

Fibrotic diseases including airway remodeling in asthma, idiopathic pulmonary fibrosis, scleroderma, asbestosis;

Pulmonary syndromes including adult respiratory distress syndrome, viral bronchiolitis, obstructive sleep apnea, chronic obstructive pulmonary disease, cystic fibrosis, and bronchopulmonary dysplasia;

Inflammatory diseases including rheumatoid arthritis, osteoarthritis, gout, glomerulonephritis, interstitial cystitis, psoriasis, inflammatory bowel disease, multiple sclerosis, inflammatory pain, systemic lupus erythematosus, transplant rejection, inflammatory and allergic ocular diseases;

Cancer including solid tumors, leukemias and lymphomas; and

Renal diseases such as glomerulonephritis.

For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased antagonist activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

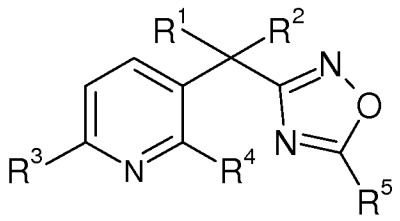
Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by *Remington: The Science and Practice of Pharmacy*, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; *Handbook of Pharmaceutical Additives*, Michael & Irene Ash (eds.), Gower, 1995; *Handbook of Pharmaceutical Excipients*, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that are required for the formulation to be efficacious.

CLAIMS

What is claimed is:

1. A compound of formula I:



I

wherein:

R^1 and R^2 are each independently hydrogen, C_{1-7} alkyl or C_{3-10} carbocycle, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is a 5-11 membered heteroaryl ring containing one to three heteroatoms selected from nitrogen, oxygen and sulfur, wherein the heteroaryl ring is optionally independently substituted with one to three groups selected from C_{1-5} alkyl, C_{1-5} alkoxy, C_{1-3} alkylhydroxy, amino, C_{1-3} alkylamino,C_{1-3} dialkylamino, oxo, -CN, halogen, and 5-6 membered heteroaryl optionally substituted with one to three methyl groups;

R^4 is hydrogen, C_{1-3} alkyl, halogen or nitrile;

R^5 is C_{1-6} alkyl, C_{3-10} carbocycle, 5-11 membered heterocycle, aryl, 5-11 membered heteroaryl, -C(O)-R^6 or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

R^6 is C_{3-8} heterocycle or –NH-5-6 membered heterocycle, each optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11} ;

$R^7$and R^8 are each independently hydrogen or C_{1-6} alkyl, wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, $-N(R^{12})(R^{13})$, 3-6 membered heterocycle, C_{1-6}alkoxy, halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-C(O)N(R^{12})(R^{13})$ or $-S(O)_nC_{1-6}$alkyl,

(g) C_{1-6}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_nC_{1-6}$alkyl,

(j) $–CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $–S(O)_2N(R^{12})(R^{13})$,

(m) a 3-10 membered heterocyclic group optionally substituted with one to three C_{1-6} alkyl groups or oxo,

(n') oxo,

(o) $–C(O)-C_{1-3}$ alkyl;

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, $–C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl C_{3-6} carbocycle and a 3-6 membered heterocyclic group, each of which is optionally independently substituted with one to three C_{1-6}alkyl groups, halogen, –OH, C_{1-6}alkoxy, $-C(O)N(R^{14})(R^{15})$, $-S(O)_nC_{1-6}$alkyl, CN, a 3-6 membered heterocyclic group, $-OC_{1-6}$alkyl, CF_3, or;

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and R^{15} are each independently selected from –H and –C_{1-6}alkyl;

n is 0, 1 or 2;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein:

R^1 and R^2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cylohexyl, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, thienyl, furanyl or thiazolyl, wherein each heteroaryl ring is optionally independently substituted with one to three groups selected from C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylhydroxy, amino, C_{1-3} alkylamino and C_{1-3} dialkylamino, oxo, -CN, halogen and 5-6 membered heteroaryl optionally substituted with one to three methyl groups; or
R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;

R^4 is hydrogen, methyl or fluoro;

R^5 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, phenyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, tetrahydropyranyl, pyrrolyl, thienyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, indolyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, -C(O)-R^6 or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

R^6 is piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl or -NH-piperadinyl each optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen or C_{1-5} alkyl wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, $-N(R^{12})(R^{13})$, 3-6 membered heterocycle, C_{1-6}alkoxy , halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-C(O)N(R^{12})(R^{13})$ or $-S(O)_nC_{1-6}$alkyl,

(g) C_{1-6}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_nC_{1-6}$alkyl,

(j) $–CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $–S(O)_2N(R^{12})(R^{13})$,

(m) a 3-8 membered heterocyclic group optionally substituted with one to three C_{1-6} alkyl groups or oxo,

(n') oxo,

(o) $–C(O)-C_{1-3}$ alkyl,

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, $–C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, C_{3-6} carbocycle, and a 3-6 membered heterocyclic group, each of which is optionally

independently substituted with one to three C_{1-6}alkyl groups, halogen, –OH, C_{1-6}alkoxy, -C(O)N(R^{14})(R^{15}), -S(O)$_n$$C_{1-6}$alkyl, CN, a 3-6 membered heterocyclic group, -OC_{1-6}alkyl, CF_3; or,

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached can form a heterocyclyl ring optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and R^{15} are each independently selected from –H and –C_{1-4}alkyl;

n is 1 or 2;
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein:

R^1 and R^2 are each independently hydrogen, methyl, ethyl, propyl, isopropyl, *tert*-butyl, cyclopropyl or cyclobutyl, with the proviso that both R^1 and R^2 are not hydrogen;
or a pharmaceutically acceptable salt thereof.

4. A compound of formula (I) according to any of the claims 1-3, wherein:

R^3 is pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl, wherein each heteroaryl ring is optionally independently substituted with one to two groups selected from C_{1-3} alkyl, C_1-C_3 alkoxy, C_{1-2} alkylhydroxy, dimethylpyrrole, oxo, -CN, halogen, C_{1-3} alkylamino and amino; or
R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;

or a pharmaceutically acceptable salt thereof.

5. A compound of formula (I) according to any of the claims 1-4, wherein:

R^5 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, -C(O)-piperizinyl, -C(O)-piperidinyl, -C(O)-NH-piperidinyl or $-NR^7R^8$, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen or C_1-C_5 alkyl wherein the alkyl group is optionally substituted with –OH or C_{1-3}alkoxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, halogen, CN, $-CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-N(R^{12})(R^{13})$, morpholinyl, piperazinyl, C_{1-6}alkoxy, $-SO_2C_{1-3}$alkyl or $-C(O)N(R^{12})(R^{13})$,

(g) C_{1-3}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_2C_{1-6}$alkyl,

(j) $-CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $-S(O)_2N(R^{12})(R^{13})$,

(m) morpholinyl, piperazinyl, piperidinyl, tetrahydropyranyl, tetrahydrothienyl, dioxotetrahydrothienyl or oxetanyl each optionally substituted with a methyl group,

(n') oxo,

(o) $-C(O)-CH_3$,

(p) C_{1-6}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, C_{3-6} carbocycle, 3-6 membered heterocycle and –C_{1-6}alkyl, wherein the alkyl group is optionally substituted with one to three halogen, –OH, C_{1-6}alkoxy, 5-6 membered heterocyclic group, -C(O)N(R^{14})(R^{15}) or -$S(O)_2C_{1-6}$alkyl; or

R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring selected from pyrrolidinyl, piperidinyl and morpholinyl, wherein each heterocyclic ring is optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and $R^{15}$are each independently selected from –H and –C_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 or 2, wherein:

R^1 and R^2 are each independently hydrogen, methyl, isopropyl, or cyclopropyl, with the proviso that both R^1 and R^2 are not hydrogen;

R^3 is pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl, wherein each heteroaryl ring is optionally independently substituted with one to two groups selected from C_{1-3} alkyl,methoxy,-CH_2OH, amino, -NH-CH_3, oxo, -CN, fluoro and 2,5- dimethylpyrrole; or R^3 is pyrrolopyrazinyl or pyrido-oxazinyl;

R^4 is hydrogen;

R^5 is pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperazinyl, pyrazolopyrimidinyl, phenyl or –NR^7R^8, wherein each R^5 is optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11};

$R^7$and R^8 are each independently hydrogen, methyl or ethyl optionally substituted with hydroxy;

R^9, R^{10} and R^{11} are independently selected from

(a) –H,

(b) -OH,

(c) halogen,

(d) -CN,

(e) $-CF_3$,

(f) C_{1-6}alkyl optionally substituted with one to three –OH, $-N(R^{12})(R^{13})$, morpholinyl, piperazinyl, C_{1-3}alkoxy, halogen, CN, $–CO_2R^{12}$, -O- C_{1-6}alkyl-O- C_{1-3}alkyl, $-SO_2CH_3$ or $-C(O)N(R^{12})(R^{13})$,

(g) C_{1-3}alkoxy,

(h) $-N(R^{12})(R^{13})$,

(i) $-S(O)_2C_{1-2}$alkyl,

(j) $–CO_2R^{12}$,

(k) $-C(O)N(R^{12})(R^{13})$,

(l) $–S(O)_2N(R^{12})(R^{13})$,

(m) morpholinyl, piperazinyl, tetrahydropyranyl, dioxotetrahydrothienyl or oxetanyl each optionally substituted with a methyl group,

(n') oxo,

(o) $–C(O)-CH_3$,

(p) C_{1-4}alkenyl substituted optionally substituted with a –OH;

R^{12} and R^{13} are each independently selected from –H, cyclopropyl, tetrahydrofuranyl, tetrahydropyranyl and $–C_{1-6}$alkyl, wherein the alkyl group is optionally independently substituted with one to three halogen, –OH, C_{1-6}alkoxy, tetrahydrofuranyl, tetrahydropyranyl, $-C(O)N(R^{14})(R^{15})$, or $-S(O)_2C_{1-6}$alkyl; or

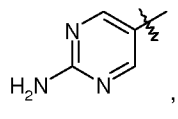
R^{12} and R^{13} taken together with the nitrogen ring to which they are attached form a heterocyclyl ring selected from pyrrolidinyl, piperidinyl and morpholinyl, wherein each heterocyclic ring is optionally substituted with one to three –OH, CN, -OC_{1-6}alkyl or oxo;

R^{14} and $R^{15}$are each independently selected from –H and –C_{1-4}alkyl;
or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 above, wherein:
R^1 is methyl,
R^2 is selected from methyl, isopropyl and cyclopropyl;
or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 6, wherein:

R^3 is selected from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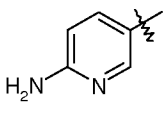
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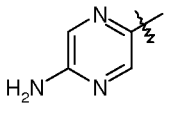
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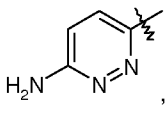
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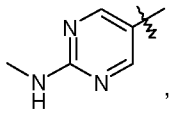
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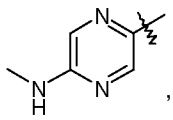
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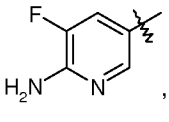
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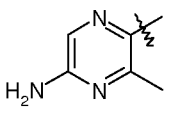
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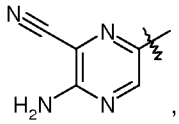
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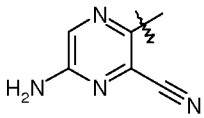
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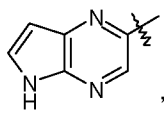
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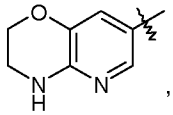
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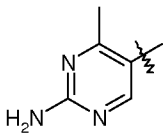
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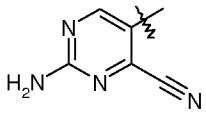

or a pharmaceutically acceptable salt thereof.

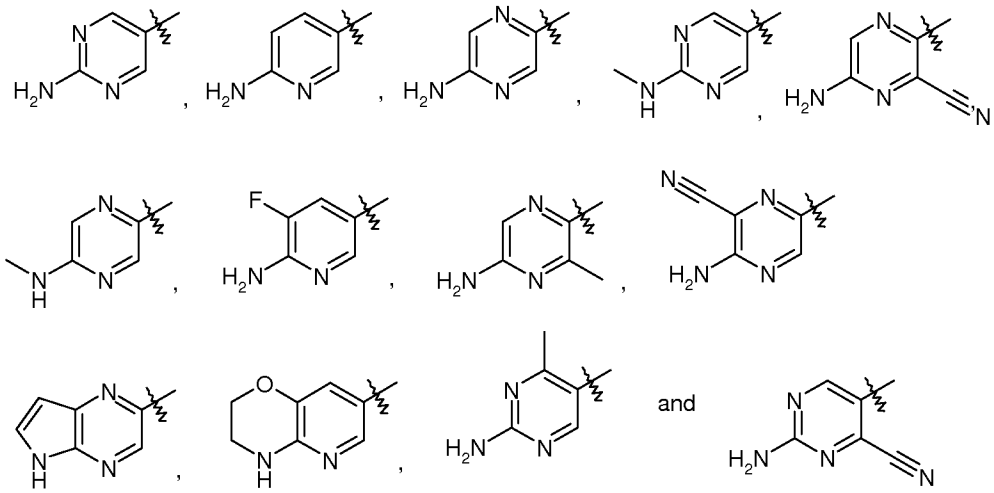
9. A compound according to claim 6, wherein:
R^5 is pyrazolyl optionally independently substituted with one to three groups selected from R^9, R^{10} and R^{11} ;
or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 6, wherein:

R^1 is methyl,

R^2 is selected from methyl, isopropyl and cyclopropyl;

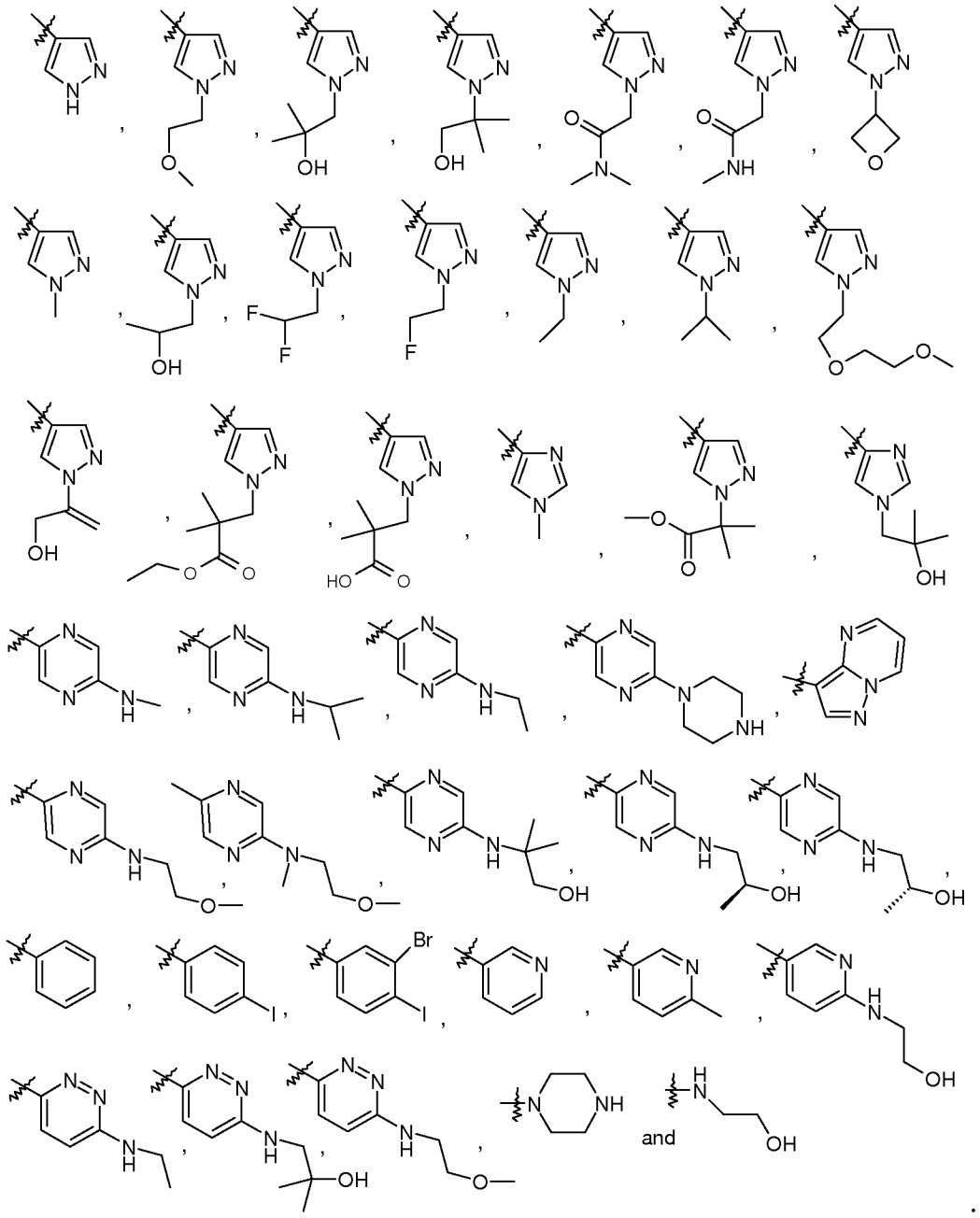
R^3 is selected from



and

R^4 is hydrogen,

R^5 is selected from



;

or pharmaceutically acceptable salts thereof.

11. A compound according to claim 10 above, wherein:

R^2 is cyclopropyl;

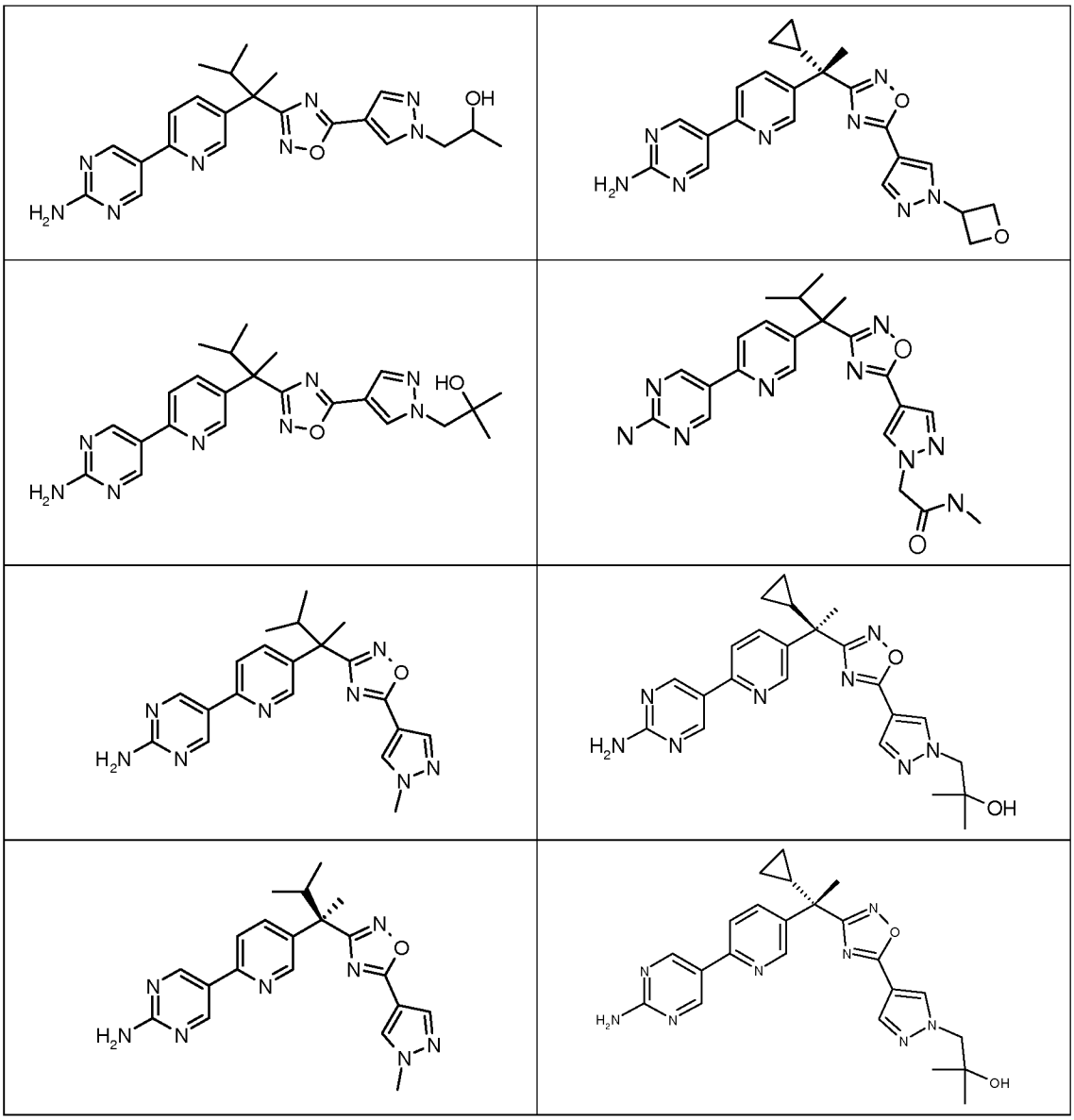
or a pharmaceutically acceptable salt thereof.

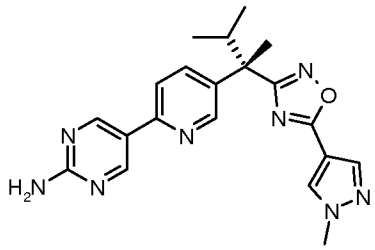
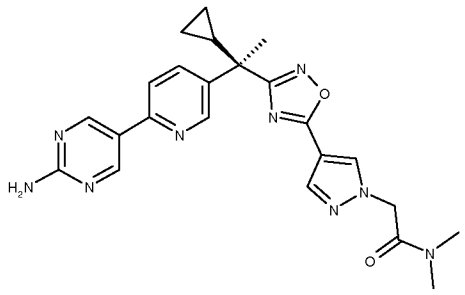
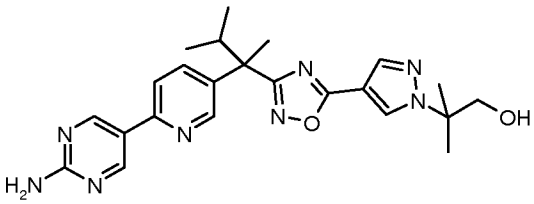
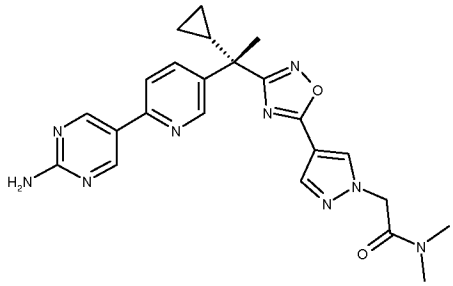
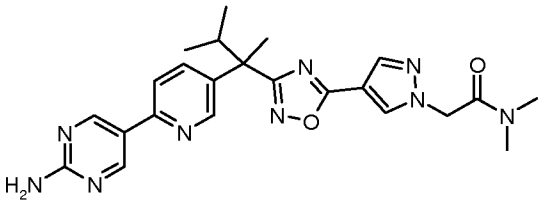
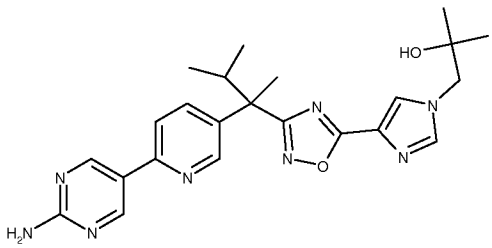
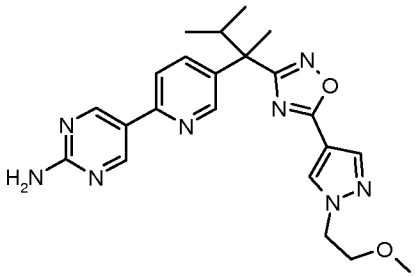
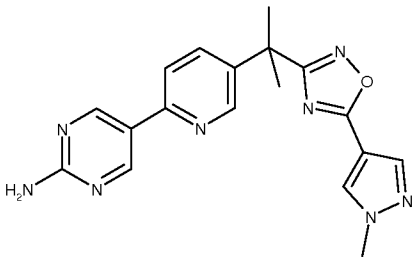
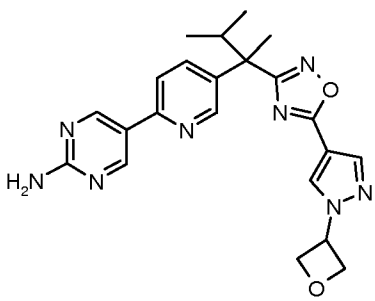
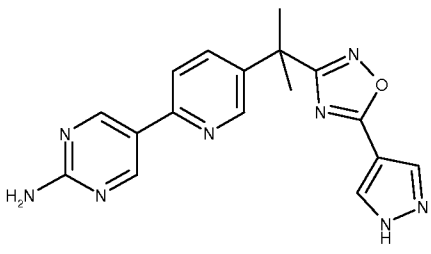
12. A compound according to claim 10, wherein:

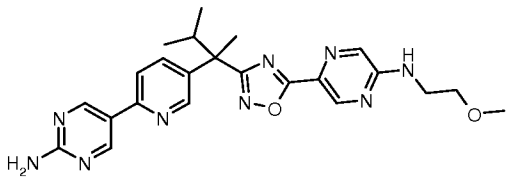
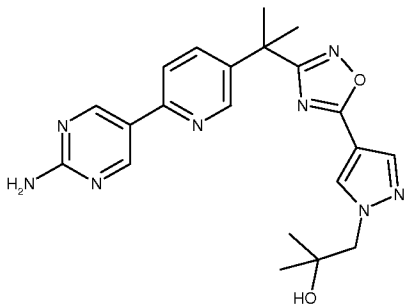
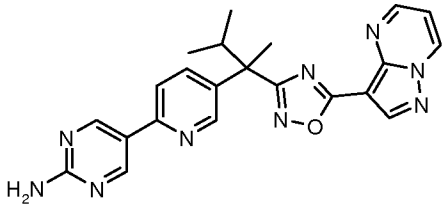
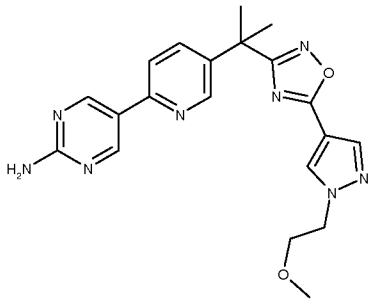
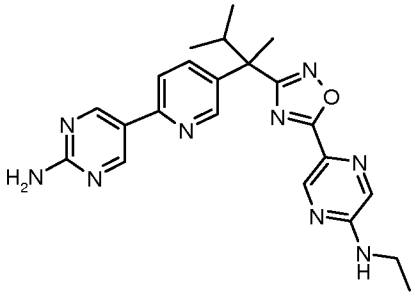
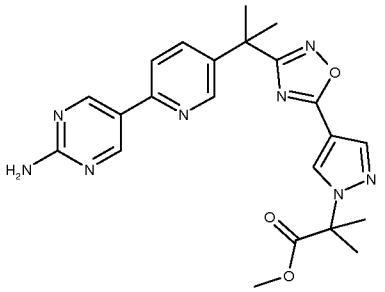
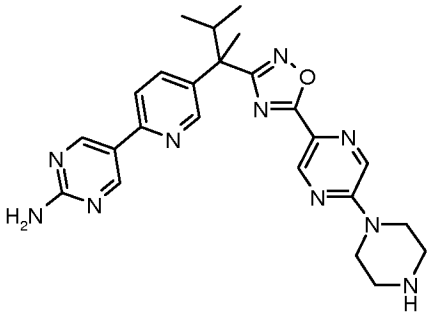
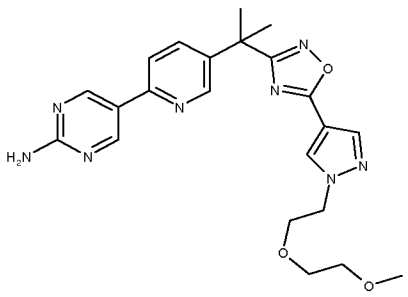
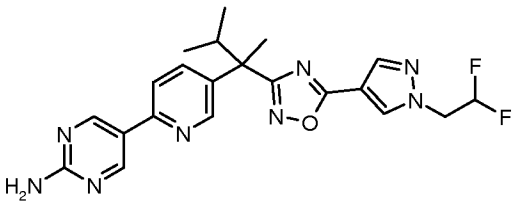
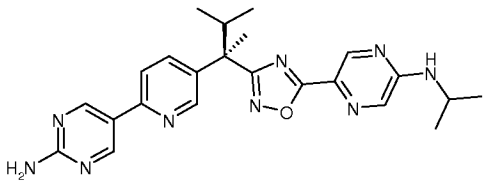
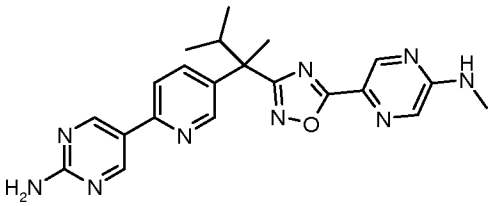
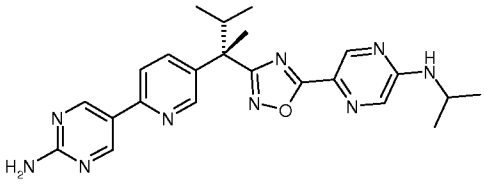
R^2 is selected from methyl and isopropyl;

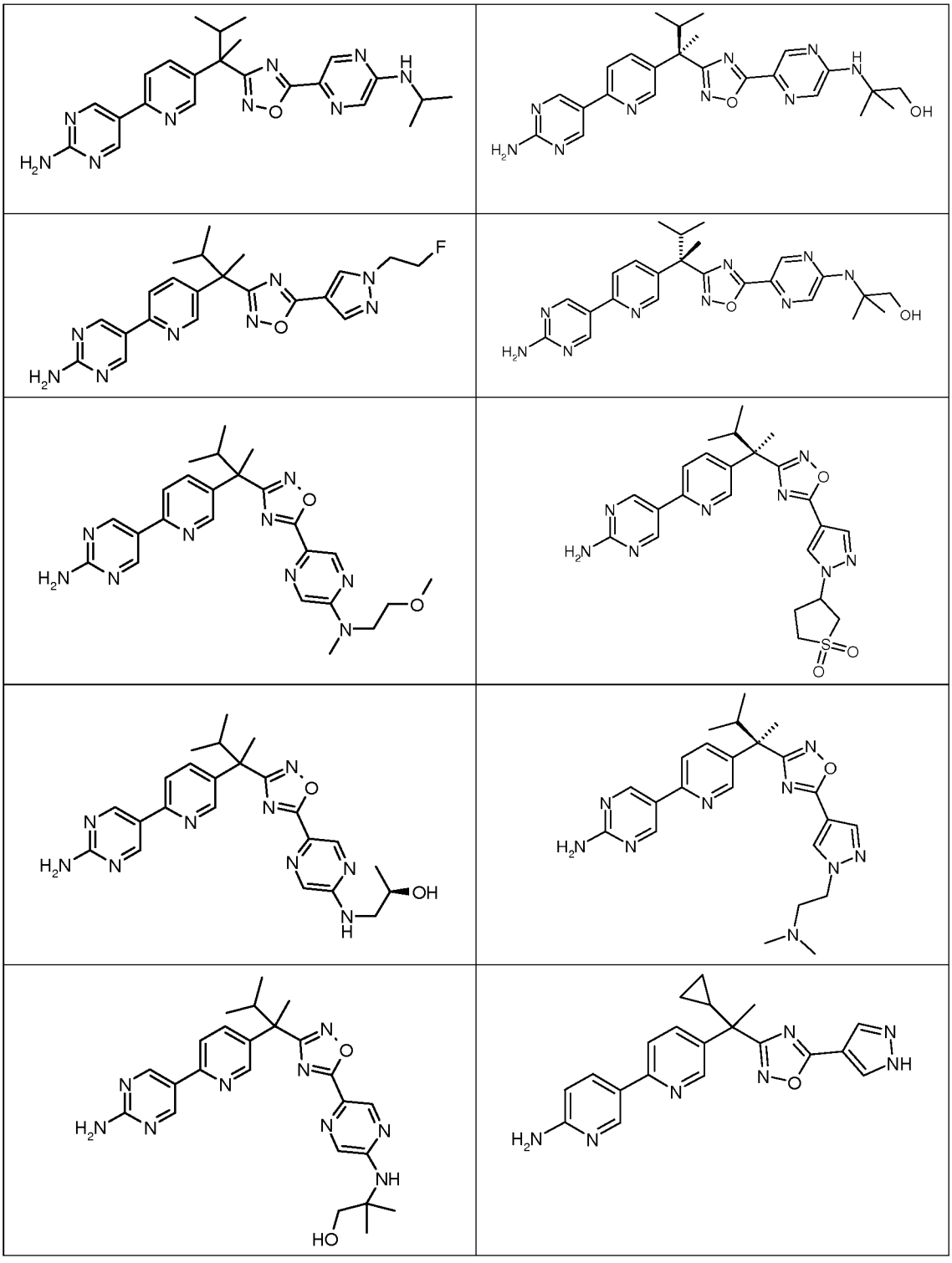
or a pharmaceutically acceptable salt thereof.

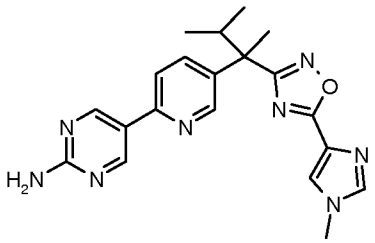
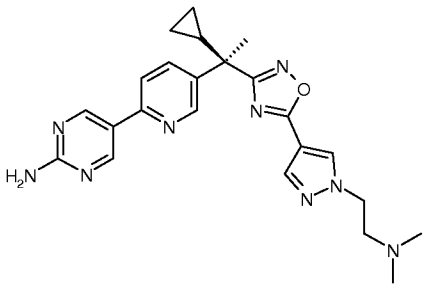
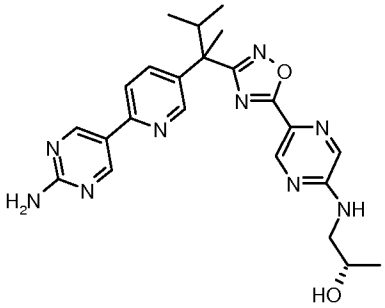
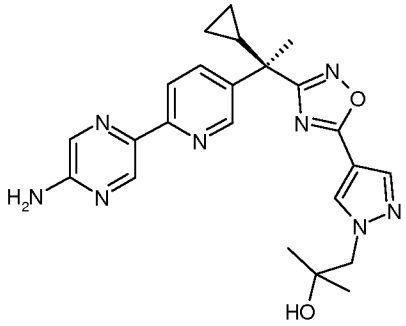
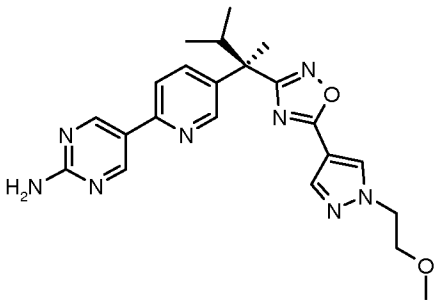
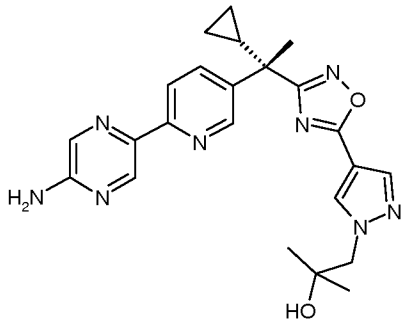
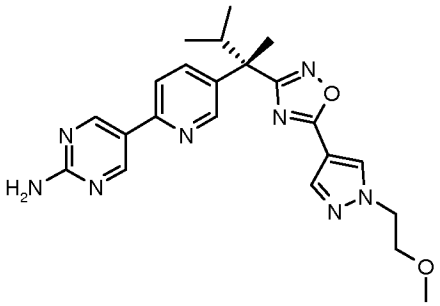
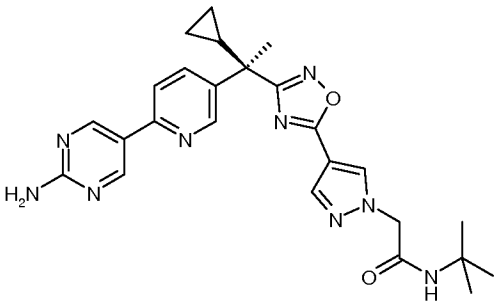
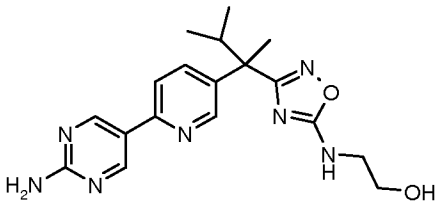
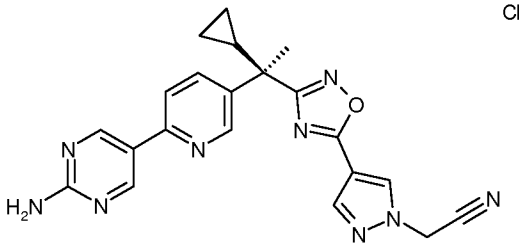
13. A compound selected from a group consisting of:

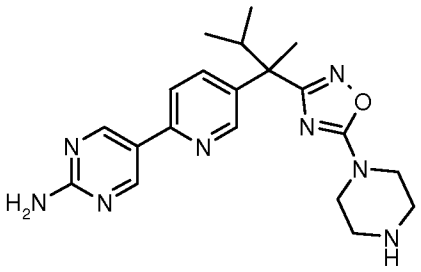
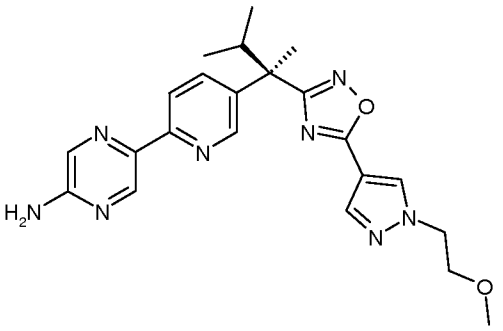
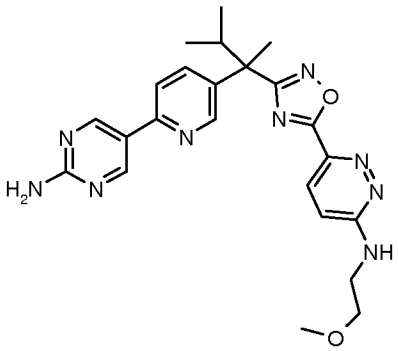
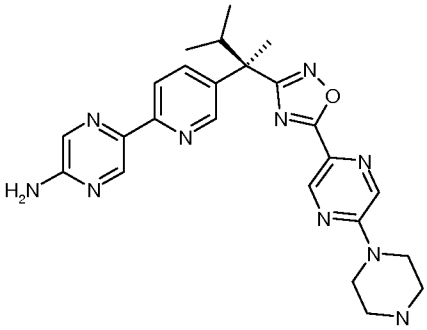
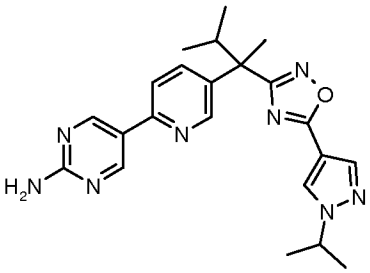
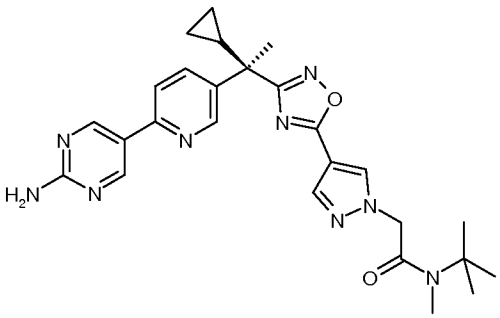
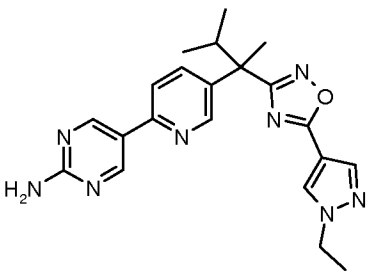
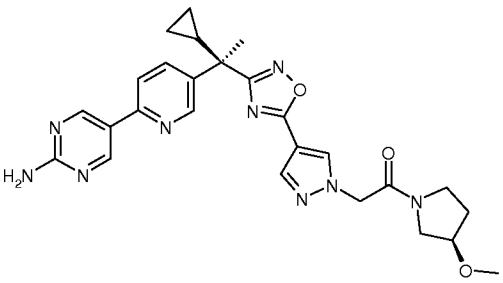
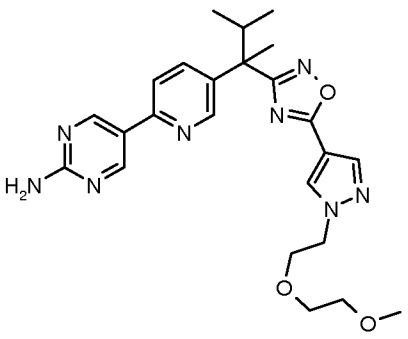
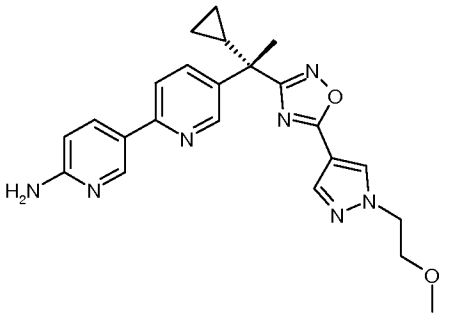


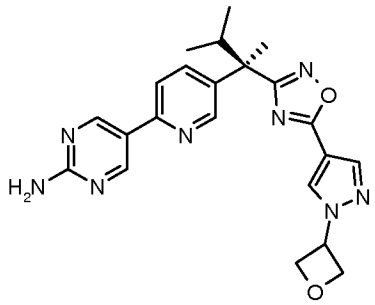
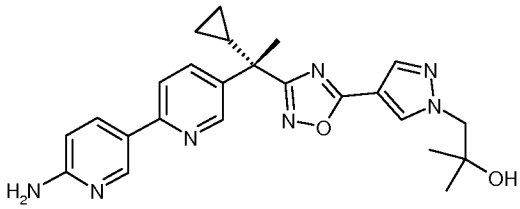
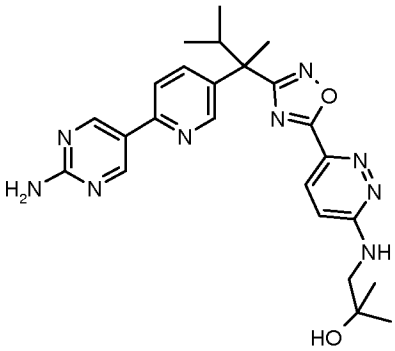
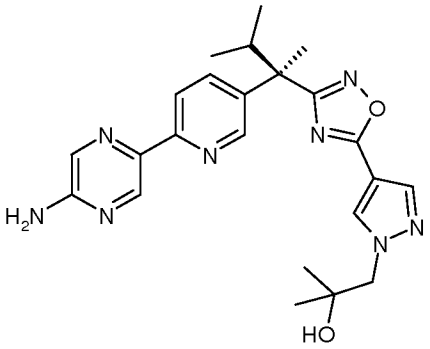
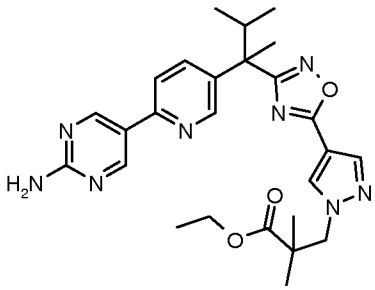
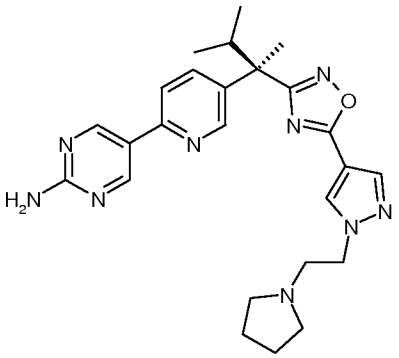
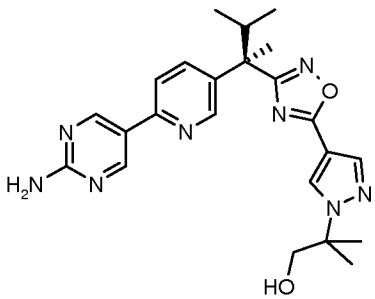
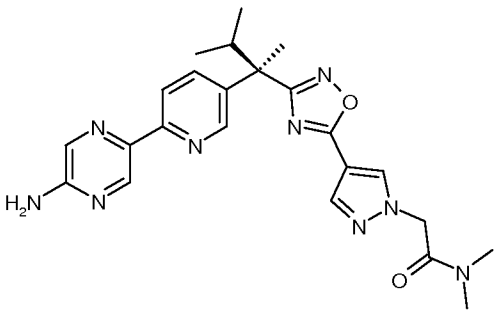
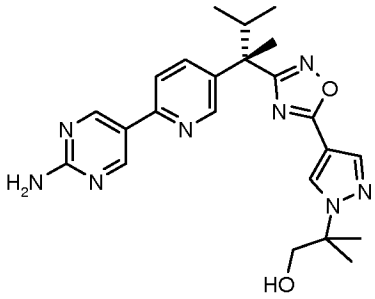
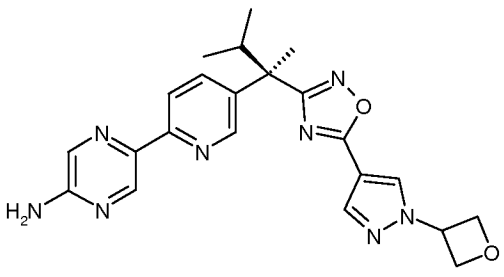
	
	
	
	
	

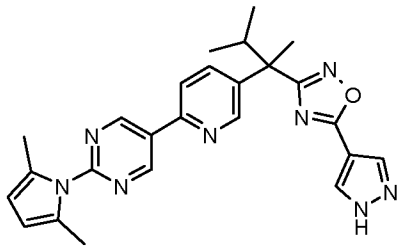
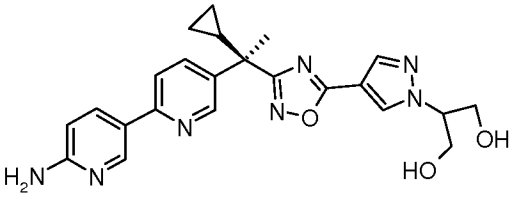
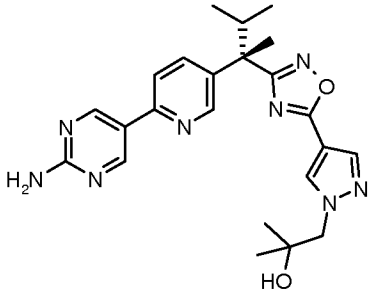
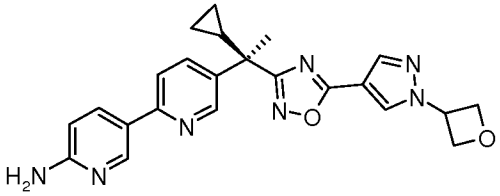
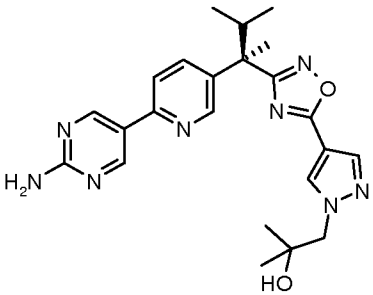
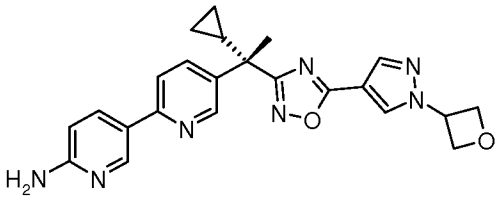
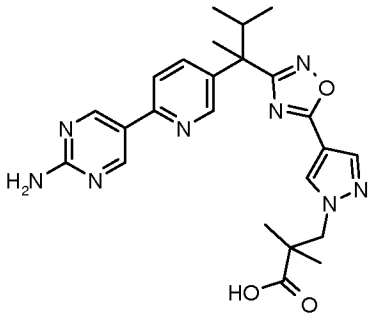
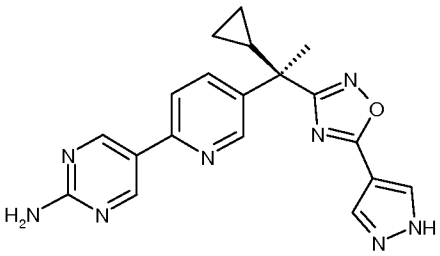
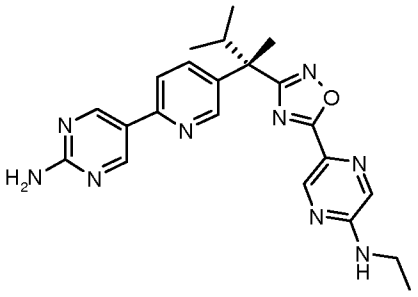
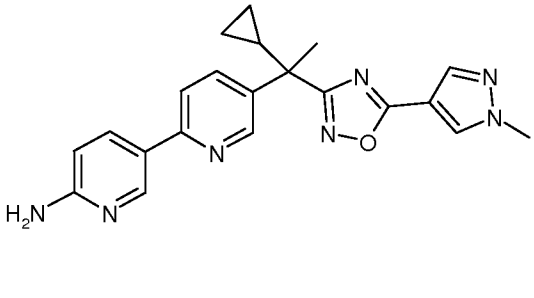
	
	
	
	
	
	

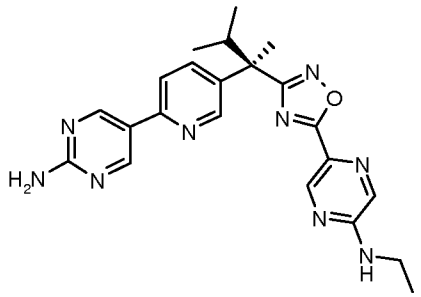
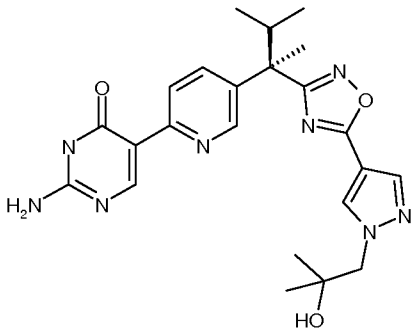
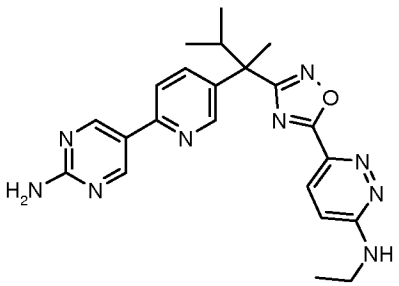
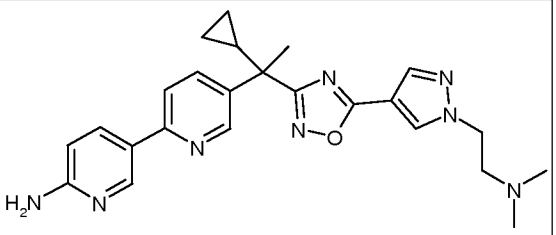
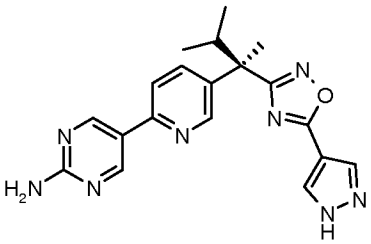
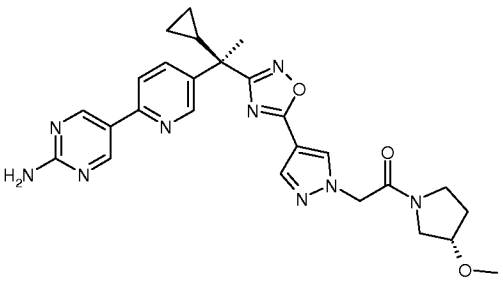
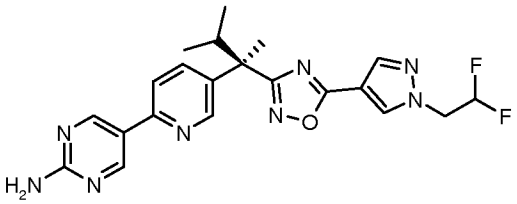
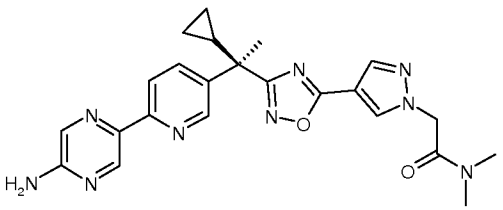
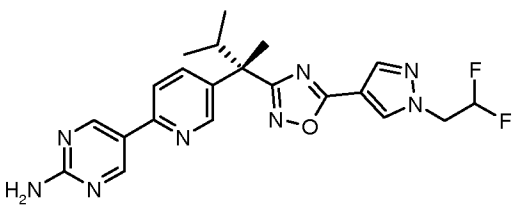
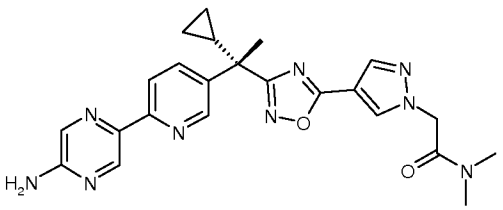


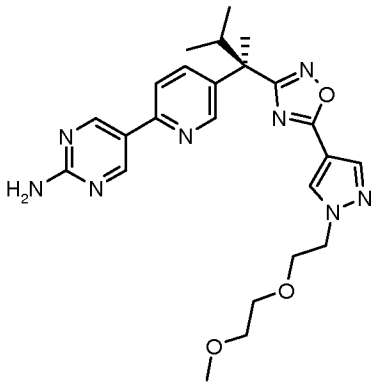
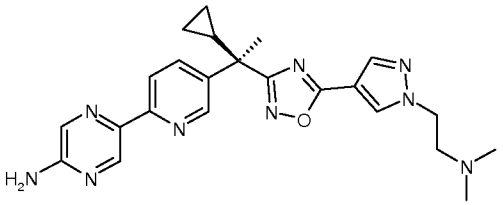
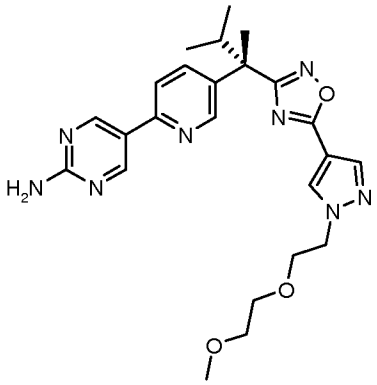
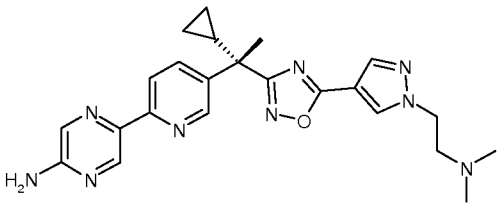
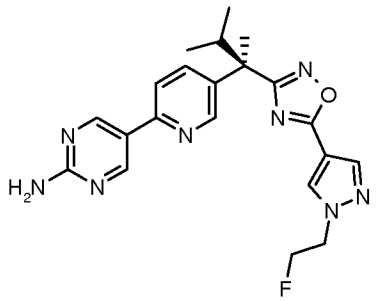
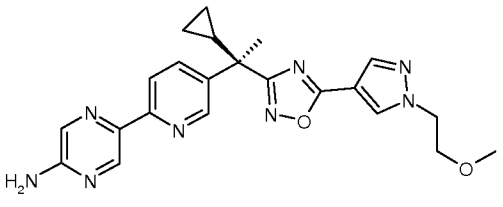
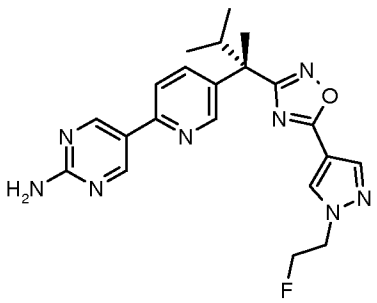
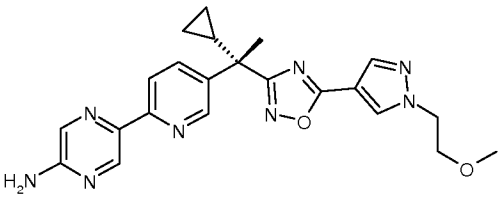
	Chiral 
	
	
	
	Chiral 

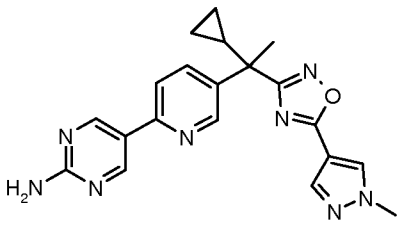
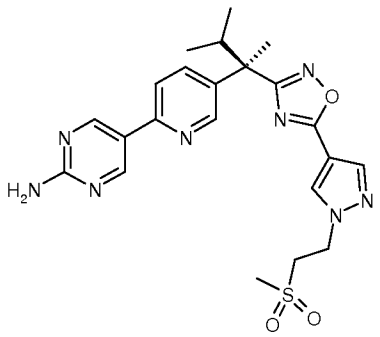
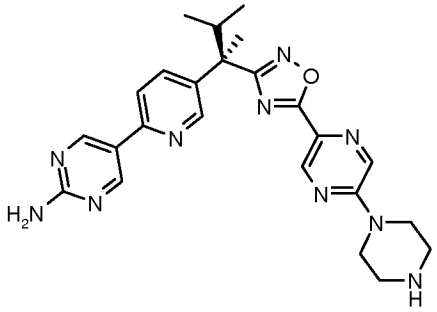
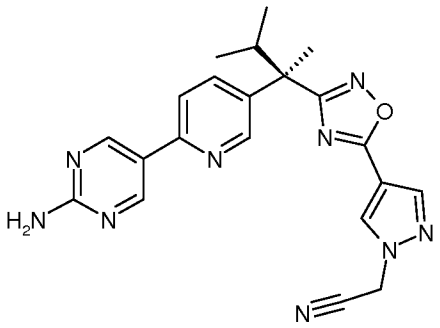
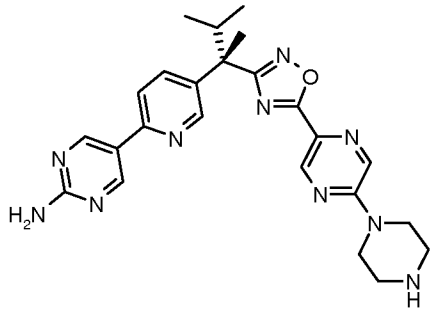
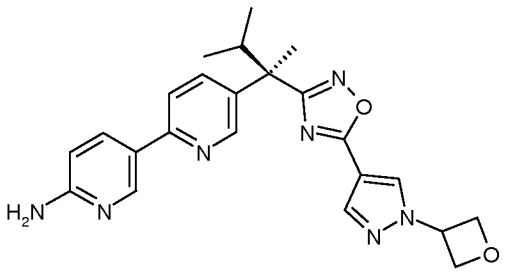
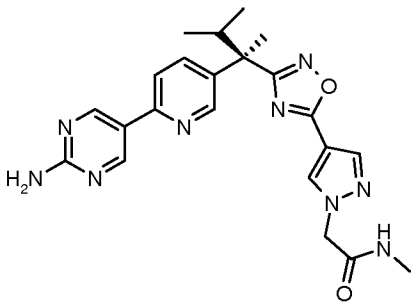
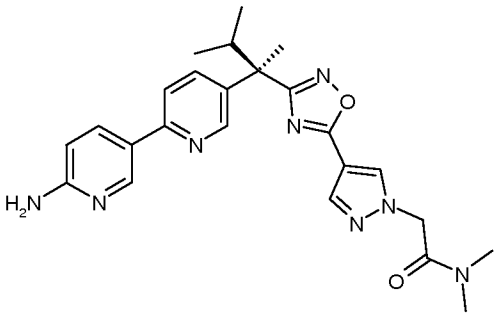
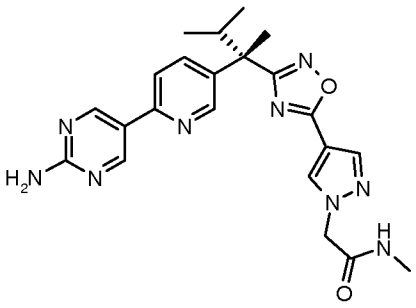
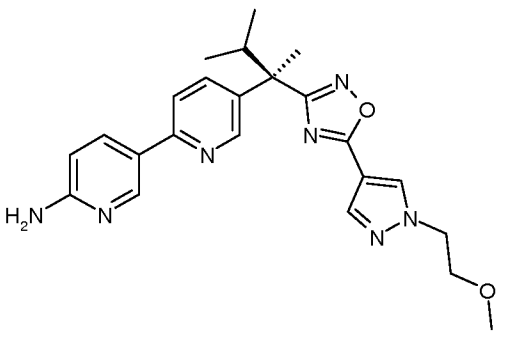
	
	
	
	
	

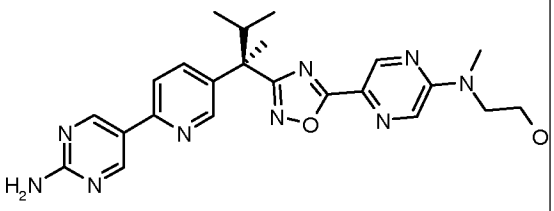
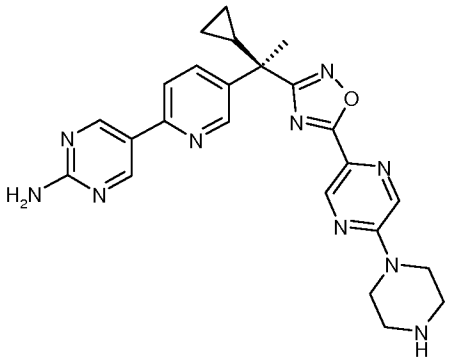
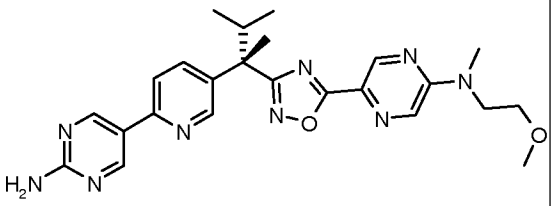
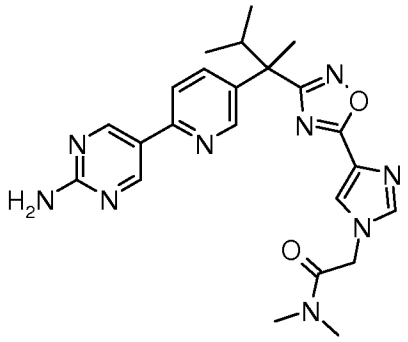
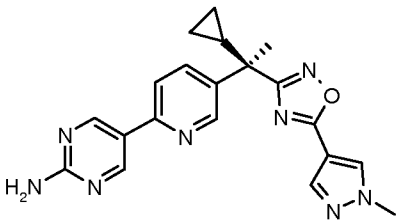
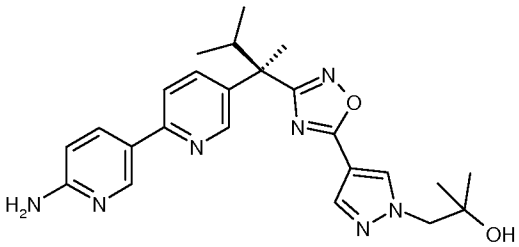
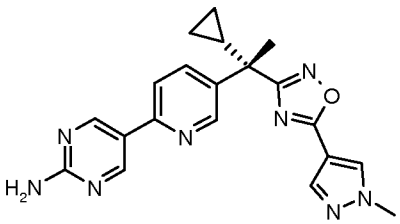
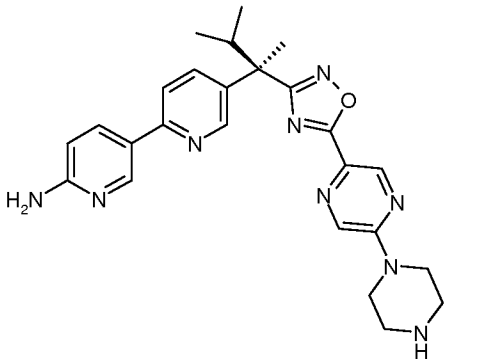
	
	
	
	
	

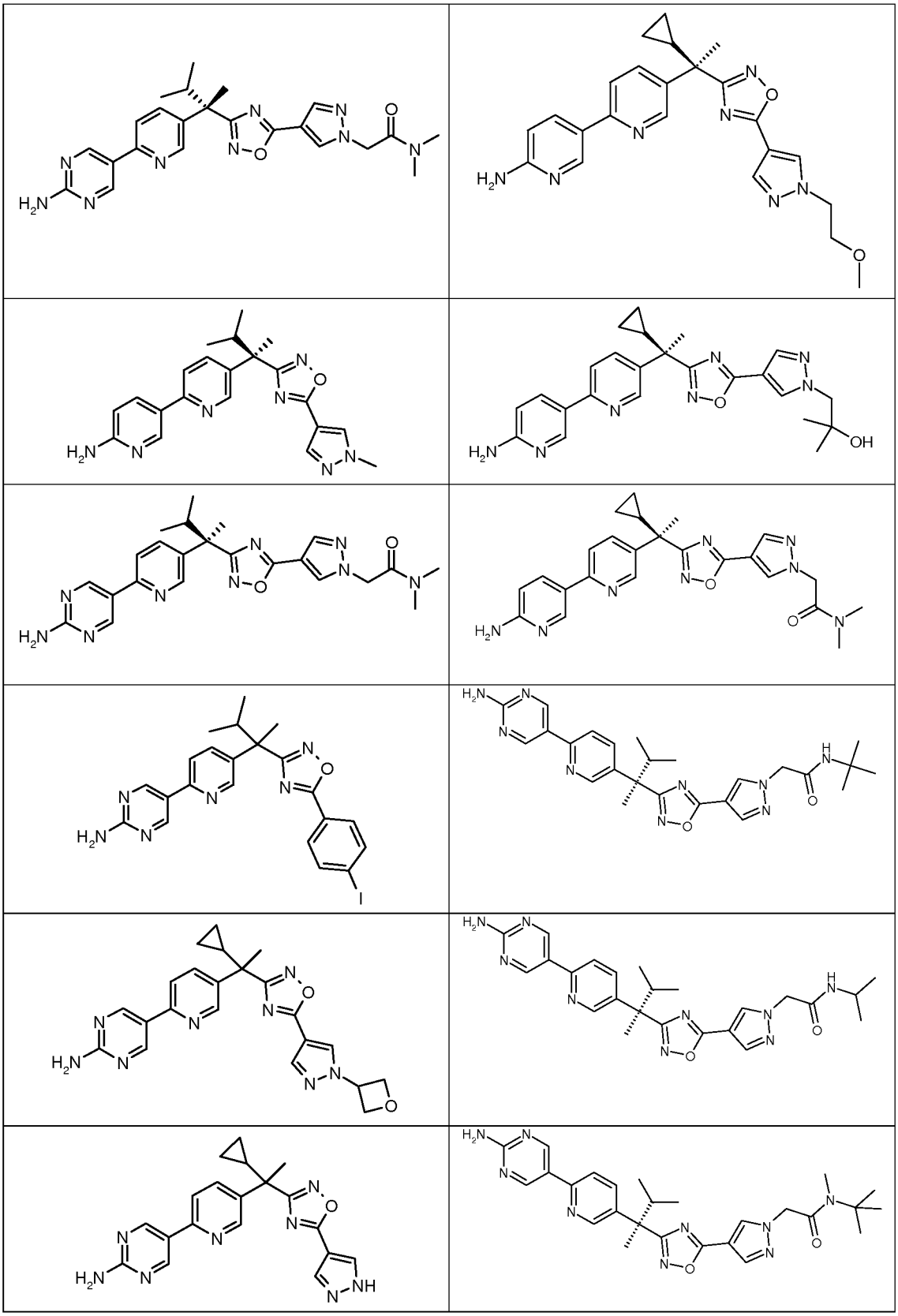
	
	
	
	
	

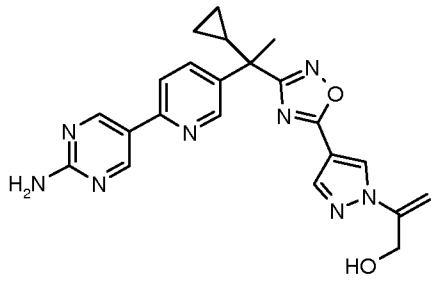
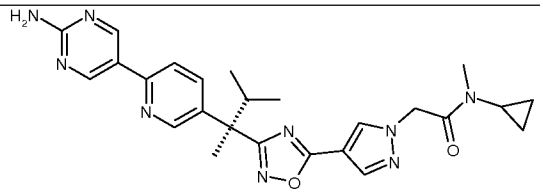
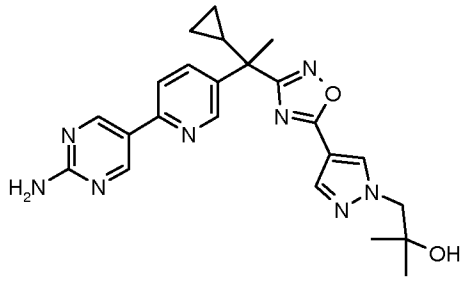
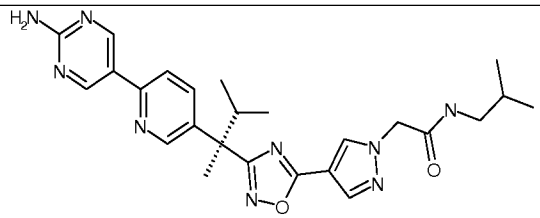
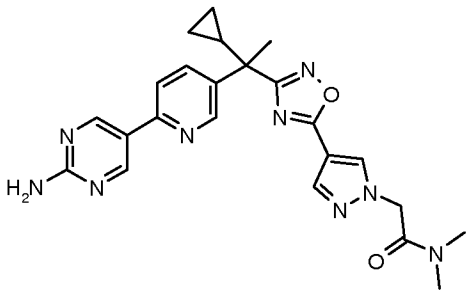
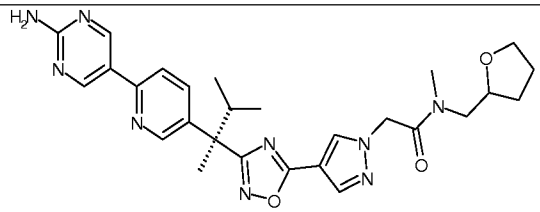
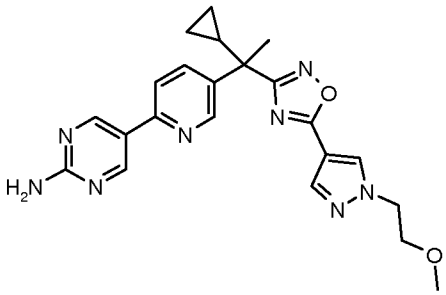
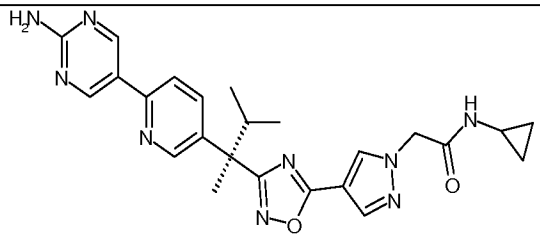
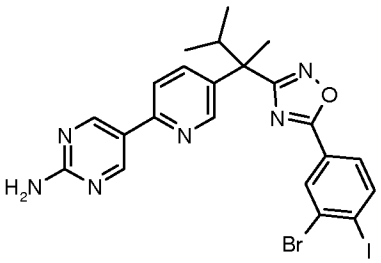
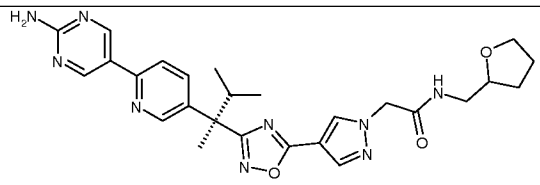
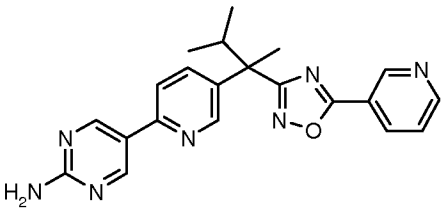
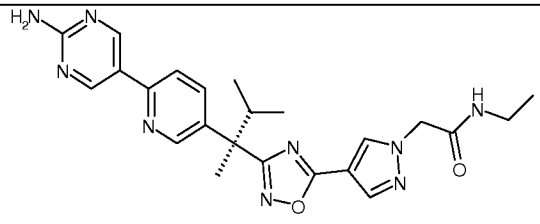
	
	
	
	
	

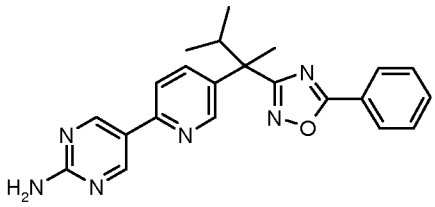
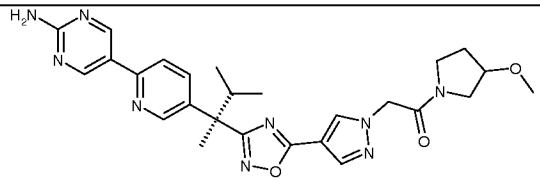
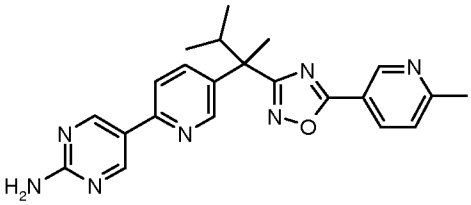
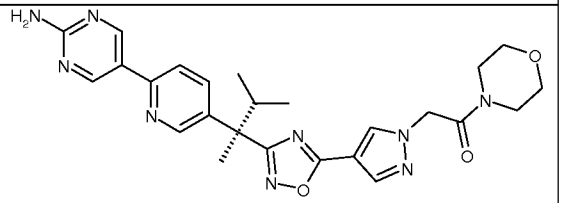
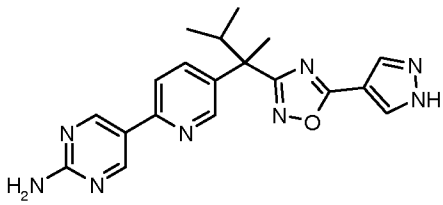
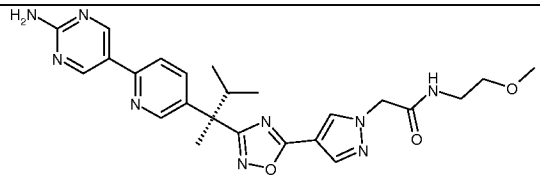
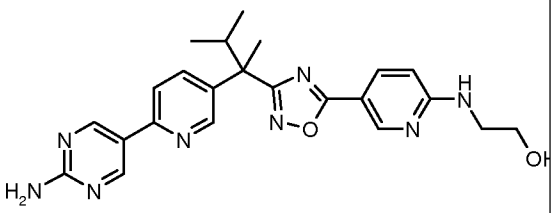
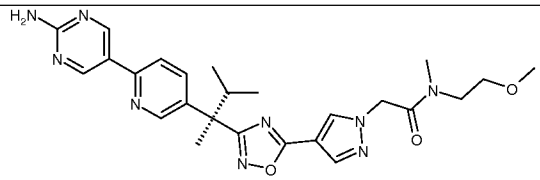
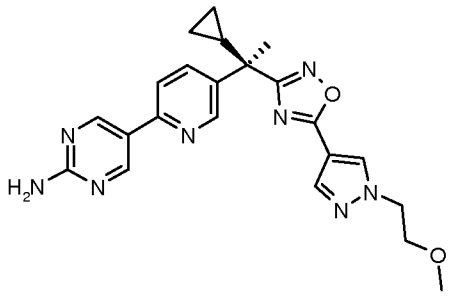
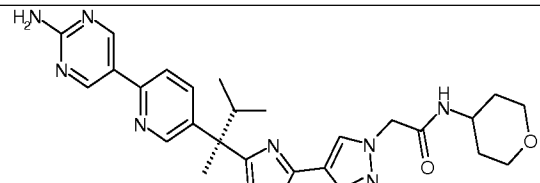
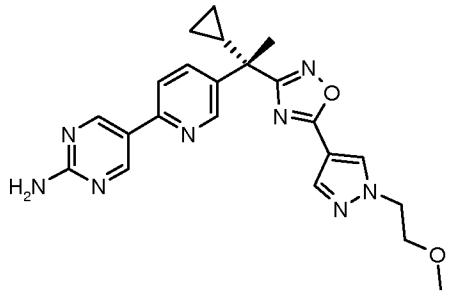
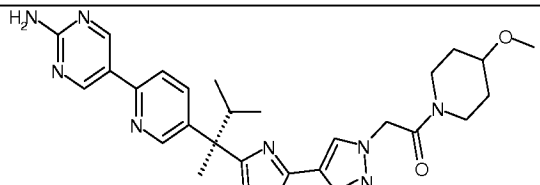
	
	
	
	

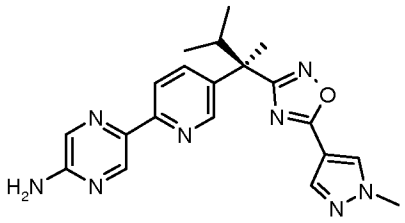
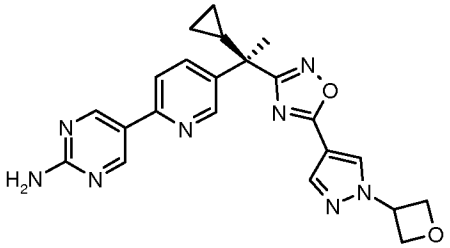
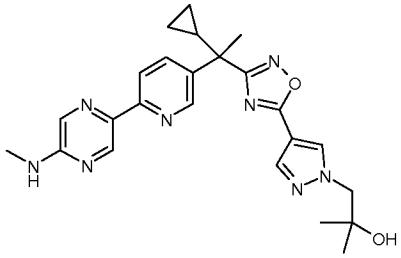
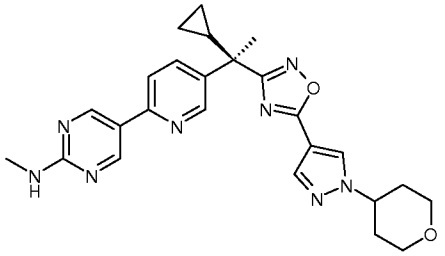
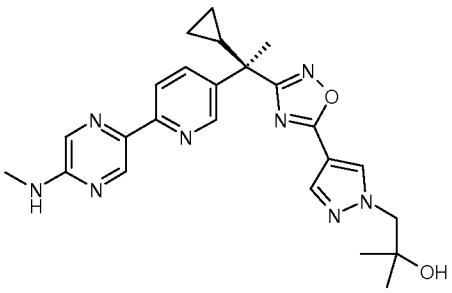
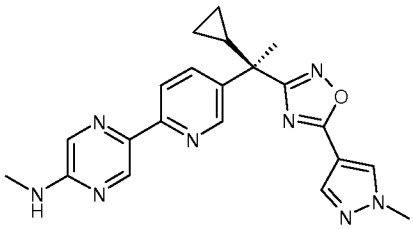
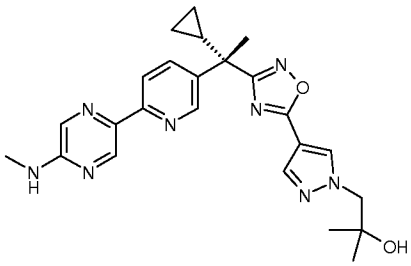
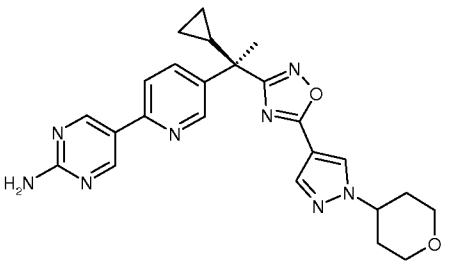
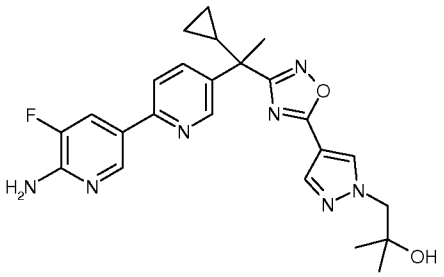
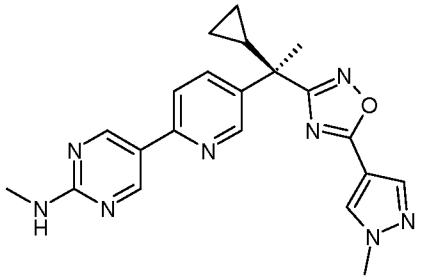
	
	
	
	
	

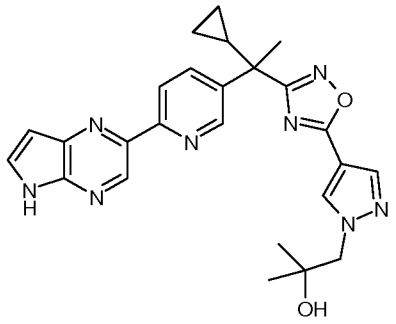
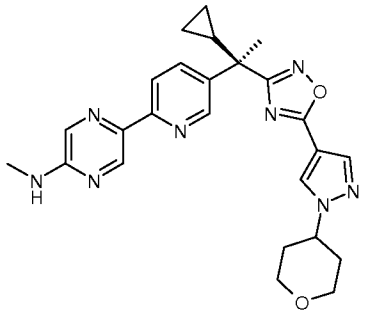
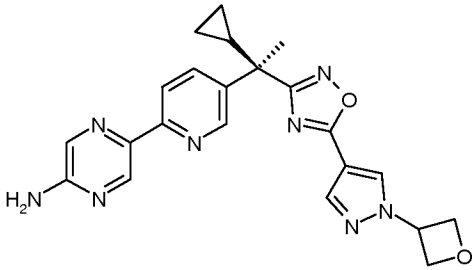
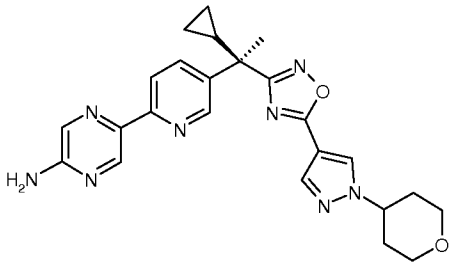
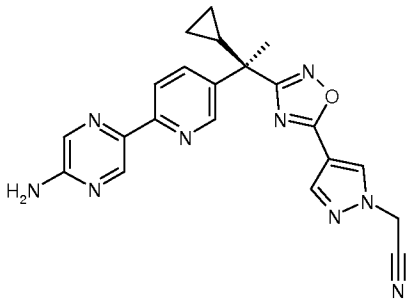
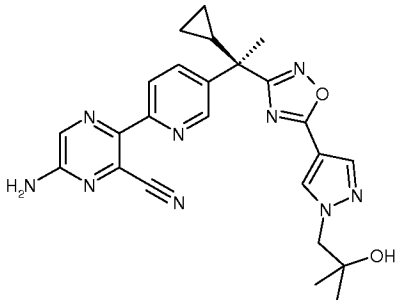
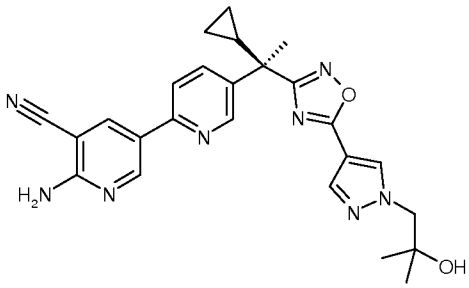
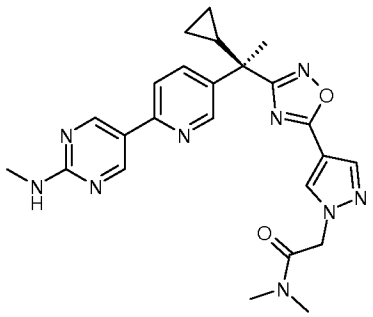
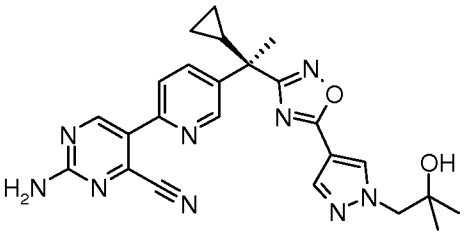
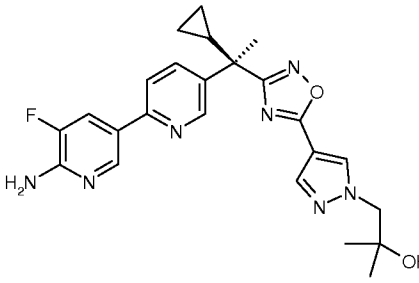
	
	
	
	

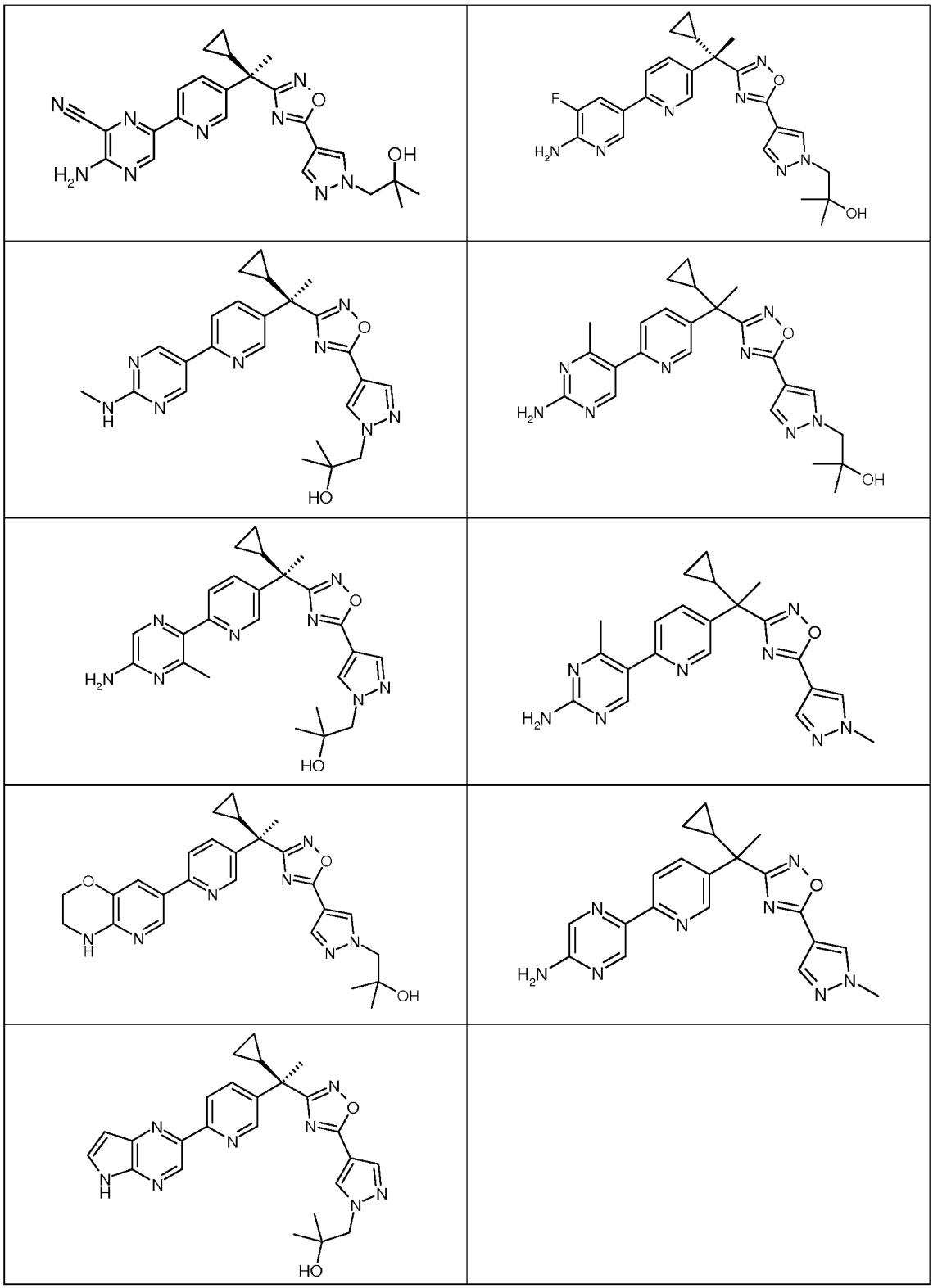


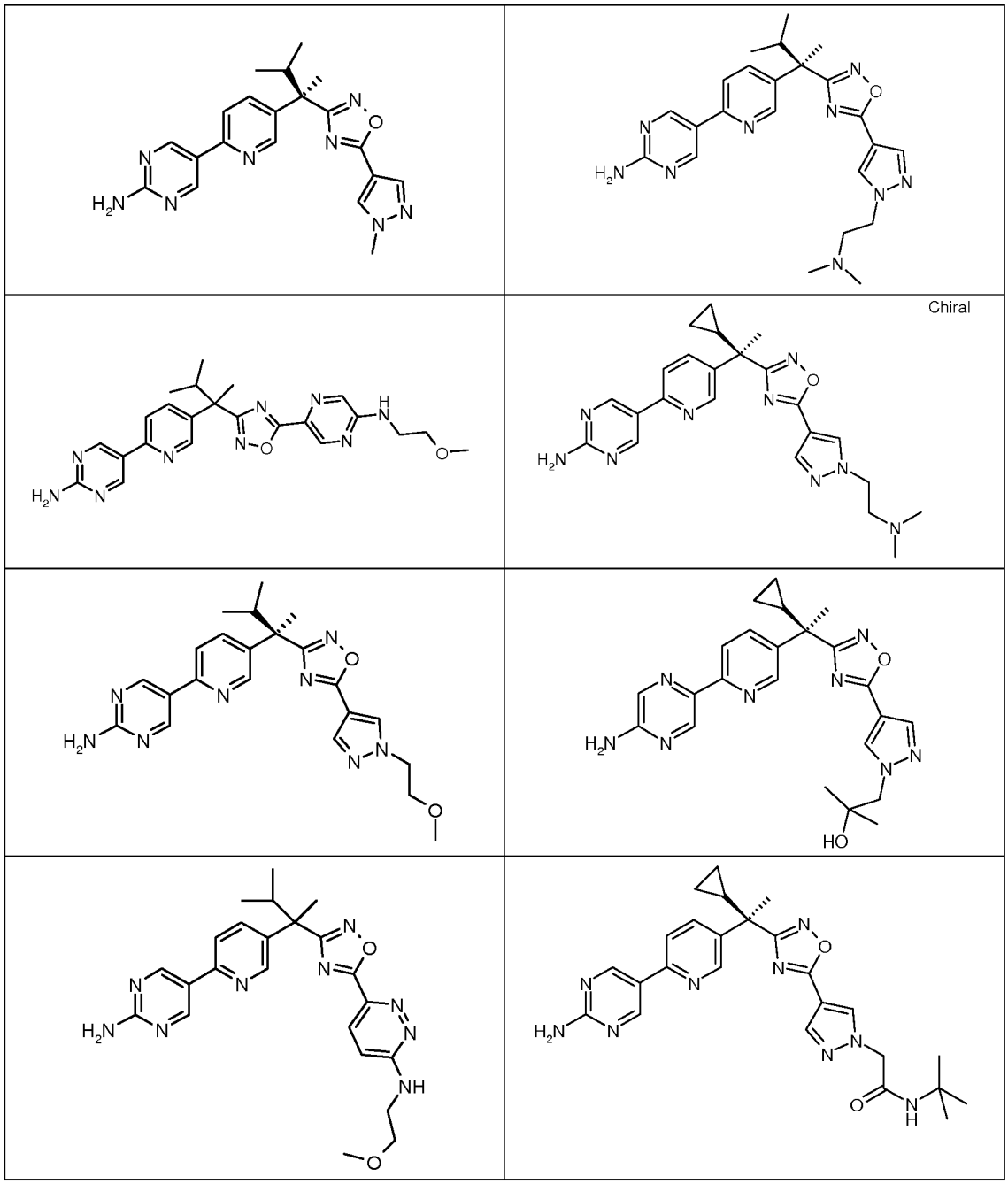
	
	
	
	
	

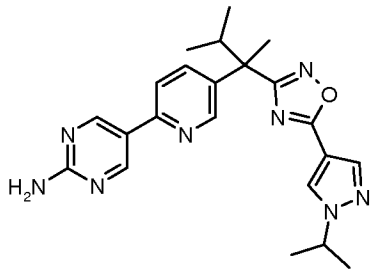
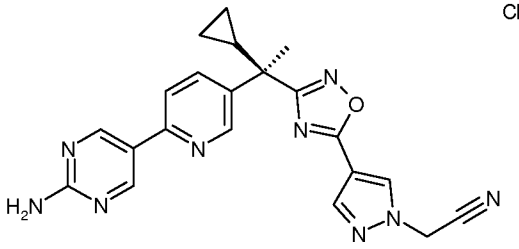
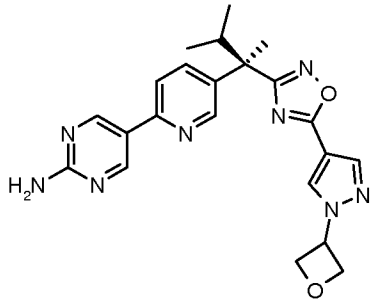
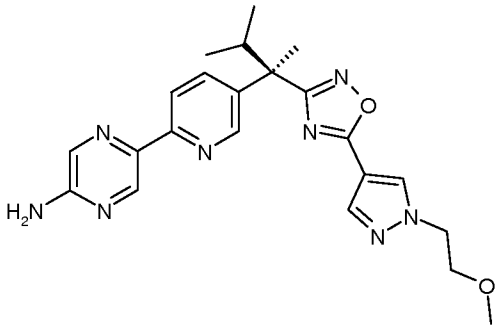
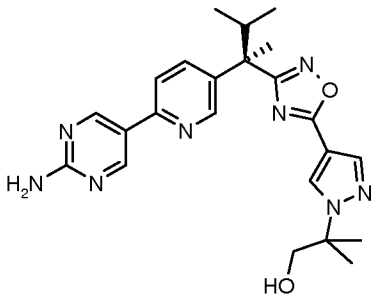
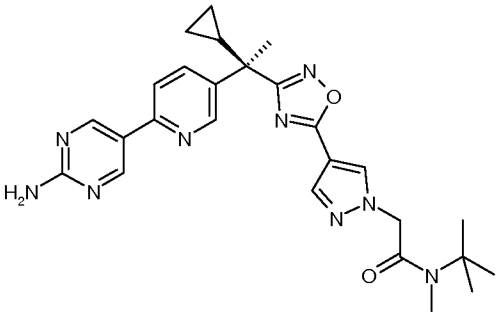
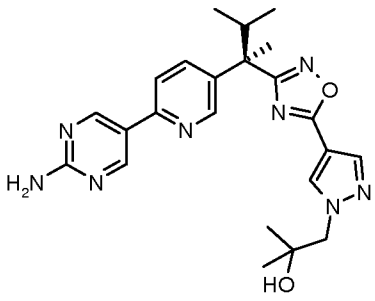
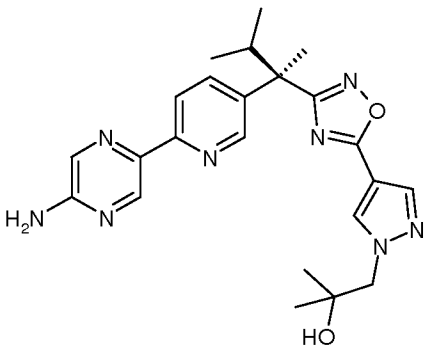
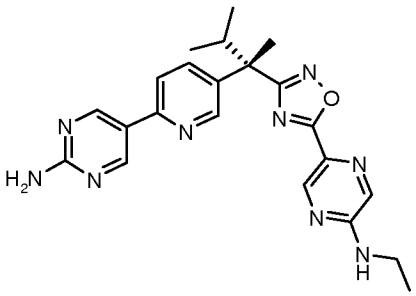
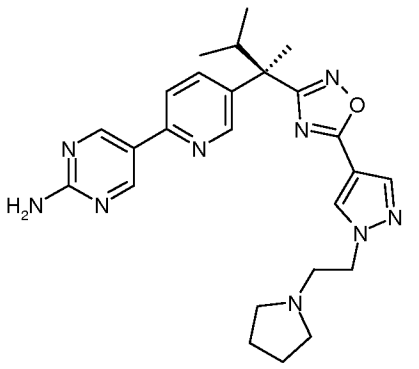
	
	
	
	
	

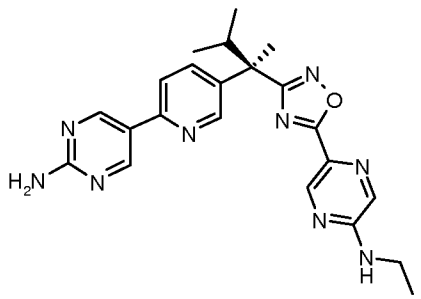
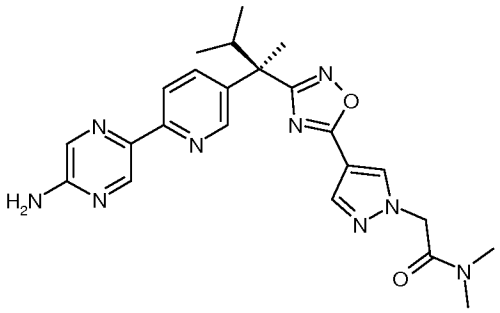
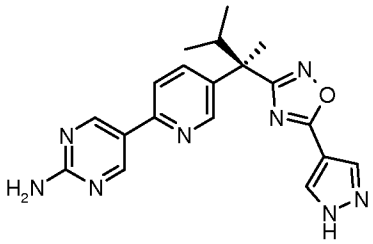
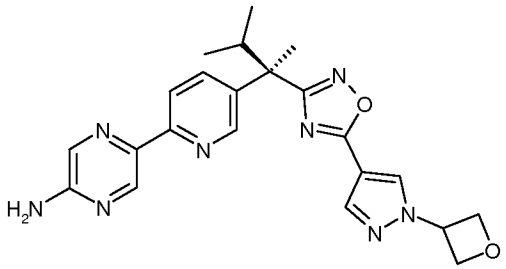
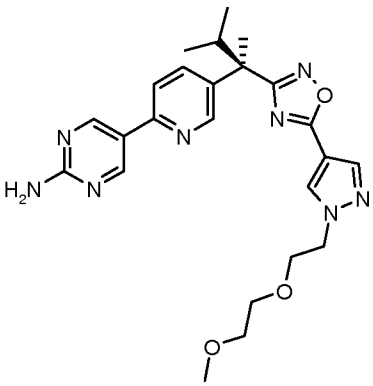
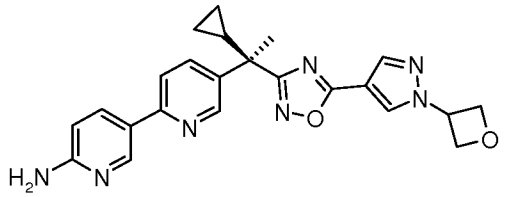
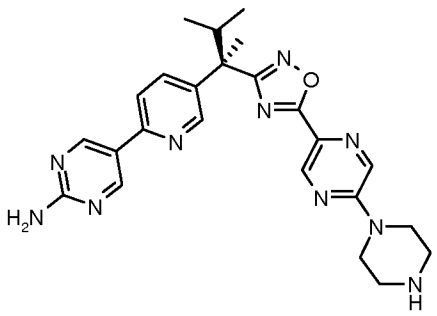
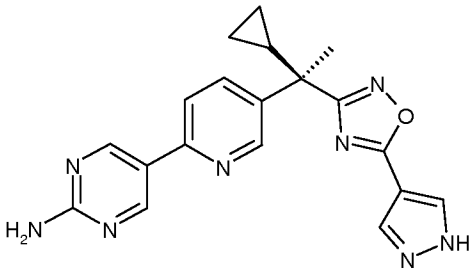
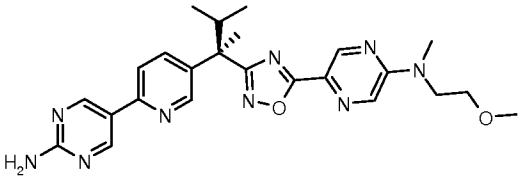
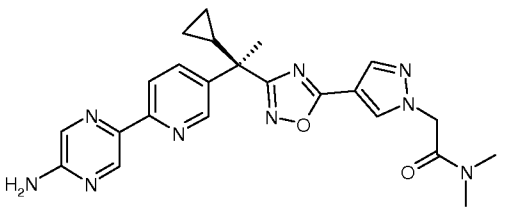


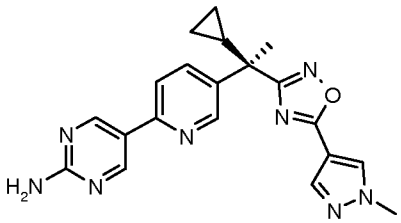
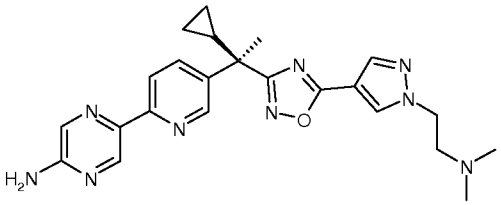
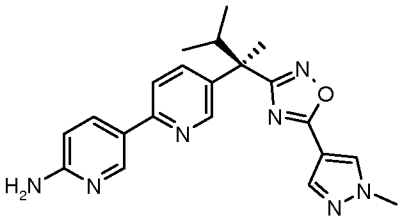
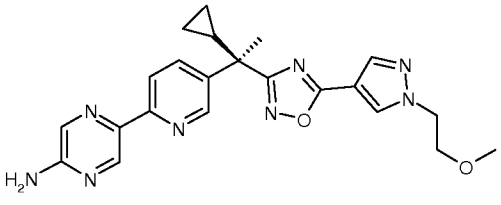
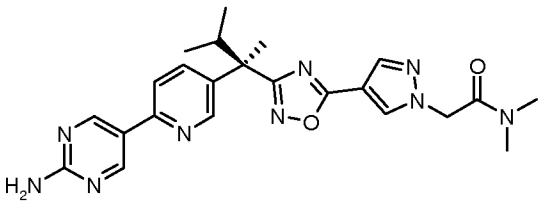
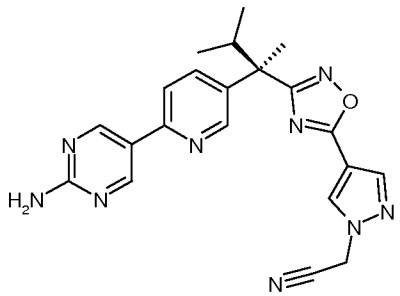
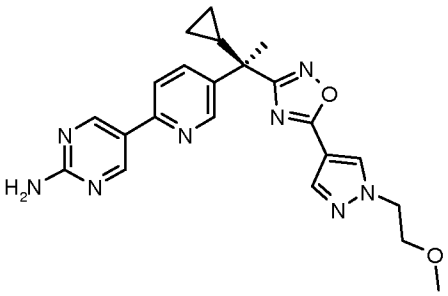
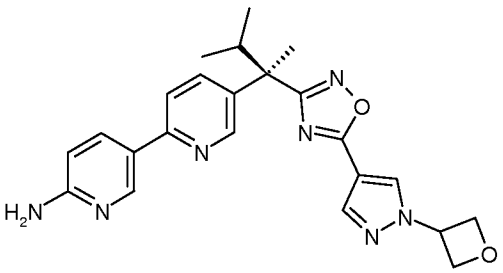
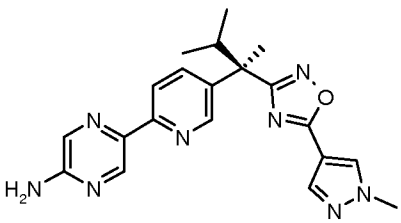
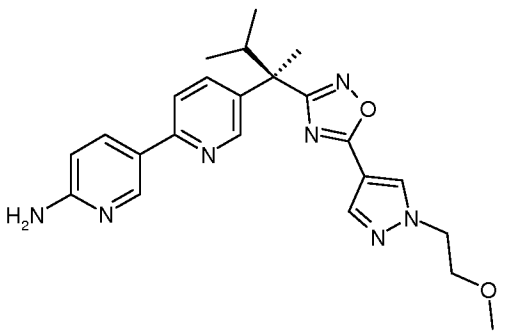
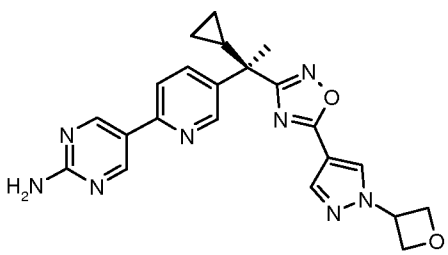
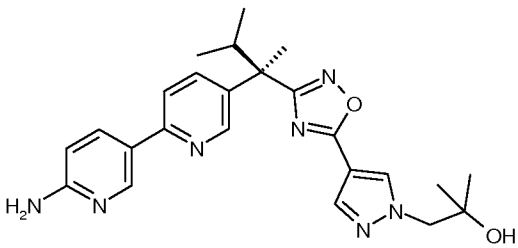
or pharmaceutically acceptable salts thereof.

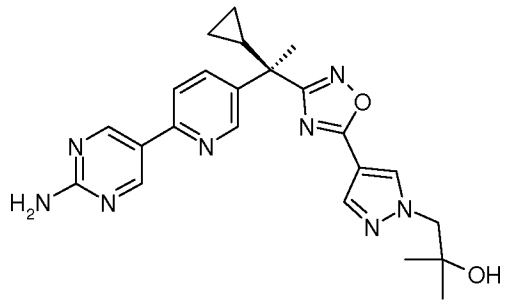
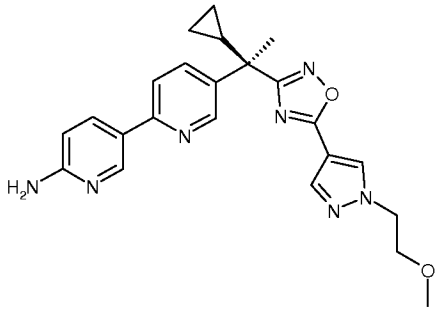
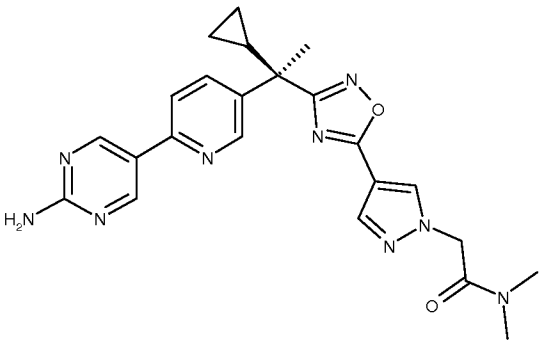
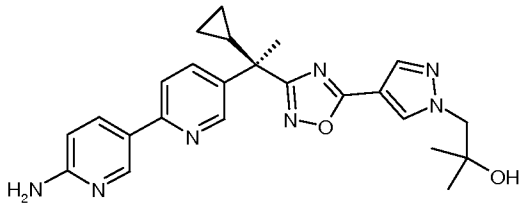
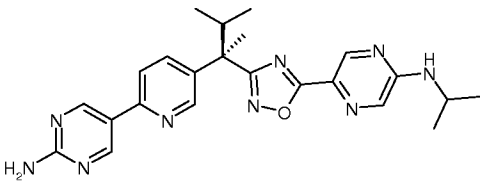
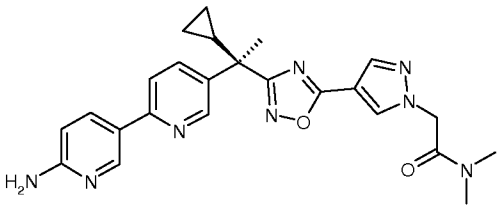
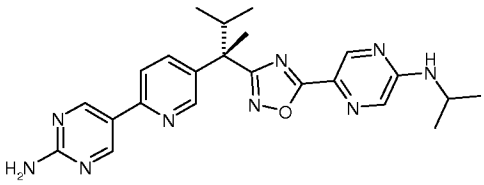
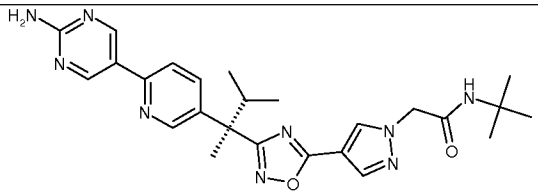
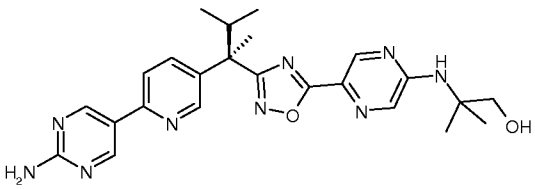
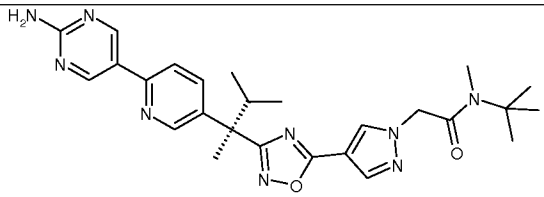
14. A compound according to claim 13, selected from a group consisting of:

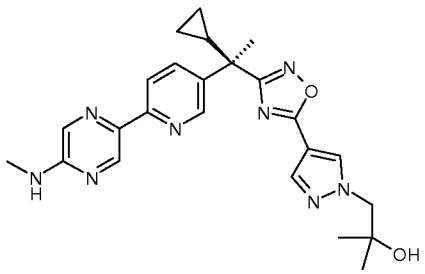
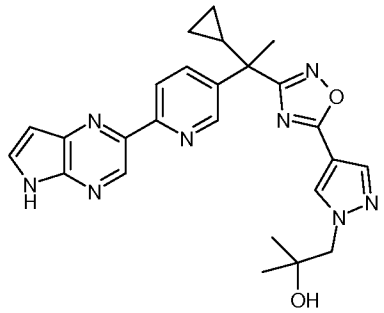
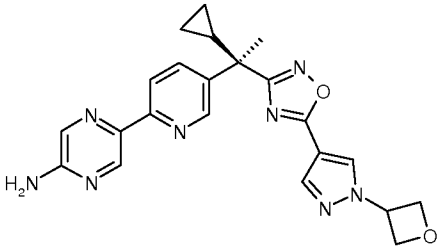
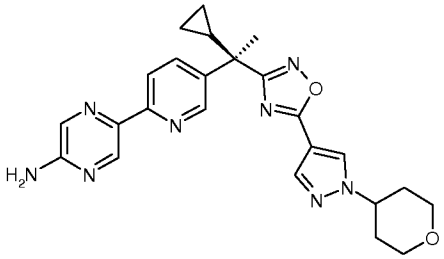
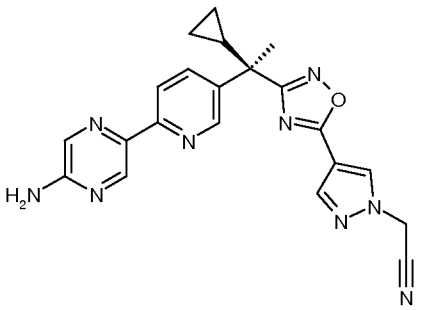
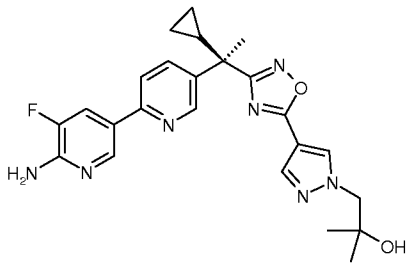
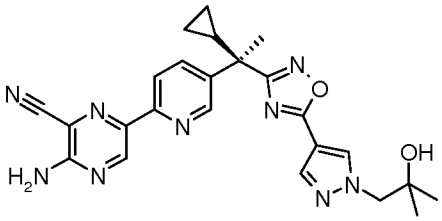
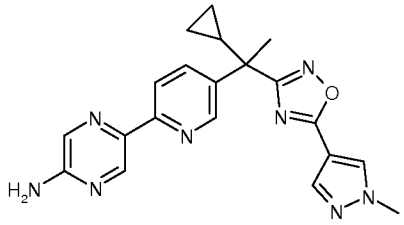
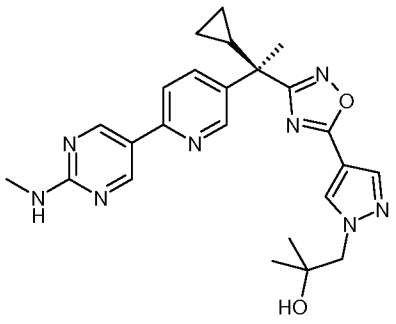
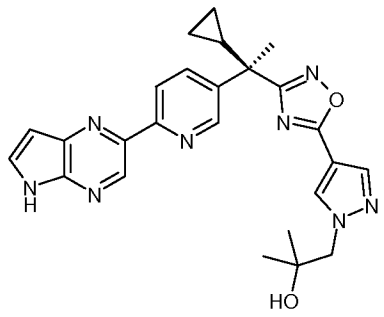


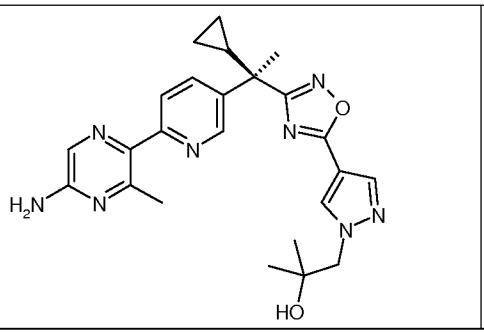
	Chira 
	
	
	
	

or pharmaceutically acceptable salts thereof.

15. A pharmaceutical composition comprising a compound according to any of the claims 1 to 14, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient and/or carrier.

16. A method of treating a leukotriene-mediated disorder comprising administering an effective amount of a compound according to any of claims 1 to 14 or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

17. The method of claim 16, wherein said leukotriene-mediated disorder is selected from cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer.

18. The method of claim 17, wherein said leukotriene-mediated disorder is Atherosclerosis.

19. A compound of any of claims 1 to 14 or a pharmaceutically acceptable salt thereof for use as a medicament.

20. A compound of any of claims 1 to 14 or a pharmaceutically acceptable salt thereof for treatment of a leukotriene-mediated disorder.

21. A compound of any of claims 1 to 14 or a pharmaceutically acceptable salt thereof for treatment of a leukotriene-mediated disorder selected from cardiovascular, inflammatory, allergic, pulmonary and fibrotic diseases, renal diseases and cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/052252

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 A61K31/4245 A61P9/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/030369 A1 (MERCK & CO INC [US]; OGAWA ANTHONY [US]; UJJAINWALLA FEROZE [US]; VAND) 13 March 2008 (2008-03-13) claim 1	1-21
A	WO 2007/056228 A2 (AMIRA PHARMACEUTICALS INC [US]; HUTCHINSON JOHN H [US]; PRASIT PETPIBO) 18 May 2007 (2007-05-18) claim 1	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 2011	02/11/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/052252

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008030369 A1	13-03-2008	AU 2007293373 A1	13-03-2008
		CA 2666686 A1	13-03-2008
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