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(54) **AMIDE DERIVATIVES AS FLT-3 MODULATORS**

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(57) **ABSTRACT**

The invention provides methods and compositions for treating conditions mediated by flt-3 wherein derivatives of amide compounds are employed. The invention also provides methods of using the compounds and/or compositions in the treatment of a variety of diseases and unwanted conditions in subjects.

AMIDE DERIVATIVES AS FLT-3 MODULATORS

[0001] This application claims priority to U.S. Provisional Application No. 60/520,273, filed Nov. 13, 2003, U.S. Provisional Application No. 60/527,094, filed Dec. 3, 2003, U.S. Provisional Application No. 60/531,243, filed Dec. 18, 2003, and U.S. Provisional Application No. 60/531,082, filed Dec. 18, 2003, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins, and can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs). Growth factor receptors with PTK activity are known as receptor tyrosine kinases. Protein receptor tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family, which includes Bcr-Abl tyrosine kinase, can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain. The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT-3, and stem cell or steel factor receptor (c-kit). A more complete listing of the known Protein receptor tyrosine kinases subfamilies is described in Plowman et al., DN&P, 7(6):334-339 (1994), which is incorporated by reference, including any drawings, as if fully set forth herein. Furthermore, for a more detailed discussion of "non-receptor tyrosine kinases", see Bolen, Oncogene, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

[0003] Hematologic cancers, also known as hematologic or hematopoietic malignancies, are cancers of the blood or bone marrow; including leukemia and lymphoma. Acute myelogenous leukemia (AML) is a clonal hematopoietic stem cell leukemia that represents ~90% of all acute leukemias in adults. See e.g., Lowenberg et al., *N. Eng. J. Med.* 341:1051-62 (1999). While chemotherapy can result in complete remissions, the long term disease-free survival rate for AML is about 14% with about 7,400 deaths from AML each year in the United States. The single most commonly mutated gene in AML is FLT3 kinase. See e.g., Abu-Duhier et al., *Br. J. Haemotol.* 111:190-05 (2000); Kiyoi et al., *Blood* 93:3074-80 (1999); Kottaridis et al., *Blood* 98:1752-59 (2001); Stirewalt et al., *Blood* 97:3589-95 (2001). Such mutations also indicate a poor prognosis for the patient.

[0004] The compounds provided by the present invention are urea derivatives of substituted aryls and hetroaryls, e.g., isoxazoles, pyrazoles and isothiazoles. Urea derivatives of pyrazoles have been reported to be selective p38 kinase inhibitors by Dumas, J., et al., *Bioorg. Medic. Chem. Lett.* 10:2051-2054 (2000). Oxazoles and isopyrazoles are suggested as blockers of cytokine production in WO 00/43384 published 27 Jul. 2000. Urea derivatives of isoxazole and pyrazoles are described as inhibitors of RAF kinase in WO 99/32106 published 1 Jul. 1999. Such compounds are also described as p38 kinase inhibitors by Dumas, J., et al., *Bioorg. Medic. Chem. Lett.* 10:2047-2050 (2000). These compounds are also suggested as p38 kinase inhibitors in PCT publication WO 99/32111 published 1 Jul. 1999.

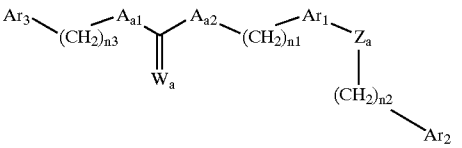
[0005] There remains a need for additional compounds that are effective in inhibiting kinase activity. Given the complexities of signal transduction with the redundancy and crosstalk between various pathways, the identification of specific kinase inhibitors permits accurate targeting with limited inhibition of other pathways, thus reducing the toxicity of such inhibitory compounds.

SUMMARY OF THE INVENTION

[0006] The present invention provides compounds which modulate kinase activity, and in some embodiments inhibit protein tyrosine kinases or a specific kinase or kinase class. In some embodiments, the compositions and methods for treating and preventing conditions and diseases, such as cancer, hematologic malignancies, cardiovascular disease, inflammation or multiple sclerosis. The compounds of the invention can be delivered alone or in combination with additional agents, and are used for the treatment and/or prevention of conditions and diseases. Unless otherwise stated, each of the substituents is as previously defined.

[0007] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

Formula A



[0008] wherein:

[0009] (a) A_{a1} is N—R_{3a} or C—$R_{(3a)2}$ and A_{a2} is N—R_{3a} or C—$R_{(3a)2}$, wherein one of A_{a1} or A_{a2} is N and one is C wherein each R_{3a} is independently a suitable substituent selected from hydrogen, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; —CN; and —NO_2; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, —$(CH_2)_z$CN where z is a whole integer, preferably from 0 to 4, =NH, —NHOH, —OH, —C(O)H, —OC(O)H, —C(O)OH, —OC(O)OH, —OC(O)O-C(O)H, —OOH, —C(NH)NH_2, —NHC(NH)NH_2, —C(S)NH_2, —NHC(S)NH_2, —NHC(O)NH_2, —S(O_2)H, —S(O)H, —NH_2, —C(O)NH_2, —OC(O)NH_2, —NHC(O)H, —NHC(O)OH,—C(O)NHC(O)H, —OS(O_2)H, —OS(O)H, —OSH, —SC(O)H, —S(O)C(O)OH, —SO_2C(O)OH, —NHSH, —NHS(O)H, —$NHSO_2$H, —C(O)SH,

—C(O)S(O)H, —C(O)S(O_2)H, —C(S)H, —C(S)OH, —C(SO)OH, —C(SO_2)OH, —NHC(S)H, —OC(S)H, —OC(S)OH, —OC(SO_2)H, —S(O_2)NH_2, —S(O)NH_2, —SNH_2, —NHCS(O_2)H, —NHC(SO)H, —NHC(S)H, and —SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, —NO_2, —CN, —$(CH_2)_z$—CN where z is a whole integer, preferably from 0 to 4, —OR_c, —NR_cOR_c, —NR_cR_c,—C(O)NR_c, —C(O)OR_c, —C(O)R_c, —$NR_cC(O)NR_cR_c$,—$NR_cC(O)R_c$, —OC(O)OR_c, —OC(O)NR_cR_c, —SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is indepenently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group; or two $R_{3a's}$ cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with one two or three suitable substituents selected from halogen, =O; =S; —CN; —NO_2, or an alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; —CN; and —NO_2; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, —$(CH_2)_z$CN where z is a whole integer, preferably from 0 to 4,

[0010] =NH, —NHOH, —OH, —C(O)H, —OC(O)H, —C(O)OH, —OC(O)OH, —OC(O)OC(O)H, —OOH, —C(NH)NH_2, —NHC(NH)NH_2, —C(S)NH_2, —NHC(S)NH_2, —NHC(O)NH_2, —S(O_2)H, —S(O)H, —NH_2, —C(O)NH_2, —OC(O)NH_2, —NHC(O)H, —NHC(O)OH, —C(O)NHC(O)H, —OS(O_2)H, —OS(O)H, —OSH, —SC(O)H, —S(O)C(O)OH, —SO_2C(O)OH, —NHSH, —NHS(O)H, —$NHSO_2$H, —C(O)SH, —C(O)S(O)H, —C(O)S(O_2)H, —C(S)H, —C(S)OH, —C(SO)OH, —C(SO_2)OH, —NHC(S)H, —OC(S)H, —OC(S)OH, —OC(SO_2)H, —S(O_2)NH_2, —S(O)NH_2, —SNH_2, —NHCS(O_2)H, —NHC(SO)H, —NHC(S)H, and —SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, —NO_2, —CN, —$(CH_2)_z$—CN where z is a whole integer, preferably from 0 to 4, —OR_c, —NR_cOR_c, —NR_cR_c, —C(O)NR_c, —C(O)OR_c, —C(O)R_c, —$NR_cC(O)NR_cR_c$, —$NR_cC(O)R_c$, —OC(O)OR_c, —OC(O)NR_cR_c, —SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

[0011] (b) Ar_1, Ar_2 and Ar_3 are each independently an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of: halogens; =O; =S; —CN; and —NO_2; and alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, —$(CH_2)_z$CN where z is a whole integer, preferably from 0 to 4, =NH, —NHOH, —OH, —C(O)H, —OC(O)H, —C(O)OH, —OC(O)OH, —OC(O)OC(O)H, —OOH, —C(NH)NH_2, —NHC(NH)NH_2, —C(S)NH_2, —NHC(S)NH_2, —NHC(O)NH_2, —S(O_2)H, —S(O)H, —NH_2, —C(O)NH_2, —OC(O)NH_2, —NHC(O)H, —NHC(O)OH, —C(O)NHC(O)H, —OS(O_2)H, —OS(O)H, —OSH, —SC(O)H, —S(O)C(O)OH, —SO_2C(O)OH, —NHSH, —NHS(O)H, —$NHSO_2$H, —C(O)SH, —C(O)S(O)H, —C(O)S(O_2)H, —C(S)H, —C(S)OH, —C(SO)OH, —C(SO_2)OH, —NHC(S)H, —OC(S)H, —OC(S)OH, —OC(SO_2)H, —S(O_2)NH_2, —S(O)NH_2, —SNH_2, —NHCS(O_2)H, —NHC(SO)H, —NHC(S)H, and —SH groups unsubstituted or substituted with one or more suitable substituents independently selected from the group consisting of halogens, =O, —NO_2, —CN, —$(CH_2)_z$—CN where z is a whole integer, preferably from 0 to 4, —OR_c, —NR_cOR_c, —NR_cR_c, —C(O)NR_c, —C(O)OR_c, —C(O)R_c, —$NR_cC(O)NR_cR_c$, —$NR_cC(O)R_c$, —OC(O)OR_c, —OC(O)NR_cR_c, —SR_c, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more substituents cyclize to form a fused or spiro polycyclic cycloalkyl, heterocycloalkyl, aryl, or heteroaryl group, where each R_c is independently selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, and unsubstituted heteroaryl, or two or more R_c groups together cyclize to form part of a heteroaryl or heterocycloalkyl group unsubstituted or substituted with an unsubstituted alkyl group;

[0012] (c) n, is 0, 1, 2, 3 or 4;

[0013] (d) n_2 is 0, 1, 2, 3 or 4;

[0014] (e) n_3 is 0, 1, 2, 3 or 4;

[0015] (f) Z_a is a bond or is selected from S, O, N, NR_c, C(O)NR_c, $NR_cC(O)$, and CR_c, wherein R_c is a suitable substituent selected from hydrogen, unsubstituted alkyl, unsubstituted alkenyl, unsubstituted

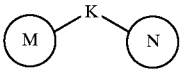
alkynyl, unsubstituted aryl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, or unsubstituted heteroaryl group; and

[0016] (g) W_a is S or O;

[0017] or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, isomer, derivative, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof.

[0018] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(IA)

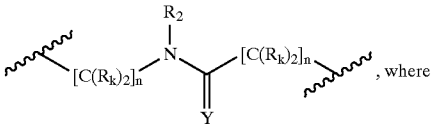


[0019] wherein:

[0020] M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

[0021] N is a substituted or unsubstituted aryl, or substituted or unsubstituted hetroaryl; and

[0022] K is



, where

[0023] Y is O or S;

[0024] each R_k is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, —$OC(O)R_2$, —NO_2, —$N(R_2)_2$, —SR_2, —$C(O)R_2$, —$C(O)_2R_2$, —$C(O)N(R_2)_2$, or —$N(R_2)C(O)R_2$,

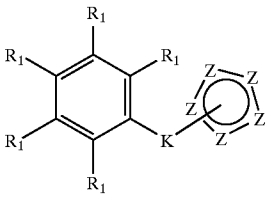
[0025] each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

[0026] each n is independently 0, 1, 2, 3 or 4;

[0027] or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

[0028] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(IB)



[0029] wherein:

[0030] each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

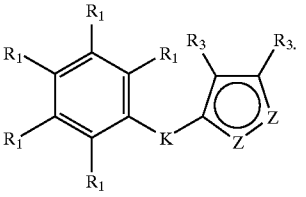
[0031] where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

[0032] each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —OR_c —OH, —$OC(O)R_c$, —NO_2, —$N(R_c)_2$, —SR_c, $S(O)_jR_c$ where j is 1 or 2, —NR_c-$C(O)R_c$, —$C(O)N(R_c)_2$, $C(O)_2R_c$, or —$C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

[0033] each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

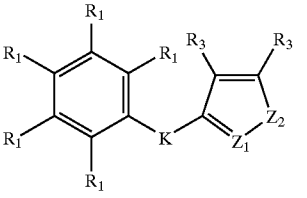
[0034] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(II)



[0035] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

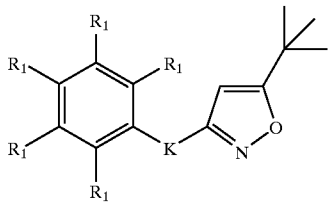
(III)



[0036] wherein Z_1 is CR_3 or N; and Z_2 is O or S.

[0037] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(IV)



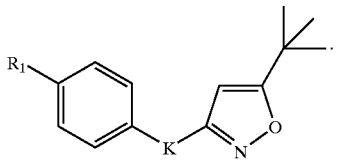
[0038] wherein:

[0039] each R_1 is independently H, halogen, substituted or unsubstituted alkyl, —O(substituted or unsubstituted alkyl), —O(substituted or unsubstituted alkenyl), —NR_c(O)O(substituted or unsubstituted alkyl), —NR_cC(O) (substituted or unsubstituted alkyl), —NR_cC(O)(substituted or unsubstituted alkenyl), —C(O)NR_c(substituted or unsubstituted alkyl), —C(O)NR_c(substituted or unsubstituted alkenyl), —NO_2, —S(═O)R_c, —SR_c, $C(O)_2R_c$, or —C(O)R_c; and

[0040] each R_2 is independently H or substituted or unsubstituted alkyl.

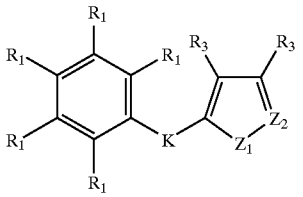
[0041] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(V)



[0042] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

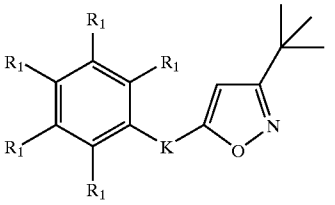
(VI)



[0043] wherein Z_1 is O or S; and Z_2 is CR_3 or N.

[0044] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(VII)



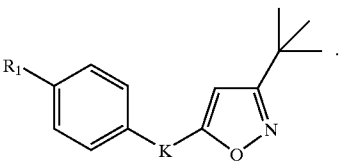
[0045] wherein:

[0046] each R_1 is independently H, halogen, substituted or unsubstituted. alkyl, —O(substituted or unsubstituted alkyl), —O(substituted or unsubstituted alkenyl), —NR_cC(O)O(substituted or unsubstituted alkyl), —NR_cC(O) (substituted or unsubstituted alkyl), —NR_cC(O)(substituted or unsubstituted alkenyl), —C(O)NR_c(substituted or unsubstituted alkyl), —C(O)NR_c(substituted or unsubstituted alkenyl), —NO_2, —S(═O)R_c, —SR_c, $C(O)_2R_c$, or —C(O)R_c; and

[0047] each R_2 is independently H or substituted or unsubstituted alkyl.

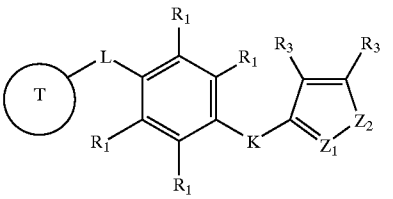
[0048] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(VIII)



[0049] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(IX)

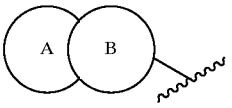


[0050] wherein:

[0051] L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, C(O)NH(substituted or unsubstituted alkylene), C(O)NH(substituted or unsubstituted alkenylene) —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

[0052] T is a mono-, bi, -or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

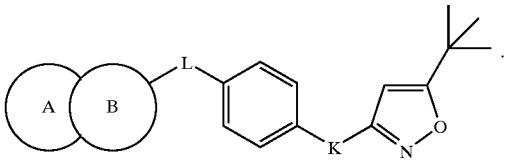
[0053] In some embodiments, T is



[0054] wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

[0055] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

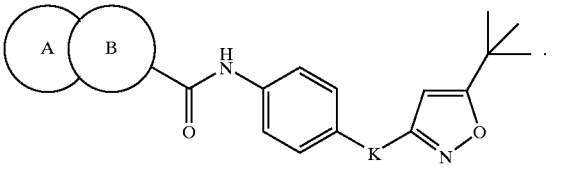
(XI)



[0056] In some embodiments, L of said compound is a covalent bond —C(O)NH(substituted or unsubstituted alkylene), —NHC(O)—, —NHC(O)(substituted or unsubstituted alkylene)-, —NH—, or —O(substituted or unsubstituted alkylene)-.

[0057] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

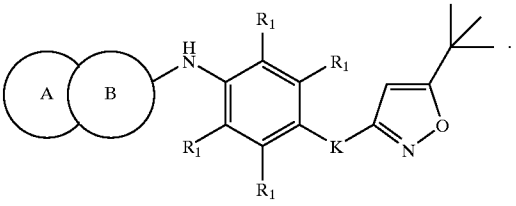
(XII)



[0058] In some embodiments, B of said compound is a substituted or unsubstituted five-membered arylene or heteroarylene. In other embodiments, B is substituted or unsubstituted thiophenylene. In still other embodiments, B is substituted or unsubstituted imidazolylene. In yet other embodiments, B is substituted or unsubstituted pyrrolylene. In still other embodiments, B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene. In some embodiments, B is substituted or unsubstituted phenylene. In other embodiments, B is substituted or unsubstituted pyridinylene, pyrimidinylene, or pyridazine.

[0059] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

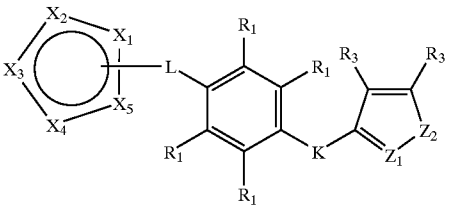
(XIII)



[0060] In some embodiments, B of said compound is a substituted or unsubstituted six-membered heteroarylene. In other embodiments, the six-membered heteroarylene is substituted or unsubstituted pyrimidinylene. In still other embodiments, L of said compound —OCH_2—. In yet other embodiments, L of said compound is —C(O)NH.

[0061] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XIV)



[0062] wherein:

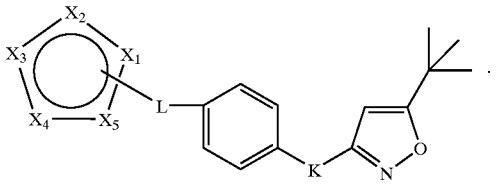
[0063] L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

[0064] each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$, or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

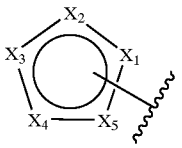
[0065] each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0066] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

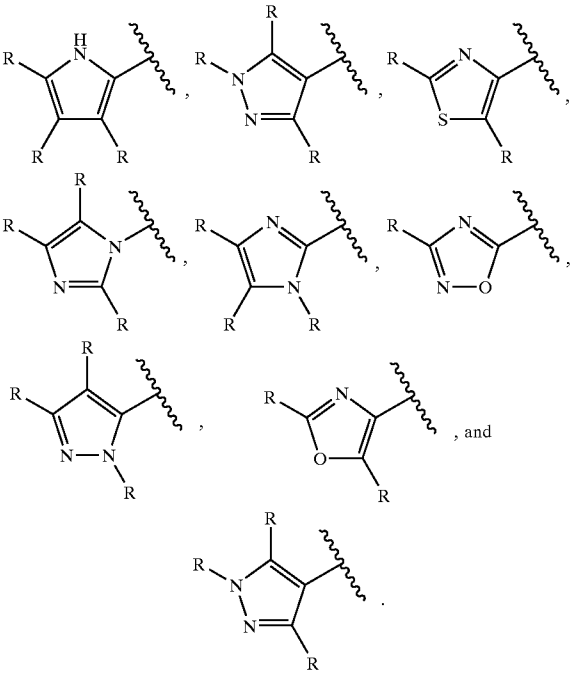
(XV)



[0067] In some embodiments, L of said compound is a covalent bond, —C(O)NH—, or —O(substituted or unsubstituted alkylene)-. In other embodiments,

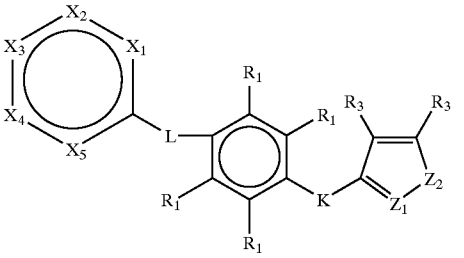


[0068] of said compound is selected from the group consisting of:



[0069] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XVI)



[0070] wherein:

[0071] L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

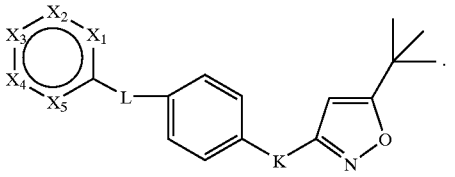
[0072] each of X_1-X_5 is independently C, CR, N—O, or N, wherein no more than two of X_1-X_5 is N, where

[0073] each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$, or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

[0074] each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

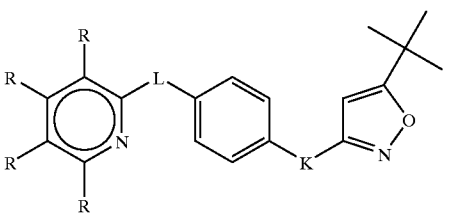
[0075] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XVII)



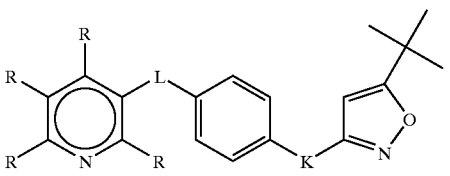
[0076] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XVIII)



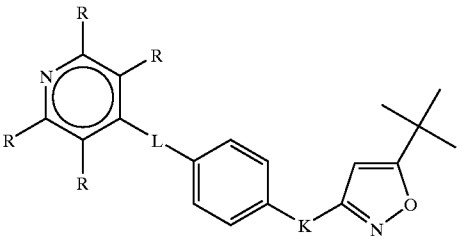
[0077] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a-flt-3 modulating compound having the structure:

(XXI)



[0078] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

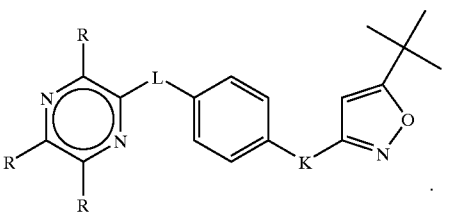
(XXII)



[0079] wherein L is —O(substituted or unsubstituted alkylene)- or —(O)(substituted or unsubstituted alkenylene)-.

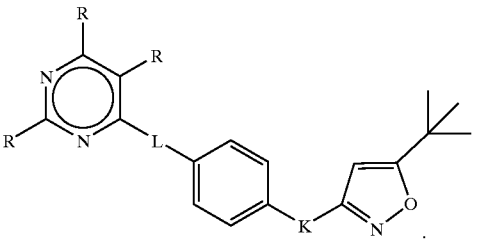
[0080] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXIII)



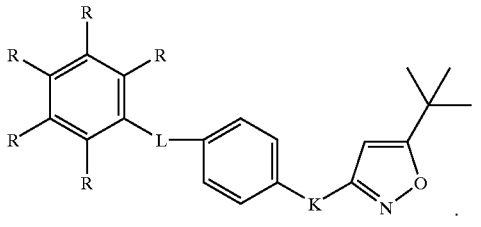
[0081] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXIV)



[0082] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

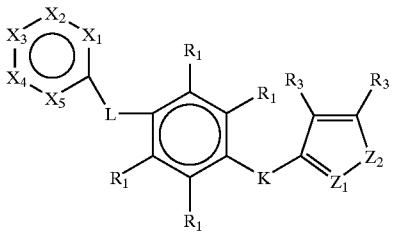
(XXV)



[0083] In some embodiments, L of said compound is —O(substituted or unsubstituted alkylene)- or —O(substituted or unsubstituted alkenylene)-. In other embodiments, L of said compound is —NHC(O)—. In still other embodiments, L of said compound is a covalent bond, substituted or unsubstituted alkylene, —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —NH(alkylene)-, —NHC(O)CH_2SCH_2C(O)NH—, and —NHC(O)(substituted alkylene)S—.

[0084] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXVI)



[0085] wherein:

[0086] L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

[0087] each of X_1-X_5 is independently C, CR, or N, wherein no more than two of X_1-X_5 is N, where

[0088] each R is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$ or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

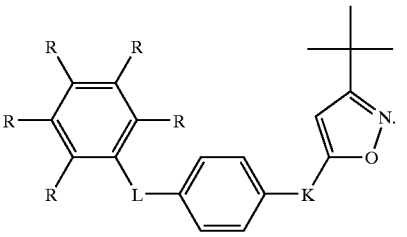
[0089] each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0090] Z_1 is O or S; and

[0091] Z_2 is CR_3 or N.

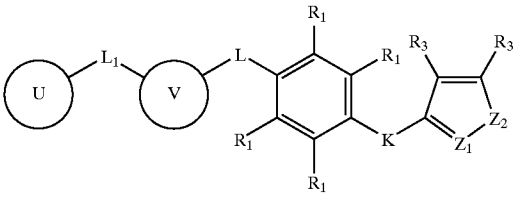
[0092] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXVII)



[0093] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XVIII)



[0094] wherein:

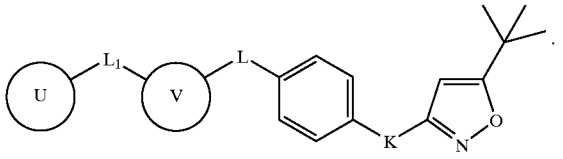
[0095] each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted-or unsubstituted alkylene), —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—;

[0096] U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

[0097] V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

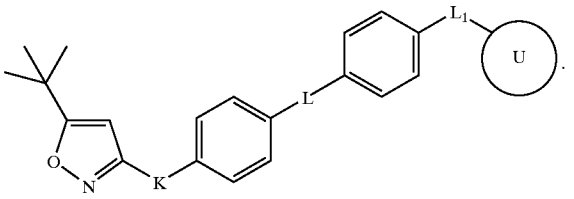
[0098] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XIX)



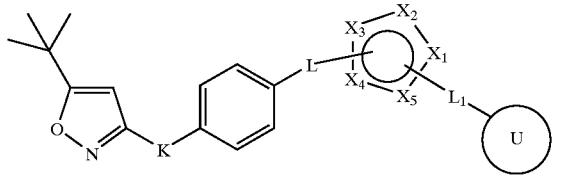
[0099] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XX)



[0100] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXXI)



[0101] wherein:

[0102] each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; and

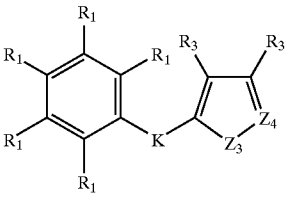
[0103] each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$ or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

[0104] each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0105] In some embodiments, U is a substituted or unsubstituted five-membered heteroaryl, substituted or unsubstituted phenyl, or substituted or unsubstituted six-membered heteroaryl.

[0106] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXIII)



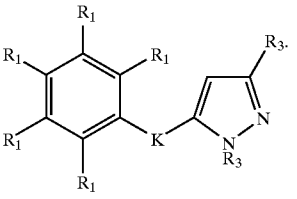
[0107] wherein:

[0108] Z_3 is NR_3, O, or S; and

[0109] Z_4 is N or CR_3.

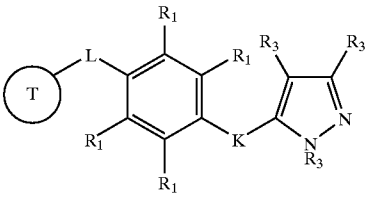
[0110] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXIV)



[0111] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(XXV)



[0112] wherein:

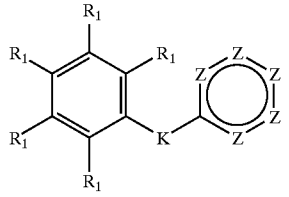
[0113] L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted

alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

[0114] T is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[0115] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(A)



[0116] wherein:

[0117] each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms where

[0118] R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

[0119] each R_k is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, $—OC(O)R_2$, $—NO_2$, $—N(R_2)_2$, $—SR_2$, $—C(O)R_2$, $—C(O)_2R_2$, $—C(O)N(R_2)_2$, or $—N(R_2)C(O)R_2$,

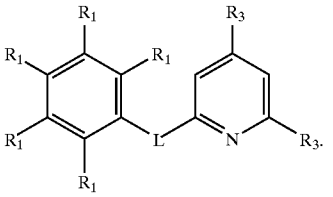
[0120] each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

[0121] each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $—OR_c$ —OH, $—OC(O)R_c$, $—NO_2$, $—N(R_c)_2$, $—SR_c$, $S(O)_jR_c$ where j is 1 or 2, $—NR_cC(O)R_c$, $—C(O)N(R_c)_2$, $—C(O)_2R_c$, or $—C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

[0122] each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0123] Provided herein are compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of a flt-3 modulating compound having the structure:

(B)



[0124] In some embodiments, the protein tyrosine kinase is selected from the fetus liver kinase ("flk") receptor subfamily, which includes kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1). In further embodiments, the protein tyrosine kinase is selected from the fibroblast growth factor ("FGF") receptor subgroup, which includes the receptors FGFR1, FGFR 2, FGFR3, and FGFR4, and the ligands, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6,and FGF7. In a still further embodiment, the protein tyrosine kinase is the tyrosine kinase growth factor receptor family, c-Met. In some embodiments, the protein tyrosine kinase is an finslike tyrosine kinase 3 receptor kinase (FLT-3 kinase).

[0125] The compounds and compositions disclosed herein may be used for the prevention or treatment of cancers such as stomach, gastric, bone, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract, ovarian, squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, leukemia, glioma, colorectal cancer, genitourinary cancer gastrointestinal cancer, or pancreatic cancer. In particular, the cancer is acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

[0126] Compositions and methods for treating a disease comprising administering to a subject in need thereof an effective amount of an fms-like tyrosine kinase 3 (FLT-3) receptor modulating compound are provided herein. In one embodiment, the disease is cancer. In other embodiments, the cancer is a malignant tumor, or a hematologic malignancy such as leukemia and lymphoma. In some embodiments, the leukemia is acute myelogenous leukemia (AML), a B-precursor cell acute lymphoblastic leukemia, myelodysplastic leukemia, T-cell acute lymphoblastic leukemia or chronic myelogenous leukemia (CML).

[0127] These and other aspects of the present invention will become evident upon reference to the following detailed description. In addition, various references are set forth

herein which describe in more detail certain procedures or compositions, and are incorporated by reference in their entirety.

DISCLOSURE OF THE INVENTION

[0128] To more readily facilitate an understanding of the invention and its preferred embodiments, the meanings of terms used herein will become apparent from the context of this specification in view of common usage of various terms and the explicit definitions of other terms provided in the glossary below or in the ensuing description.

[0129] Glossary of Terms

[0130] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a,""an" and "the" include plural referents unless the context clearly dictates otherwise. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (1992) "ADVANCED ORGANIC CHEMISTRY 3RD ED." Vols. A and B, Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed.

[0131] The term "modulator" means a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, agonist, antagonist, and the like.

[0132] The term "agonist" means a molecule such as a compound, a drug, an enzyme activator or a hormone that enhances the activity of another molecule or the activity of a receptor site etiehr directly or indirectly.

[0133] The term "antagonist" means a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone, that diminishes or prevents the action of another molecule or the activity of a receptor site either directly or indirectly.

[0134] The terms "effective amount" or "therapeutically effective amount" refer to a sufficient amount of the agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic use is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

[0135] As used herein, the terms "treat" or "treatment" are synonymous with the term "prevent" and are meant to indicate a postponement of development of diseases, preventing the development of diseases, and/or reducing severity of such symptoms that will or are expected to develop. Thus, these terms include ameliorating existing disease symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease, relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder.

[0136] By "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0137] "Carrier materials" include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. "Pharmaceutically compatible carrier materials" may comprise, e.g., acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy,* Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences,* Mack Publishing Co., Easton, Pa. 1975; Liberman, H. A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms,* Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems,* Seventh Ed. (Lippincott Williams & Wilkins1999).

[0138] As used herein, the term "subject" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the present invention, the mammal is a human.

[0139] The term "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4,-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid,

muconic acid, and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[0140] As used herein, the term "biological sample" is broadly defined to include any cell, tissue, organ or multicellular organism. A biological sample can be derived, for example, from cell or tissue cultures in vitro. Alternatively, a biological sample can be derived from a living organism or from a population of single cell organisms.

[0141] As used herein, the term "linker" means any divalent linking moiety used to connect, join, or attach two chemical groups. For example, linkers may be used to join two cyclic groups, such as to join two aryl groups (e.g., phenyl), an aryl group to a cycloalkyl group, an aryl group to a heterocyclyl group, a cycloalkyl group to a cycloalkyl group, a cycloalkyl group to a heterocyclyl group, and the like. Representative linkers include, but are not limited to, a covalent bond, -(substituted or unsubstituted alkylene)-, -(substituted or unsubstituted alkenylene)-, -(substituted or unsubstituted alkynylene)-, -(substituted or unsubstituted cycloalkylene)-, -(substituted or unsubstituted heterocyclylene)-, -(substituted or unsubstituted arylene)-, and -(substituted or unsubstituted heteroarylene)-. Exemplary linkers also include —O—, —S—, —S(O)—, —$S(O)_2$—, —$S(O)_3$—, —C(O)—, —NH—, —N═, —N═N—, ═N—N═, —C(O)NH—, —S(O)NH—, and the like. Additional examples of linkers include —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkylene)-, —C(O)(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—, —NHC(O)(substituted or unsubstituted alkenylene)-, and the like. Linkers, as represented herein, embrace divalent moieties in any chemically feasible directionality. For example, compounds comprising a linker —C(O)NH— which attaches two aryl groups, Ar_1 to Ar_2, include Ar_1—C(O)NH—Ar_2 as well as Ar_1—NHC(O)—Ar_2.

[0142] As used herein, the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0143] As used herein, "alkyl" means a straight chain or branched, saturated or unsaturated chain having from 1 to 10 carbon atoms. Representative saturated alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl, and longer alkyl groups, such as heptyl, and octyl. An alkyl group can be unsubstituted or substituted. Unsaturated alkyl groups include alkenyl groups and alkynyl groups, discussed below. Alkyl groups containing three or more carbon atoms may be straight, branched or cyclized.

[0144] As used herein, "lower alkyl" means an alkyl having from 1 to 5 carbon atoms.

[0145] As used herein, an "alkenyl group" includes a monovalent unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to, (C_2-C_8) alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted.

[0146] As used herein, "alkynyl group" includes a monovalent unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C_2-C_6)alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted.

[0147] The terms "trifluoromethyl,""sulfonyl," and "carboxyl" include CF_3, SO_3H, and CO_2H, respectively.

[0148] The term "alkoxy" as used herein includes —O-(alkyl), wherein alkyl is defined above.

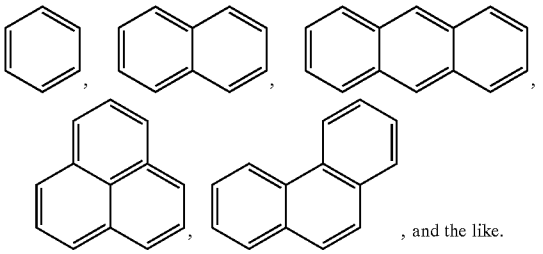
[0149] As used herein, "alkoxyalkoxy" includes —O-(alkyl)-O-(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

[0150] As used herein, "alkoxycarbonyl" includes-C(O)O-(alkyl), wherein alkyl is defined above.

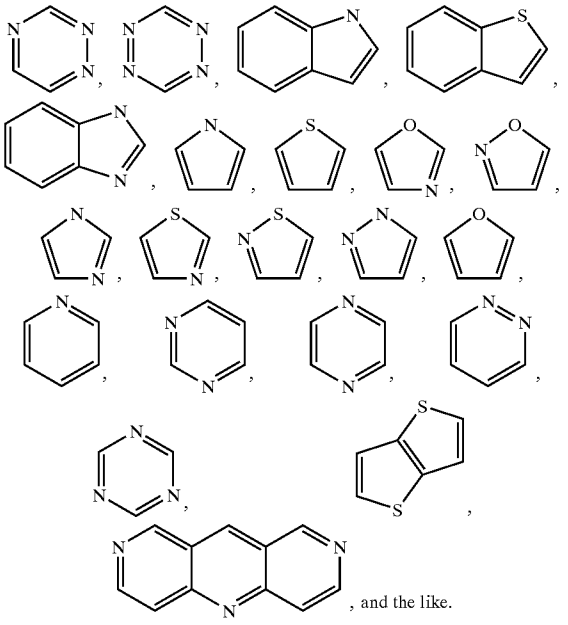
[0151] As used herein, "alkoxycarbonylalkyl" includes -(alkyl)-C(O)O-(alkyl), wherein alkyl is defined above.

[0152] As used herein, "alkoxyalkyl" means -(alkyl)-O-(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

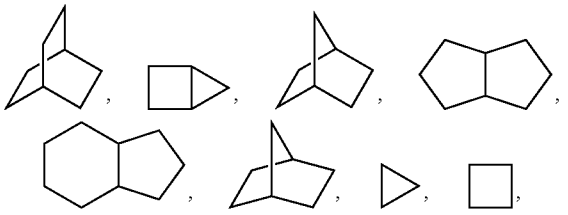
[0153] As used herein, the term "aryl" (Ar) refers to a monocyclic, or fused or spiro polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12 ring atoms per ring. Illustrative examples of aryl groups include the following moieties:



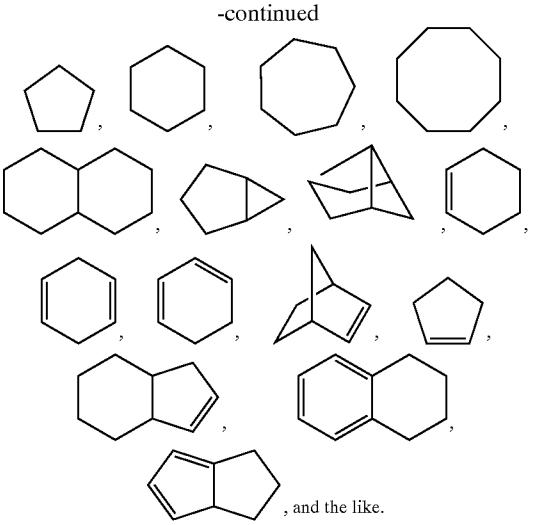
[0154] As used herein, the term "heteroaryl" (heteroAr) refers to a monocyclic, or fused or spiro polycyclic, aromatic heterocycle (ring structure having ring atoms selected from carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per ring. Illustrative examples of aryl groups include the following moieties:



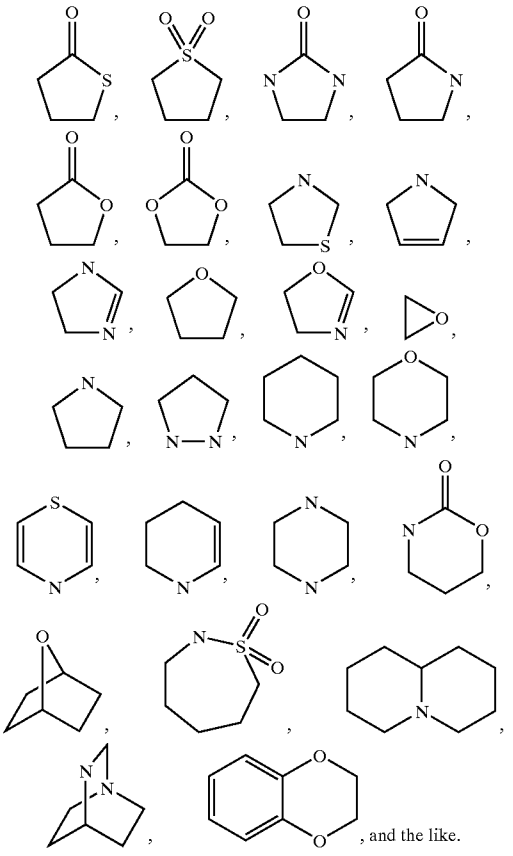
[0155] As used herein, the term "cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or Spiro polycyclic, carbocycle having from 3 to 12 ring atoms per ring. Illustrative examples of cycloalkyl groups include the following moieties:



-continued



[0156] As used herein, the term "heterocycloalkyl" refers to a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring selected from C atoms and N, O, and S heteroatoms. Illustrative examples of heterocycloalkyl groups include:



[0157] As used herein, "aryloxy" includes —O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted.

[0158] As used herein, "arylalkyl" includes -(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0159] As used herein, "arylalkyloxy" includes —O-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0160] As used herein, "cycloalkyl" includes a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of cycloalkyl groups include, but are not limited to, (C_3-C_7)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

[0161] As used herein, "cycloalkyloxy" includes —O-(cycloalkyl), wherein cycloalkyl is defined above.

[0162] As used herein, "cycloalkylalkyloxy" includes —O-(alkyl)-(cycloalkyl), wherein cycloalkyl and alkyl are defined above.

[0163] As used herein, the term "alkylidene" includes the divalent radical —C_nH_{2n}—, wherein n is an integer from 1 to 8, such as —CH_2—, —CH_2CH_2—, —CH_2—CH_2—CH_2—, —$CH_2CH_2CH_2CH_2$—, —$CH_2CH_2CH_2CH_2CH_2$—, and the like, unsubstituted or substituted with one or more alkyl groups.

[0164] As used herein, "heteroatom-containing alkylidene" includes an alkylidene wherein at least one carbon atom is replaced by a heteroatom selected from nitrogen, oxygen, or sulfur, such as —$CH_2CH_2OCH_2CH_2$—, and the like, unsubstituted or substituted with one or more alkyl groups.

[0165] As used herein, "aminoalkoxy" includes —O-(alkyl)-NH_2, wherein alkyl is defined above.

[0166] As used herein, "mono-alkylamino" includes —NH(alkyl), wherein alkyl is defined above.

[0167] As used herein, "di-alkylamino" includes —N(alkyl)(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

[0168] As used herein, "mono-alkylaminoalkoxy" includes —O-(alkyl)-NH(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

[0169] As used herein, "di-alkylaminoalkoxy" includes —O-(alkyl)N(alkyl)(alkyl), wherein each "alkyl" is independently an alkyl group defined above.

[0170] As used herein, "arylamino" includes —NH(aryl), wherein aryl is defined above.

[0171] As used herein, "arylalkylamino" includes —NH-(alkyl)-(aryl), wherein alkyl and aryl are defined above.

[0172] As used herein, "alkylamino" includes —NH(alkyl), wherein alkyl is defined above.

[0173] As used herein, "cycloalkylamino" includes —NH-(cycloalkyl), wherein cyclohexyl is defined above.

[0174] As used herein, "cycloalkylalkylamino" includes —NH-(alkyl)-(cycloalkyl), wherein alkyl and cycloalkyl are defined above.

[0175] As used herein, "aminoalkyl" includes -(alkyl)-NH_2, wherein alkyl is defined above.

[0176] As used herein, "mono-alkylaminoalkyl" includes -(alkyl)-NH(alkyl),wherein each "alkyl" is independently an alkyl group defined above.

[0177] As used herein, "di-alkylaminoalkyl" includes -(alkyl)-N(alkyl)(alkyl),wherein each "alkyl" is independently an alkyl group defined above.

[0178] The term "whole integer" is intended to include whole numbers. For example, a whole integer from 0 to 4 would include 0, 1, 2, 3, and 4.

[0179] Sulfonyl refers to the presence of a sulfur atom, which is optionally linked to another moiety such as an aliphatic group, an aromatic group, an aryl group, an alicyclic group, or a heterocyclic group. Aryl or alkyl sulfonyl moieties have the formula —SO_2R_d, and alkoxy moieties have the formula —O—R_d—, wherein R_d is alkyl, as defined above, or is aryl wherein aryl is phenyl, optionally substituted with 1-3 substituents independently selected from halo (fluoro, chloro, bromo or iodo), lower alkyl (1-6C) and lower alkoxy (1-6C).

[0180] As used herein, the term "substituted" means that the specified group or moiety bears one or more suitable substituents.

[0181] As used herein, the term "unsubstituted" means that the specified group bears no substituents.

[0182] As used herein, the term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents.

[0183] Molecular embodiments of the present invention may possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[0184] Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini et al., Chem, Rev, 1996, 96, 3147-3176 and references cited therein.

[0185] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0186] To more readily facilitate an understanding of the invention and its preferred embodiments, the meanings of terms used herein will become apparent from the context of this specification in view of common usage of various terms and the explicit definitions of other terms provided in the glossary below or in the ensuing description.

[0187] Compounds

[0188] In one aspect, the present invention is directed to compounds, compositions, and methods for treating conditions associated with abnormal kinase activity. In one embodiment, compounds useful in the invention are derivatives of isoxazoles, pyrazoles and isothiazoles. When the compounds of the invention contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers.

[0189] Thus, the invention provides methods for modulating various kinases by providing an effective amount of a compound of the formulas described herein.

[0190] Salts of the compounds may be used for therapeutic and prophylactic purposes, where the salt is preferably a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example Q-toluenesulphonic, acids.

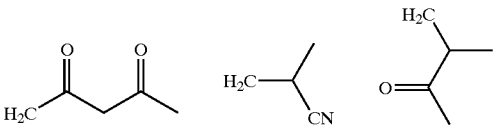
[0191] A "prodrug" refers to a drug or compound in which the pharmacological action results from conversion by metabolic processes within the body. Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. Additionally, prodrugs can increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, e.g., Fedorak et al., Am. J. Physiol., 269:G210-218 (1995); McLoed et al., Gastroenterol, 106:405-413 (1994); Hochhaus et al., Biomed. Chrom., 6:283-286 (1992); J. Larsen and H. Bundgaard, Int. J. Pharmaceutics, 37, 87 (1987); J. Larsen et al., Int. J. Pharmaceutics, 47, 103 (1988); Sinkula et al., J. Pharm. Sci., 64:181-210 (1975); T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987. Prodrug forms of the above described compounds, wherein the prodrug is metabolized in vivo to produce a derivative as set forth above are included within the scope of the claims. Indeed, some of the above-described derivatives may be a prodrug for another derivative or active compound.

[0192] The invention further provides for the optical isomers of the compounds disclosed herein, especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the invention, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein.

[0193] In another aspect, compositions containing the above described analogs and derivatives are provided. Preferably, the compositions are formulated to be suitable for pharmaceutical or clinical use by the inclusion of appropriate carriers or excipients.

[0194] Groups such as carbonyl, carboxyl, alkoxy, amino, and cyano groups, etc., as shown in the formula above, need not be directly bound to the para position; they may be included elsewhere in the alkyl, alkenyl or alkynyl substituent. Thus, also acceptable substituents are the following representative forms:

[0195] $-CH_2NHCH_3$; $-CH_2OCH_3$; $-CH_2SCH_3$; $-NHCH_3$; $-CH_2CH_3$; $-OCH_2CH_3$; $-SCH_2CH_2CH_3$; $-CH{=}CHCH_2NH_2$; $-CH_2CH_2OH$;



[0196] $-CH_2CH_2CH_2SH$; $-CH_2OC(O)CH_3$; $-CH_2NHC(O)CH_2C(O)CH_3$; $-NHC(O)CH_2CH_2CH_3$ each of which may further be substituted with a cycloalkyl, heterocycloalkyl, aryl or heteroaryl group.

[0197] It will also be evident that these substituents include, for example, trifluoromethyl, difluoromethyl and fluoromethyl (alkyl substituted by halo) and trifluoromethoxy, difluoromethoxy and fluoromethoxy (alkyl where one carbon is replaced by O and is further substituted by halo).

[0198] Compounds of the invention which contain carboxyl groups or which contain amino groups may be supplied in the forms of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of carboxylic acids include inorganic salts such as salts of sodium, potassium, calcium, magnesium and the like or salts formed with organic bases such as caffeine. Salts of amines are acid addition salts formed from inorganic acids such as hydrochloric, sulfuric, phosphoric acids or may be salts of organic acids such as acetates, maleates, propionates, and the like.

[0199] The invention also provides prodrug forms of the compounds described herein, wherein the prodrug is metabolized in vivo to produce a derivative as set forth above. Indeed, some of the above described derivatives may be a prodrug for another derivative or active compound. The invention further provides for the optical isomers of the compounds disclosed herein, especially those resulting from the chiral carbon atoms in the molecule. In additional embodiments of the invention, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are provided.

[0200] In another aspect of the invention, compositions containing the above described analogs and derivatives are

provided. Preferably, the compositions are formulated to be suitable for pharmaceutical or clinical use by the inclusion of appropriate carriers or excipients.

[0201] In yet another aspect of the invention, pharmaceutical formulations are provided comprising at least one compound described above, or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

[0202] The compounds of the invention, especially when used in the invention methods and compositions, may be "conjugated"—that is they may be coupled to additional moieties that do not destroy their ability to modulate kinases. For example, the compounds might be coupled to a label such as a radioactive label, a fluorescent label and the like, or may be coupled to targeting agents such as antibodies or fragments, or to fragments to aid purification such as FLAG or a histidine tag. The compounds may also be coupled to specific binding partners such as biotin for use in assay procedures or to moieties that alter their biological half-lives such as polyethylene glycol. Thus, the methods of the invention employ the invention compounds per se as well as conjugates thereof.

[0203] Synthesis of Compounds

[0204] Compounds of the present invention may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. See, e.g., March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 3rd Ed., Vols. A and B (Plenum 1992), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 2nd Ed. (Wiley 1991). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein.

[0205] The compounds of the invention are synthesized by methods well known in the art. The compounds of the invention are ureas or cyclic forms thereof and can be synthesized using generally known procedures for urea synthesis.

[0206] In one group of methods, an amine is reacted with an isocyanate in an aprotic solvent. Typically, in some embodiments, a molar excess of the amine is used in the presence of an aprotic solvent and the reaction is conducted at room temperature. The reaction mixture is then poured into water and precipitated with salt to recover the crude product which is then purified according to standard methods.

[0207] In alternative methods, the ureas are formed from two separate amine reactants in the presence of a condensing agent such as 1,1,carbonyldiimidazole (CDI) in the presence of an inert nonpolar solvent such as dichloromethane. One of the amines is first added to a solution of CDI in solvent under cooling conditions and then stirred at room temperature with the other amine. After removal of solvent, the crude product can be purified using standard procedures.

[0208] In still another method, one of the amines is added in an aprotic solvent to a solution of triphosgene and then treated with the other amine reactant dissolved in an inert solvent in the presence of base such as triethylamine. After reaction at room temperature, the mixture may be diluted with, for example, ethylacetate and washed with water and brine, dried and purified.

[0209] In still another method, one of the amine components is treated with 4-nitrophenylchloroformate in the presence of mild base in a solvent such as N-methylpyrrolidone (NMP). The other amine is then added and the reaction mixture heated, then cooled, poured into water, extracted into chloroform and further purified.

[0210] Alternatively, the urea may be formed by the reaction of an amine with the counterpart halo acylamine which is formed from the parent amine by treatment with phosgene and base in an inert solvent such as methylene dichloride or by reacting an amine with its counterpart amine with an acyl amine containing an alternate leaving group formed by reaction of that amine with 4-nitrophenylchloroformate in the presence of an amine base and in an inert solvent.

[0211] Details of these methods can be found in Matsuno et al. *J Med. Chem.* 45:3057-66 (2002); Matsuno et al. *J. Med. Chem.* 45:4513-23 (2002); and and Pandley et al., *J. Med. Chem.* 45:3772-93 (2002).

[0212] Cyclized forms of the ureas may be obtained by treating the formed urea with dibromo derivatives of the bridge, typically in the presence of a strong base and in an inert aprotic polar solvent.

[0213] The ureas may be converted to thioureas by treating with Lawesson's reagent in the presence of toluene.

[0214] For compounds having the moiety Ar^1-L-Ar^2 is obtained by first protecting the amino group of p-hydroxy aniline destined to become Ar^1 with a protecting agent such as Boc and then coupling the hydroxy group of Ar^1 to an aryl alkyl halide. This coupling is conducted in the presence of strong base and in an aprotic solvent. After deprotection, the urea is formed by reaction with the isoxazole isocyanate. These techniques are exemplified below.

[0215] Selected examples of covalent linkages and precursor functional groups which yield them are given in the Table entitled "Examples of Covalent Linkages and Precursors Thereof." Precursor functional groups are shown as electrophilic groups and nucleophilic groups. The functional group on the organic substance may be attached directly, or attached via any useful spacer or linker as defined below.

TABLE 1

Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids

TABLE 1-continued

Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols

[0216] In general, carbon electrophiles are susceptible to attack by complementary nucleophiles, including carbon nucleophiles, wherein an attacking nucleophile brings an electron pair to the carbon electrophile in order to form a new bond between the nucleophile and the carbon electrophile.

[0217] Suitable carbon nucleophiles include, but are not limited to alkyl, alkenyl, aryl and alkynyl Grignard, organolithium, organozinc, alkyl-, alkenyl , aryl- and alkynyl-tin reagents (organostannanes), alkyl-, alkenyl-, aryl- and alkynyl-borane reagents (organoboranes and organoboronates); these carbon nucleophiles have the advantage of being kinetically stable in water or polar organic solvents. Other carbon nucleophiles include phosphorus ylids, enol and enolate reagents; these carbon nucleophiles have the advantage of being relatively easy to generate from precursors well known to those skilled in the art of synthetic organic chemistry. Carbon nucleophiles, when used in conjunction with carbon electrophiles, engender new carbon-carbon bonds between the carbon nucleophile and carbon electrophile.

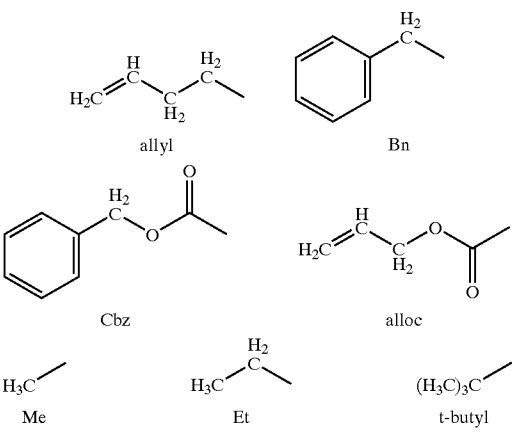
[0218] Non-carbon nucleophiles suitable for coupling to carbon electrophiles include but are not limited to primary and secondary amines, thiols, thiolates, and thioethers, alcohols, alkoxides, azides, semicarbazides, and the like. These non-carbon nucleophiles, when used in conjunction with carbon electrophiles, typically generate heteroatom linkages (C—X—C), wherein X is a hetereoatom, e.g, oxygen or nitrogen.

[0219] The term "protecting group" refers to chemical moieties that block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. It is preferred that each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

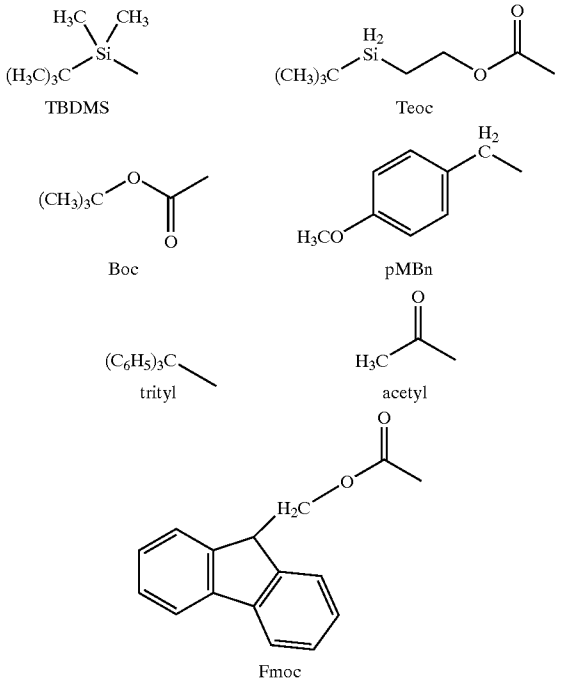
[0220] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester derivatives as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[0221] Allyl blocking groups are useful in then presence of acid- and base-protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pdo-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[0222] Typically blocking/protecting groups may be selected from:



-continued



[0223] Other protecting groups are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated herein by reference in its entirety.

[0224] Biological Activity

[0225] Protein kinases (PKs) play a role in signal transduction pathways regulating a number of cellular functions, such as cell growth, differentiation, and cell death. PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. Abnormal PK activity has been related to disorders ranging from relatively non life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). In addition, a variety of tumor types have dysfunctional growth factor receptor tyrosine kinases, resulting in inappropriate mitogenic signaling. Protein kinases are believed to be involved in many different cellular signal transduction pathways. In particular, protein tyrosine kinases (PTK) are attractive targets in the search for therapeutic agents, not only for cancer, but also against many other diseases. Blocking or regulating the kinase phosphorylation process in a signaling cascade may help treat conditions such as cancer or inflammatory processes.

[0226] Protein tyrosine kinases are a family of tightly regulated enzymes, and the aberrant activation of various members of the family is one of the hallmarks of cancer. The protein-tyrosine kinase family includes Bcr-Abl tyrosine kinase, and can be divided into subgroups that have similar structural organization and sequence similarity within the kinase domain. The members of the type III group of receptor tyrosine kinases include the platelet-derived growth factor (PDGF) receptors (PDGF receptors α and β), colony-stimulating factor (CSF-1) receptor (CSF-1R, c-Fms), FLT-3, and stem cell or steel factor receptor (c-kit).

[0227] The compounds, compositions, and methods provided herein are useful to modulate the activity of kinases including, but not limited to, ERBB2, ABL1, AURKA, CDK2, EGFR, FGFR1, LCK, MAPK14, PDGFR, KDR, ABL1, BRAF, ERBB4, FLT3, KIT, and RAF1. In some embodiments, the compositions and methods provided herein modulate the activity of a mutant kinase.

[0228] Inhibition by the compounds provided herein can be determined using any suitable assay. In one embodiment, inhibition is determined in vitro. In a specific embodiment, inhibition is assessed by phosphorylation assays. Any suitable phosphorylation assay can be employed. For example, membrane autophosphorylation assays, receptor autophosphorylation assays in intact cells, and ELISA's can be employed. See, e.g., Gazit, et al., J. Med. Chem. (1996) 39:2170-2177, Chapter 18 in CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Ausubel, et al., eds. 2001). Cells useful in such assays include cells with wildtype or mutated forms. In one embodiment, the wildtype is a kinase that is not constitutively active, but is activated with upon dimerization. For example, the mutant FLT3 kinase is constitutively active via internal tandem duplication mutations or point mutations in the activation domain. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc. Exemplary cells include Ba/F3 or 32Dc13 cells transduced with, e.g., MSCV retroviral constructs FLT3-ITD (Kelly et al., 2002); Molm-13 and Molm14 cell line (Fujisaki Cell Center, Okayama, Japan); HL60 (AML-M3), AML193 (AML-M5), KG-1, KG-1a, CRL-1873, CRL-9591, and THP-1 (American Tissue Culture Collection, Bethesda, Md.); or any suitable cell line derived from a patient with a hematopoietic malignancy.

[0229] In some embodiments, the compounds described herein significantly inhibit receptor tyrosine kinases. A significant inhibition of a receptor tyrosine kinase activity refers to an IC_{50} of less than or equal to 100 μM. Preferably, the compound can inhibit activity with an IC_{50} of less than or equal to 50 μM, more preferably less than or equal to 10 μM, more preferably less than 1 μM, or less than 100 nM, most preferably less than 50 nM. Lower IC_{50}'s are preferred because the IC_{50} provides an indication as to the in vivo effectiveness of the compound. Other factors known in the art, such as compound half-life, biodistribution, and toxicity should also be considered for therapeutic uses. Such factors may enable a compound with a lower IC_{50} to have greater in vivo efficacy than a compound having a higher IC_{50} Preferably, a compound that inhibits activity is administered at a dose where the effective tyrosine phosphorylation, i.e., IC_{50}, is less than its cytotoxic effects, LD_{50}.

[0230] In some embodiments, the compounds selectively inhibit one or more kinases. Selective inhibition of a kinase, such as FLT3, p38 kinase, STK10, MKNK2, Bcr-Abl, c-kit, or PDGFR, is achieved by inhibiting activity of one kinase, while having an insignificant effect on other members of the superfamily.

[0231] FLT-3

[0232] FLT3 kinase is a tyrosine kinase receptor involved in the regulation and stimulation of cellular proliferation. See e.g., Gilliland et al., *Blood* 100:1532-42 (2002). The FLT3 kinase is a member of the class III receptor tyrosine

kinase (RTKIII) receptor family and belongs to the same subfamily of tyrosine kinases as c-kit, c-fms, and the platelet-derived growth factor a and B receptors. See e.g., Lyman et al., FLT3 *Ligand in THE CYTOKINE HANDBOOK* 989 (Thomson et al., eds. 4th Ed.) (2003). The FLT3 kinase has five immunoglobulin-like domains in its extracellular region as well as an insert region of 75-100 amino acids in the middle of its cytoplasmic domain. FLT3 kinase is activated upon the binding of the FLT3 ligand, which causes receptor dimerization. Dimerization of the FLT3 kinase by FLT3 ligand activates the intracellular kinase activity as well as a cascade of downstream substrates including Stat5, Ras, phosphatidylinositol-3-kinase (PI3K), PLCγ, Erk2, Akt, MAPK, SHC, SHP2, and SHIP. See e.g., Rosnet et al., *Acta Haematol.* 95:218 (1996); Hayakawa et al., *Oncogene* 19:624 (2000); Mizuki et al., *Blood* 96:3907 (2000); and Gilliand et al., *Curr. Opin. Hematol.* 9: 274-81 (2002). Both membrane-bound and soluble FLT3 ligand bind, dimerize, and subsequently activate the FLT3 kinase.

[**0233**] In normal cells, immature hematopoietic cells, typically CD34+ cells, placenta, gonads, and brain express FLT3 kinase. See, e.g., Rosnet, et al., *Blood* 82:1110-19 (1993); Small et al., *Proc. Natl. Acad. Sci. U.S.A.* 91:459-63 (1994); and Rosnet et al., *Leukemia* 10:238-48 (1 996). However, efficient stimulation of proliferation via FLT3 kinase typically requires other hematopoietic growth factors or interleukins. FLT3 kinase also plays a critical role in immune function through its regulation of dendritic cell proliferation and dilferentiation. See e.g., McKenna et al., Blood 95:3489-97 (2000).

[**0234**] Numerous hematologic malignancies express FLT3 kinase, the most prominent of which is AML. See e.g., Yokota et al., Leukemia 11:1605-09 (1997). Other FLT3 expressing malignancies include B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias. See e.g., Rasko et al., Leukemia 9:2058-66 (1995).

[**0235**] FLT3 kinase mutations associated with hematologic malignancies are activating mutations. In other words, the FLT3 kinase is constitutively activated without the need for binding and dimerization by FLT3 ligand, and therefore stimulates the cell to grow continuously.

[**0236**] Several studies have identified inhibitors of FLT3 kinase activity that also inhibit the kinase activity of related receptors, e.g., VEGF receptor (VEGFR), PDGF receptor (PDGFR), and kit receptor kinases. See e.g., Mendel et al., *Clin. Cancer Res.* 9:327-37 (2003); O'Farrell et al., *Blood* 101:3597-605 (2003); and Sun et al., *J. Med. Chem.* 46:1116-19 (2003). Such compounds effectively inhibit FLT3 kinase-mediated phosphorylation, cytokine production, cellular proliferation, resulting in the induction of apoptosis. See e.g., Spiekermann et al., *Blood* 101:1494-1504 (2003). Moreover, such compounds have potent antitumor activity in vitro and in vivo.

[**0237**] In some embodiments, the kinase is a class III receptor tyrosine kinase (RTKIII). In other embodiments, the kinase is a tyrosine kinase receptor intimately involved in the regulation and stimulation of cellular proliferation. In still other embodiments, the kinase is a fms-like tyrosine kinase 3 receptor (FLT-3 kinase). In this context, inhibition and reduction of the activity of FLT-3 kinase refers to a lower level of measured activity relative to a control experiment in which the protein, cell, or subject is not treated with the test compound, whereas an increase in the activity of FLT-3 kinase refers to a higher level of measured activity relative to a control experiment. In particular embodiments, the reduction or increase is at least 10%. One of skill in the art will appreciate that reduction or increase in the activity of FLT-3 kinase of at least 20%, 50%, 75%, 90% or 100% or any integer between 10% and 100% may be preferred for particular applications.

[**0238**] Compounds provided herein are useful in treating conditions characterized by inappropriate FLT3 activity such as proliferative disorders. FLT3 activity includes, but is not limited to, enhanced FLT3 activity resulting from increased or de novo expression of FLT3 in cells, increased FLT3 expression or activity, and FLT3 mutations resulting in constitutive activation. The existence of inappropriate or abnormal FLT3 ligand and FLT3 levels or activity can be determined using well known methods in the art. For example, abnormally high FLT3 levels can be determined using commercially available ELISA kits. FLT3 levels can be determined using flow cytometric analysis, immunohistochemical analysis, and in situ hybridization techniques.

[**0239**] An inappropriate activation of the FLT3 can be determined by an increase in one or more of the activities occurring subsequent to FLT3 binding: (1) phosphorylation or autophosphorylation of FLT3; (2) phosphorylation of a FLT3 substrate, e.g., Stat5, Ras; (3) activation of a related complex, e.g., PI3K; (4) activation of an adaptor molecule; and (5) cellular proliferation. These activities are readily measured by well known methods in the art.

[**0240**] Formulations

[**0241**] The compounds described herein can be used to prepare a medicament, such as by formulation into pharmaceutical compositions for administration to a subject using techniques generally known in the art. A summary of such pharmaceutical compositions may be found, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. The compounds of the invention can be used singly or as components of mixtures. Preferred forms of the compounds are those for systemic administration as well as those for topical or transdermal administration. Formulations designed for timed release are also within the scope of the invention. Formulation in unit dosage form is also preferred for the practice of the invention.

[**0242**] In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packeted tablets or capsules, and powders in vials or ampoules.

[**0243**] The compounds described herein may be labeled isotopically (e.g. with a radioisotope) or by any other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels. The compositions may be in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. Suitable excipients or carriers are, for example, water, saline, dextrose, glycerol, alcohols, aloe vera gel, allantoin, glycerin, vitamin A and E oils, mineral

oil, propylene glycol, PPG-2 myristyl propionate, and the like. Of course, these compositions may also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[0244] Methods for the preparation of compositions comprising the compounds described herein include formulating the derivatives with one or more inert, pharmaceutically acceptable carriers to form either a solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein.

[0245] A carrier of the invention can be one or more substances which also serve to act as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, or tablet disintegrating agent. A carrier can also be an encapsulating material.

[0246] In powder forms of the invention's compositions, the carrier is preferably a finely divided solid in powder form which is interdispersed as a mixture with a finely divided powder from of one or more compound. In tablet forms of the compositions, one or more compounds is intermixed with a carrier with appropriate binding properties in suitable proportions followed by compaction into the shape and size desired. Powder and tablet form compositions preferably contain between about 5 to about 70% by weight of one or more compound. Carriers that may be used in the practice of the invention include, but are not limited to, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

[0247] The compounds of the invention may also be encapsulated or microencapsulated by an encapsulating material, which may thus serve as a carrier, to provide a capsule in which the derivatives, with or without other carriers, is surrounded by the encapsulating material. In an analogous manner, cachets comprising one or more compounds are also provided by the instant invention. Tablet, powder, capsule, and cachet forms of the invention can be formulated as single or unit dosage forms suitable for administration, optionally conducted orally.

[0248] In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted. One or more compounds are then dispersed into the melted material by, as a non-limiting example, stirring. The non-solid mixture is then placed into molds as desired and allowed to cool and solidify.

[0249] Non-limiting compositions in liquid form include solutions suitable for oral or parenteral administration, as well as suspensions and emulsions suitable for oral administration. Sterile aqueous based solutions of one or more compounds, optionally in the presence of an agent to increase solubility of the derivative(s), are also provided. Non-limiting examples of sterile solutions include those comprising water, ethanol, and/or propylene glycol in forms suitable for parenteral administration. A sterile solution of the invention may be prepared by dissolving one or more compounds in a desired solvent followed by sterilization, such as by filtration through a sterilizing membrane filter as a non-limiting example. In another embodiment, one or more compounds are dissolved into a previously sterilized solvent under sterile conditions.

[0250] A water based solution suitable for oral administration can be prepared by dissolving one or more compounds in water and adding suitable flavoring agents, coloring agents, stabilizers, and thickening agents as desired. Water based suspensions for oral use can be made by dispersing one or more compounds in water together with a viscous material such as, but not limited to, natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, and other suspending agents known to the pharmaceutical field.

[0251] In therapeutic use, the compounds of the invention are administered to a subject at dosage levels of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day. For example, a human subject of approximately 70 kg, this is a dosage of from 35 mg to 560 mg per day. Such dosages, however, may be altered depending on a number of variables, not limited to the activity of the compound used, the condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the condition being treated, and the judgment of the practitioner.

[0252] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon.

[0253] Methods of Use

[0254] By modulating kinase activity, the compounds disclosed herein can be used to treat a variety of diseases. Suitable conditions characterized by undesirable protein-kinase activity can be treated by the compounds presented herein. As used herein, the term "condition" refers to a disease, disorder, or related symptom where inappropriate kinase activity is present. In some embodiments, these conditions are characterized by aggressive neovasculaturization including tumors, especially acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs). In some embodiments, a FLT3 modulating compounds may be used to treat tumors. The ability of compounds that inhibit FLT3 kinase activity to treat tumors has been established. Compounds having this property include SU5416 (Sugen), PKC412 (Novartis), GTP-14564 and CT53518 (Millennium). See e.g., Giles et al., Blood 102:795-801 (2003); Weisberg et al., Cancer Cell 1:433-43 (2002); Murata et al., J. Biol. Chem. 278:32892-98 (2003); and Kelly et al., Cancer Cell 1:421-32 (2002).

[0255] Compounds presented herein are useful in the treatment of a variety of biologically aberrant conditions or disorders related to tyrosine kinase signal transduction. Such disorders pertain to abnormal cell proliferation, differentiation, and/or metabolism. Abnormal cell proliferation may result in a wide array of diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis).

[0256] In various embodiments, compounds presented herein regulate, modulate, and/or inhibit disorders associated with abnormal cell proliferation by affecting the enzymatic activity of one or more tyrosine kinases and interfering with the signal transduced by said kinase. More particularly, the present invention is directed to compounds which regulate, modulate said kinase mediated signal transduction pathways as a therapeutic approach to cure leukemia and many kinds of solid tumors, including but not limited to carcinoma, sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma, melanoma and myoblastoma. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreas cancers, colon cancers, blood cancers, lung cancers and bone cancers.

[0257] In other embodiments, compounds herein are useful in the treatment of cell proliferative disorders including cancers, blood vessel proliferative disorders, fibrotic disorders, and mesangial cell proliferative disorders. Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferation disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage, and ocular diseases, like diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness. Conversely, disorders related to the shrinkage, contraction or closing of blood vessels, such as restenosis, are also implicated.

[0258] Fibrotic disorders refer to the abnormal formation of extracellular matrix. Examples of fibrotic disorders include hepatic cirrhosis and mesangial cell proliferative disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis. Other fibrotic disorders implicated include atherosclerosis (see, below).

[0259] Mesangial cell proliferative disorders refer to disorders brought about by abnormal proliferation of mesangial cells. Mesangial proliferative disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection, and glomerulopathies. The cell proliferative disorders which are indications of the present invention are not necessarily independent. For example, fibrotic disorders may be related to, or overlap, with blood vessel proliferative disorders. For example, atherosclerosis results, in part, in the abnormal formation of fibrous tissue within blood vessels.

[0260] Compounds of the invention can be-administered to a subject upon determination of the subject as having a disease or unwanted condition that would benefit by treatment with said derivative. The determination can be made by medical or clinical personnel as part of a diagnosis of a disease or condition in a subject. Non-limiting examples include determination of a risk of acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

[0261] The methods of the invention can comprise the administration of an effective amount of one or more compounds as disclosed herein, optionally in combination with one or more other active agents for the treatment of a disease or unwanted condition as disclosed herein. The subject is preferably human, and repeated administration over time is within the scope of the present invention.

[0262] The present invention thus also provides compounds described above and their salts or solvates and pharmaceutically acceptable salts or solvates thereof for use in the prevention or treatment of disorders mediated by aberrant protein tyrosine kinase activity such as human malignancies and the other disorders mentioned above. The compounds of the present invention are especially useful for the treatment of disorders caused by aberrant kinase activity such as breast, ovarian, gastric, pancreatic, non-small cell lung, bladder, head and neck cancers, and psoriasis. The cancers include hematologic cancers, for example, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs).

[0263] A further aspect of the invention provides a method of treatment of a human or animal subject suffering from a disorder mediated by aberrant protein tyrosine kinase activity, including susceptible malignancies, which comprises administering to the subject an effective amount of a compound described above or a pharmaceutically acceptable salt or solvate thereof.

[0264] A further aspect of the present invention provides the use of a compound described above, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of cancer and malignant tumors. The cancer can be stomach, gastric, bone, ovary, colon, lung, brain, larynx, lymphatic system, genitourinary tract, ovarian, squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, small-cell lung cancer, leukemia, acute myelogenous leukemia (AML), B-precursor cell acute lymphoblastic leukemias, myelodysplastic leukemias, T-cell acute lymphoblastic leukemias, and chronic myelogenous leukemias (CMLs), glioma, colorectal cancer, genitourinary cancer gastrointestinal cancer, or pancreatic cancer.

[0265] In accordance with the present invention, compounds provided herein are useful for preventing and treating conditions associated with ischemic cell death, such as myocardial infarction, stroke, glaucoma, and other neurodegenerative conditions. Various neurodegenerative conditions which may involve apoptotic cell death, include, but are not limited to, Alzheimer's Disease, ALS and motor neuron degeneration, Parkinson's disease, peripheral neuropathies, Down's Syndrome, age related macular degeneration (ARMD), traumatic brain injury, spinal cord injury, Huntington's Disease, spinal muscular atrophy, and HIV encephalitis. The compounds described in detail above can be used in methods and compositions for imparting neuroprotection and for treating neurodegenerative diseases.

[0266] The compounds described herein, can be used in a pharmaceutical composition for the prevention and/or the treatment of a condition selected from the group consisting of arthritis (including osteoarthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis and rheumatoid arthritis), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neurodegenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders, and septic shock, arthritis, fever, common cold, pain and cancer in a mammal, preferably a human, cat, livestock or a dog, comprising an amount of a compound described herein or a pharmaceutically acceptable salt thereof effective in such prevention and/or treatment optionally with a pharmaceutically acceptable carrier.

[0267] A further aspect of the present invention provides the use of a compound described above, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of psoriasis.

[0268] As one of skill in the art will recognize, the compounds can be administered before, during or after the occurrence of a condition or a disease, and the timing of administering the composition containing a compound can vary. Thus, for example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions and diseases in order to prevent the occurrence of the disorder. The compounds and compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, preferably within the first 48 hours of the onset of the symptoms, more preferably within the first 6 hours of the onset of the symptoms, and most preferably within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as, for example, an intravenous injection, a bolus injection, infusion over 5 min. to about 5 hours, a pill, a capsule, transdermal patch, buccal delivery, and the like, or a combination thereof. A compound is preferably administered as soon as is practicable after the onset of a condition or a disease is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. As one of skill in the art will recognize, the length of treatment can vary for each subject, and the length can be determined using the known criteria. For example, the compound or a formulation containing the compound can be administered for at least 2 weeks, preferably about 1 month to about 5 years, and more preferably from about 1 month to about 3 years.

[0269] Kits/Articles of Manufacture

[0270] For use in the therapeutic applications described herein, kits and articles of manufacture are also within the scope of the invention. Such kits can comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method of the invention. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers can be formed from a variety of materials such as glass or plastic.

[0271] For example, the container(s) can comprise one or more compounds of the invention, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container can be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods of the present invention.

[0272] A kit of the invention will typically may comprise one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound of the invention. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[0273] A label can be on or associated with the container. A label can be on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label can be associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. A label can be used to indicate that the contents are to be used for a specific therapeutic application. The label can also indicate directions for use of the contents, such as in the methods described herein.

[0274] The terms "kit" and "article of manufacture" may be used as synonyms.

EXAMPLES

[0275] The present invention is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. For all formulations herein, multiple doses may be proportionally compounded as is known in the art.

[0276] The invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation. Thus, it will be appreciated by those of skill in the art that conditions such as choice of solvent, temperature of reaction, volumes, reaction time may vary while still producing the desired compounds. In addition, one of skill in the art will also appreciate that many of the reagents provided in the following examples may be substituted with other suitable reagents. See, e.g., Smith & March, *Advanced Organic Chemistry,* 5th ed. (2001).

Example A

Synthesis of Isoxazole-Amides

[0277] Compounds A1 through A240 are synthesized by methods known in the art or described herein. The structures are shown below in Table A:

TABLE A

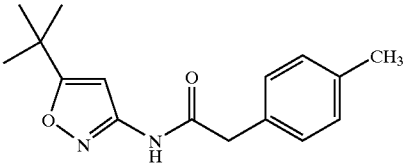
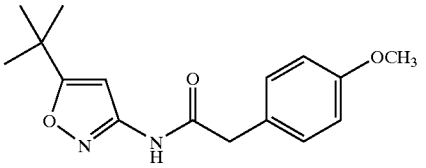
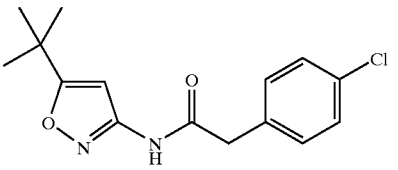
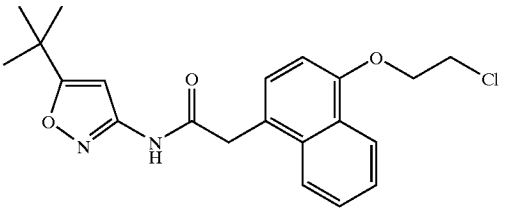
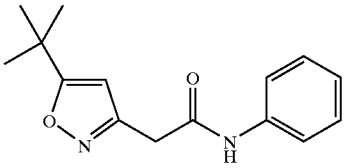
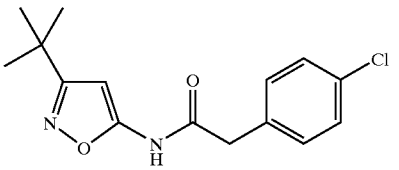
NO.	STRUCTURE
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TABLE A-continued

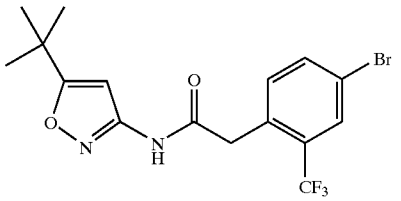
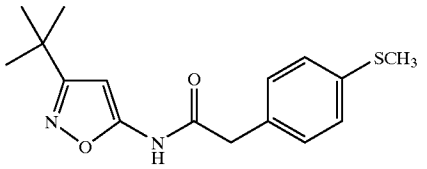
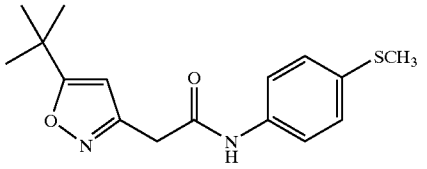
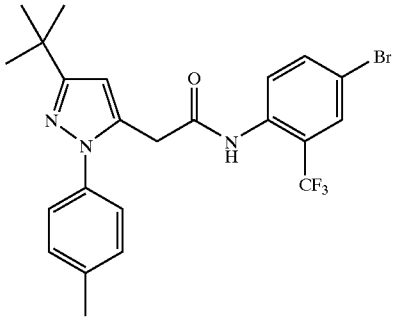
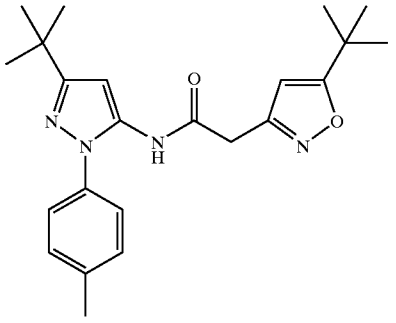
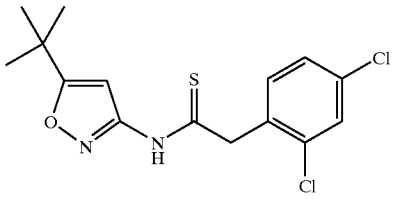
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TABLE A-continued

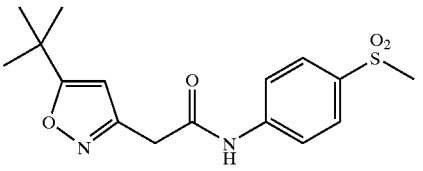
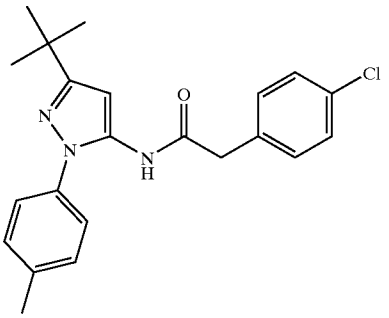
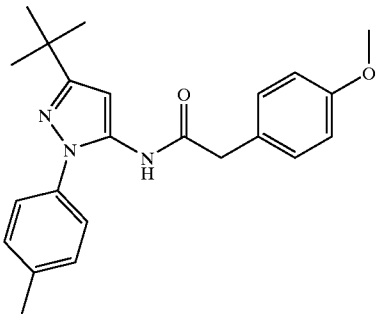
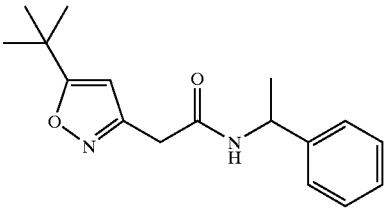
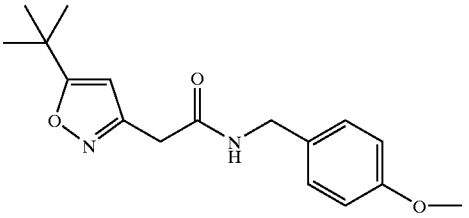
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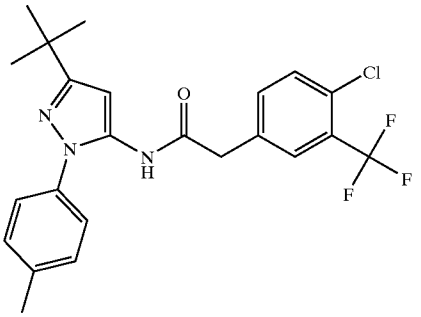
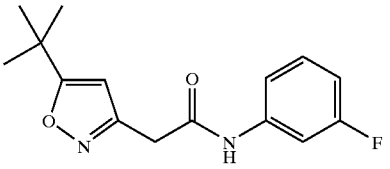
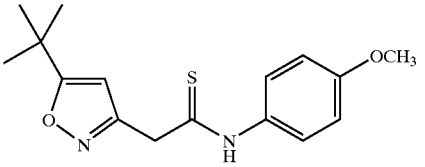
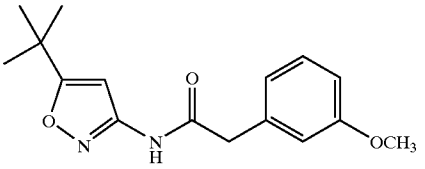
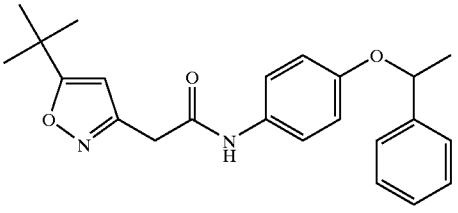
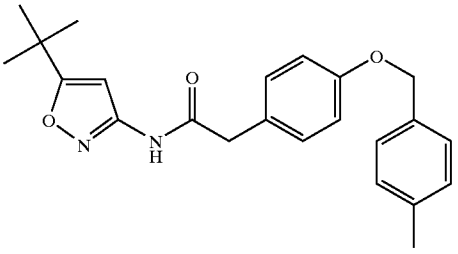
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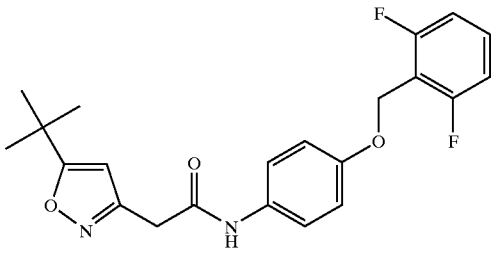
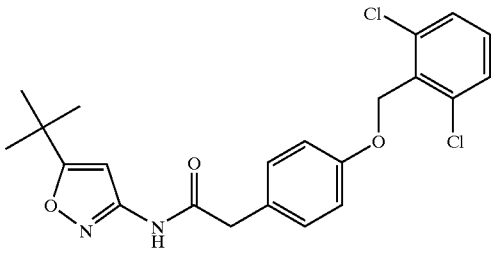
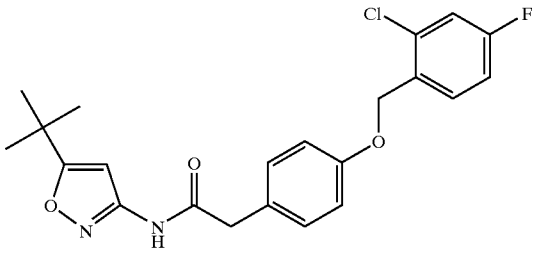
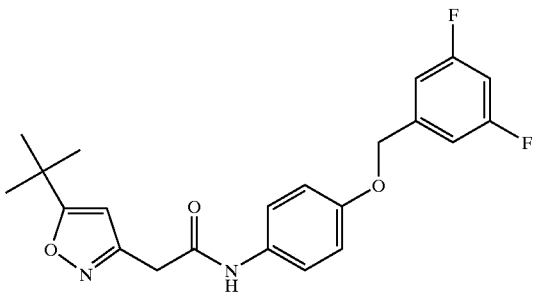
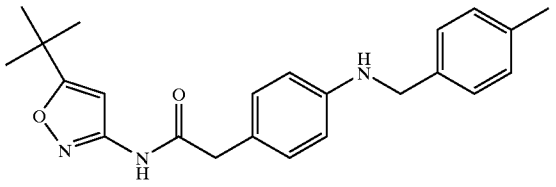
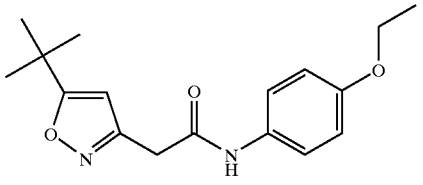
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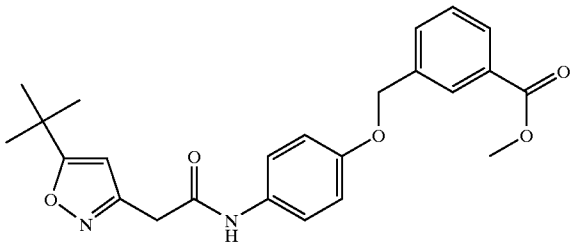
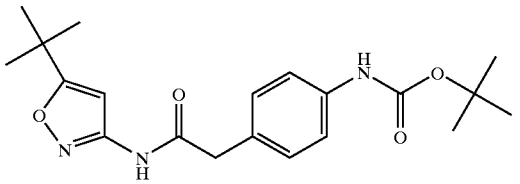
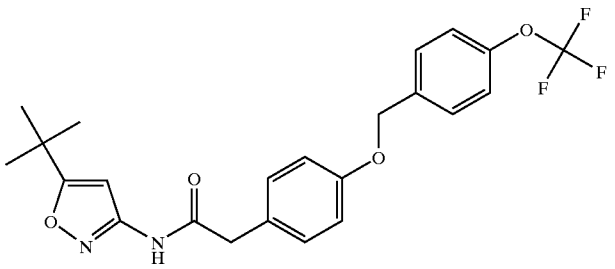
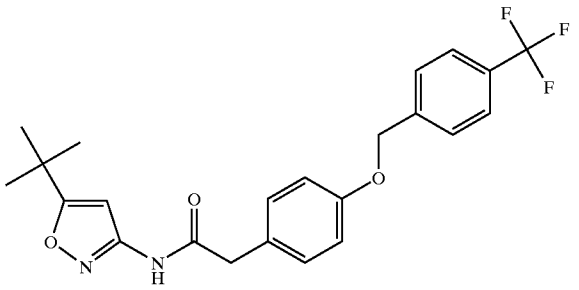
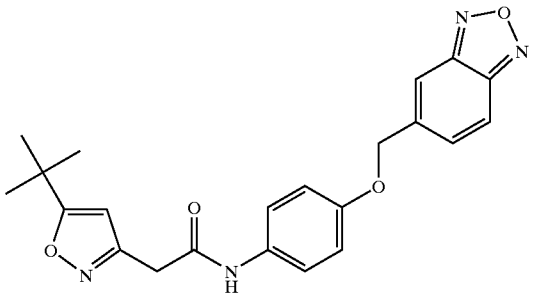
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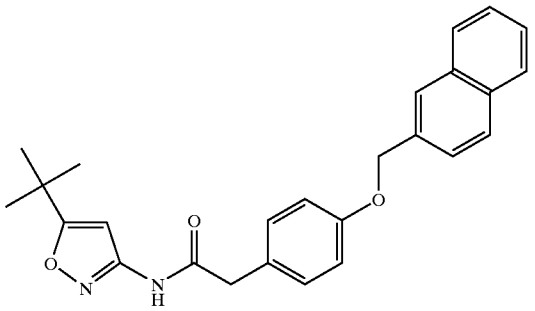
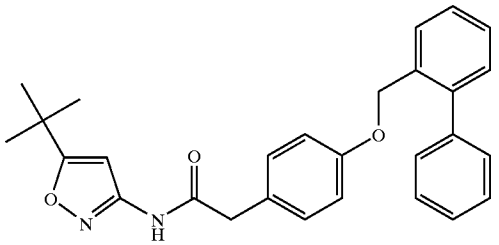
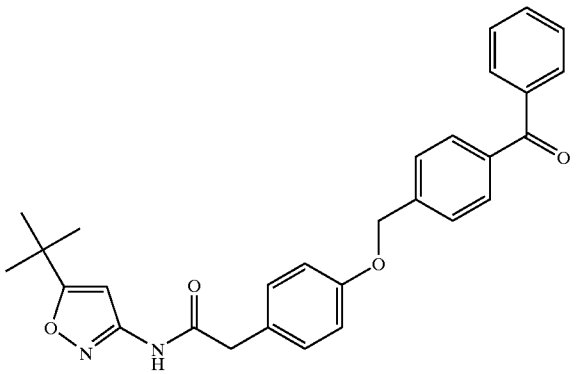
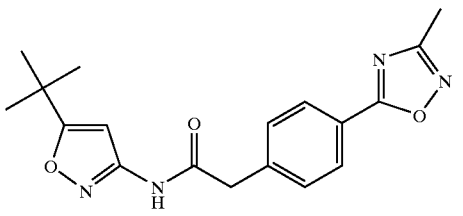
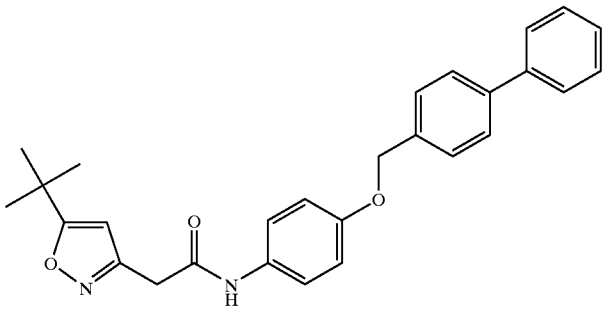
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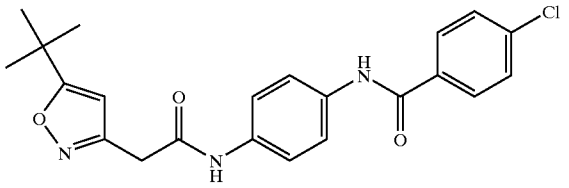
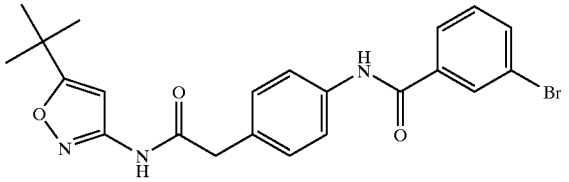
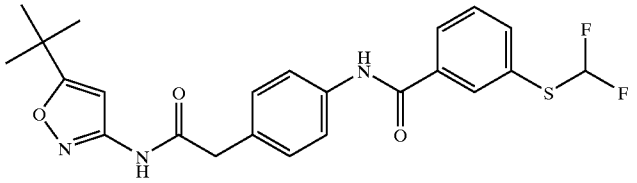
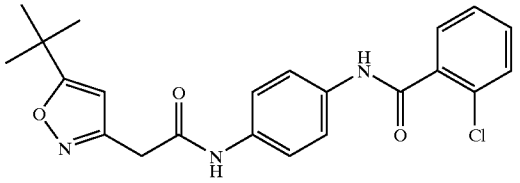
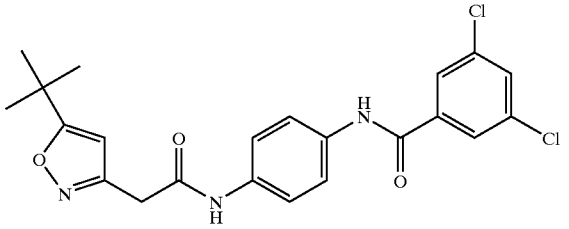
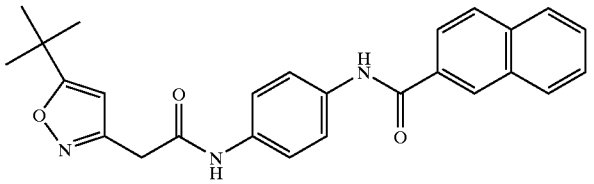
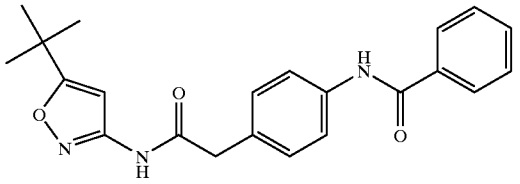
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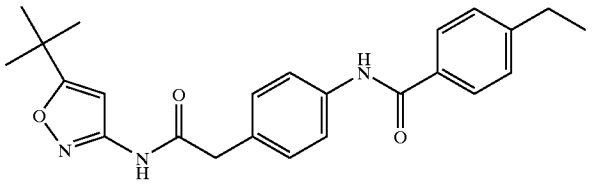
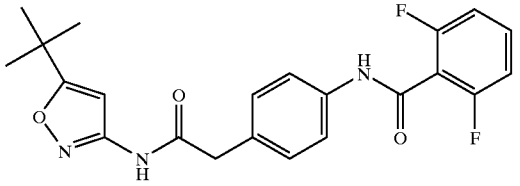
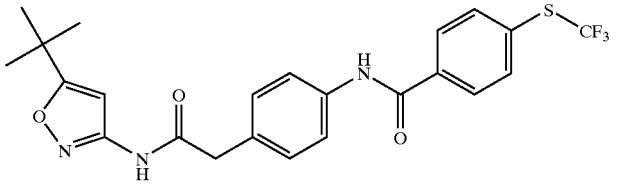
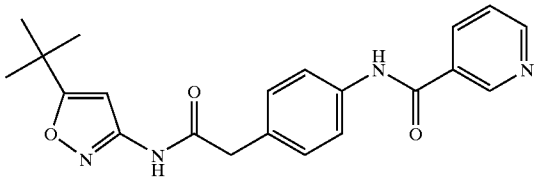
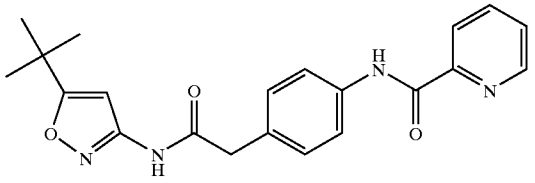
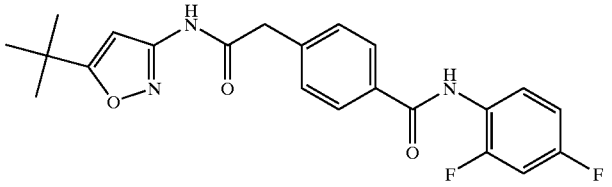
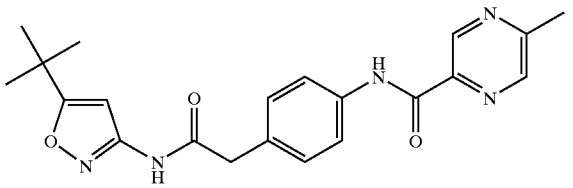
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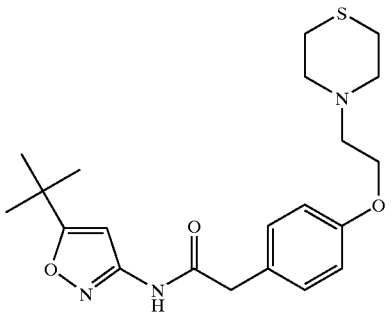
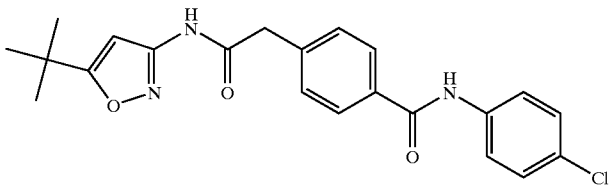
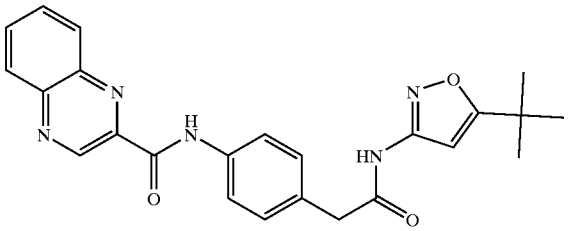
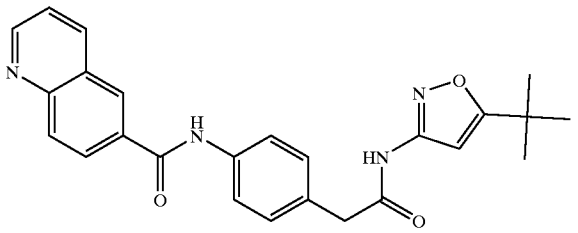
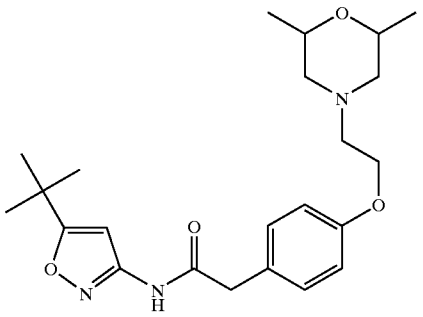
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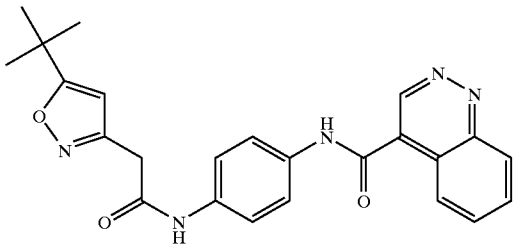
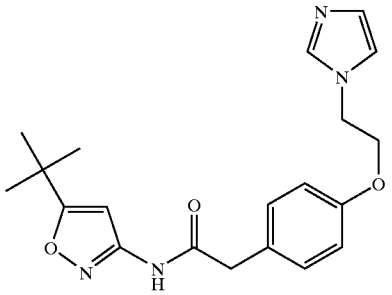
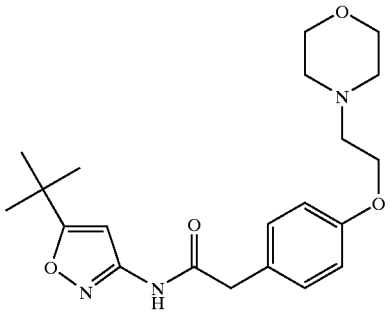
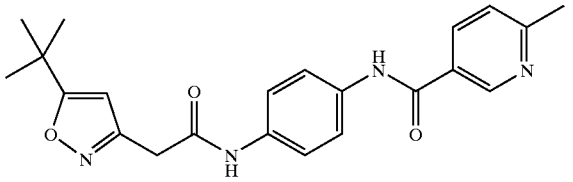
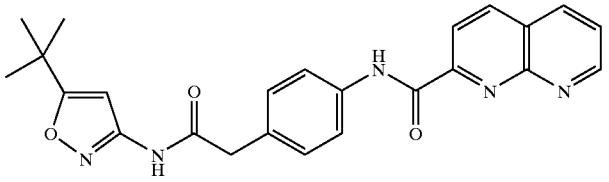
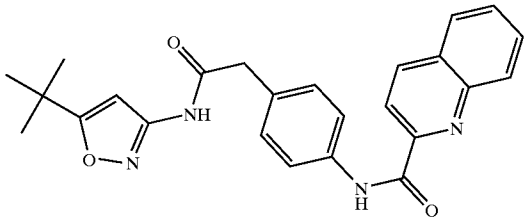
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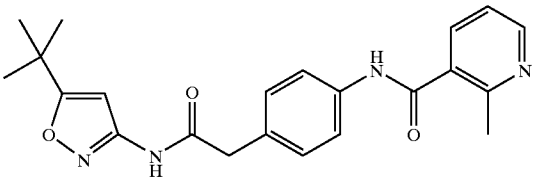
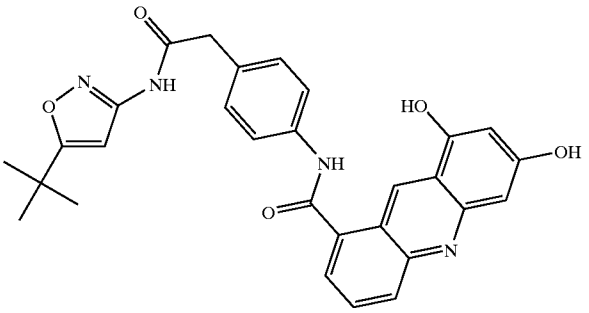
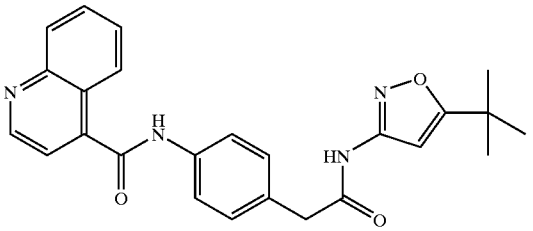
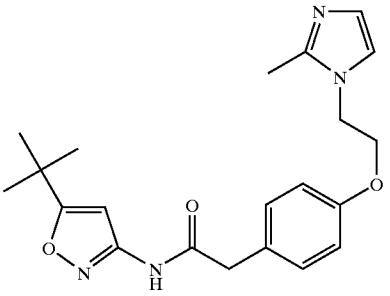
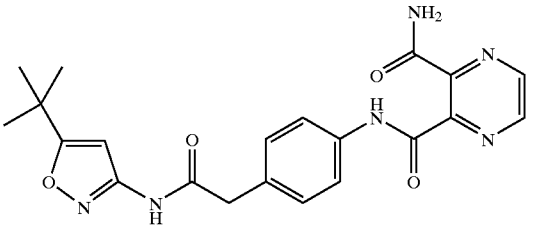
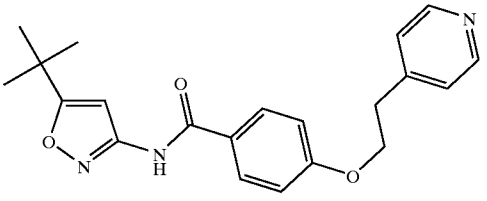
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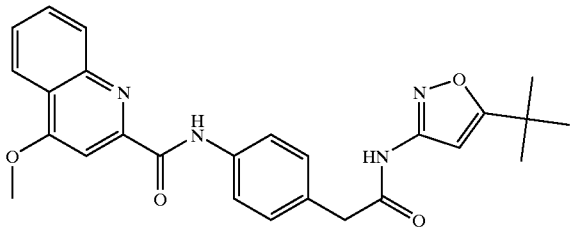
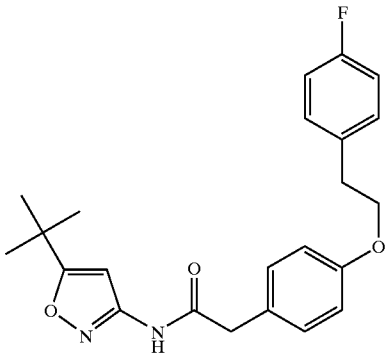
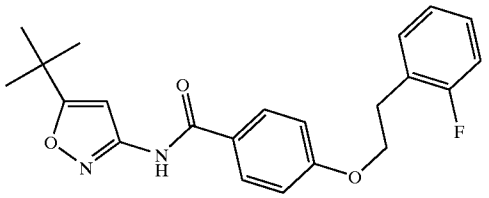
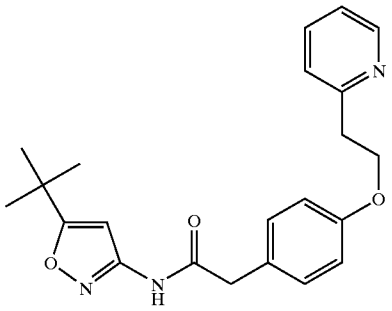
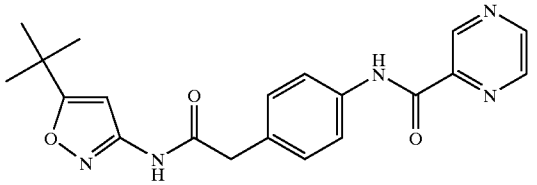
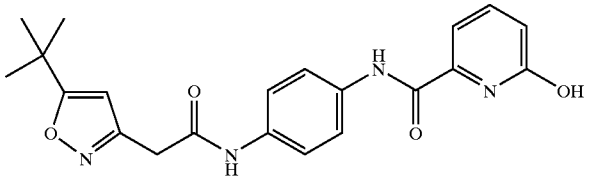
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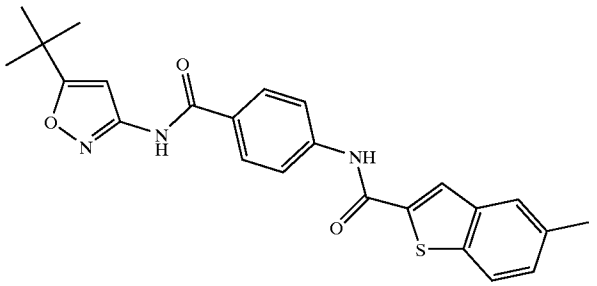
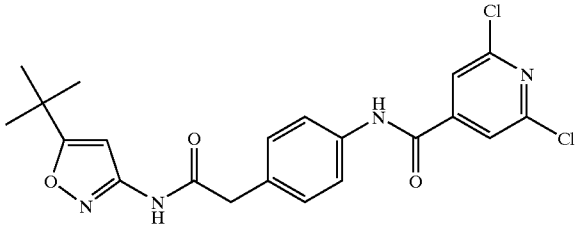
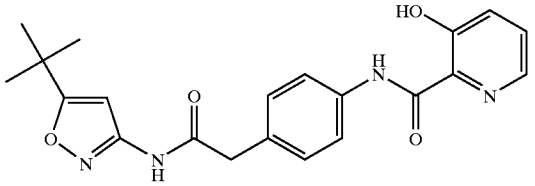
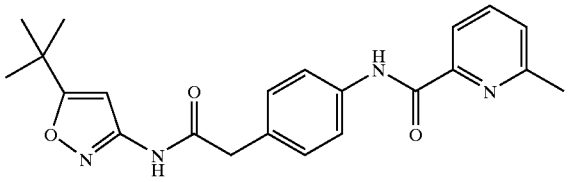
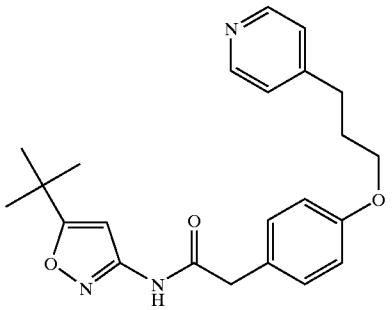
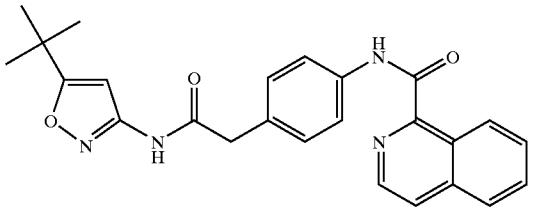
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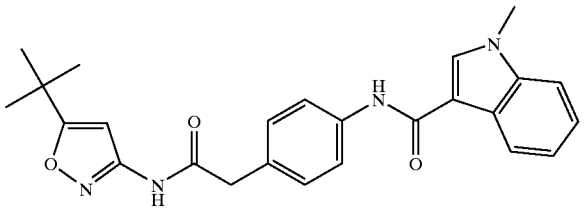
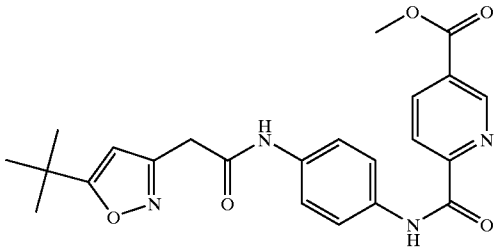
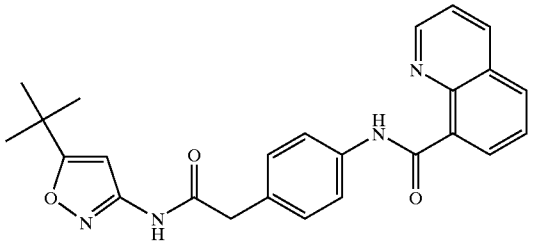
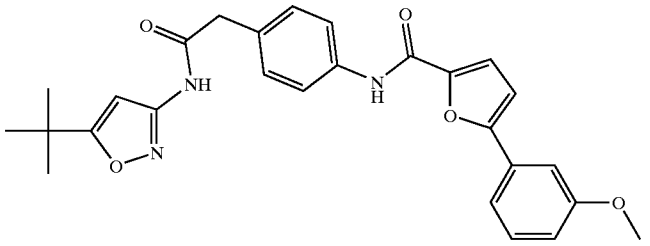
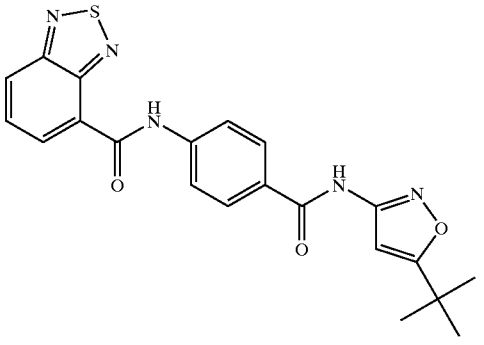
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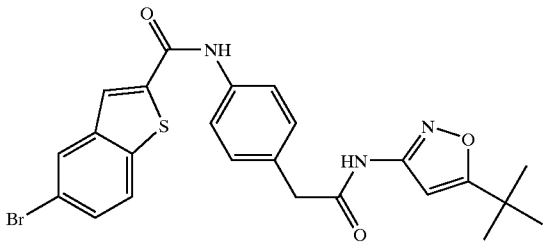
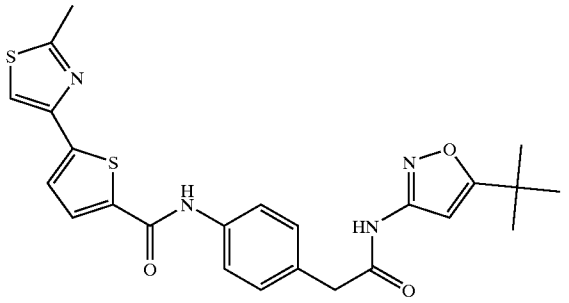
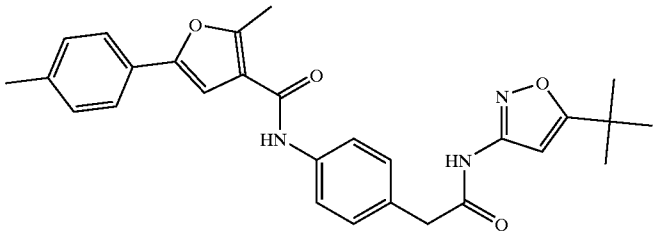
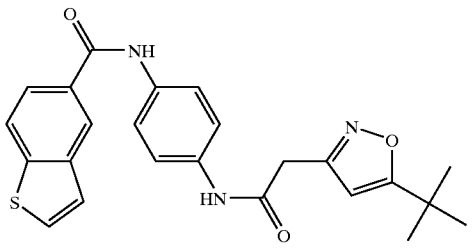
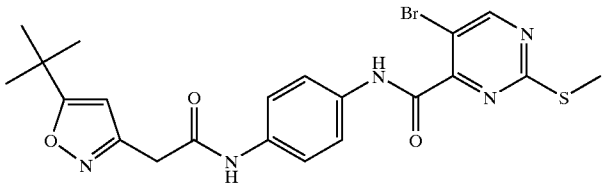
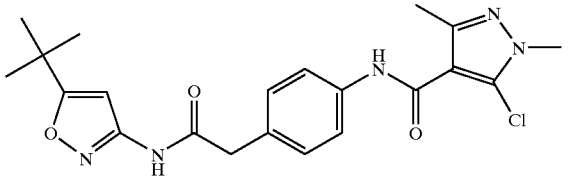
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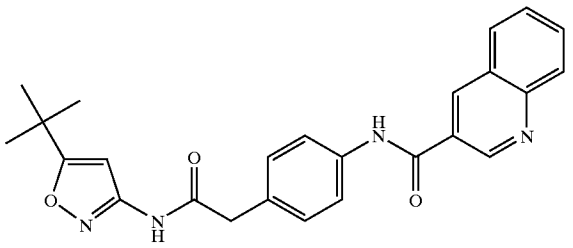
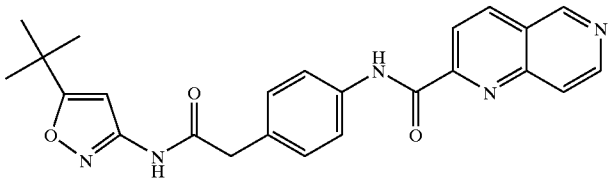
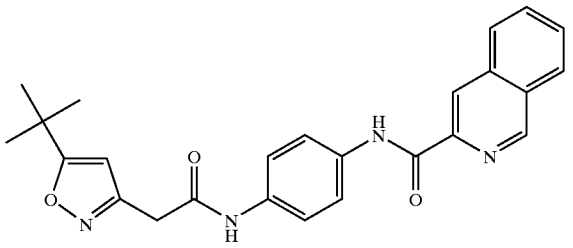
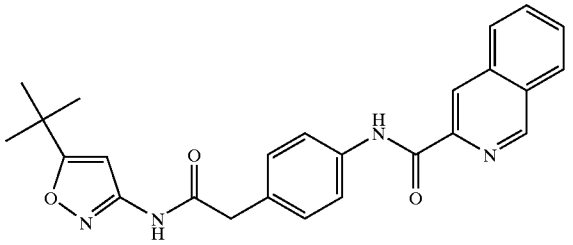
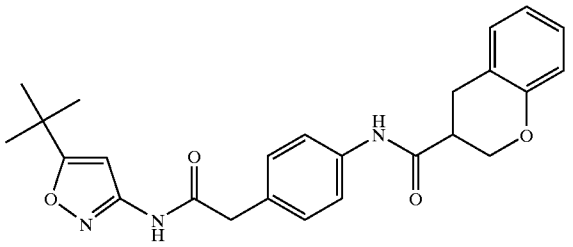
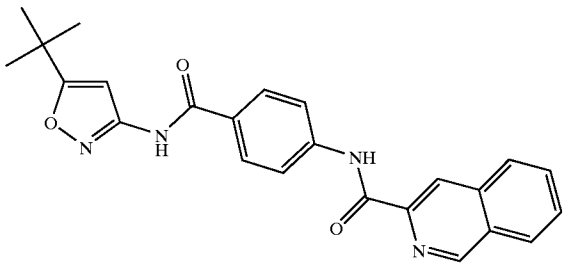
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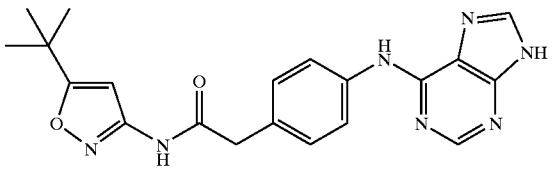
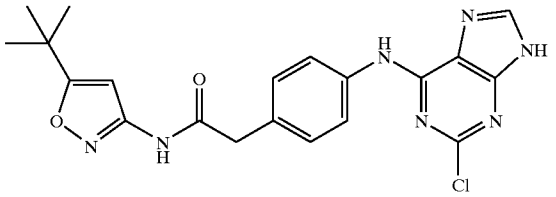
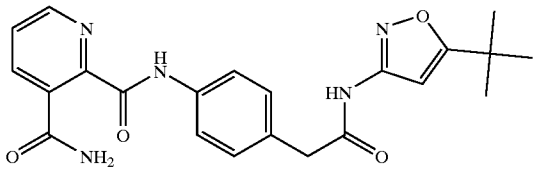
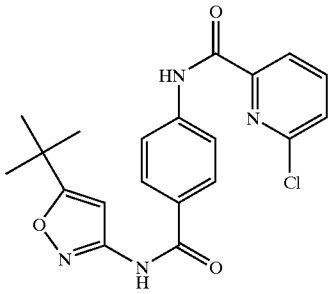
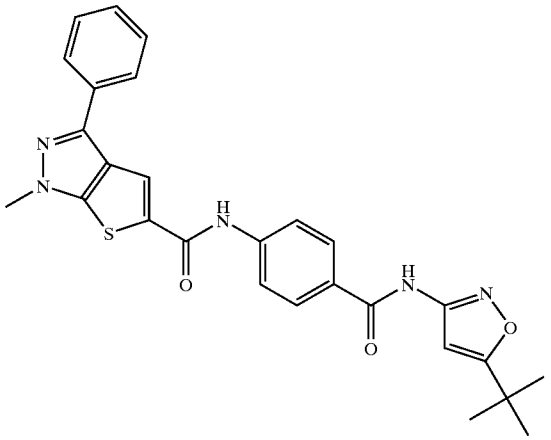
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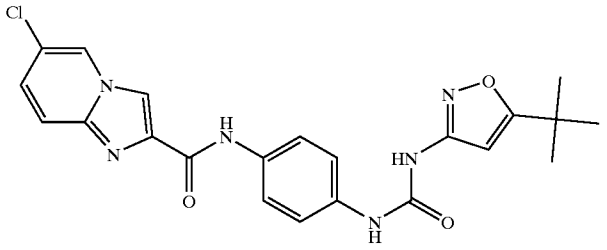
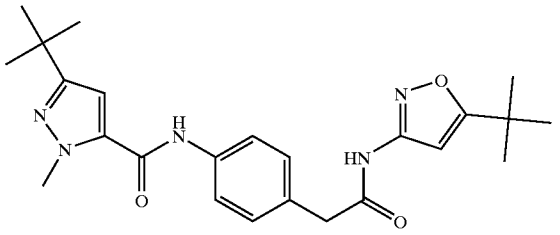
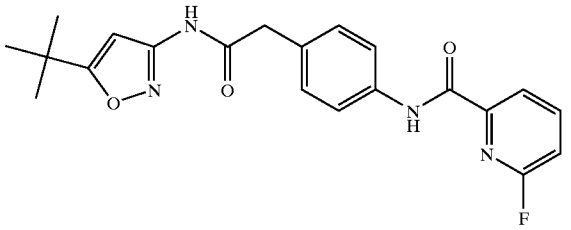
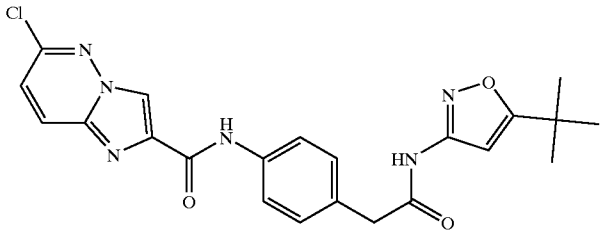
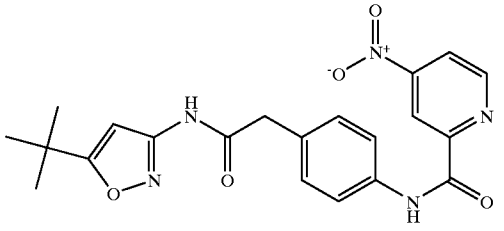
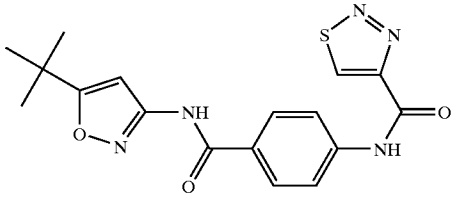
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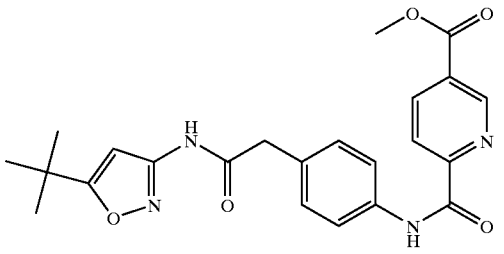
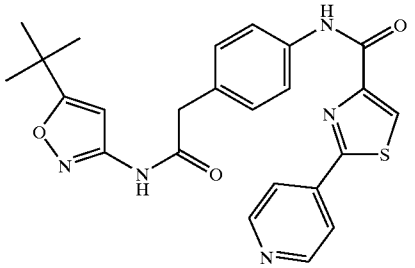
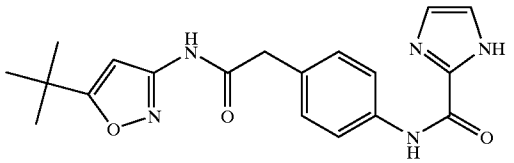
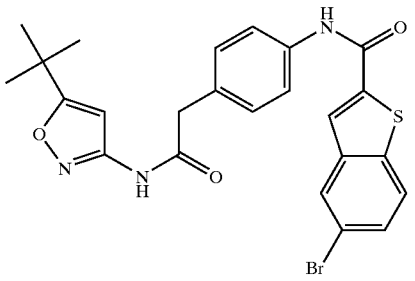
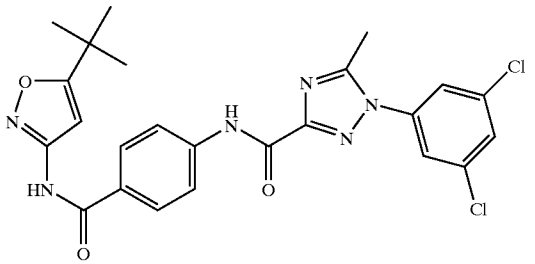
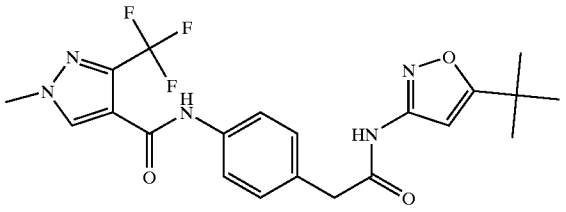
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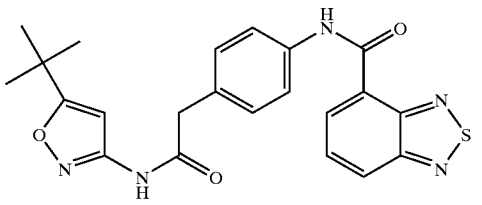
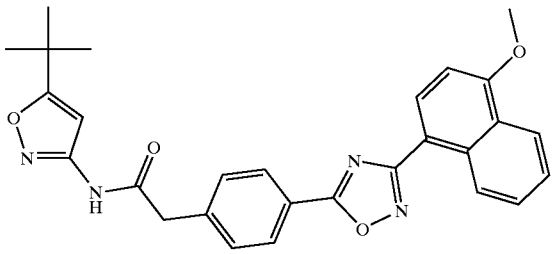
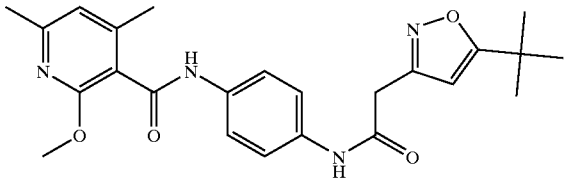
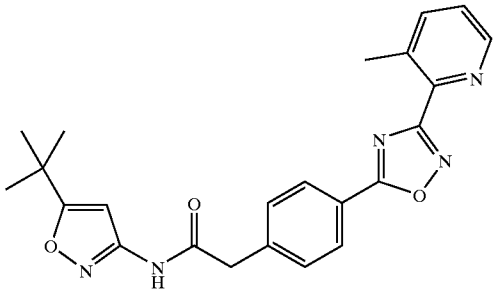
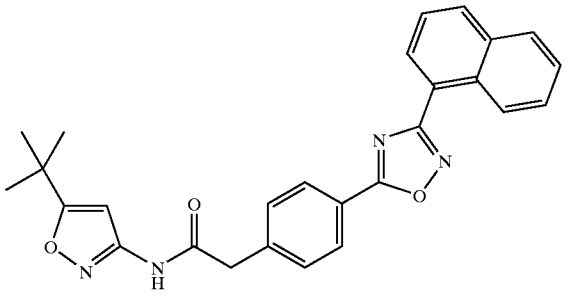
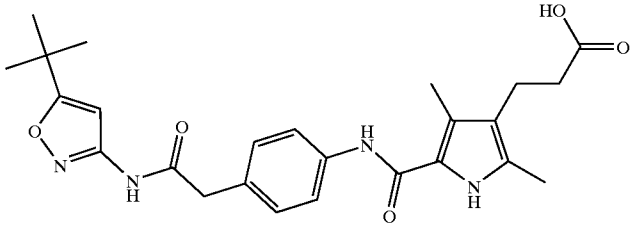
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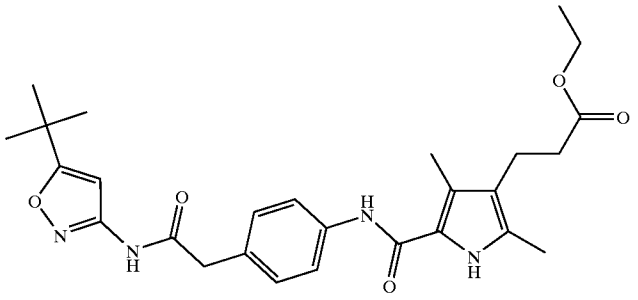
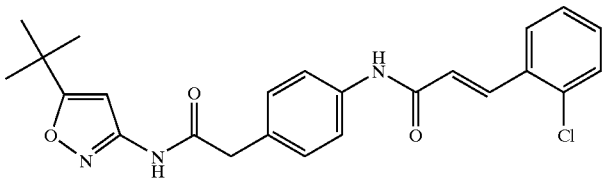
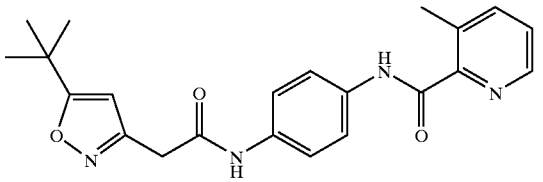
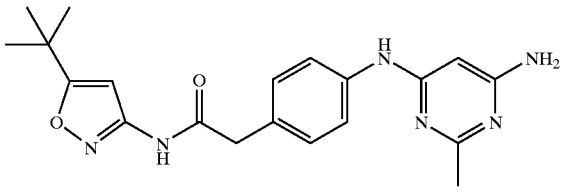
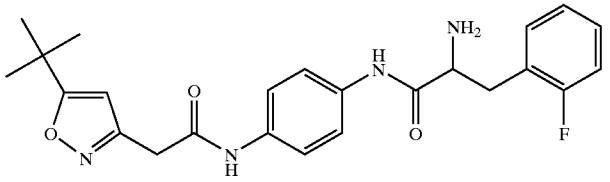
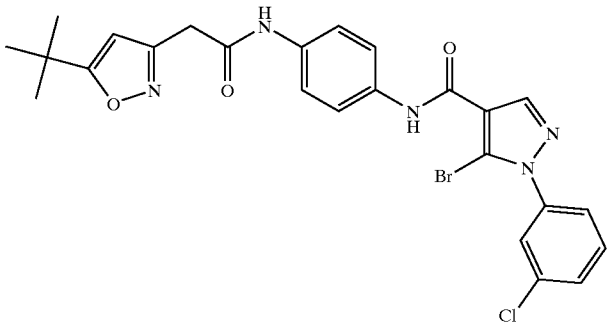
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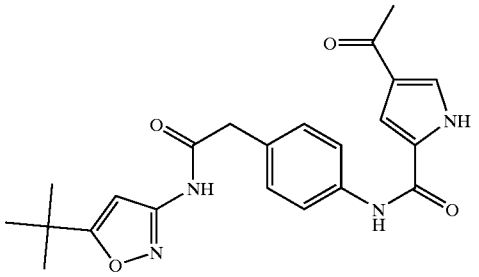
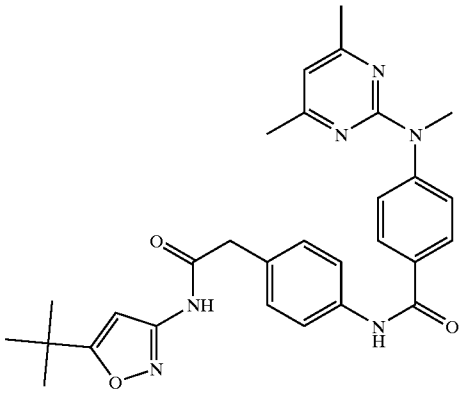
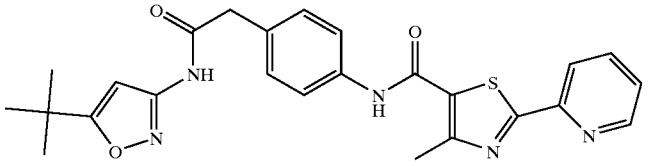
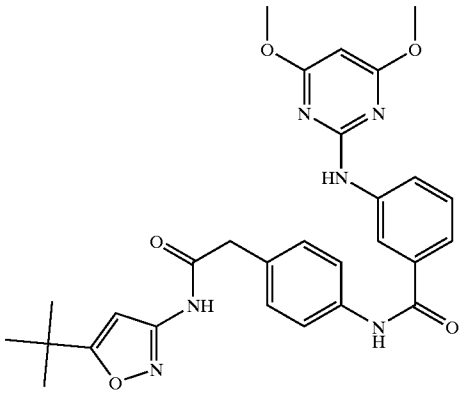
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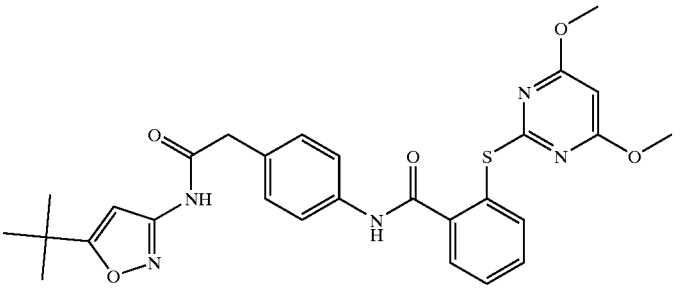
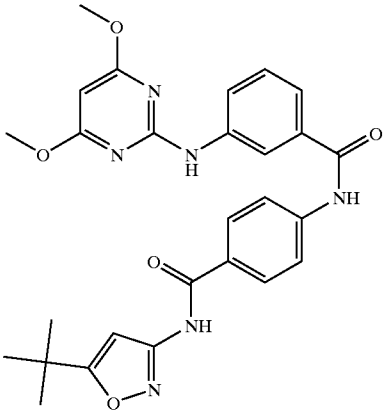
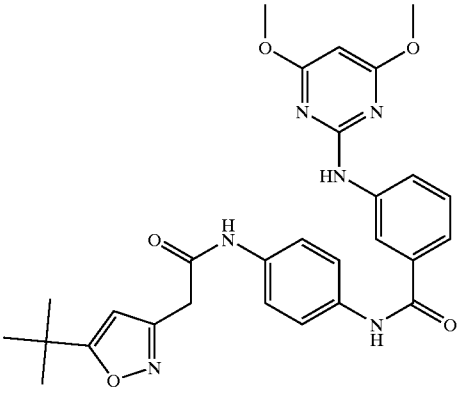
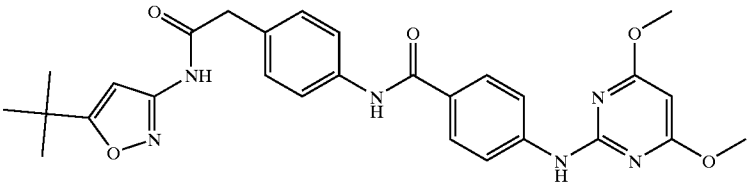
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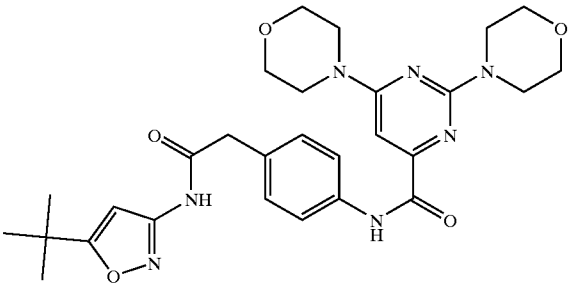
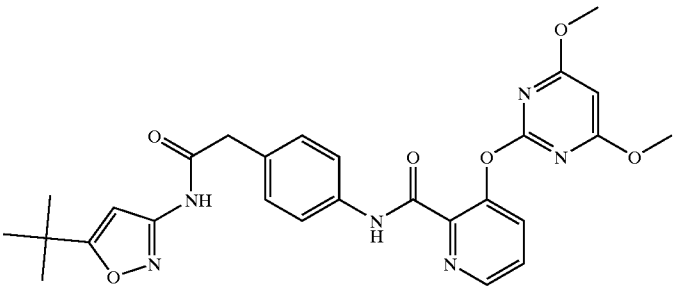
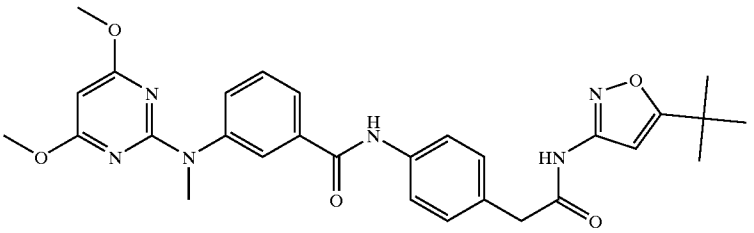
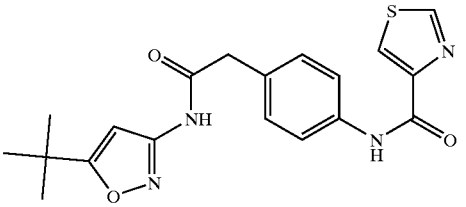
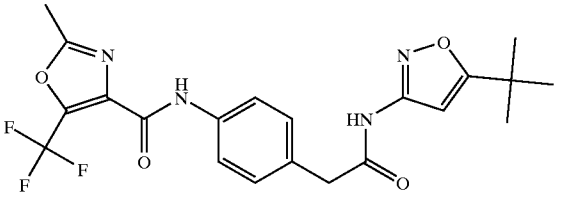
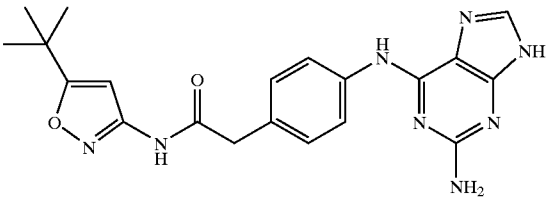
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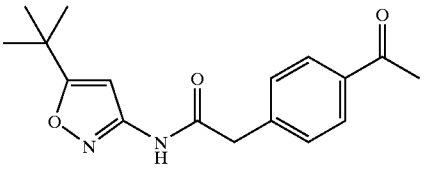
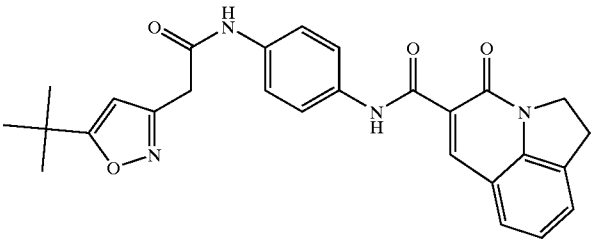
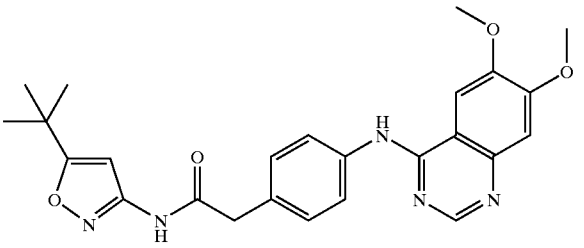
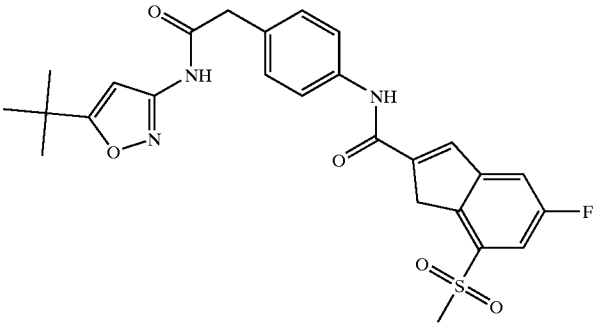
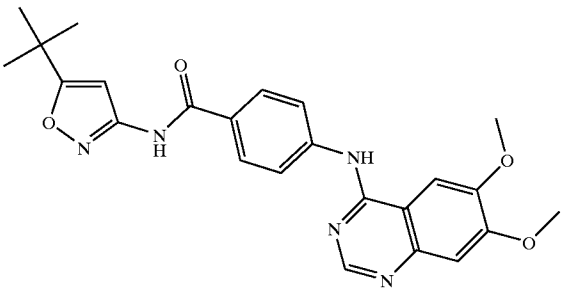
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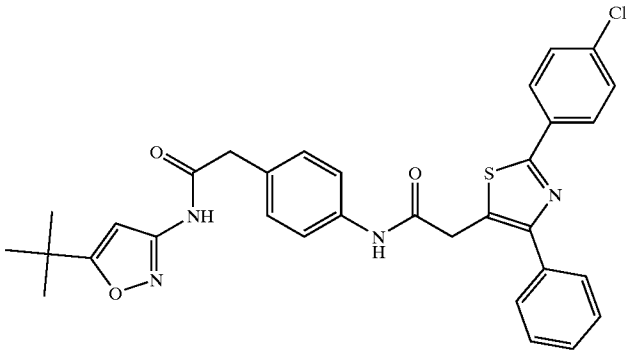
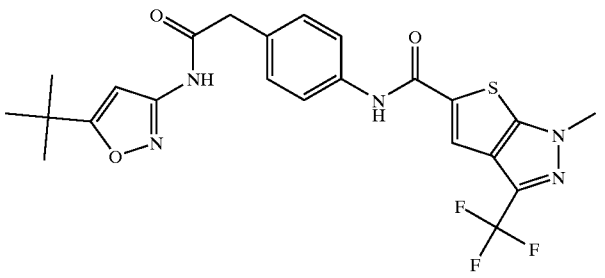
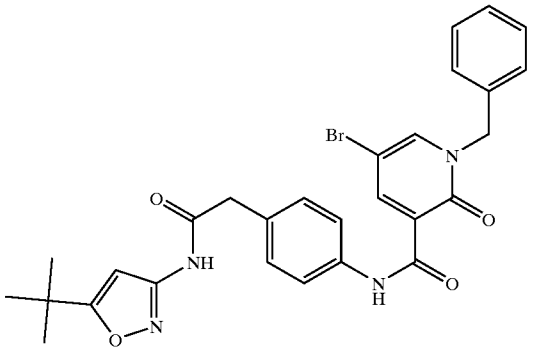
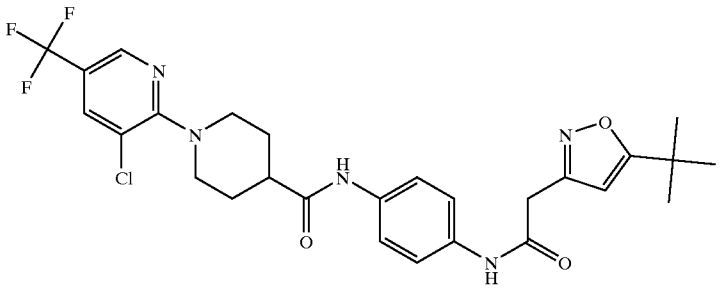
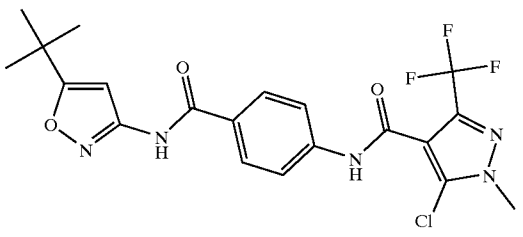
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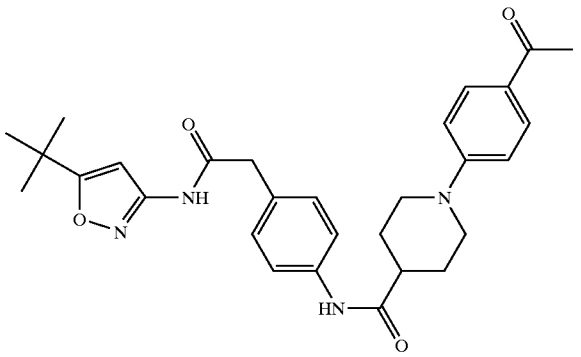
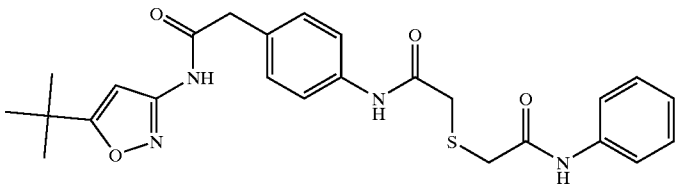
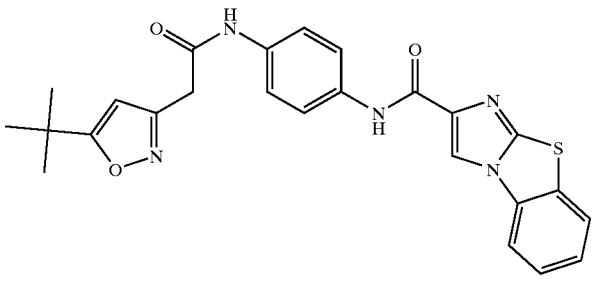
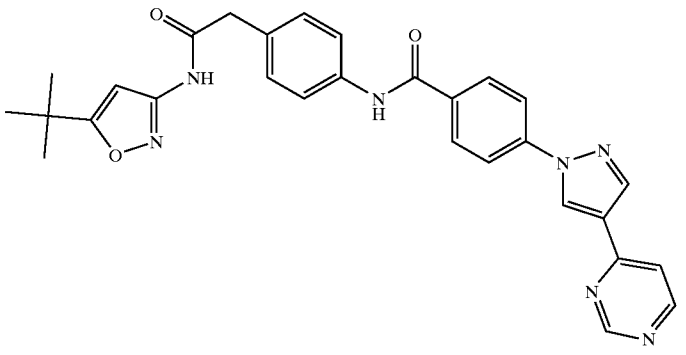
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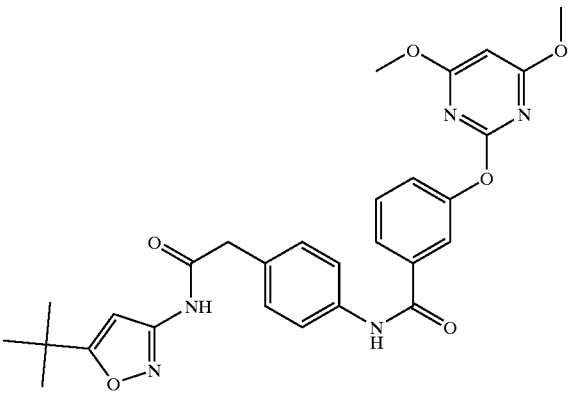
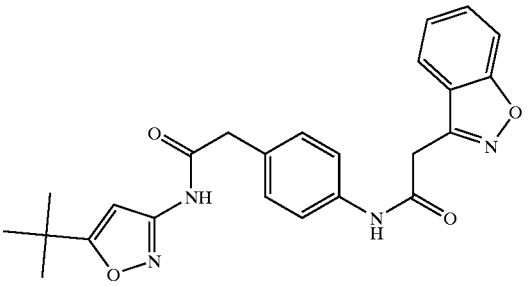
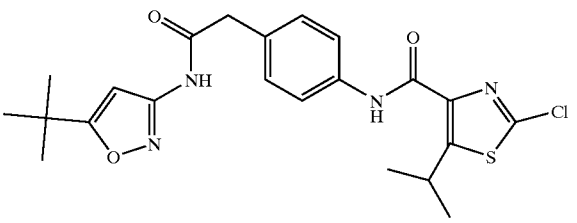
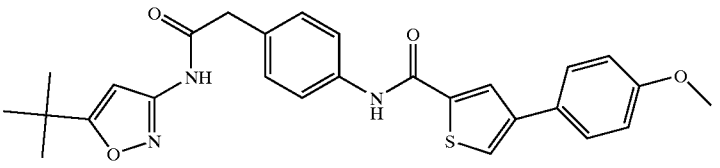
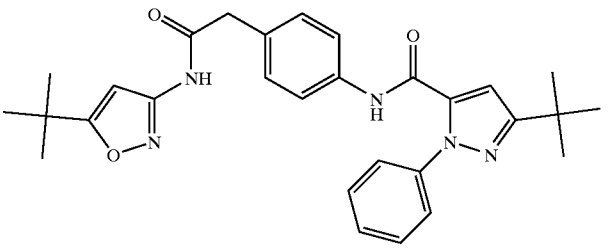
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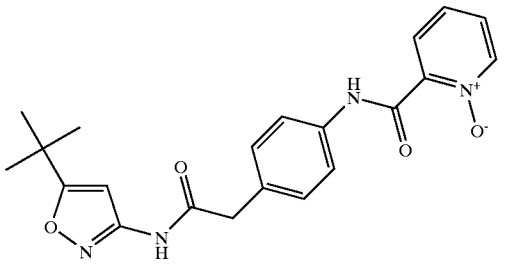
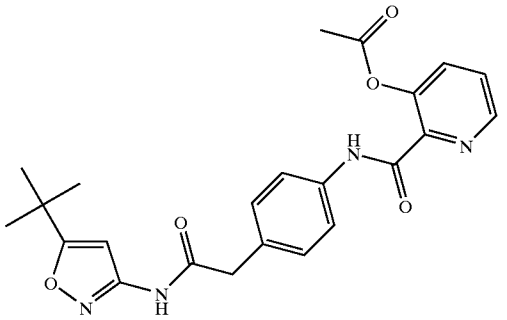
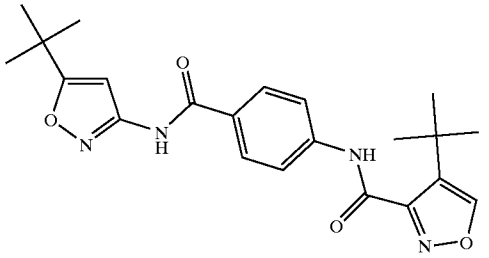
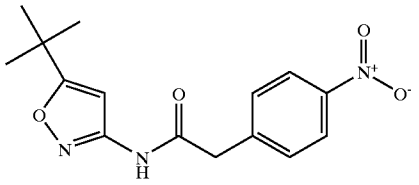
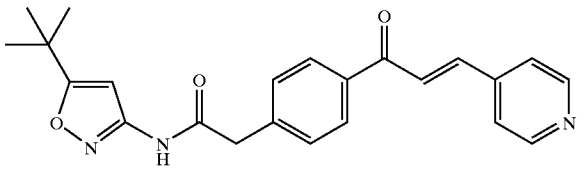
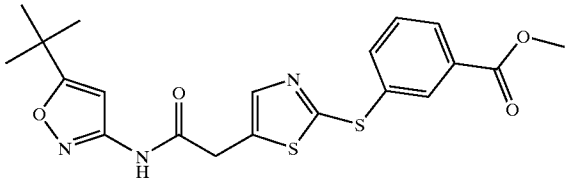
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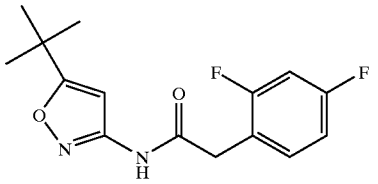
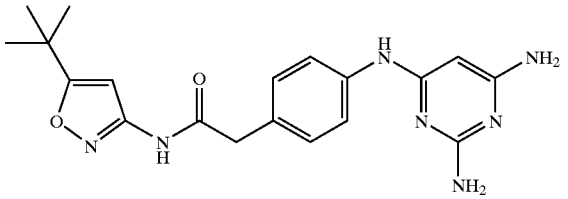
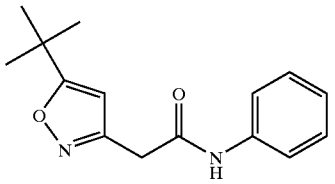
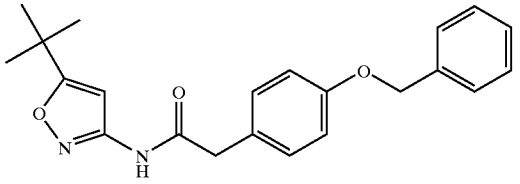
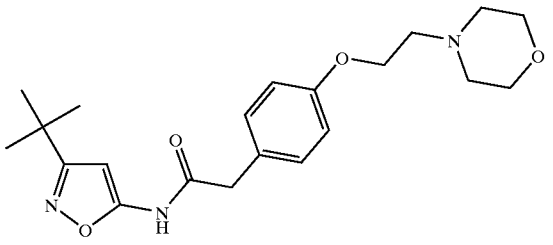
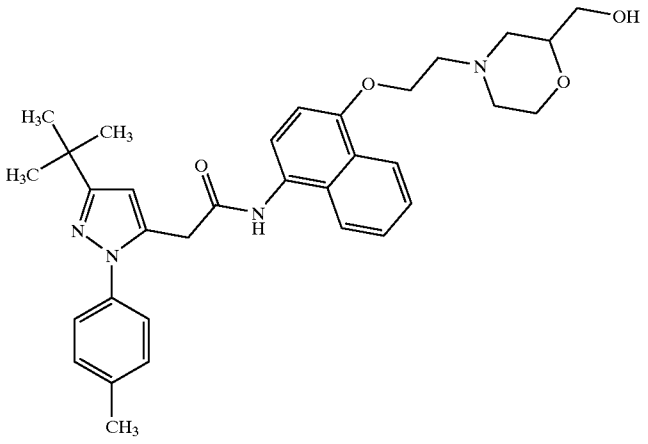
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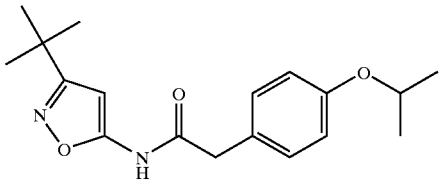
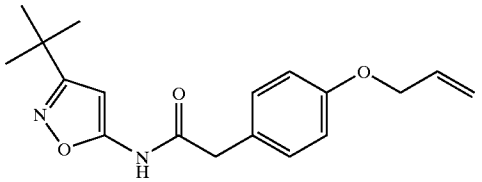
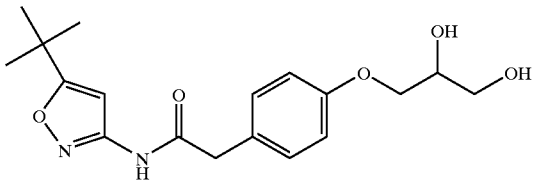
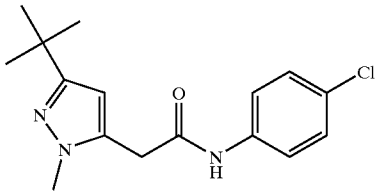
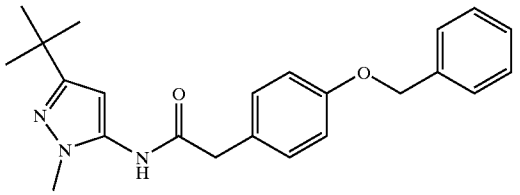
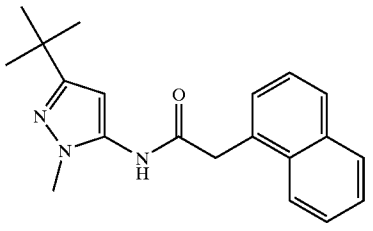
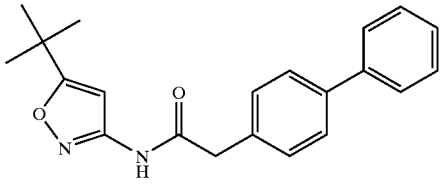
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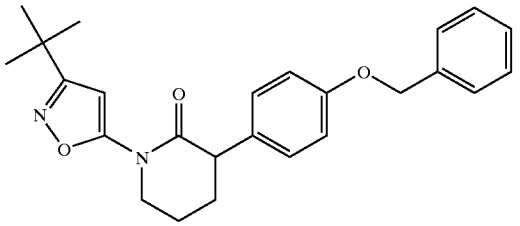
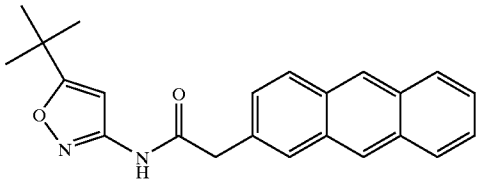
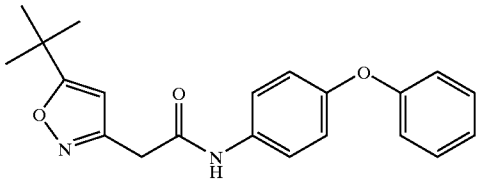
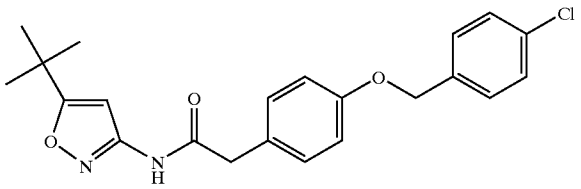
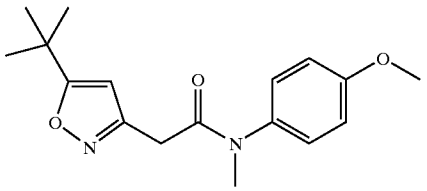
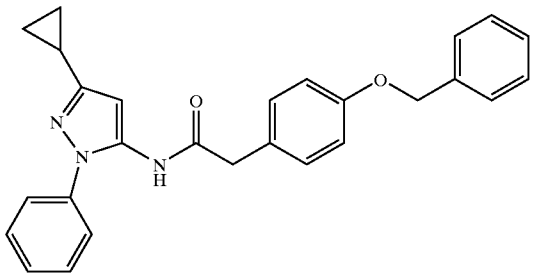
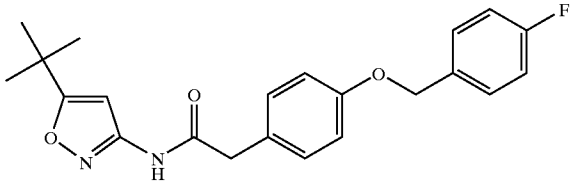
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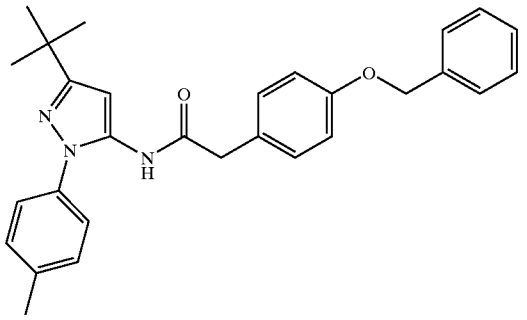
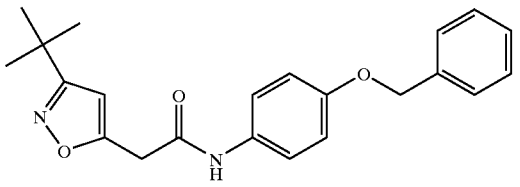
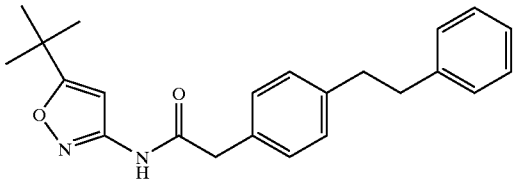
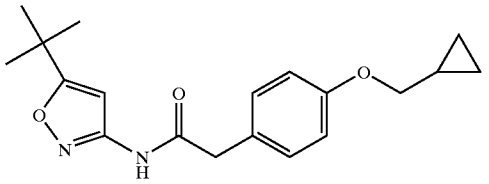
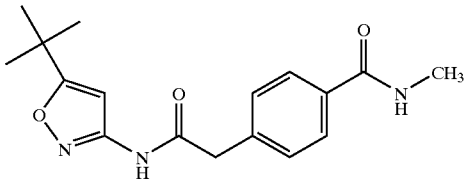
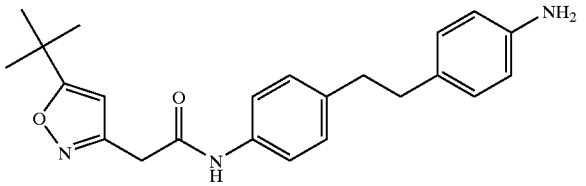
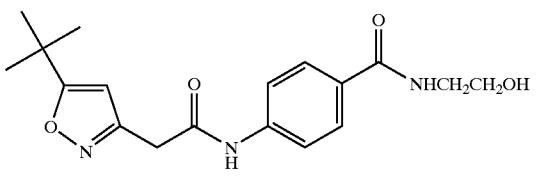
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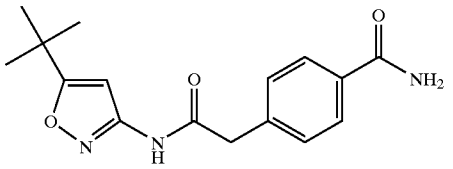
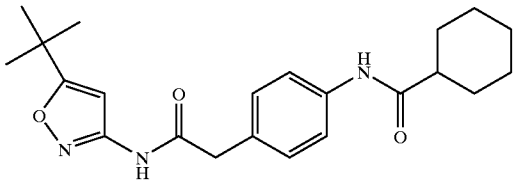
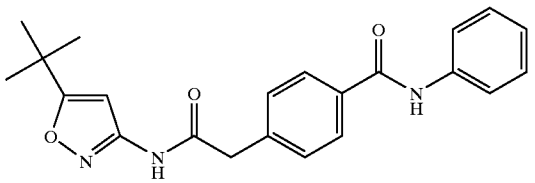
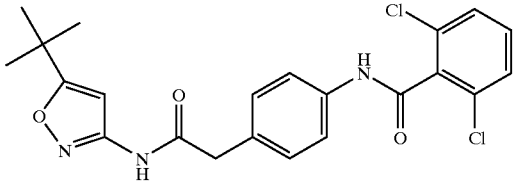
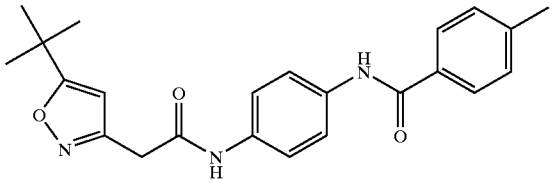
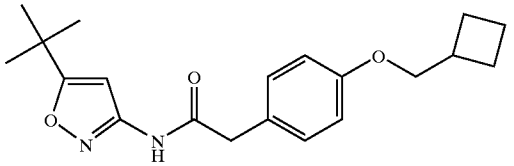
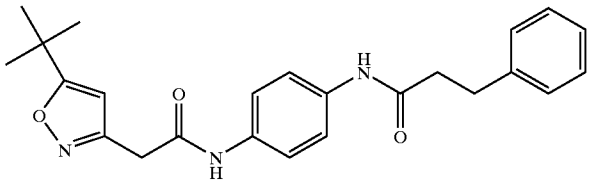
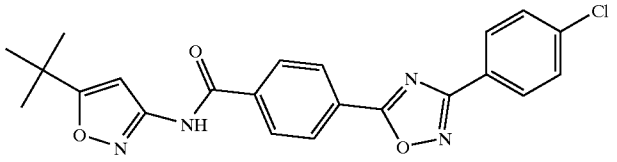
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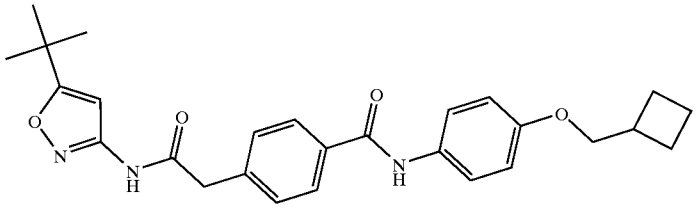
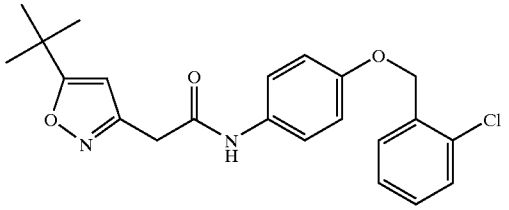
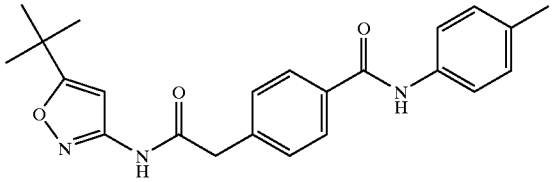
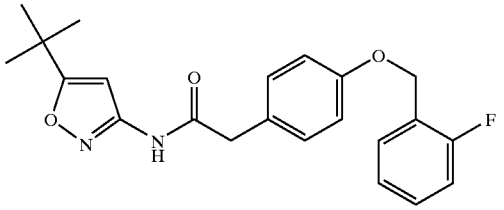
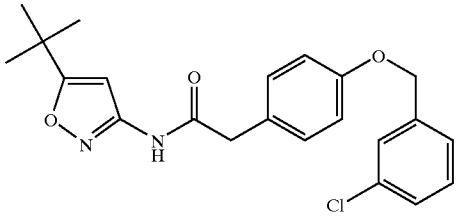
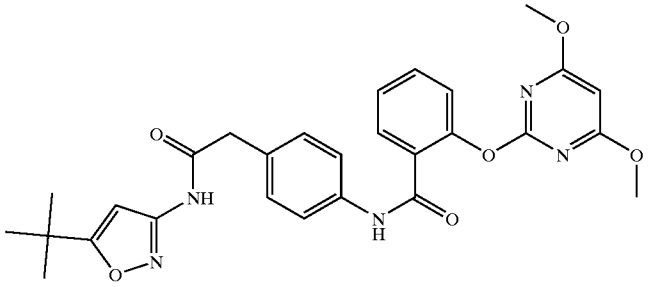
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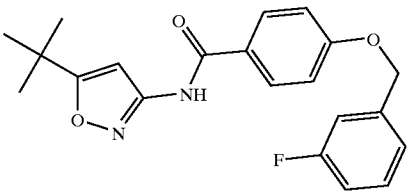
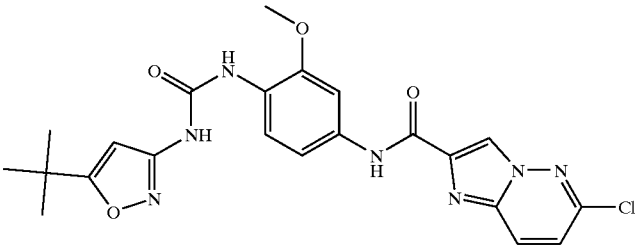
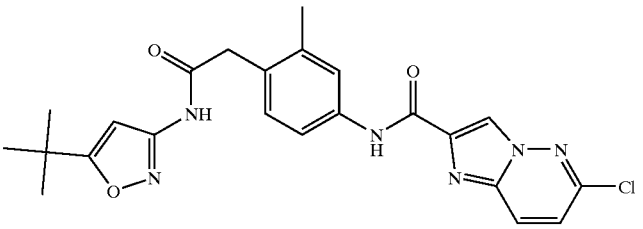
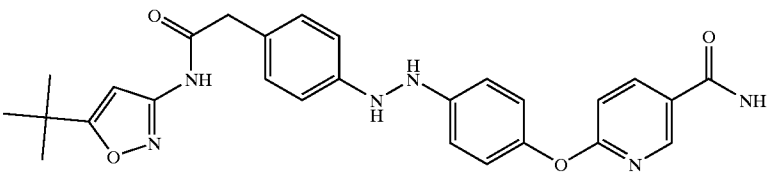
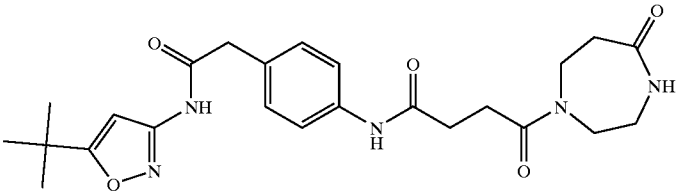
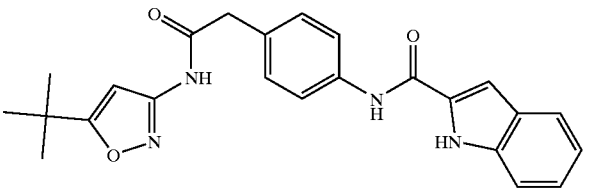
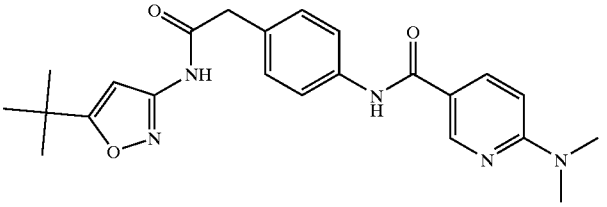
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A215	

TABLE A-continued

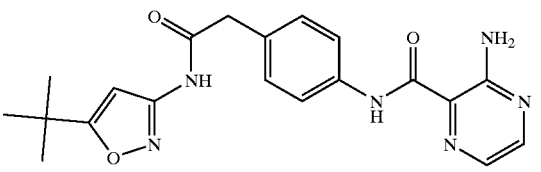
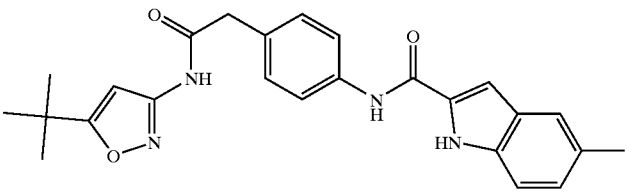
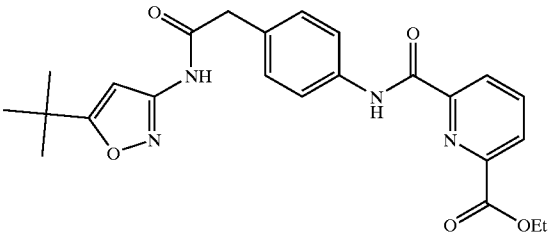
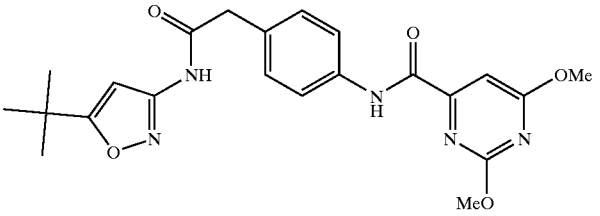
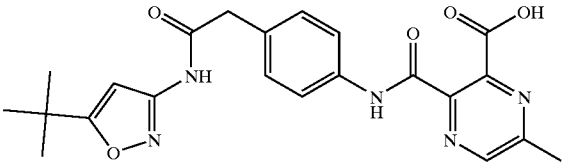
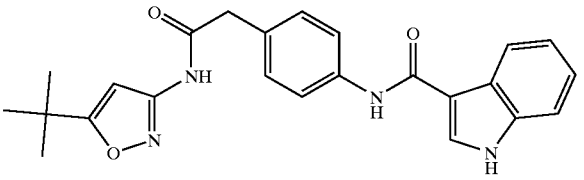
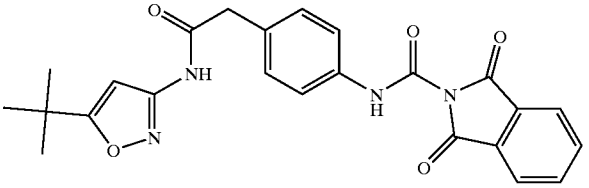
NO.	STRUCTURE
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TABLE A-continued

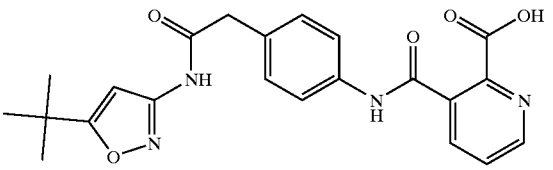
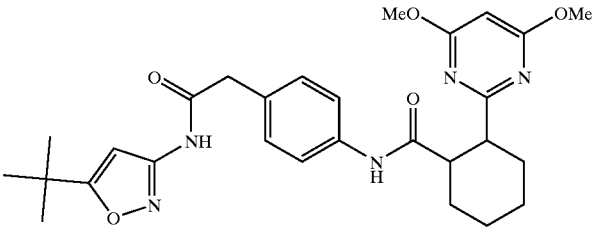
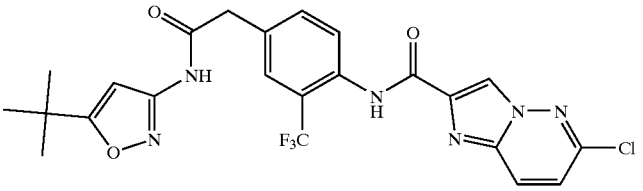
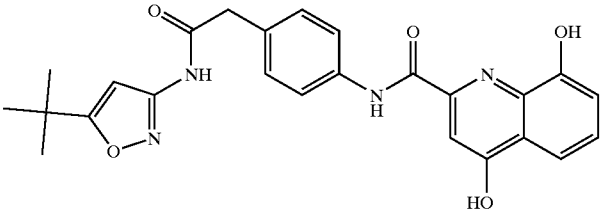
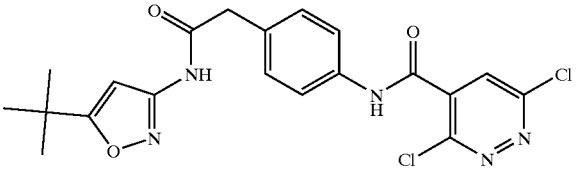
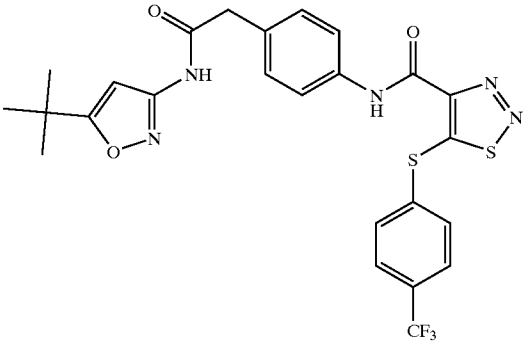
NO.	STRUCTURE
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TABLE A-continued

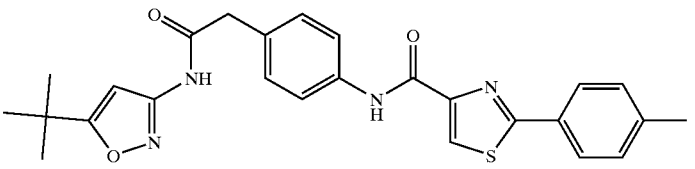
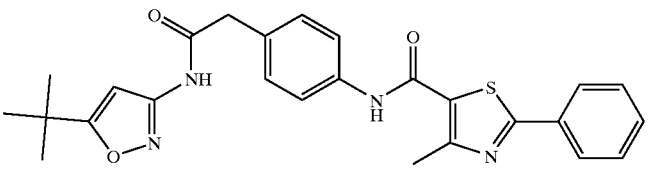
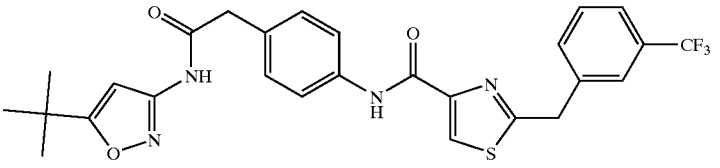
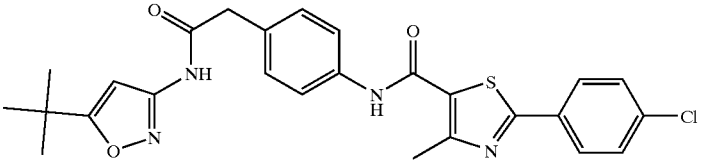
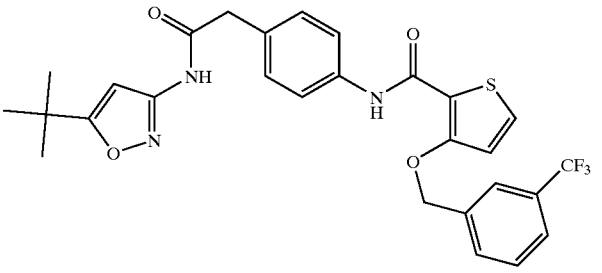
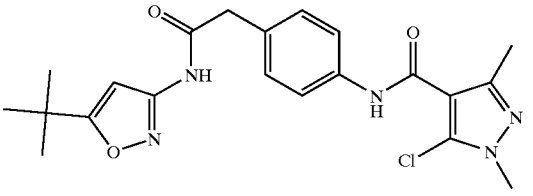
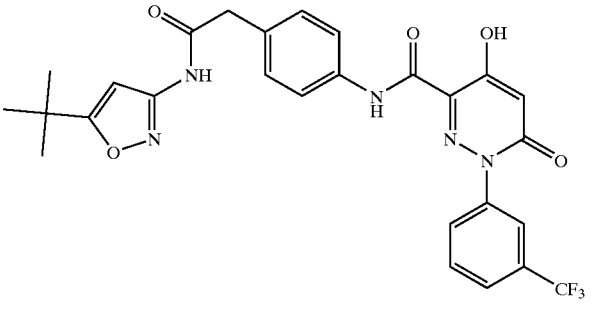
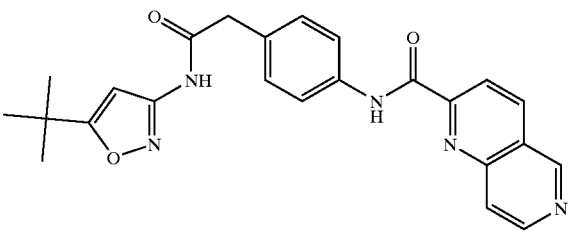
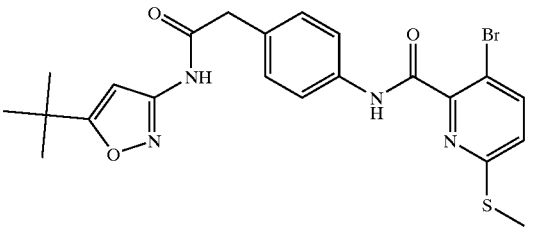
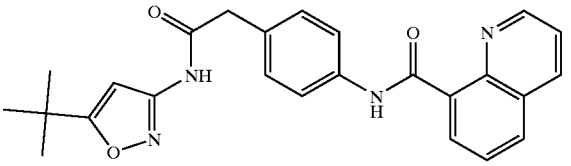
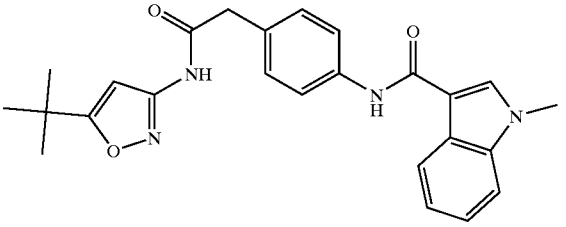
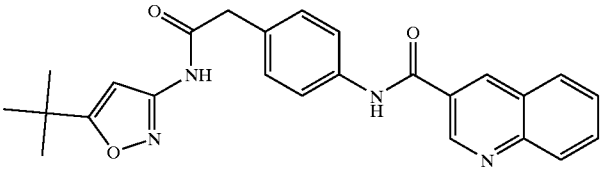
NO.	STRUCTURE
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A230	
A231	
A232	
A233	
A234	
A235	

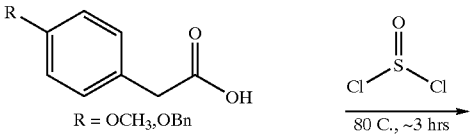
TABLE A-continued

NO.	STRUCTURE
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A239	
A240	

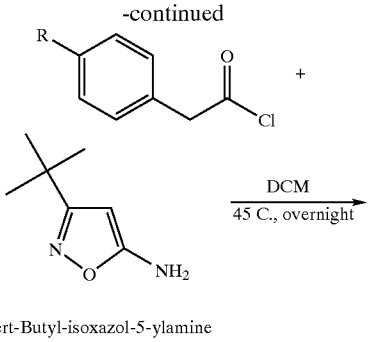
Example B

Exemplary Synthesis of Isoxazole-Amides

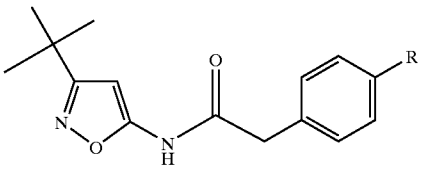
[0278]



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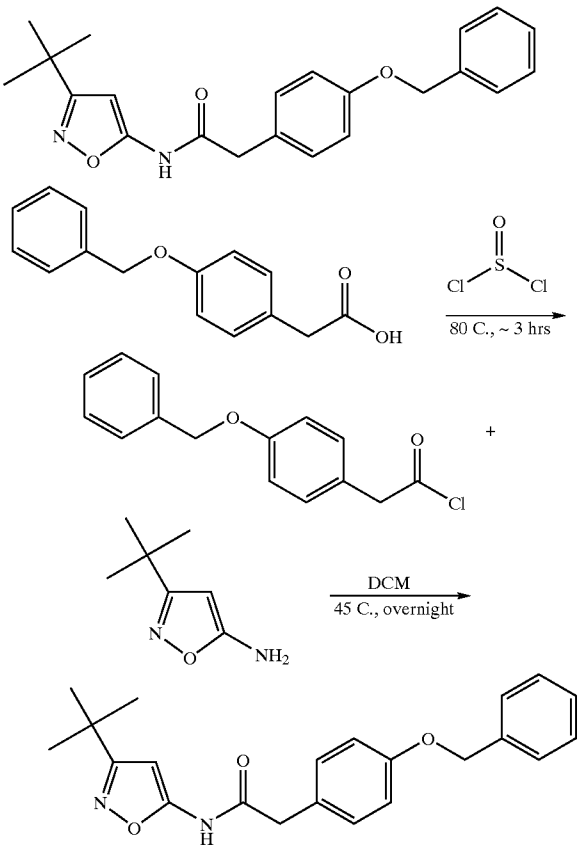
-continued



[0279] In a 40 mL vial, 1 mL of thionyl chloride was added to 0.2 mmol para-substituted phenylacetic acid. The vial was capped and stirred at 80° C. for approximately three hours. The completion of the reaction was checked by TLC. The excess thionyl chloride was removed in vacuo. The residue was dissolved in dichloromethane and added to a mixture of 3-tert-butyl-isoxazol-5-ylamine (0.2 mmol) and DIEA (0.2 mmol). The reaction was stirred overnight at 45° C. The solvent was removed under vacuum and the product was purified by HPLC.

Synthesis of Compound B1: N-(3-tert-butylisoxazol-5-yl)-2-(4-(benzyloxy)phenyl)acetamide

[0280]



[0281] (4-Benzyloxy-phenyl)-acetic acid (50 mg, 0.2 mmol, 1 eq) was stirred with 1 mL of thionyl chloride at 80° C. for approximately three hours. The completion of the reaction was checked by TLC. Excess thionyl chloride was removed in vacuo, the residue was dissolved in dichloromethane and added to a mixture of 3-tert-butyl-isoxazol-5-ylamine (28mg, 0.2 mmol, 1 eq) and DIEA (35 μL, 0.2 mmol, 1 eq). The reaction was stirred overnight at 45° C. The solvent was removed and the product purified by HPLC. Yield: 42 mg (57%), LC/MS [MH^+]365.

[0282] Compounds B2 through B16 were synthesized in a manner analogous to Compound B1 using similar starting materials and reagents. The structures are shown below in Table B:

TABLE B

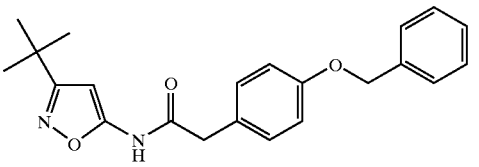
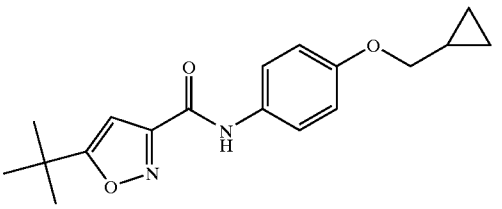
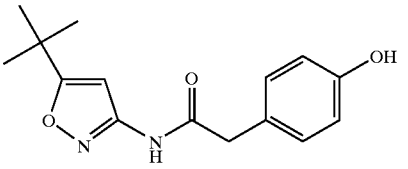
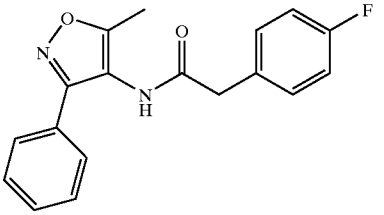
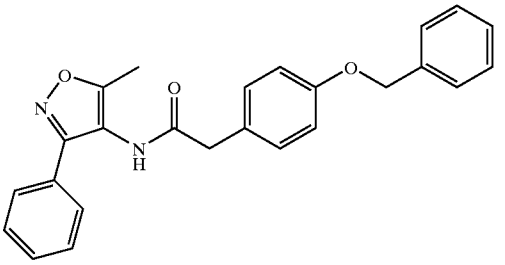
NO.	CHEMICAL STRUCTURE
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B2	
B3	
B4	
B5	

TABLE B-continued

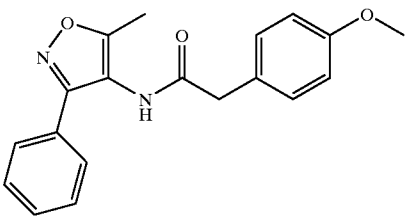
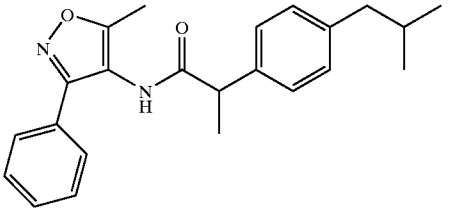
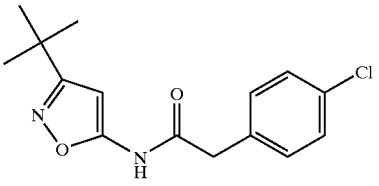
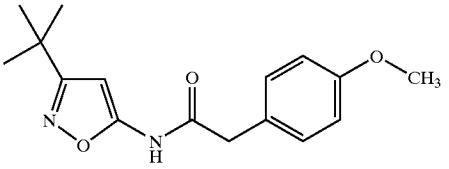
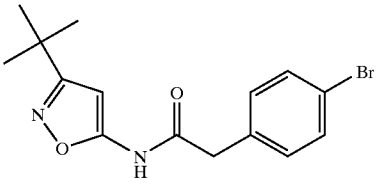
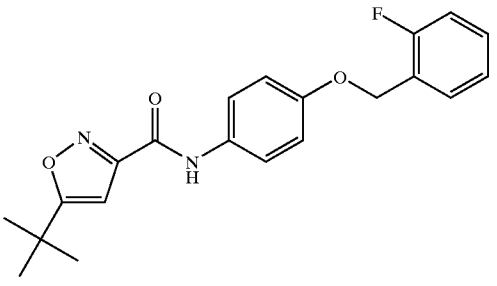
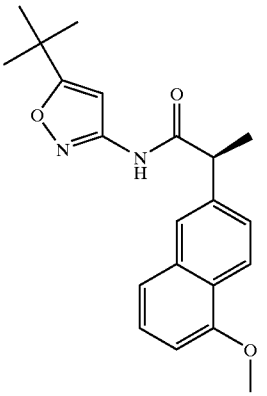
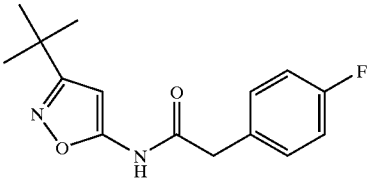
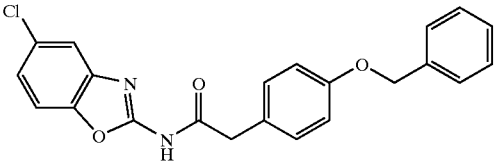
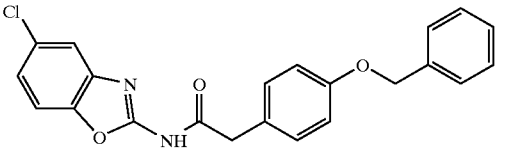
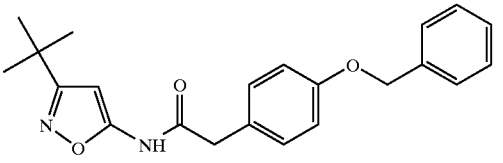
NO.	CHEMICAL STRUCTURE
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B7	
B8	
B9	
B10	
B11	

TABLE B-continued

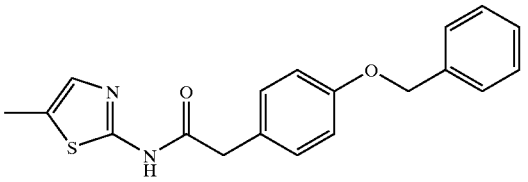
NO.	CHEMICAL STRUCTURE
B12	
B13	
B14	
B15	
B16	

Example C

Synthesis of thiazole-amides

Synthesis of Compound C1: 2-(4-(benzyloxy)phenyl)-N-(5-methylthiazol-2-yl)acetamide

[0283]



[0284] Compound C1 was prepared in strict analogy to compound B1 using 2-amino-5-methylthiazole as starting material instead of 3-tert-butyl-isoxazol-5-ylamine.

[0285] Compounds C2 through C6 were synthesized in a manner analogous to Compound C1 using similar starting materials and reagents. The structures are shown below in Table C:

TABLE C

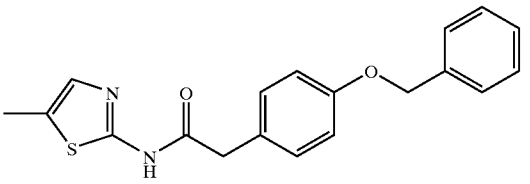
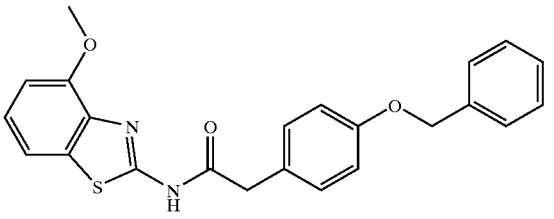
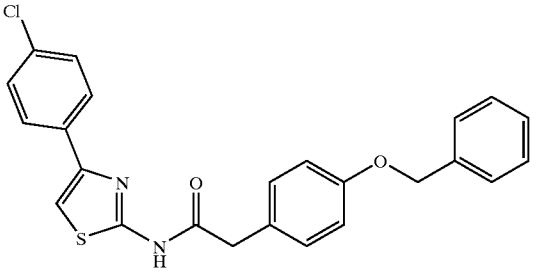
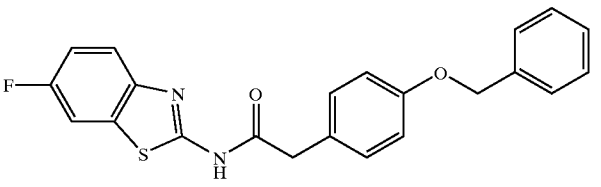
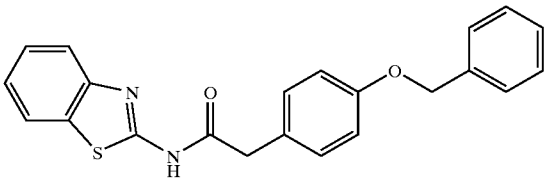
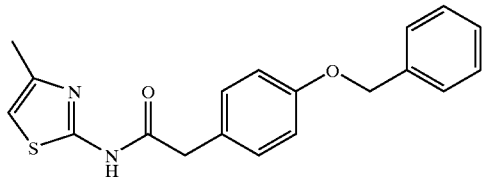
NO.	CHEMICAL STRUCTURE
C1	
C2	
C3	
C4	
C5	

TABLE C-continued

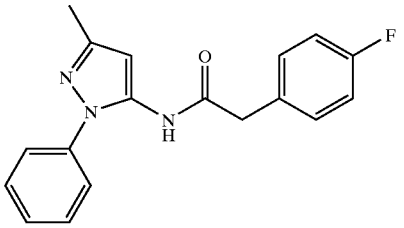
NO.	CHEMICAL STRUCTURE
C6	

Example E

Synthesis of Di-Phenyl Ureas

Synthesis of Compound E1: 2-(4-Fluoro-phenyl)-N-(5-methyl-2-phenyl-2H-pyrazol-3-)-acetamide

[0286]



[0287] Compound E1 was prepared in strict analogy to compound B1 using 5-methyl-2-phenyl-2H-pyrazol-3-ylamine and 4-fluorophenylacetic acid as starting materials.

[0288] Compounds E2 through E20 were synthesized in a manner analogous to Compound E1 using similar starting materials and reagents. The structures are shown below in Table E:

TABLE E

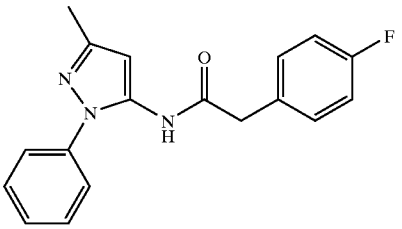
NO.	CHEMICAL STRUCTURE
E1	

TABLE E-continued

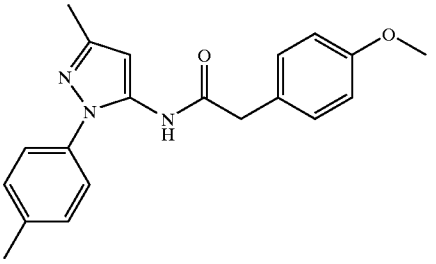
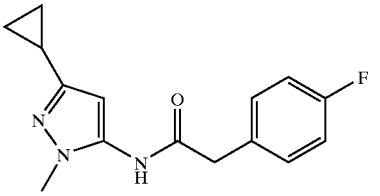
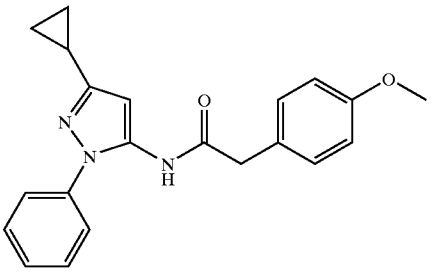
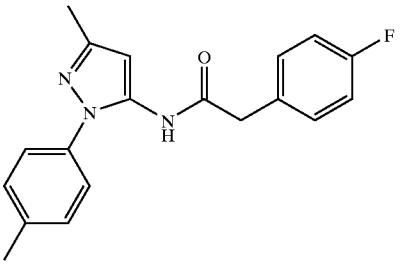
NO.	CHEMICAL STRUCTURE
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E3	
E4	
E5	

TABLE E-continued

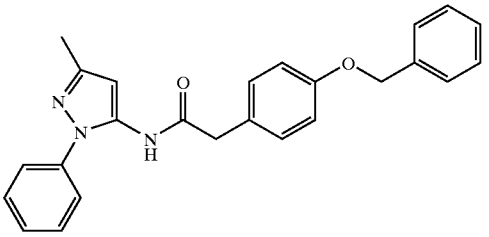
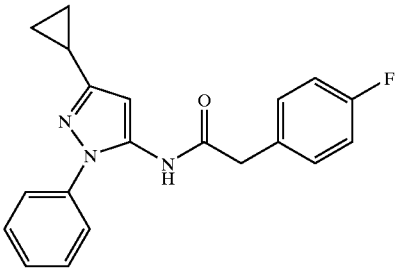
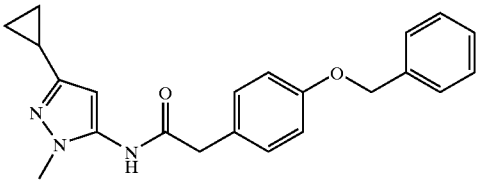
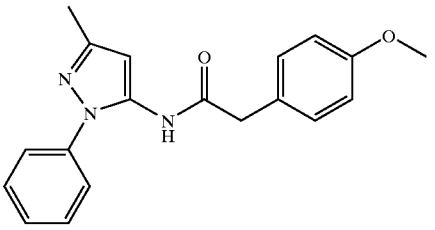
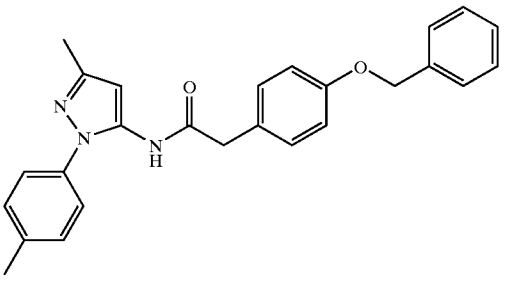
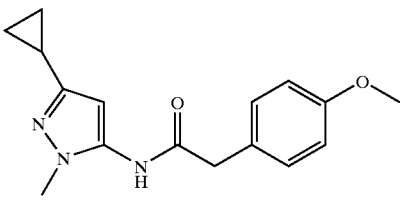
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E7	
E8	
E9	
E10	
E11	

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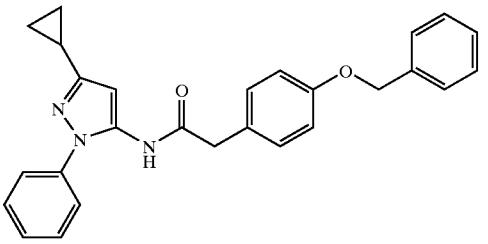
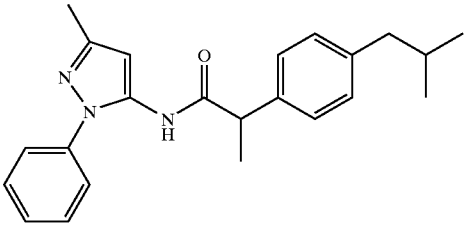
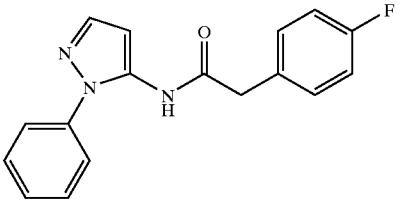
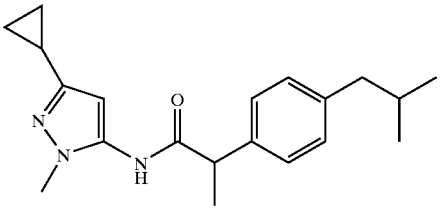
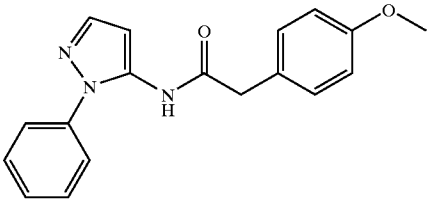
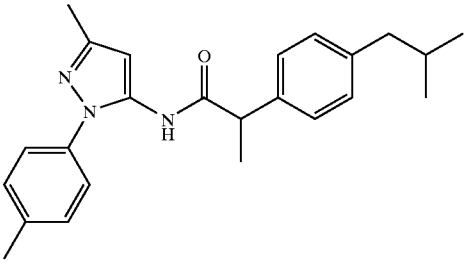
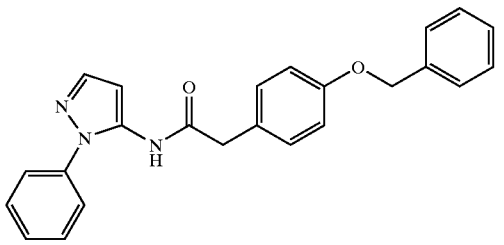
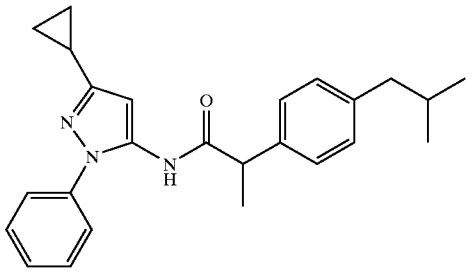
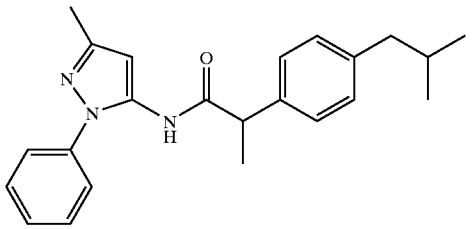
NO.	CHEMICAL STRUCTURE
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E13	
E14	
E15	
E16	
E17	

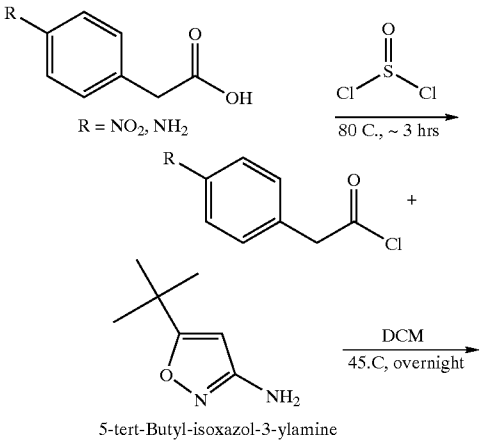
TABLE E-continued

NO.	CHEMICAL STRUCTURE
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E19	
E20	

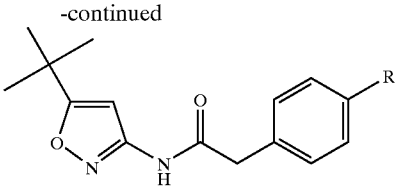
Example F

Synthesis of Isoxazole-Bis-Amides

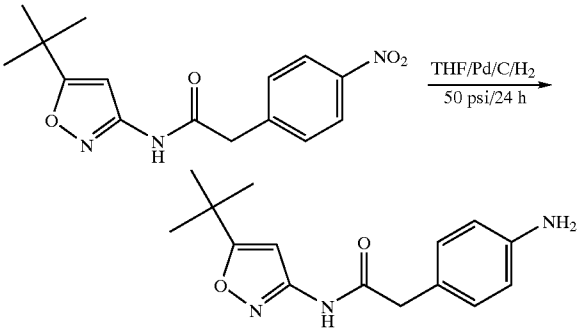
[0289]



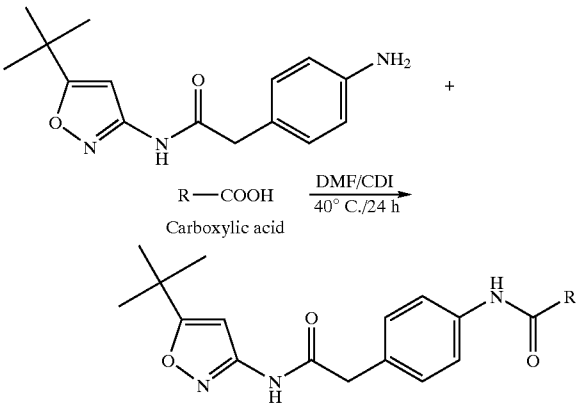
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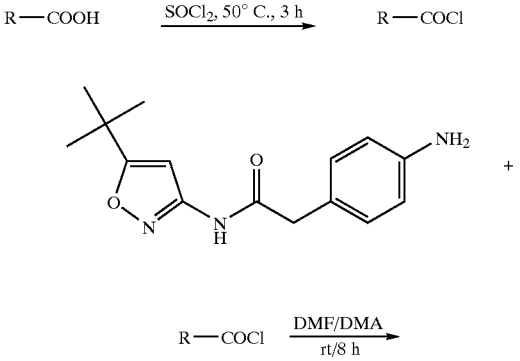
[0290] In a vial thionyl chloride was added to a para-substituted phenylacetic acid. The vial was capped and stirred at 80° C. for approximately three hours. The completion of the reaction was checked by TLC, and the excess thionyl chloride removed in vacuo. The residue was dissolved in dichloromethane and added to a mixture 5-tert-butyl-isoxazol-3-ylamine and DIEA. The reaction was stirred overnight at 45° C. The solvent was removed under vacuum and the product was purified by HPLC.



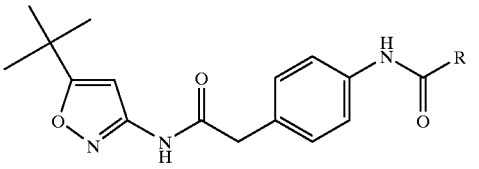
[0291] For the case of R═NO_2, reduction to the amine was carried out prior to reaction with an activated carboxylic acid. 1.5 gm of 1-(5-tert-butyl-isoxazol-3-yl)-3-(4-nitro-phenyl)-amide was dissolved in 50 ml THF and 0.1 g of 10% Pd/C is added. The solution was stirred under hydrogen at 50 psi. for 24 hours then filtered through a Celite pad. The organic solvent was evaporated under vacuum and the resulting residue was triturated with ethyl acetate.



[0292] 1 equivalent of the carboxylic acid and 1.1 equivalent of CDI were dissolved in dry DMF and stirred at 40° C. for 2 h, then 1 equivalent of the substituted aniline was added. The reaction mixture was stirred at 40° C. overnight and the final product was purified by preparative HPLC.



-continued



[0293] Alternatively, 1 equivalent of the carboxylic acid and 1.1 equivalent of thionyl chloride were heated in a sealed tube at 50 C for 3 h. The excess thionyl chloride was evaporated, 1 equivalent of aniline in DMF was added, and the solution stirred at room temperature for 8 h. The final product was purified by preparative HPLC.

[0294] Compounds F1 through F5 are synthesized in a manner analogous to those shown above using similar starting materials and reagents. The structures are shown below in Table F:

TABLE F

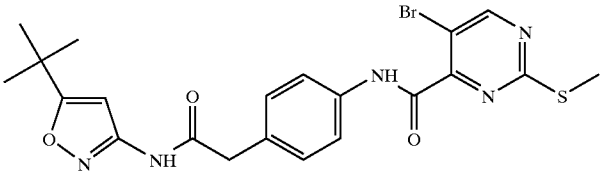
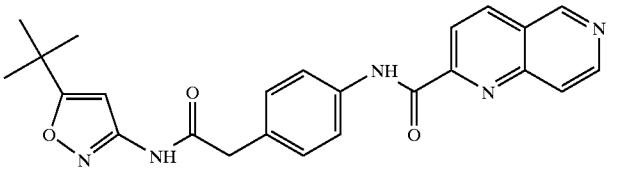
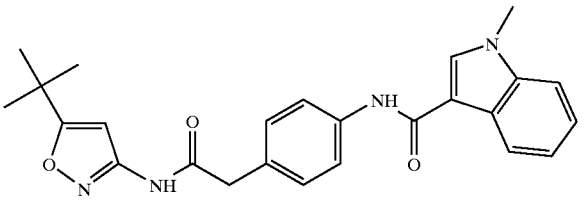
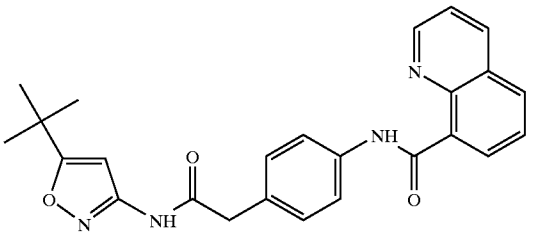
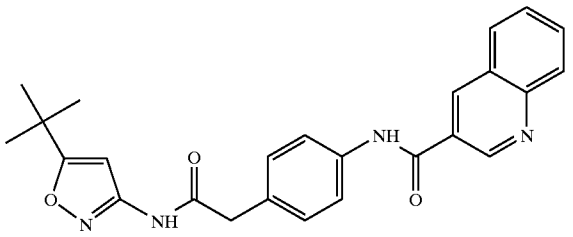
NO.	CHEMICAL STRUCTURE
F1	
F2	
F3	
F4	

TABLE F-continued

NO.	CHEMICAL STRUCTURE
F5	

[0295] Binding Constant (K_d) Measurements for Small-Molecule-Kinase Interactions

[0296] Methods for measuring binding affinities for interactions between small molecules and kinases including FLT3, c-KIT, ABL(T3341) [a.k.a. ABL(T315I)], VEGFR2 (a.k.a. KDR), and EGFR are described in detail in U.S. application Ser. No. 10/873,835, which is incorporated by reference herein in its entirety. The components of the assays include human kinases expressed as fusions to T7 bacteriophage particles and immobilized ligands that bind to the ATP site of the kinases. For the assay, phage-displayed kinases and immobilized ATP site ligands are combined with the compound to be tested. If the test compound binds the kinase it competes with the immobilized ligand and prevents binding to the solid support. If the compound does not bind the kinase, phage-displayed proteins are free to bind to the solid support through the interaction between the kinase and the immobilized ligand. The results are read out by quantitating the amount of fusion protein bound to the solid support, which is accomplished by either traditional phage plaque assays or by quantitative PCR (qPCR) using the phage genome as a template. To determine the affinity of the interactions between a test molecule and a ,kinase, the amount of phage-displayed kinase bound to the solid support is quantitated as a function of test compound concentration. The concentration of test molecule that reduces the number of phage bound to the solid support by 50% is equal to the K_d for the interaction between the kinase and the test molecule. Typically, data are collected for twelve concentrations of test compound and, the resultant binding curve is fit to a non-cooperative binding isotherm to calculate K_d.

[0297] Described in the exemplary assays below is data from binding with varying kinases. Binding values are reported as follows "+" for representative compounds exhibiting a binding dissociation constant (Kd) of 10,000 nM or higher; "++"for representative compounds exhibiting a Kd of 1,000 nM to 10,000 nM; "+++"for representative compounds exhibiting a Kd of 100 nM to 1,000 nM; and "++++"for representative compounds exhibiting a Kd of less than 100 nM. The term "ND" represents non-determined values.

The Affinity of the Compounds for FLT3

[0298] The ability of FLT3 kinase inhibitors to inhibit cellular proliferation was also examined. MV4:11 was a cell line derived from a patient with acute myelogenous leukemia. It expressed a mutant FLT3 protein that was constitutively active. MV4:11 cells were grown in the presence of candidate FLT3 inhibitor molecules, resulting in significantly decreased proliferation of the leukemia-derived cells in the presence of compound. Inhibition of FLT3 kinase activity prevented proliferation of these cells, and thus the MV4:11 cell line can be used a model for cellular activity of small molecule inhibitors of FLT3.

[0299] FLT3 Assay Using MV4,11 Cells

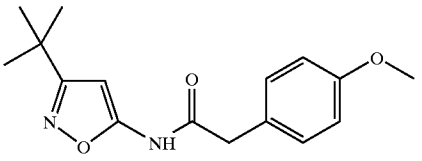
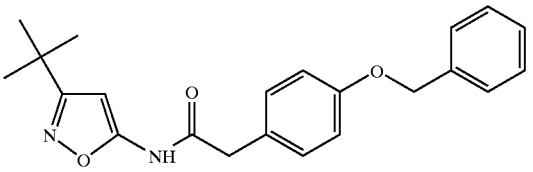
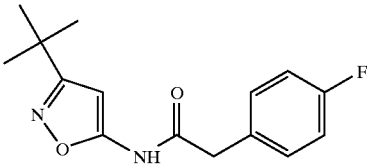
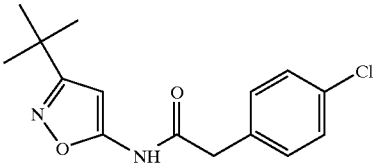
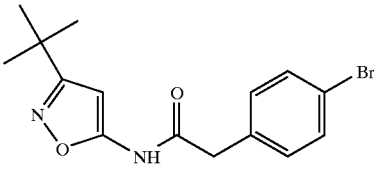
[0300] MV4,11 cells were grown in an incubator @ 37° C. in 5% CO_2 in Medium 2 (RPM 10% FBS, 4 mM glutamine, Penn/Strep). The cells were counted daily and the cell density was kept between 1e5 and 8e5 cells/ml.

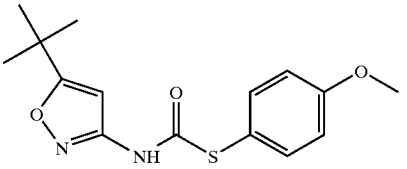
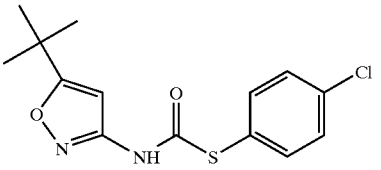
[0301] Day One: Enough cells were harvested for experiments to be conducted in 50 ml conical tubes. The harvested cells were spun at 500 g for 5 min at 4° C., the supernatant was then aspirated and the cells were resuspended in the starting volume of 1× PBS. The cells were again spun at 500 g for 5 min at 4° C. and the supernatant again aspirated. The cells were then resuspended in medium 3 (DMEM w/glut, 10% FBS, Penn/Strep) to a density of 4e5 cells/ml and incubated @ 37° C. in 5% CO_2 O/N.

[0302] Day Two: The cells were counted and enough medium 3 was added to decrease density to 2e5 cells/ml. 50 ul (10,000 cells) was aliquoted into each well of a 96 well optical plate using multichannel pipetman. The compound plate was then set up by aliquoting 3 μl of negative control (DMSO) into column 1 of a 96 well 300 ul polypropylene plate, aliquoting 3 μl of positive control (10 mM AB20121) into column 12 of plate, and aliquoting 3 μl of appropriate compounds from serial dilutions into columns 2-11. To each well, 150 μl of Medium 3 was added and 50 μl of compound/medium mixture from compound plate into rows of optical plate in duplicate. The cells were then incubated @ 37° C. in 5% CO_2 for 3 days.

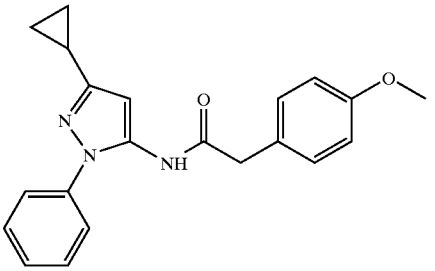
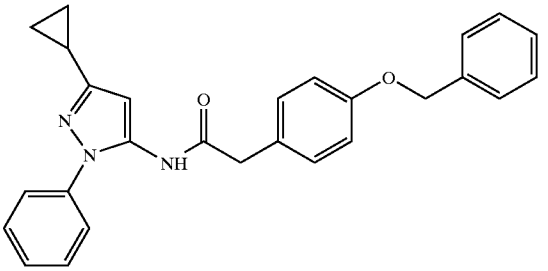
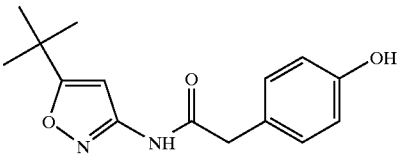
[0303] Day Five: MTS was thawed in a H_2O bath. 20 μl of MTS was added to each well of optical plate and the cells were incubated @ 37° C. in 5% CO_2 for 2 hours. The plate was then placed on a plate shaker for 30 seconds on high speed.

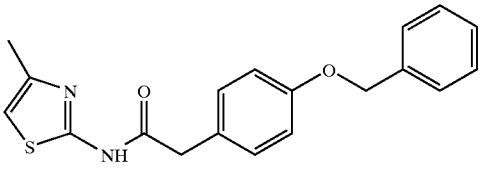
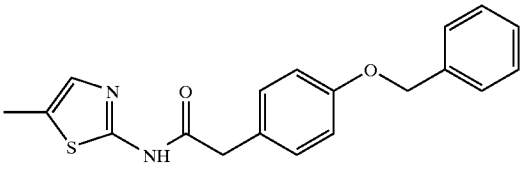
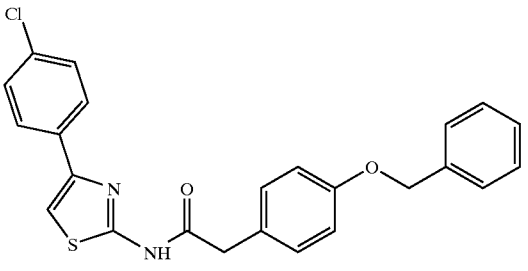
[**0304**] Data for some of the compounds is provided below:

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	++++	++++
	++++	ND
	++++	ND
	++++	ND

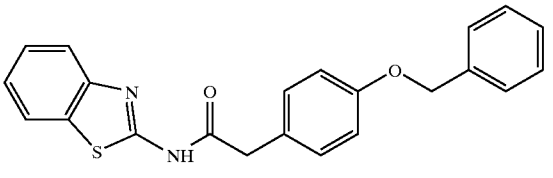
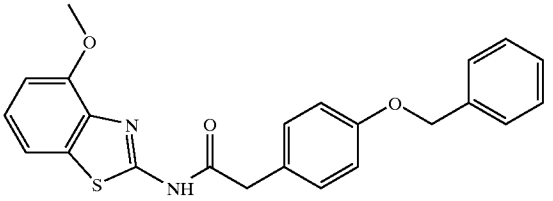
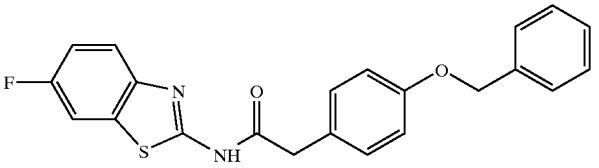
Compound Structure	Binding Assay: FLT 3(DKIN)
	++
	++

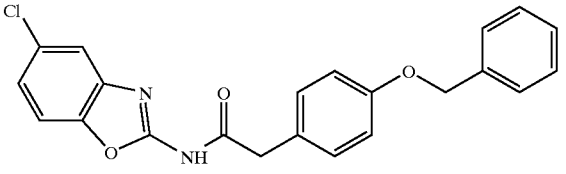
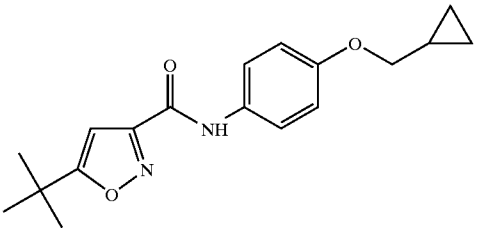
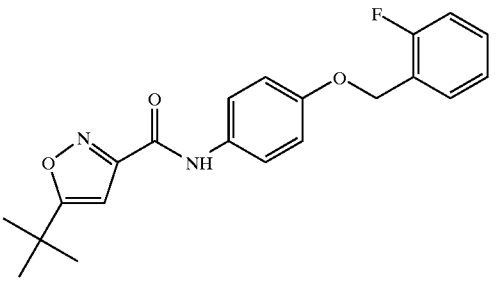
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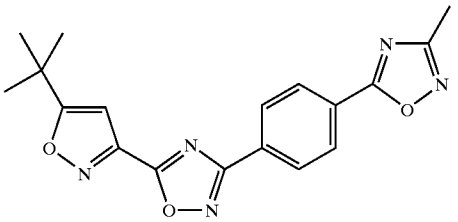
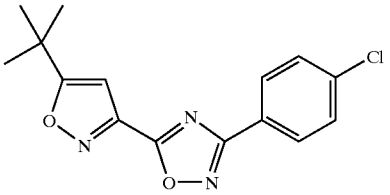
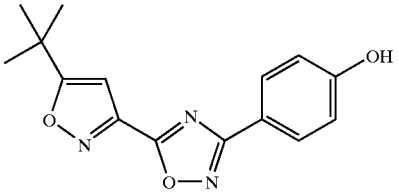
Compound Structure	Binding Assay: FLT 3(DKIN)
	+
	+
	+

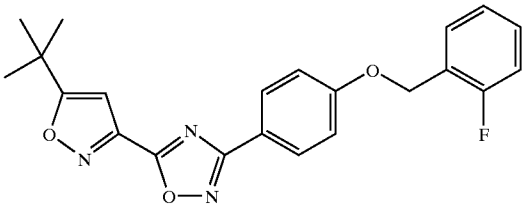
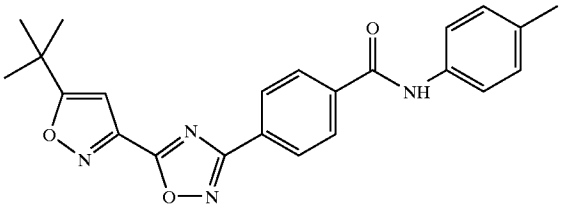
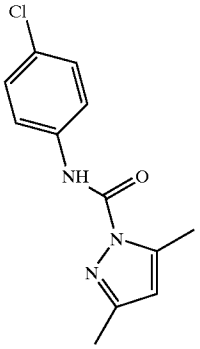
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		+
		+
		+

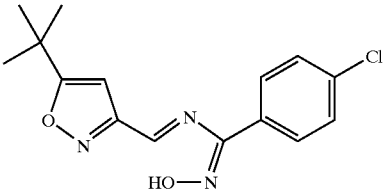
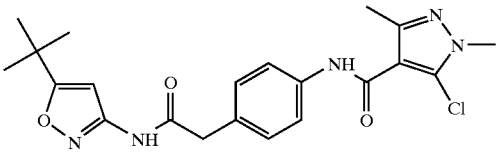
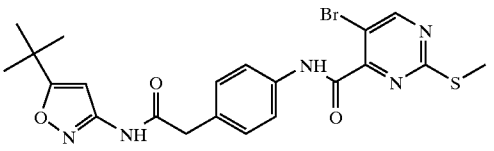
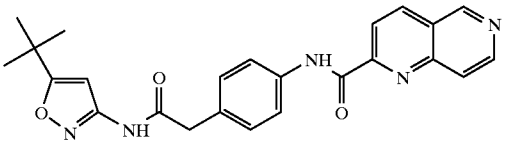
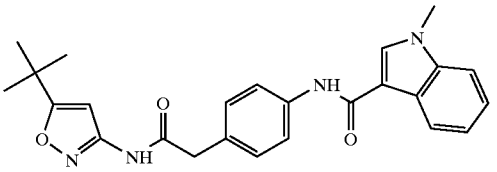
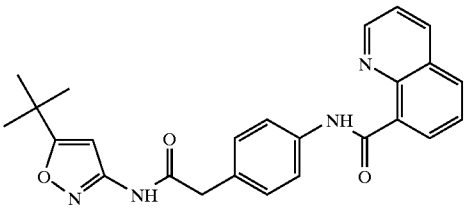
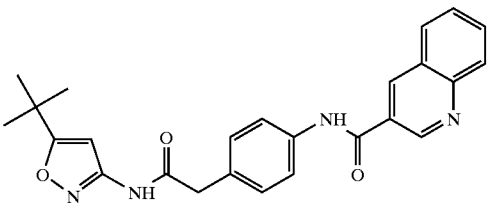
Compound Structure	Binding Assay: FLT 3(DKIN)	Cell Assay: CS 0001: IC50
	+++	ND
	+	++
	++	++

-continued

	+	+
	+	+
	+	++

Compound	Binding Assay: FLT	Cell Assay: CS
	+	+++
	+	+++
	+	+

-continued

			++		++
Binding Compound Structure	Cell Assay: FLT 3(DKIN)	Cell Assay: CS 0001: IC50	Cell Assay: CS 0005: IC50	Binding Assay: CS 0002: IC50	Assay: FLT 3(JMminus)
	ND	+++	ND	+	++++
	ND	++++	ND	+	++++
	ND	++++	ND	+	++++
	ND	++++	ND	+	++++
	ND	++	ND	+	+++
	ND	++++	ND	+	++++

[0305] All references cited herein, including patents, patent applications, and publications, are herby incorporated by reference in their entireties, whether previously specifically incorporated or not.

[0306] Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the

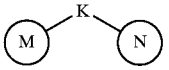
spirit and scope of the invention and without undue experimentation.

[0307] While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

What is claimed is:

1. A method of modulating flt-3 kinase, said method comprising administering an effective amount of a compound corresponding to Formula (IA):

(IA)

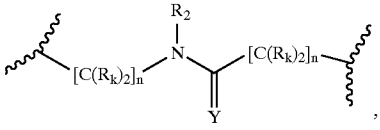


wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl, or substituted or unsubstituted hetroaryl; and

K is



, where

Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, —$OC(O)R_2$, —NO_2, —$N(R_2)_2$, —SR_2, —$C(O)R_2$, —$C(O)_2R_2$, —$C(O)N(R_2)_2$, or —$N(R_2)C(O)R_2$,

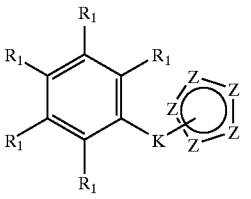
each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

2. The method of claim 1, wherein said compound corresponds to Formula (IB):

(IB)



wherein:

each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms and wherein no two adjacent Z's are O or S,

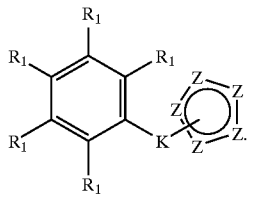
where R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl; and

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, —OR_c —OH, —$OC(O)R_c$, —NO_2, —$N(R_c)_2$, —SR_c, $S(O)_jR_c$ where j is 1 or 2, —$NR_cC(O)R_c$, —$C(O)N(R_c)_2$, $C(O)_2R_c$, or —$C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

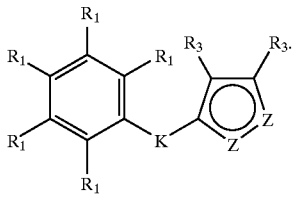
3. The method of claim 2, wherein said compound corresponds to Formula (I):

(I)



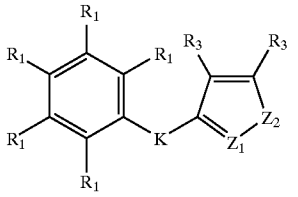
4. The method of claim 3, wherein said compound corresponds to Formula (II):

(II)



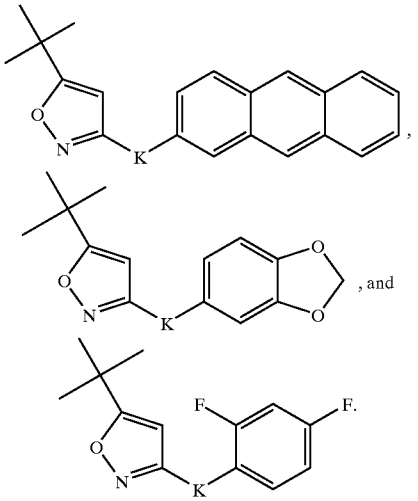
5. The method of claim 4, wherein said compound corresponds to Formula (III):

(III)



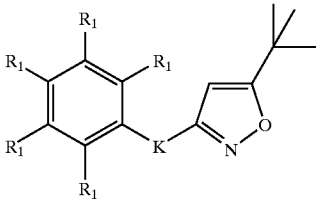
wherein Z_1 is CR_3 or N; and Z_2 is O or S.

6. The method of claim 5, wherein said compound is selected from the group consisting of:



7. The method of claim 5, wherein said compound corresponds to Formula (IV):

(IV)



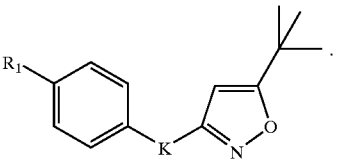
wherein:

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, —O(substituted or unsubstituted alkyl), —O(substituted or unsubstituted alkenyl), —$NR_cC(O)O$(substituted or unsubstituted alkyl), —$NR_cC(O)$ (substituted or unsubstituted alkyl), —$NR_cC(O)$(substituted or unsubstituted alkenyl), —$C(O)NR_c$(substituted or unsubstituted alkyl), —$C(O)NR_c$(substituted or unsubstituted alkenyl), —NO_2, —$S(=O)R_c$, —SR_c, $C(O)_2R_c$, or —$C(O)R_c$; and

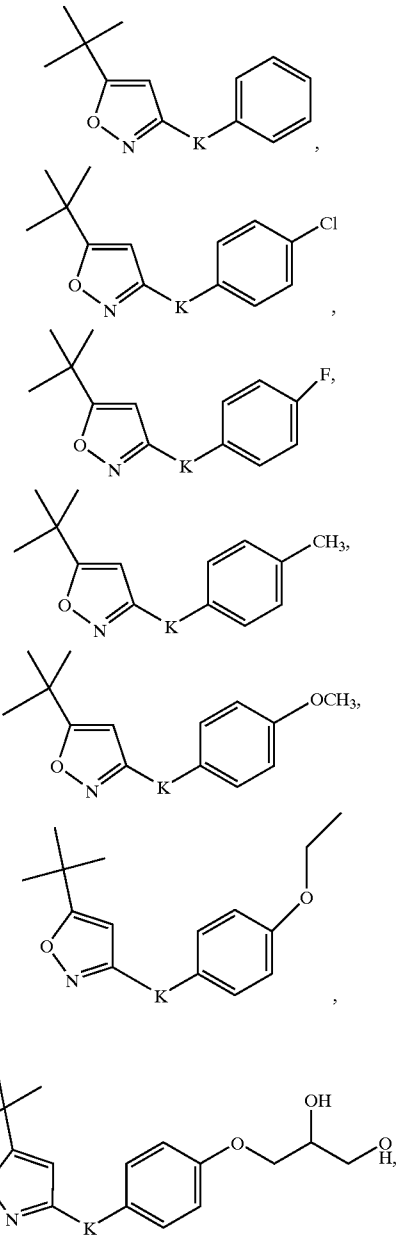
each R_2 is independently H or substituted or unsubstituted alkyl.

8. The method of claim 7, wherein said compound corresponds to Formula (V):

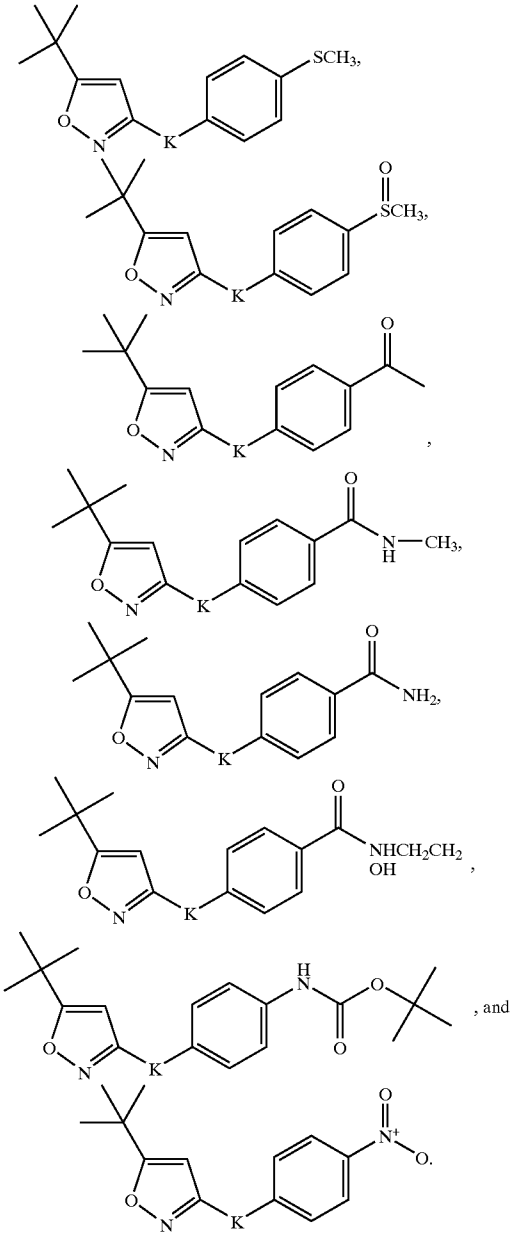
(V)



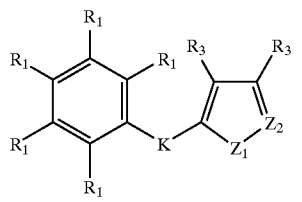
9. The method of claim 8, wherein said compound is selected from the group consisting of:



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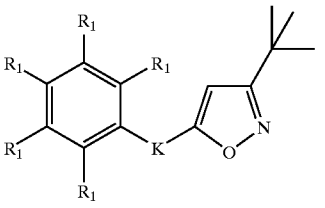
10. The method of claim 4, wherein said compound corresponds to Formula (VI):



(VI)

wherein Z_1 is O or S; and Z_2 is CR_3 or N.

11. The method of claim 10, wherein said compound corresponds to Formula (VII):



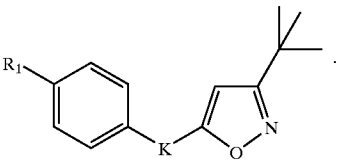
(VII)

wherein:

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, —O(substituted or unsubstituted alkyl), —O(substituted or unsubstituted alkenyl), —$NR_cC(O)O$(substituted or unsubstituted alkyl), —$NR_cC(O)$ (substituted or unsubstituted alkyl), —$NR_cC(O)$(substituted or unsubstituted alkenyl), —$C(O)NR_c$(substituted or unsubstituted alkyl), —$C(O)NR_c$(substituted or unsubstituted alkenyl), —NO_2, —$S(=O)R_c$, —SR_c, $C(O)_2R_c$, or —$C(O)R_c$; and

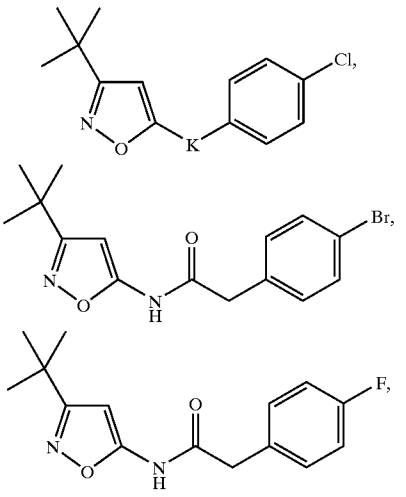
each R_2 is independently H or substituted or unsubstituted alkyl.

12. The method of claim 10, wherein said compound corresponds to Formula (VIII):

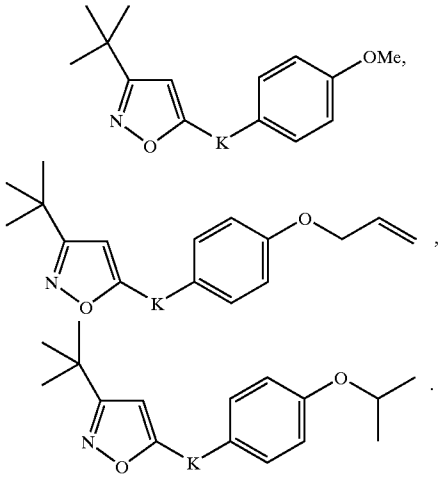


(VIII)

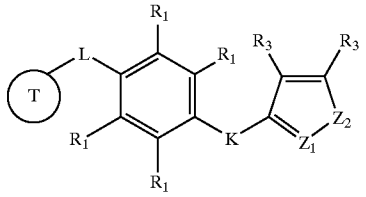
13. The method of claim 12, wherein said compound is selected from the group consisting of:



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14. The method of claim 5, wherein said compound corresponds to Formula (IX):



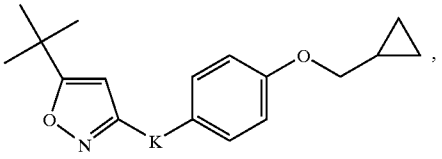
(IX)

wherein:

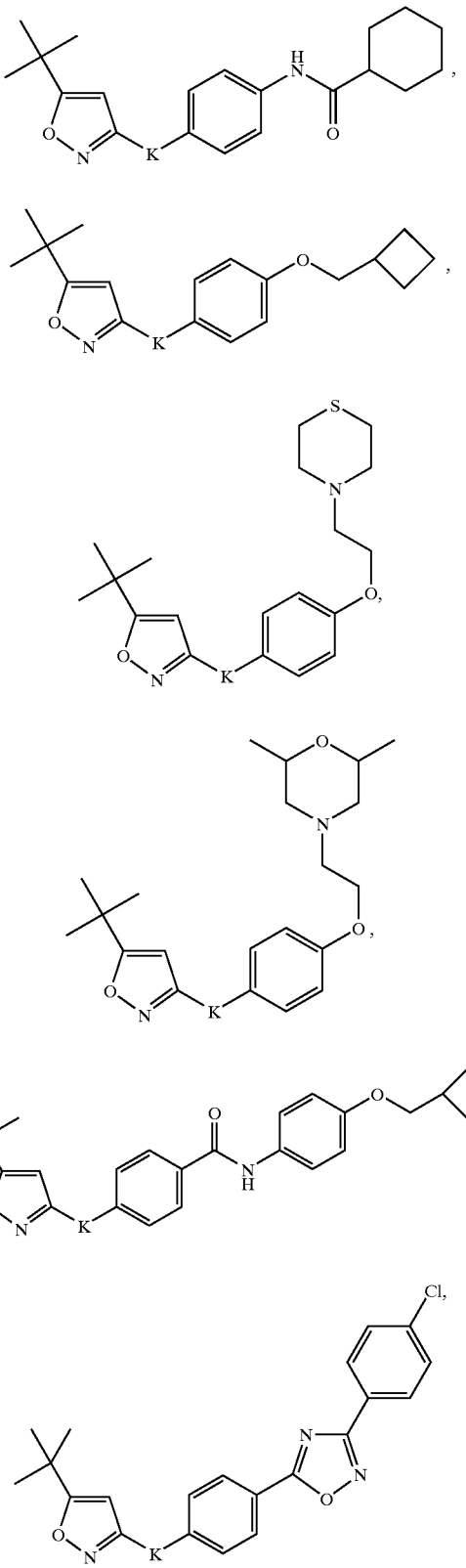
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

T is a mono-, bi, -or tricyclic, substituted or unsubstituted cycloalkyl, heterocyclyl, aryl, or heteroaryl.

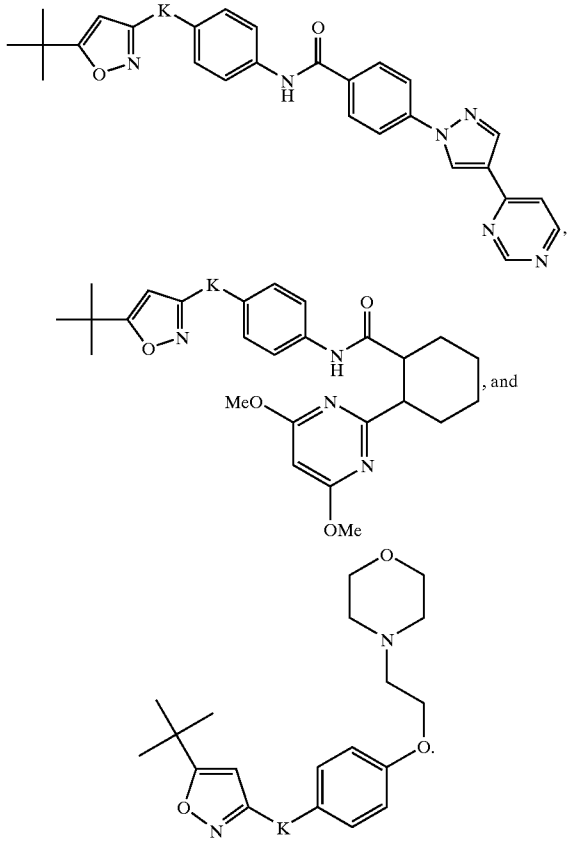
15. The method of claim 14, wherein said compound is selected from the group consisting of:



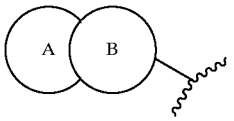
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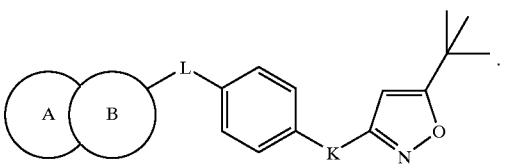
16. The method of claim 14, wherein T of said compound corresponds to Formula (X):



(X)

wherein A is a substituted or unsubstituted five or six-membered heterocyclyl, aryl, or heteroaryl; and B is a substituted or unsubstituted five or six-membered heterocyclene, arylene, or heteroarylene, wherein A and B together form a fused two ring moiety.

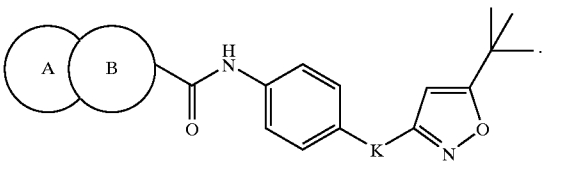
17. The method of claim 16, wherein said compound corresponds to Formula (XI):



(XI)

18. The method of claim 17, wherein L of said compound is a covalent bond —C(O)NH(substituted or unsubstituted alkylene)-, —NHC(O)—, —NHC(O)(substituted or unsubstituted alkylene)-, —NH—, or —O(substituted or unsubstituted alkylene)-.

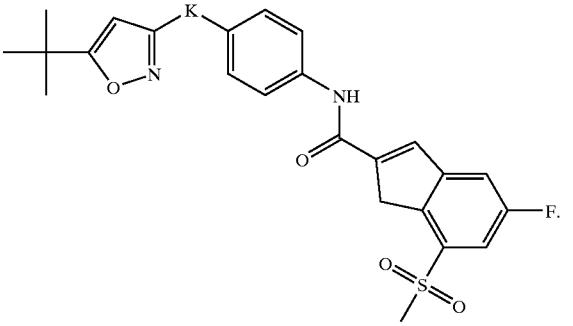
19. The method of claim 18, wherein said compound corresponds to Formula (XII):



(XII)

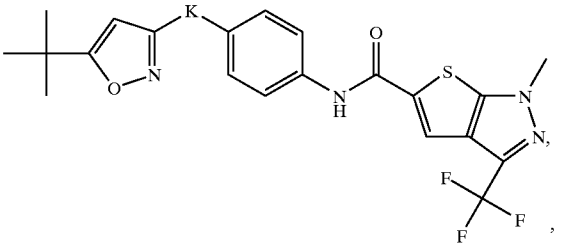
20. The method of claim 19, wherein B of said compound is a substituted or unsubstituted five-membered arylene or heteroarylene.

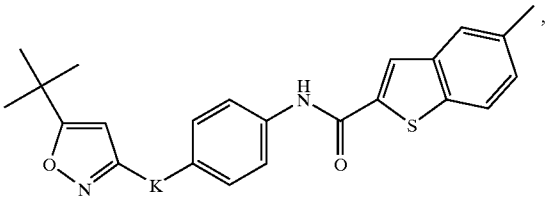
21. The method of claim 20, wherein said compound is:



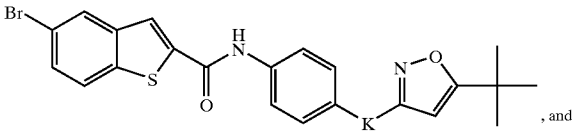
22. The method of claim 20, wherein B is substituted or unsubstituted thiophenylene.

23. The method of claim 22, wherein said compound is selected from the group consisting of:

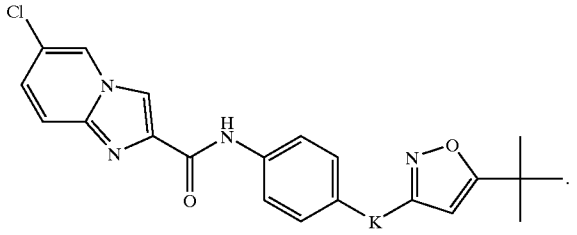




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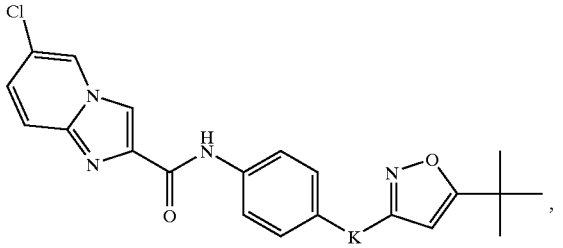
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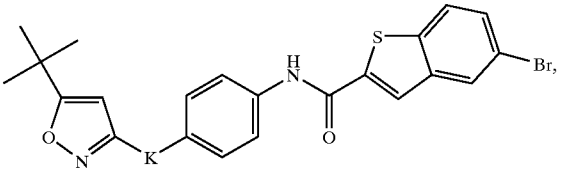
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24. The method of claim 20, wherein B is substituted or unsubstituted imidazolylene.

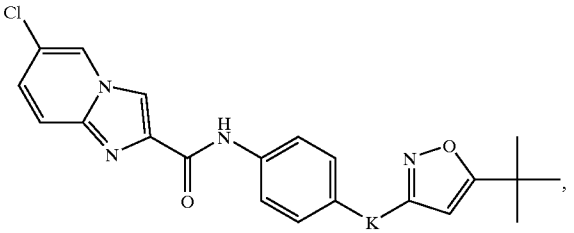
25. The method of claim 24, wherein said compound is selected from the group consisting of:



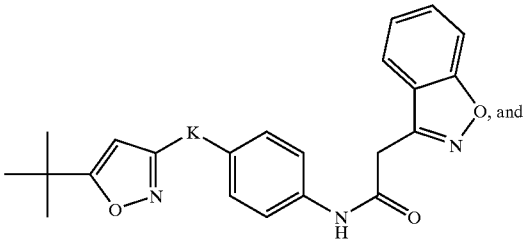
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Br,

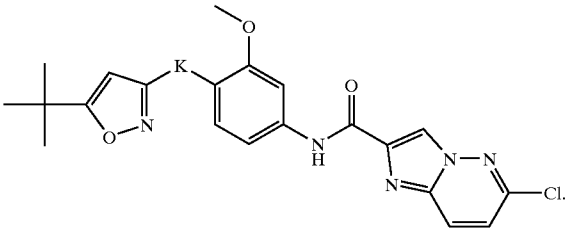


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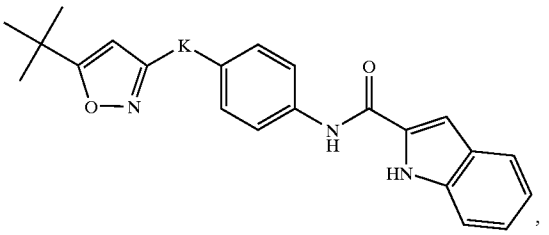
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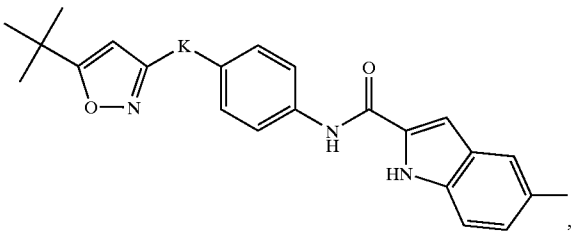
Cl.

26. The method of claim 20, wherein B is substituted or unsubstituted pyrrolylene.

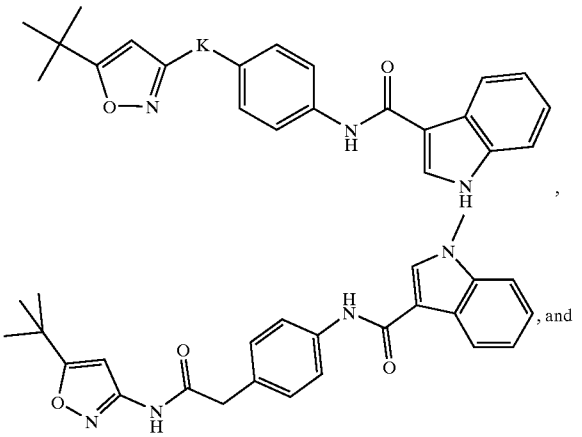
27. The method of claim 26, wherein said compound is selected from the group consisting of:



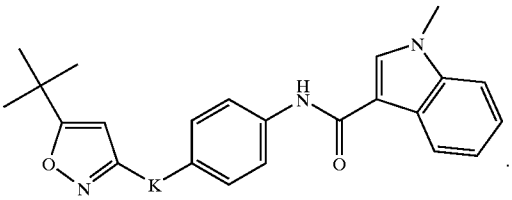
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, and

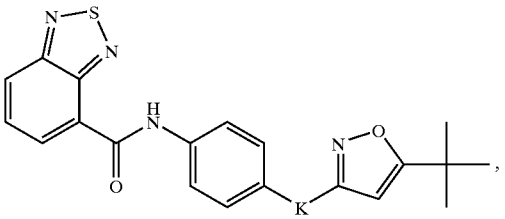


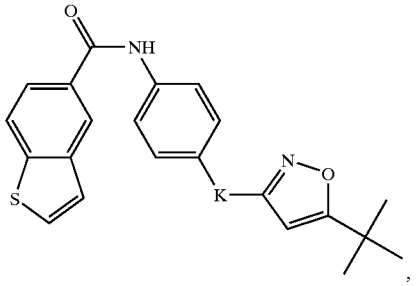
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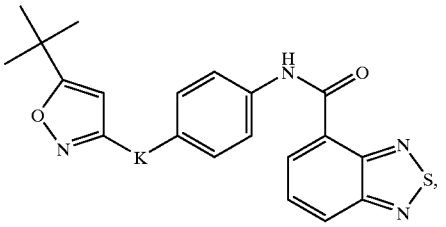
28. The method of claim 19, wherein B of said compound is a substituted or unsubstituted 6-membered arylene or heteroarylene.

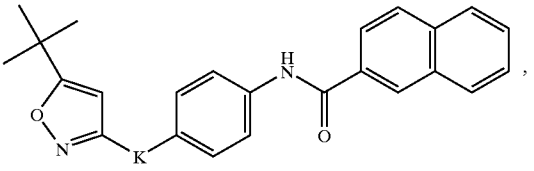
29. The method of claim 28, wherein B is substituted or unsubstituted phenylene.

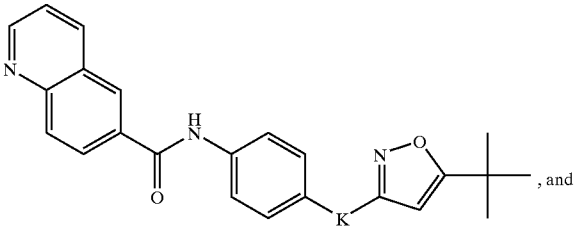
30. The method of claim 29, wherein said compound is selected from the group consisting of:



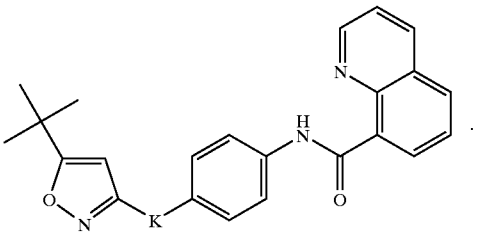








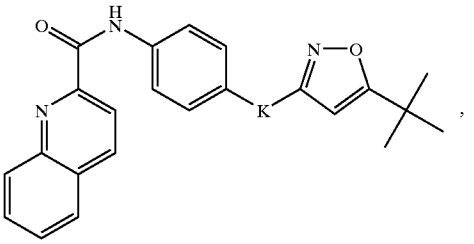
, and

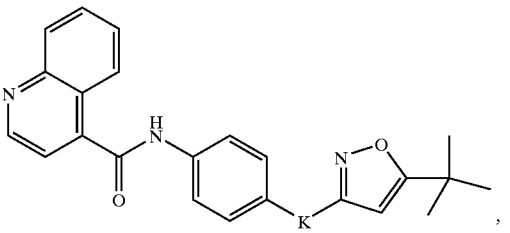


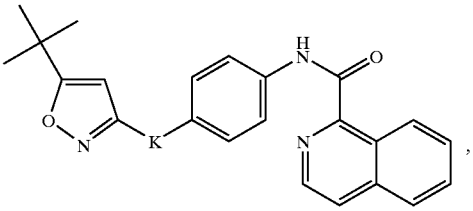
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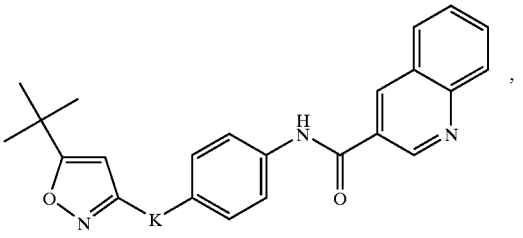
31. The method of claim 28, wherein B is substituted or unsubstituted pyridinylene, pyrimidinylene, or pyridazine.

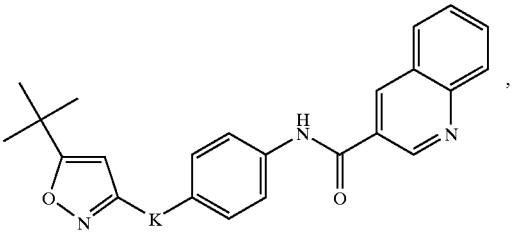
32. The method of claim 31, wherein said compound is selected from the group consisting of:

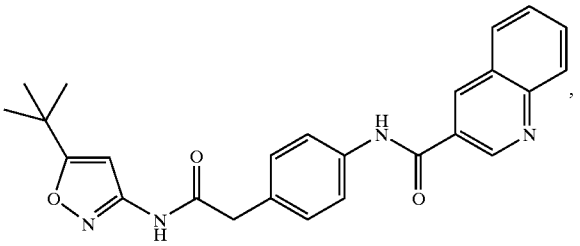




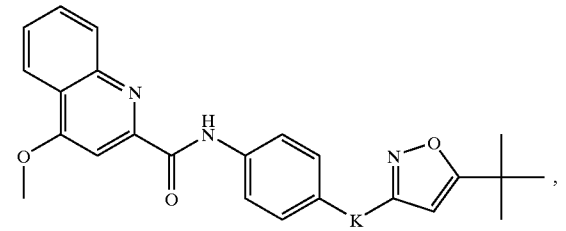


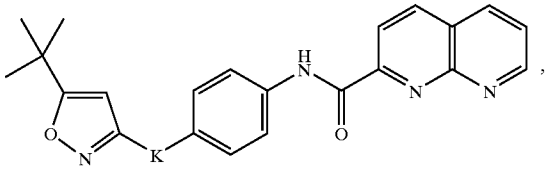


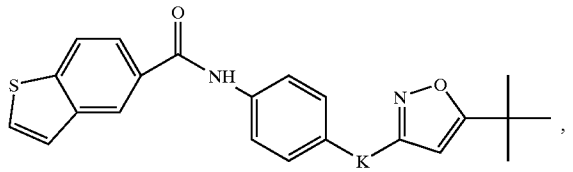


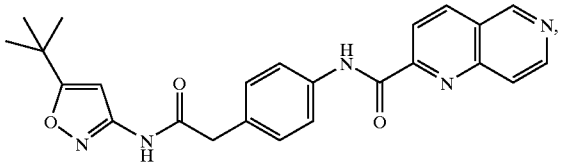


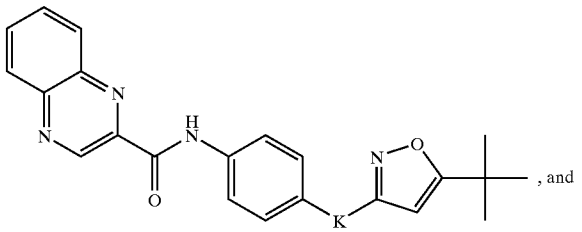
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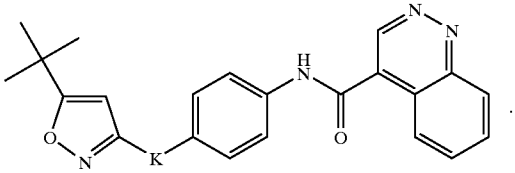








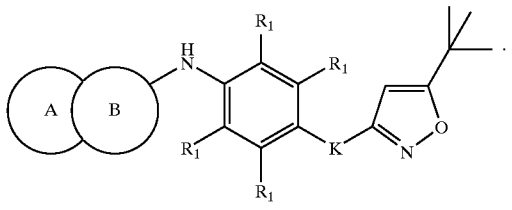
, and



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33. The method of claim 18, wherein said compound corresponds to Formula (XIII):

(XIII)

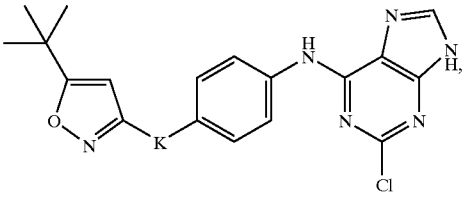


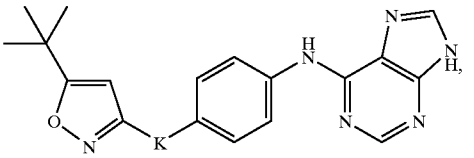
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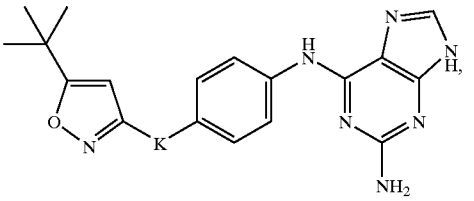
34. The method of claim 33, wherein B of said compound is a substituted or unsubstituted six-membered heteroarylene.

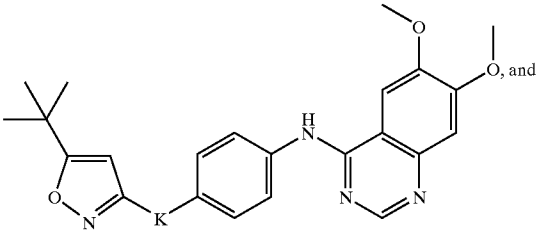
35. The method of claim 34, wherein said six-membered heteroarylene is substituted or unsubstituted pyrimidinylene.

36. The method of claim 35, wherein said compound is selected from the group consisting of:

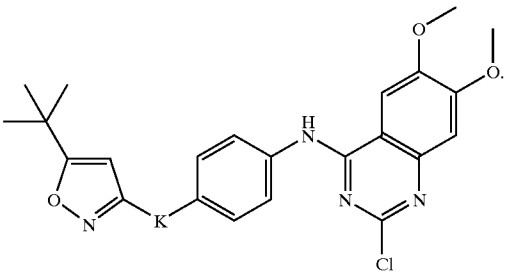








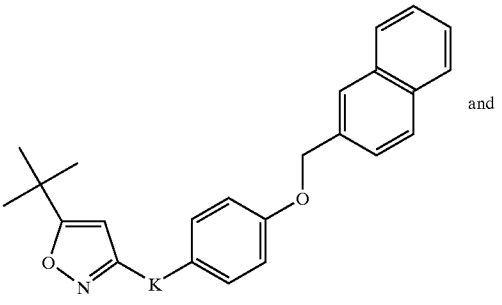
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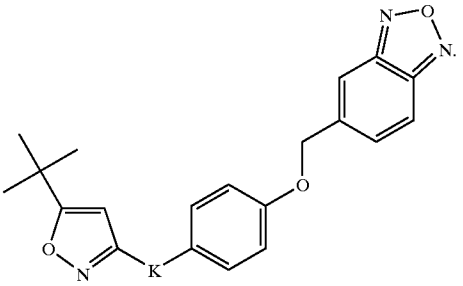
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37. The method of claim 18, wherein L of said compound —OCR_2—.

38. The method of claim 37, wherein said compound is selected from the group consisting of:

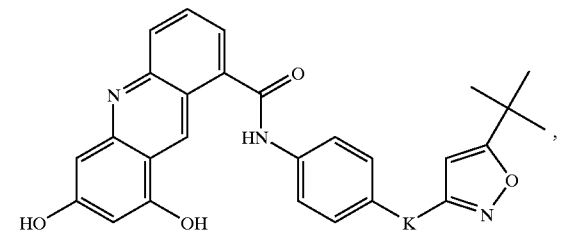


and

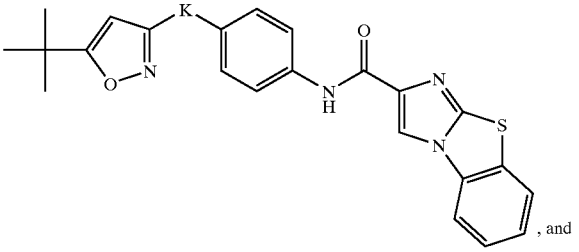


39. The method of claim 14, wherein L of said compound is —C(O)NH.

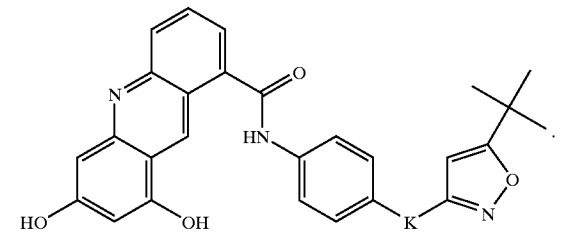
40. The method of claim 39, wherein said compound is selected from the group consisting of:



,

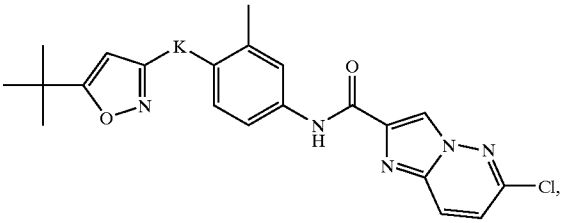


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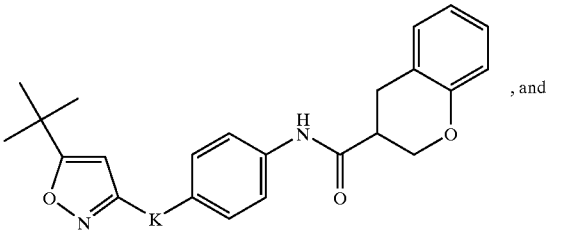


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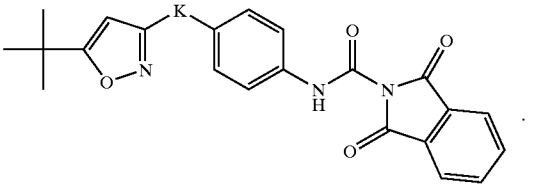
41. The method of claim 14, wherein said compound is selected from the group consisting of:



Cl,



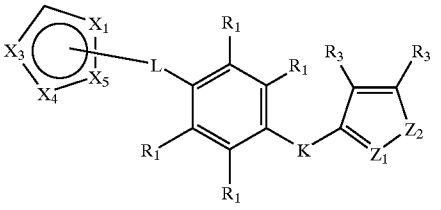
, and



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42. The method of claim 5, wherein said compound corresponds to Formula (XIV):

(XIV)



wherein:

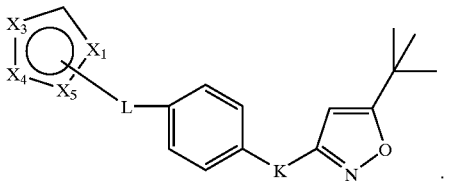
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; where each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$, or —$C(O)R_d$, or two adja-

cent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

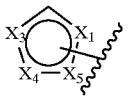
43. The method of claim 42, wherein said compound corresponds to Formula (XV):



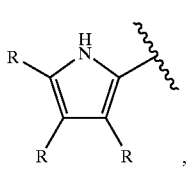
(XV)

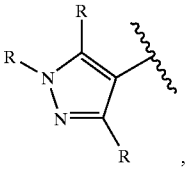
44. The method of claim 43, wherein L of said compound is a covalent bond, —C(O)NH—, or —O(substituted or unsubstituted alkylene)-.

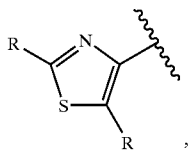
45. The method of claim 44, wherein

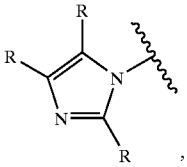


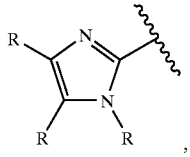
of said compound is selected from the group consisting of:

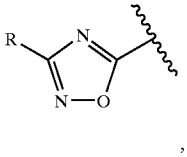


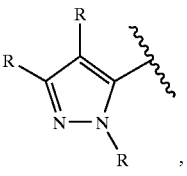


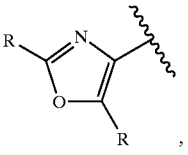






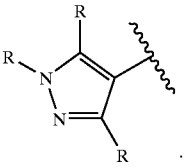




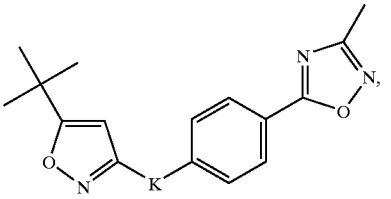


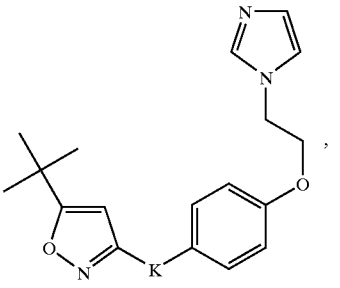
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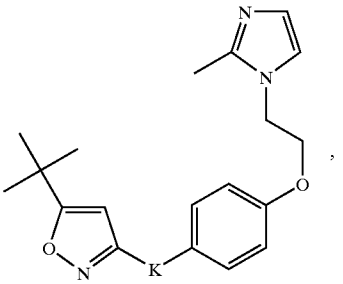
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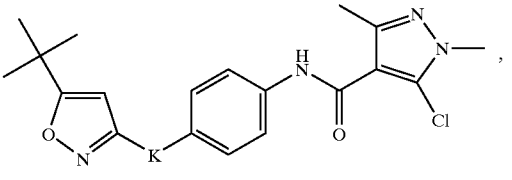


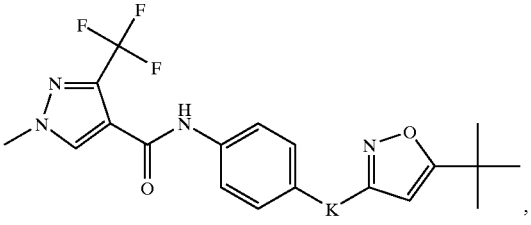
46. The method of claim 45, wherein said compound is selected from the group consisting of:



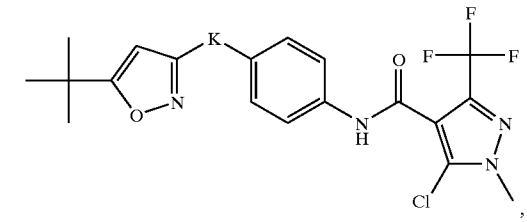


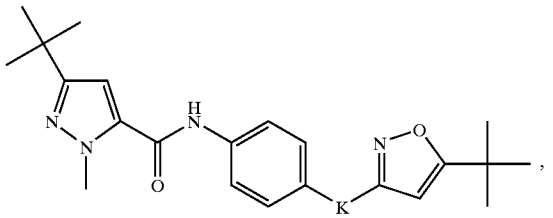


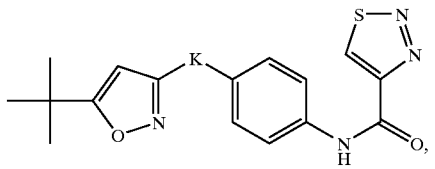


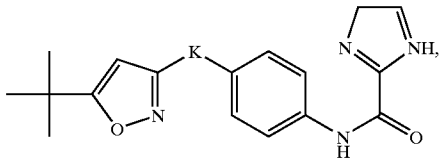


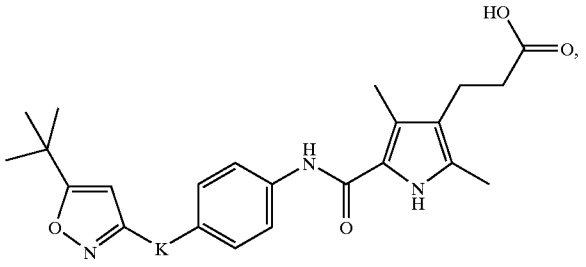
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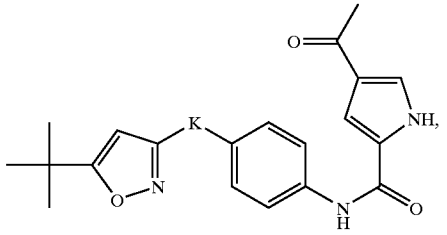


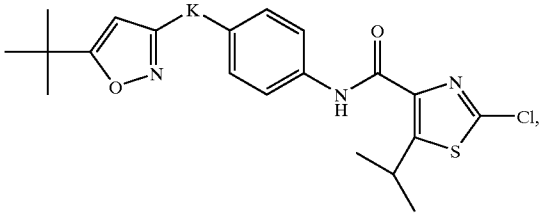




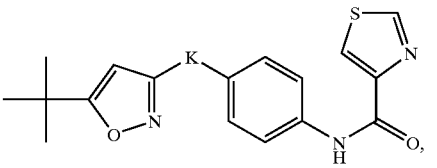


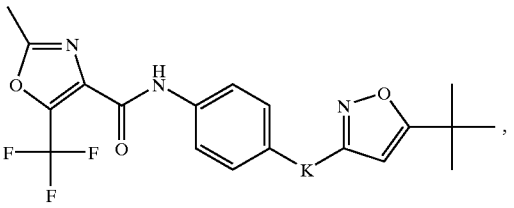


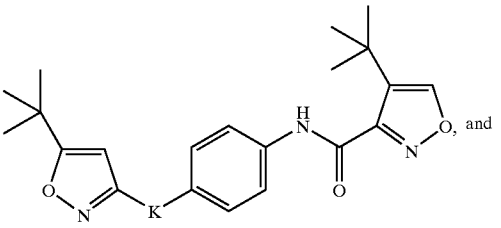


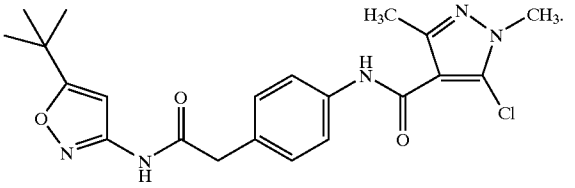


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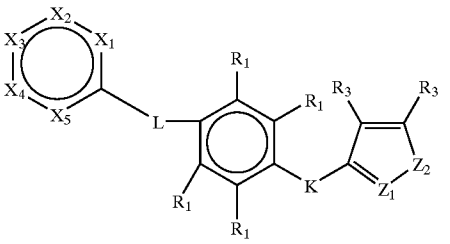






47. The method of claim 5, wherein said compound corresponds to Formula (XVI):

(XVI)



wherein:

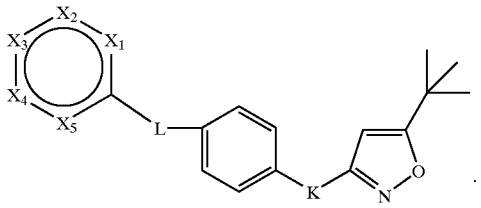
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

each of X_1-X_5 is independently C, CR, N—O, or N, wherein no more than two of X_1-X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)P_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$, or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

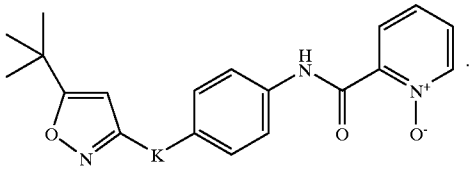
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

48. The method of claim 47, wherein said compound corresponds to Formula (XVII):

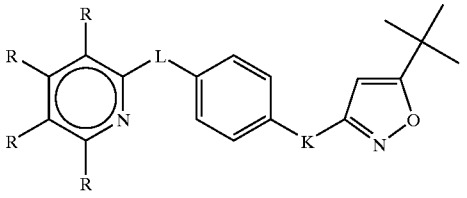


(XVII)

49. The method of claim 48, wherein said compound is:

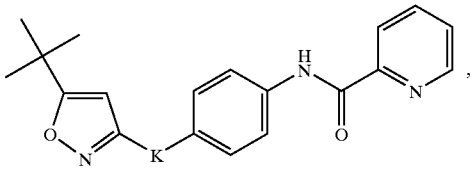


50. The method of claim 48, wherein said compound corresponds to Formula (XVIII):

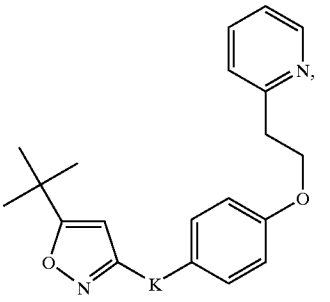


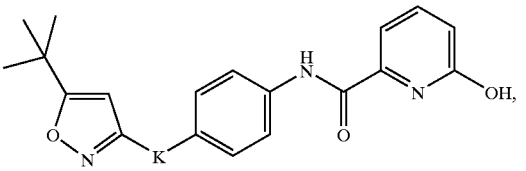
(XVIII)

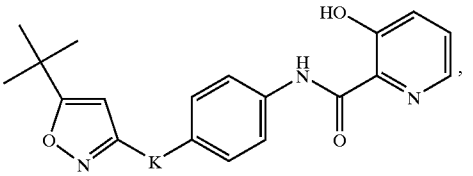
51. The method of claim 50, wherein said compound is selected from the group consisting of:

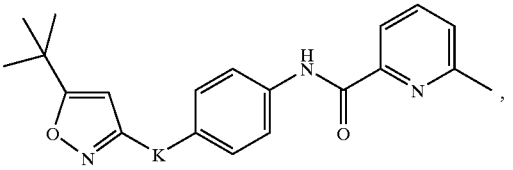


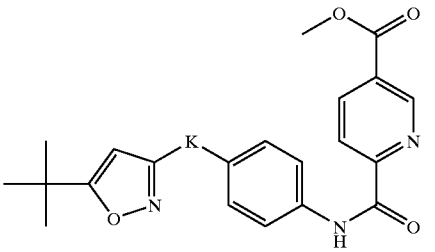
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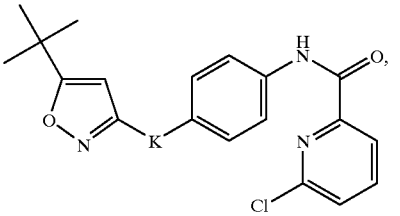


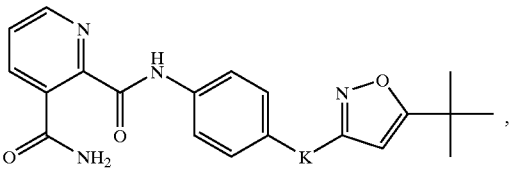




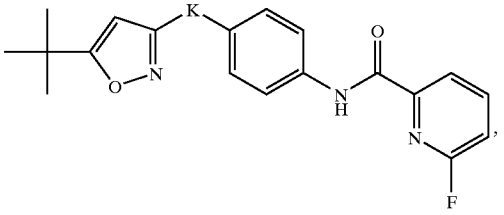


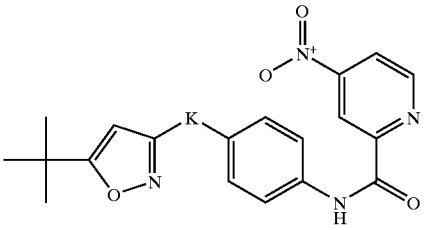


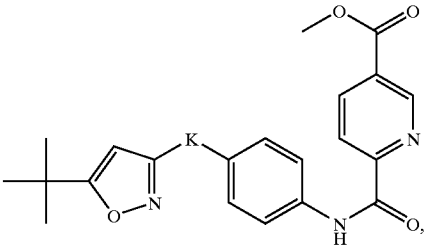


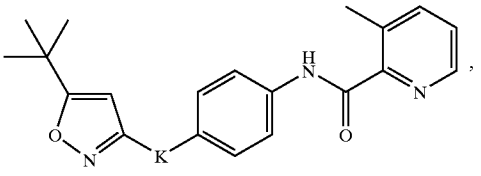


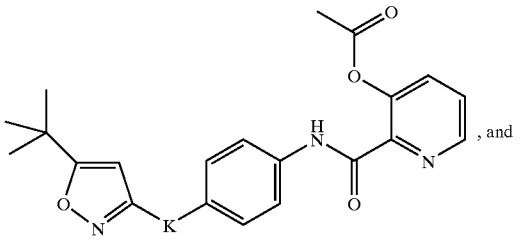
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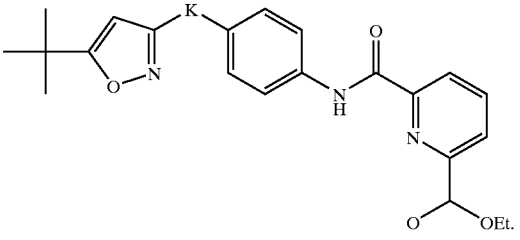






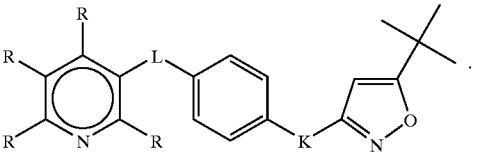




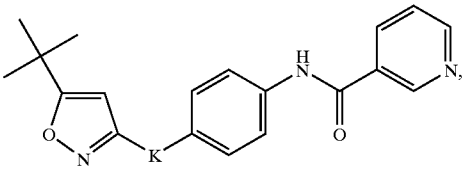


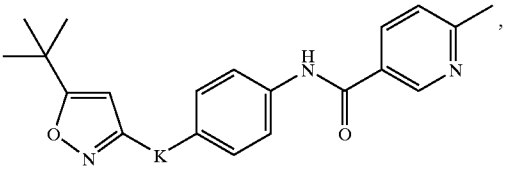
52. The method of claim 48, wherein said compound corresponds to Formula (XXI):

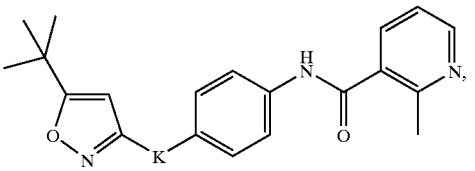
(XXI)

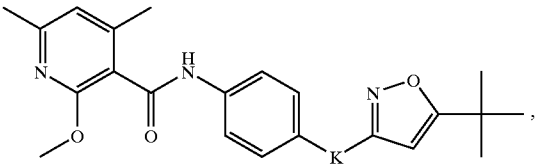


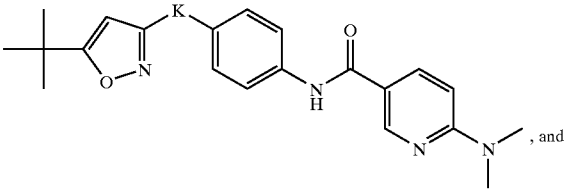
53. The method of claim 52, wherein said compound is selected from the group consisting of:

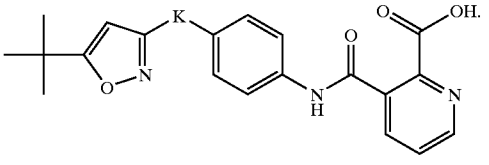






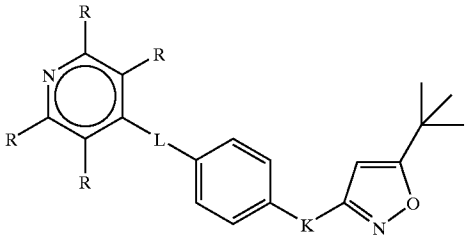






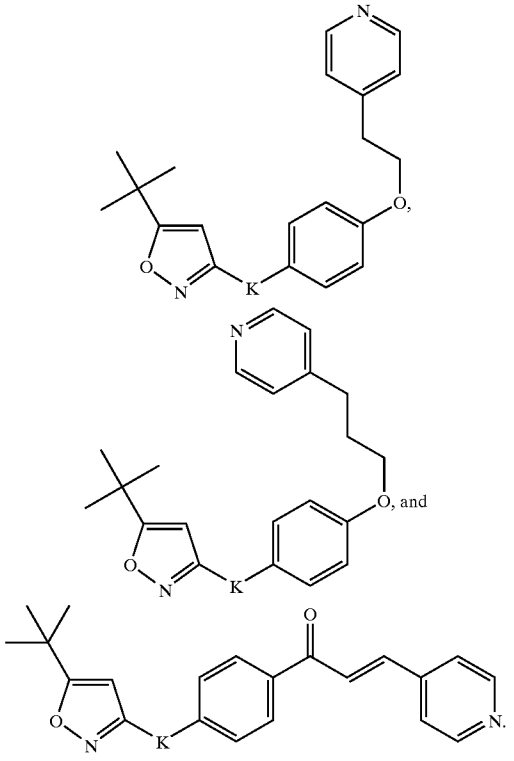
54. The method of claim 48, wherein said compound corresponds to Formula (XXII):

(XXII)



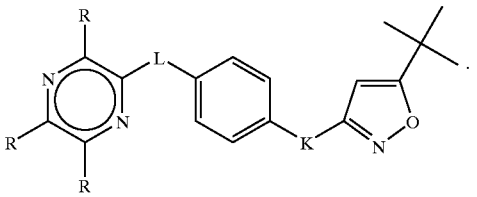
wherein L is —O(substituted or unsubstituted alkylene)- or —(O)(substituted or unsubstituted alkenylene)-.

55. The method of claim 54, wherein said compound is selected from the group consisting of:

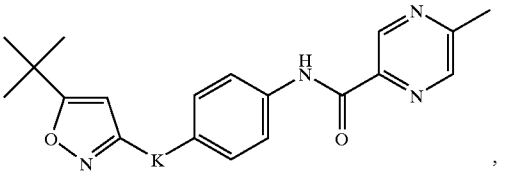


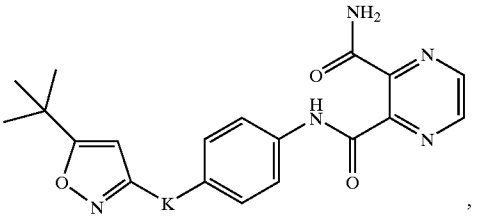
56. The method of claim 48, wherein said compound corresponds to Formula (XXIII):

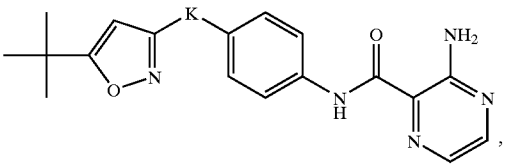
(XXIII)

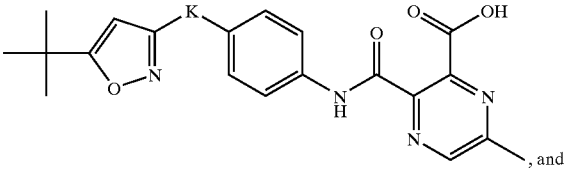


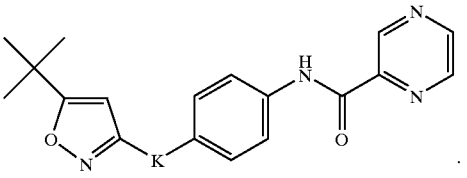
57. The method of claim 56, wherein said compound is selected from the group consisting of:





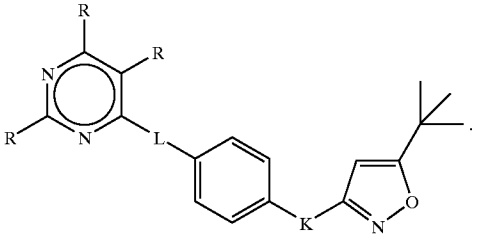




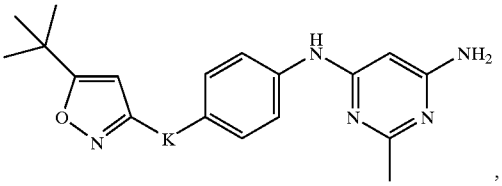


58. The method of claim 48, wherein said compound corresponds to Formula (XXIV):

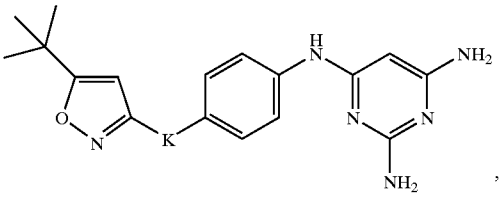
(XXIV)



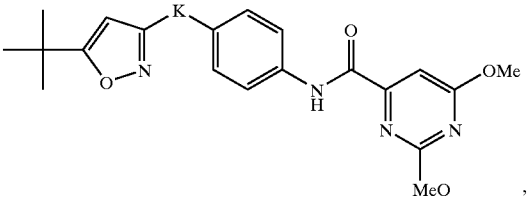
59. The method of claim 58, wherein said compound is selected from the group consisting of:



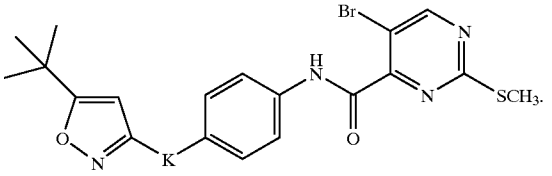
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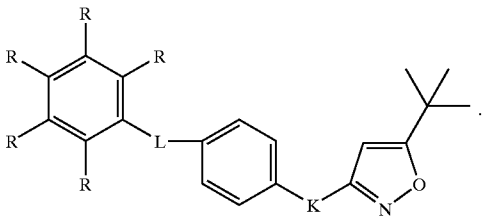


, and



60. The method of claim 48, wherein said compound corresponds to Formula (XXV):

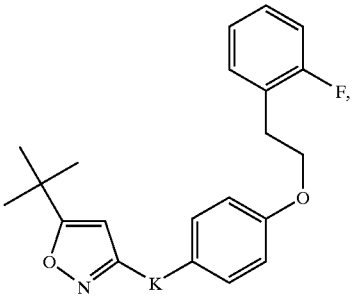
(XXV)



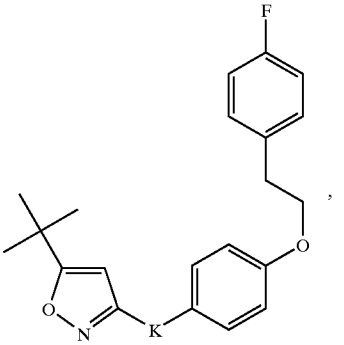
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61. The method of claim 60, wherein L of said compound is —O(substituted or unsubstituted alkylene)- or —O(substituted or unsubstituted alkenylene)-.

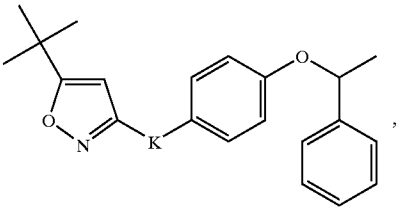
62. The method of claim 61, wherein said compound is selected from the group consisting of:



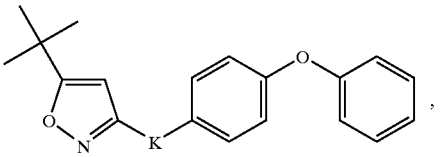
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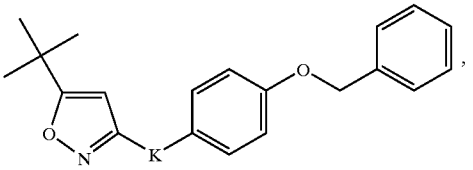
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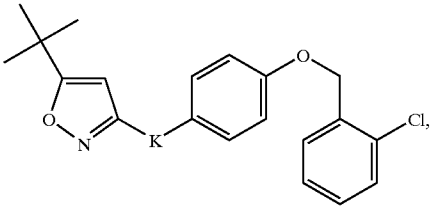
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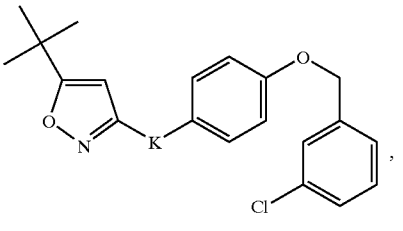
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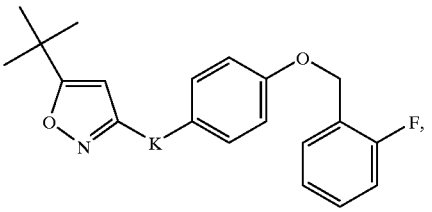
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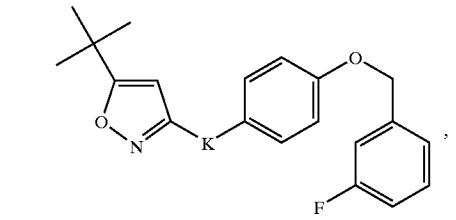
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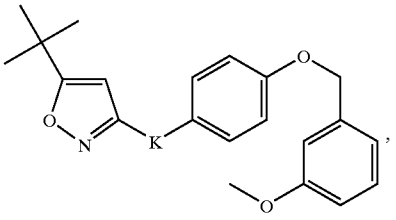


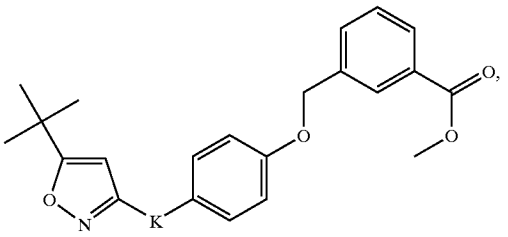
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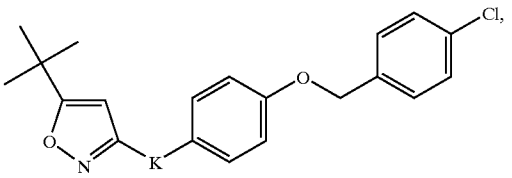


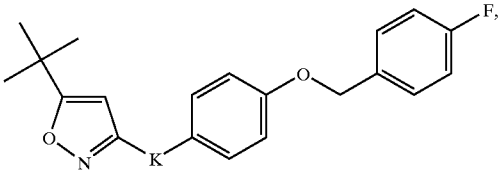
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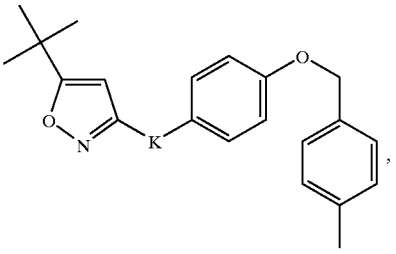


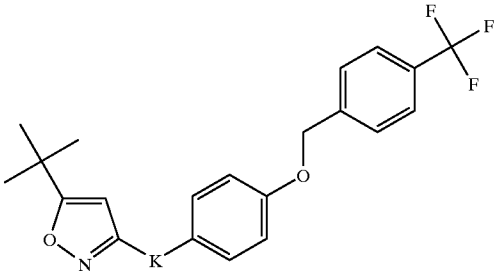




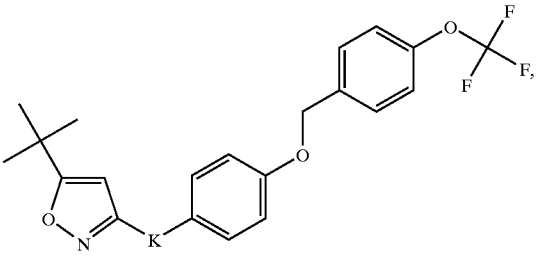


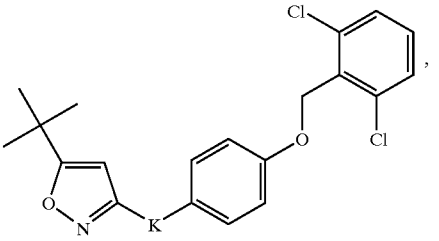


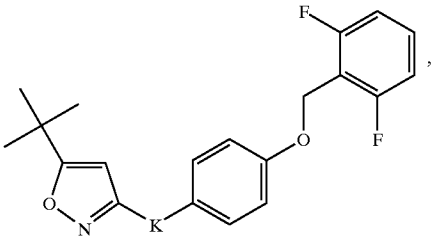


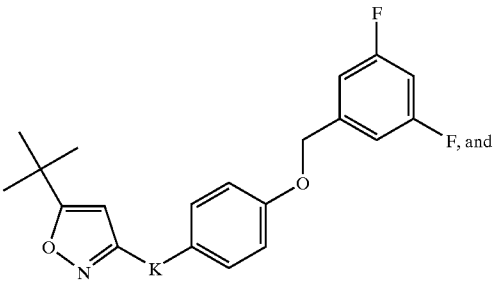


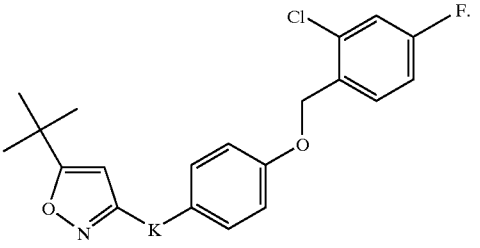
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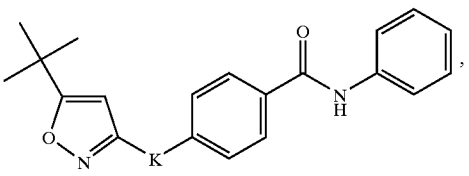




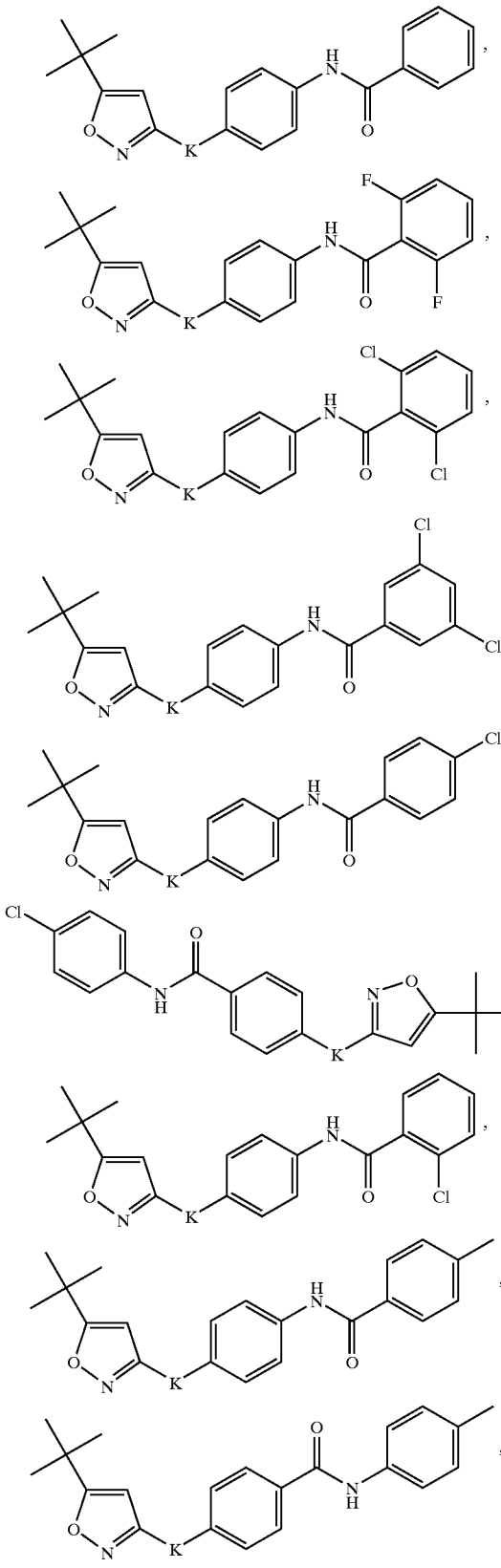


63. The method of claim 60, wherein L of said compound is —NHC(O)—.

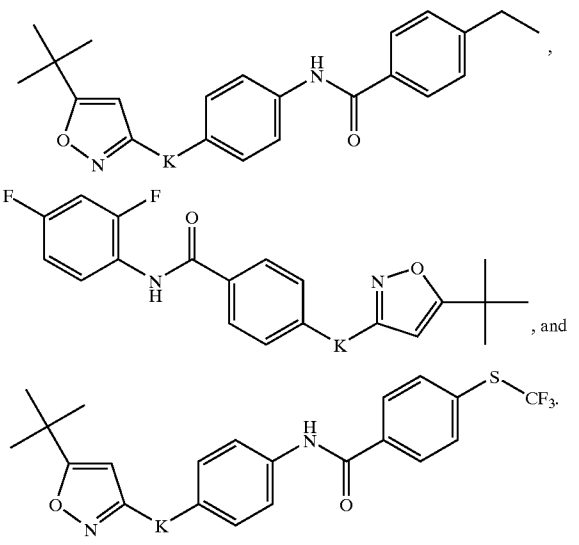
64. The method of claim 63, wherein said compound is selected from the group consisting of:



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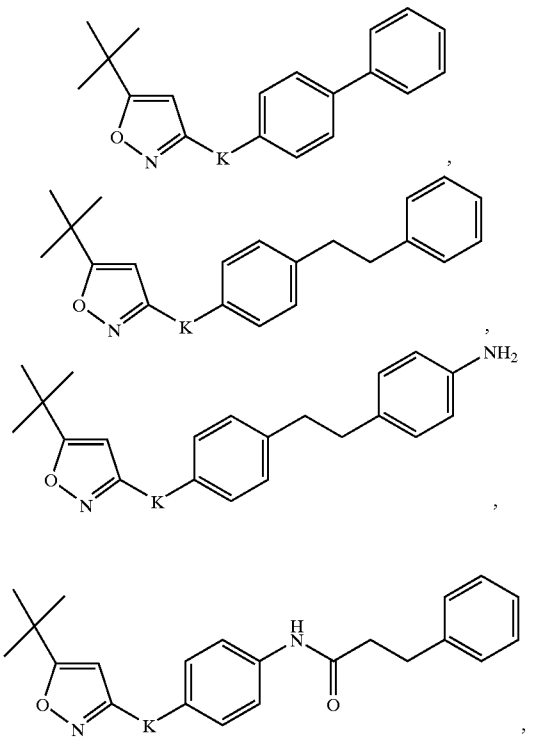


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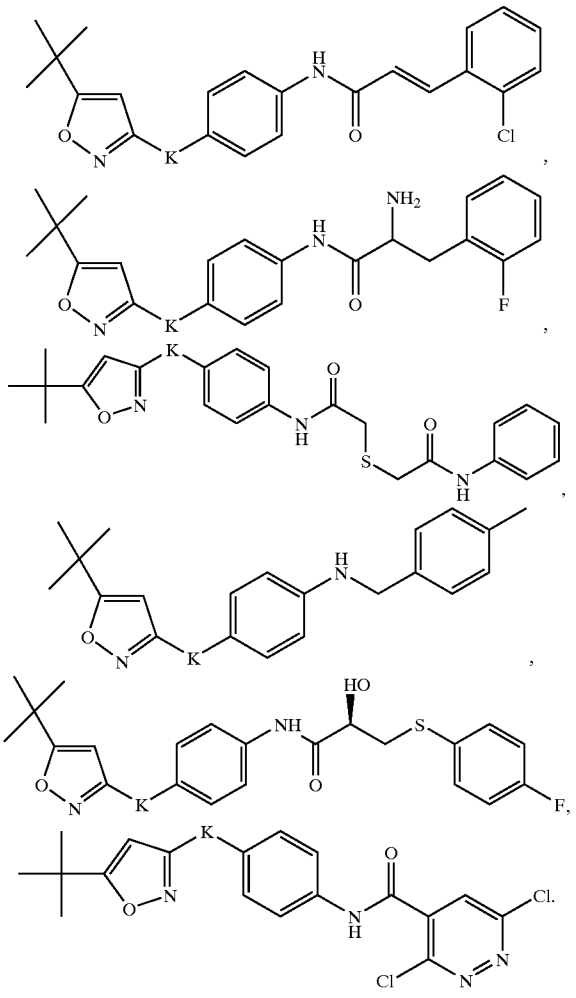


65. The method of claim 60, wherein L of said compound is a covalent bond, substituted or unsubstituted alkylene, —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —NH(alkylene)-, —NHC(O)$CH_2SCH_2C(O)NH$—, and —NHC(O)(substituted alkylene)S—.

66. The method of claim 65, wherein said compound is selected from the group consisting of:

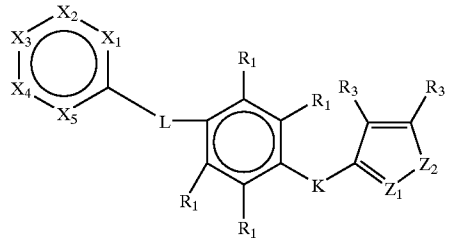


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67. The method of claim 10, wherein said compound corresponds to Formula (XXVI):

(XXVI)



wherein:

L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

each of X_1-X_5 is independently C, CR, or N, wherein no more than two of X_1-X_5 is N, where

each R is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —$NR_dC(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$ or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

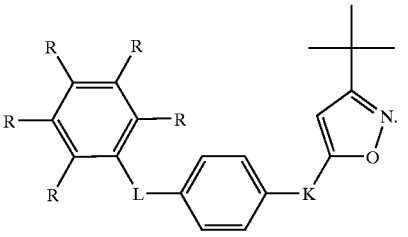
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

Z_1 is O or S; and

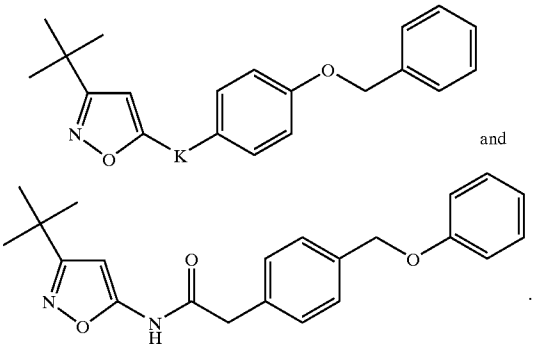
Z_2 is CR_3 or N.

68. The method of claim 67, wherein said compound corresponds to Formula (XXVII):

(XXVII)



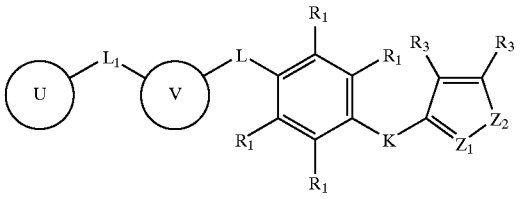
69. The method of claim 68, wherein said compound is selected from the group consisting of:



and

70. The method of claim 5, wherein said compound corresponds to Formula (XVIII):

(XVIII)



wherein:

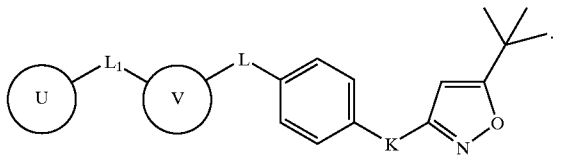
each of L and L_1 is independently a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene), —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S-(substituted or unsubstituted alkylene)C(O)NH—;

U is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

V is a substituted or unsubstituted cycloalkylene, heterocyclene, arylene, or heteroarylene.

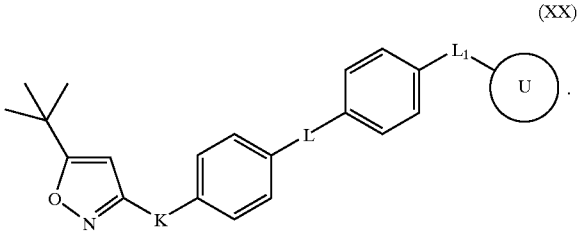
71. The method of claim 70, wherein said compound corresponds to Formula (XIX):

(XIX)

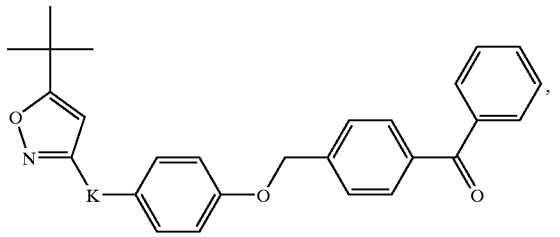


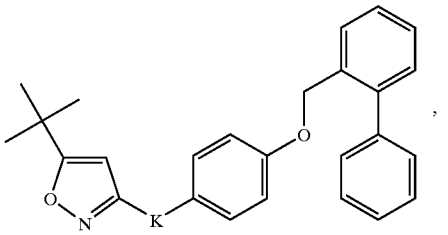
72. The method of claim 71, wherein said compound corresponds to Formula (XX):

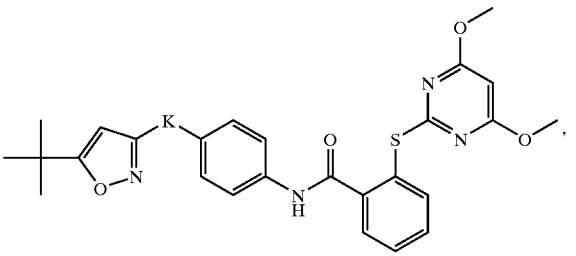
(XX)

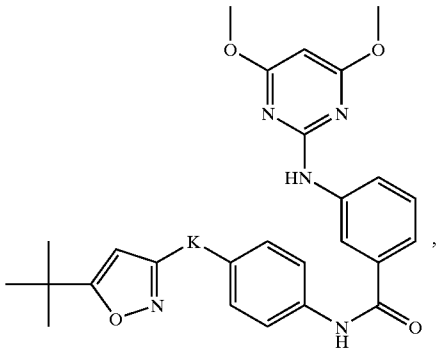


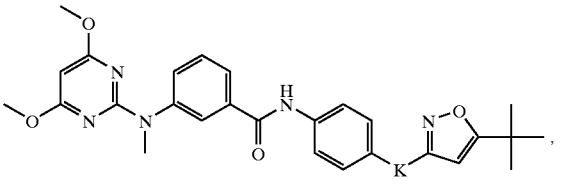
73. The method of claim 72, wherein said compound is selected from the group consisting of:

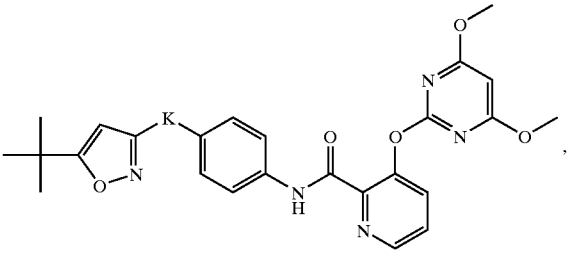




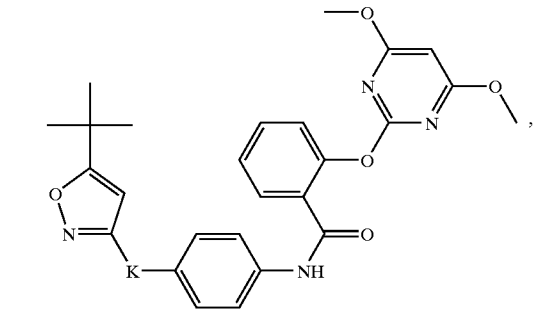


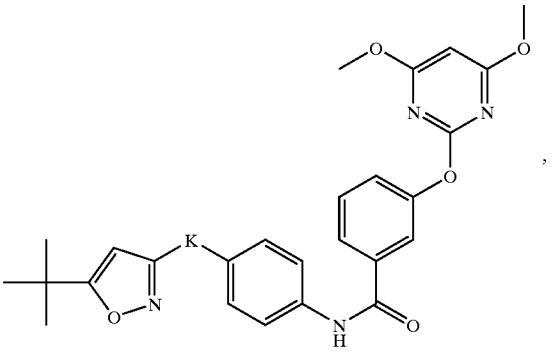


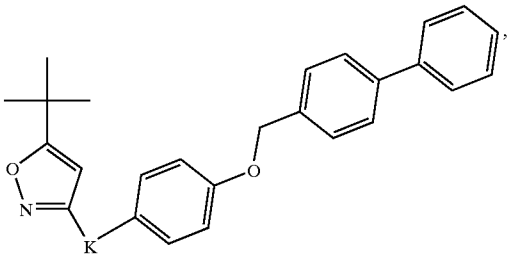


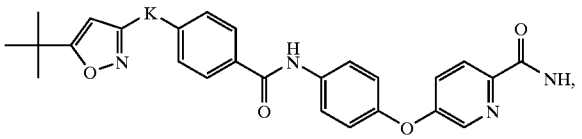


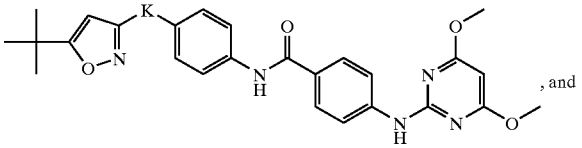
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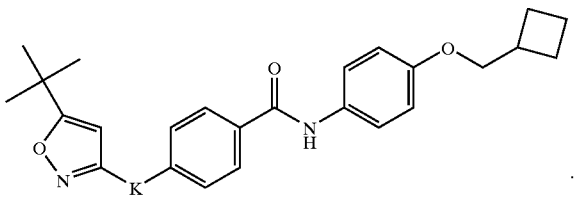






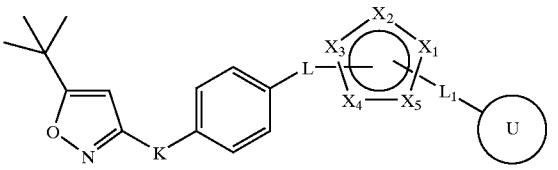






74. The method of claim 71, wherein said compound corresponds to Formula (XXXI):

(XXXI)



wherein:

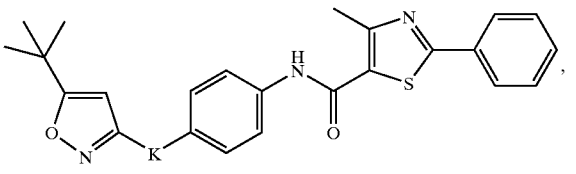
each of X_1-X_5 is independently C, CR, N, NR, S, or O, wherein no more than three of X_1-X_5 is a heteroatom, and no two adjacent ring atoms are O or S; and

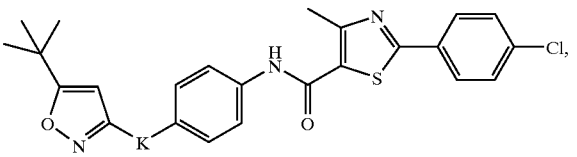
each R is independently H, halogen, substituted or unsubstituted alkyl, —OR_d, substituted or unsubstituted alkoxy, —$OC(O)R_d$, —NO_2, —$N(R_d)_2$, —SR_d, —$S(O)_jR_d$ where j is 1 or 2, —NR_d $C(O)R_d$, —$C(O)_2R_d$, —$C(O)N(R_d)_2$ or —$C(O)R_d$, or two adjacent R's are taken together to form a substituted or unsubstituted aryl or hetroaryl, where

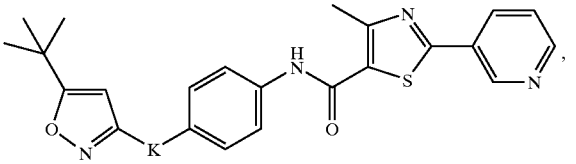
each R_d is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

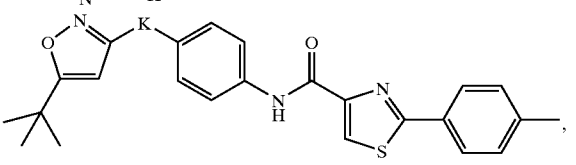
76. The method of claim **75**, wherein U is a substituted or unsubstituted five-membered heteroaryl, substituted or unsubstituted phenyl, or substituted or unsubstituted six-membered heteroaryl.

77. The method of claim 76, wherein said compound is selected from the group consisting of:

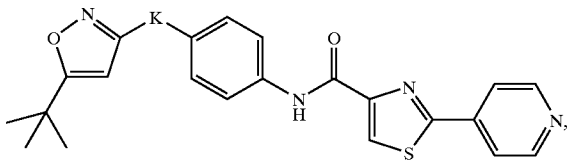


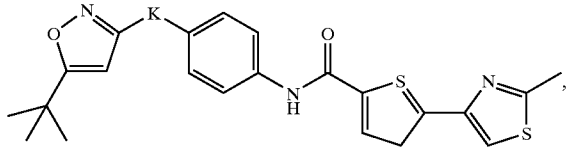


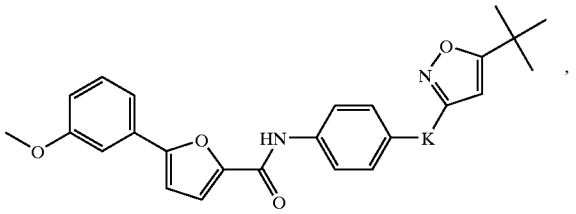


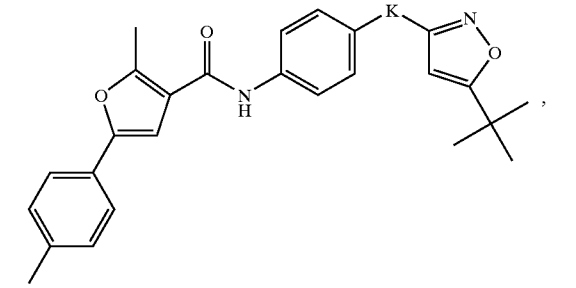


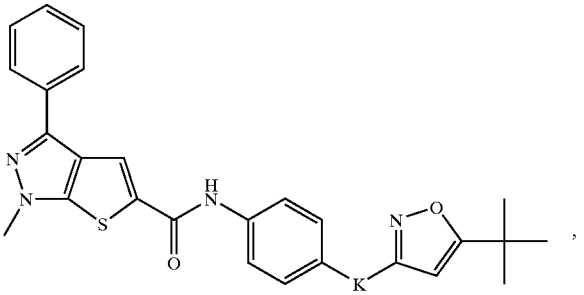
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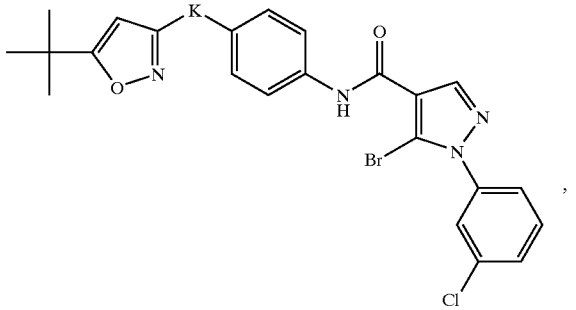


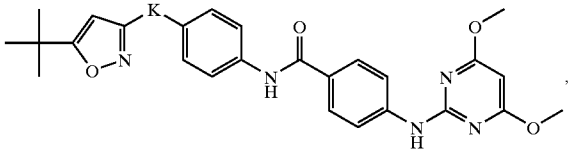




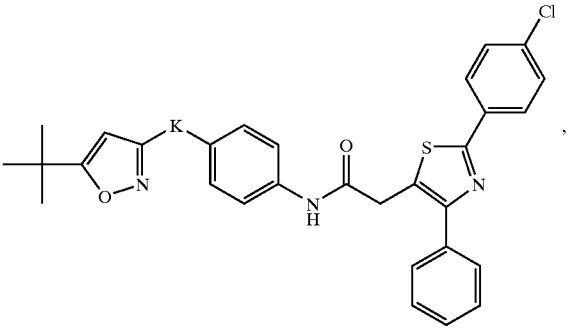


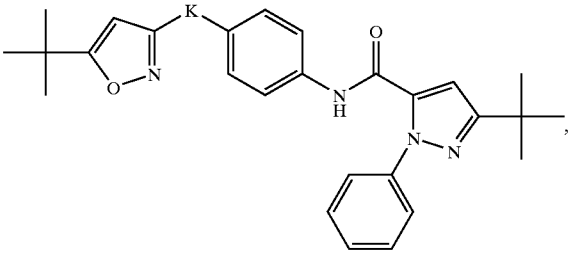


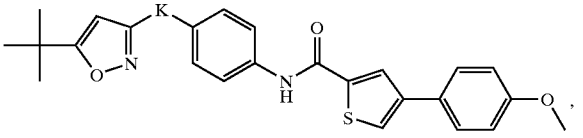


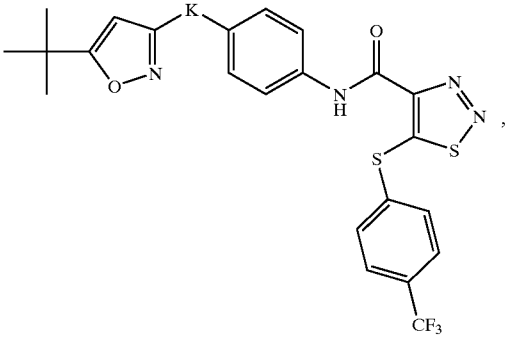


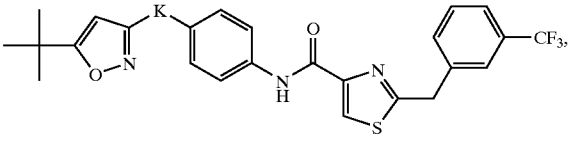
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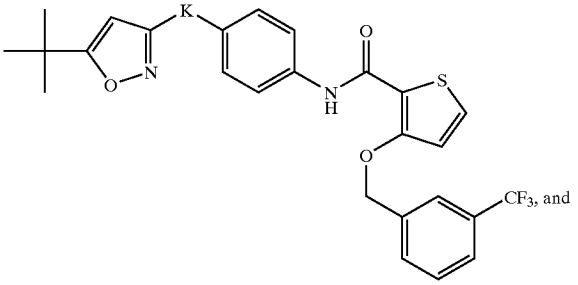






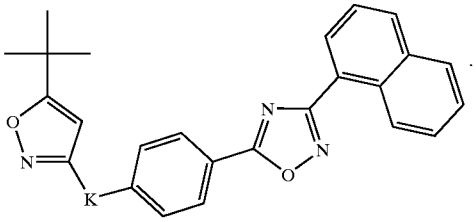




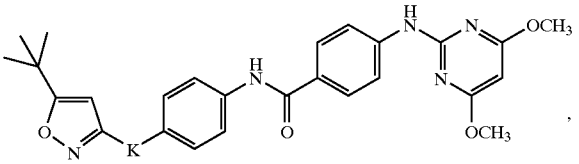


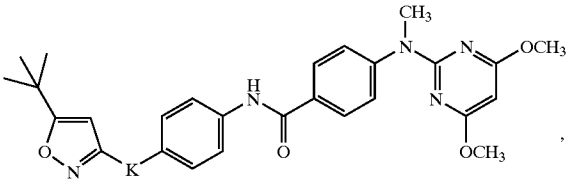
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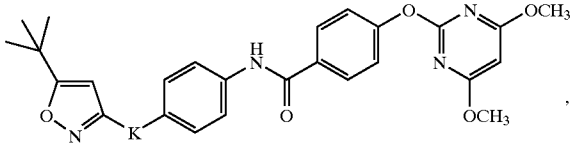
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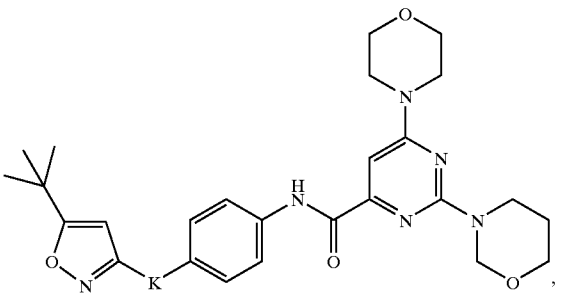


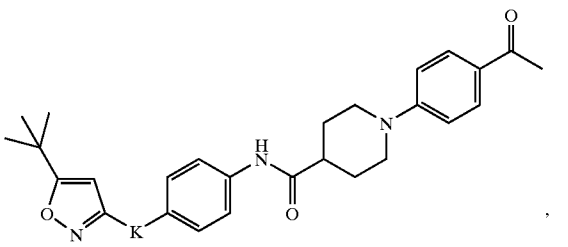
78. The method of claim 71, wherein said compound is selected from the group consisting of:



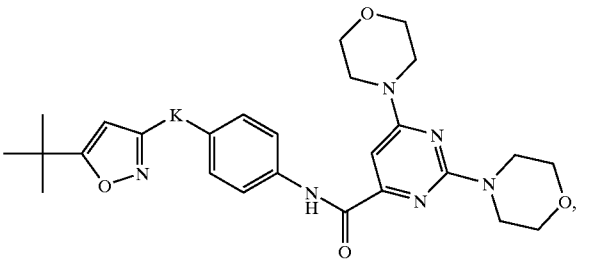


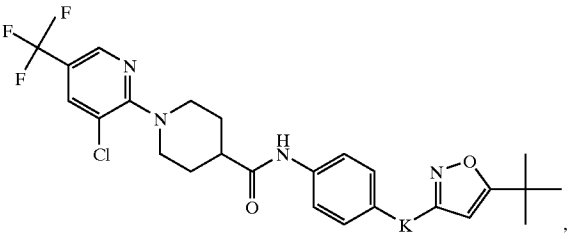


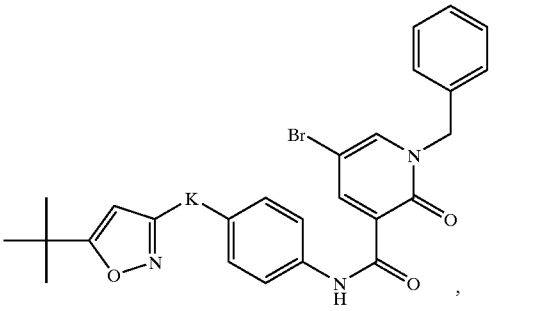


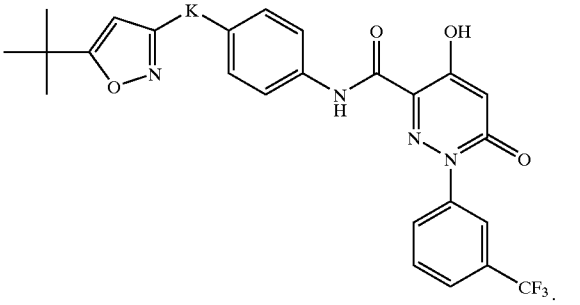


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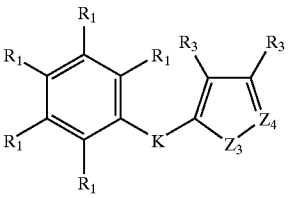






79. The method of claim 4, wherein said compound corresponds to Formula (XXIII):

(XXIII)



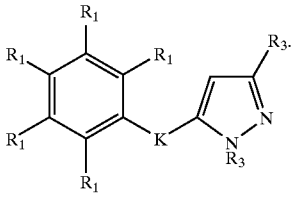
wherein:

Z_3 is NR_3, O, or S; and

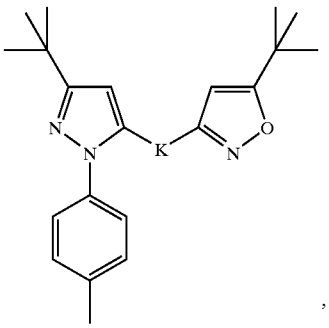
Z_4 is N or CR_3.

80. The method of claim 79, wherein said compound corresponds to Formula (XXIV):

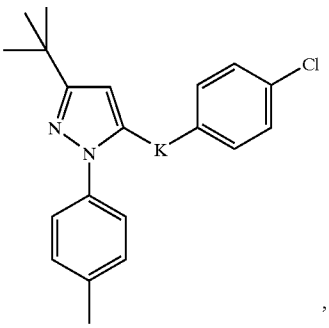
(XXIV)



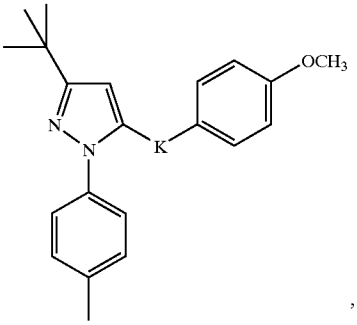
81. The method of claim 80, wherein said compound is selected from the group consisting of:



,

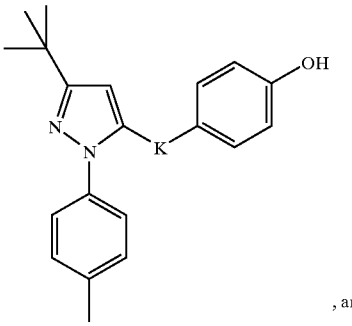


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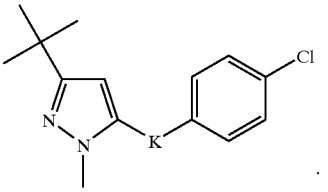


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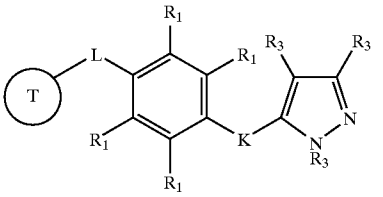
, and



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82. The method of claim 80, wherein said compound corresponds to Formula (XXV)

(XXV)

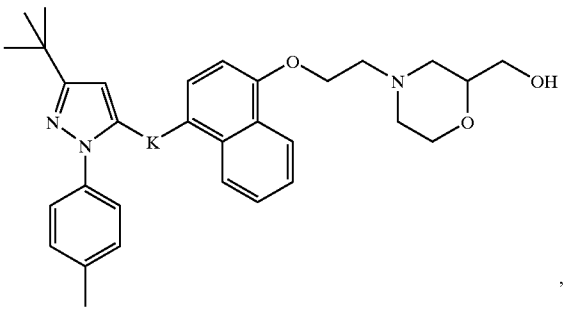


wherein:

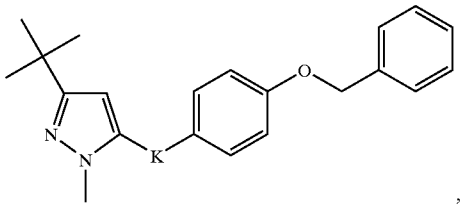
L is a linker selected from the group consisting of a covalent bond, substituted or unsubstituted alkenylene, substituted or unsubstituted alkylene, —C(O)NH—, —C(O)—, —NH—, —O—, —S—, —O(substituted or unsubstituted alkylene)-, —N(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkylene)-, —C(O)NH(substituted or unsubstituted alkenylene)- —NHC(O)(substituted or unsubstituted alkylene)-, —NHC(O)(substituted or unsubstituted alkenylene)-, —C(O)(substituted or unsubstituted alkenylene)-, and —NHC(O)(substituted or unsubstituted alkylene)S(substituted or unsubstituted alkylene)C(O)NH—; and

T is a substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

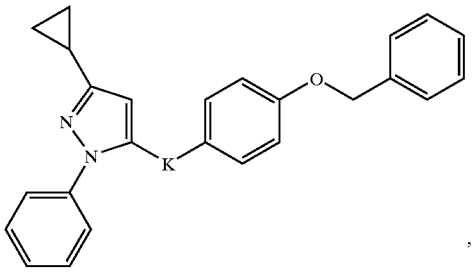
83. The method of claim 82, wherein said compound is selected from the group consisting of:



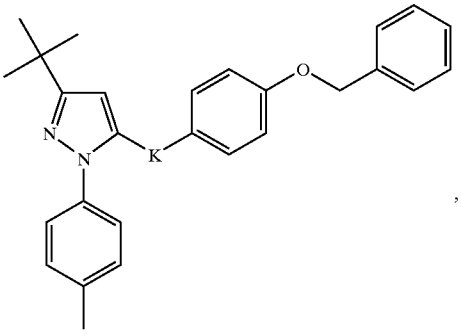
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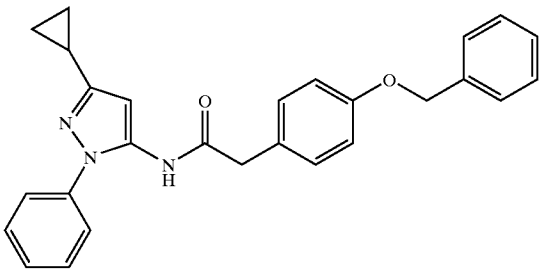
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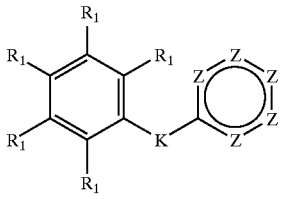
, and



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84. The method of claim 1, wherein said compound corresponds to Formula (A):

(A)



wherein:

each Z is independently C, CR_3, N, NR_3, O, or S, provided that no more than two Z's are heteroatoms where

R_3 is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

each R_k is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, $—OC(O)R_2$, $—NO_2$, $—N(R_2)_2$, $—SR_2$, $—C(O)R_2$, $—C(O)_2R_2$, $—C(O)N(R_2)_2$, or $—N(R_2)C(O)R_2$,

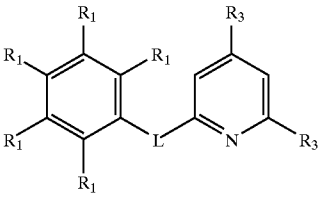
each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each R_1 is independently H, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $—OR_c$ —OH, $—OC(O)R_c$, $—NO_2$, $—N(R_c)_2$, $—SR_c$, $S(O)_jR_c$ where j is 1 or 2, $—NR_cC(O)R_c$, $—C(O)N(R_c)_2$, $C(O)_2R_c$, or $—C(O)R_c$; or two adjacent R_1's, are taken together to form a substituted or unsubstituted aryl or heteroaryl, where

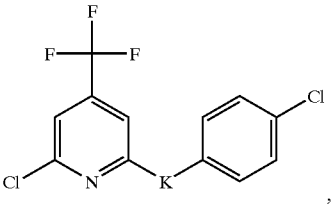
each R_c is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

85. The method of claim 84, wherein said compound corresponds to Formula (B):

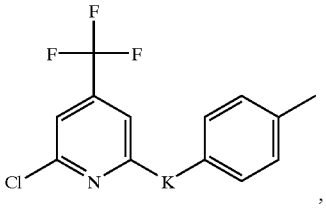
(B)



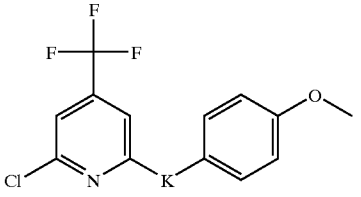
86. The method of claim 84, wherein said compound is selected from the group consisting of:



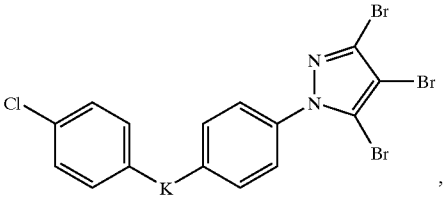
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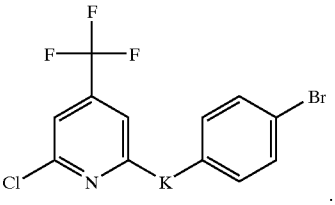
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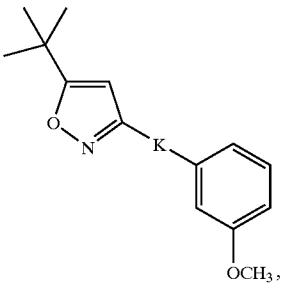


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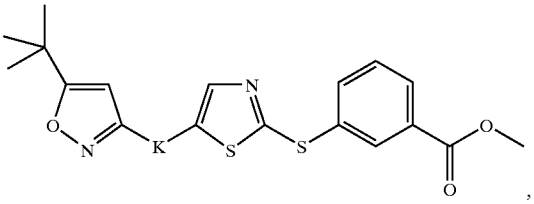


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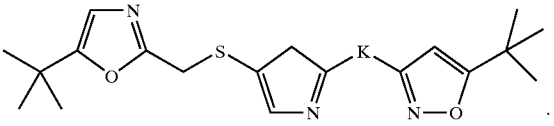
87. The method of claim 1, wherein said compound is selected from the group consisting of:



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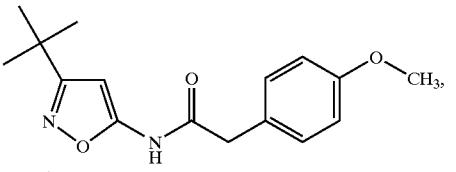


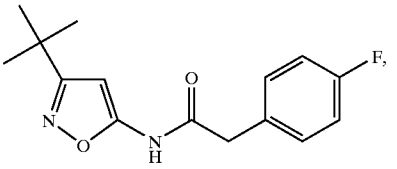
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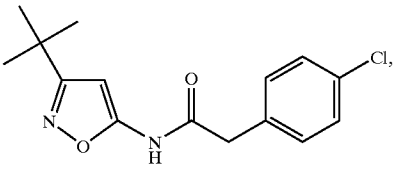


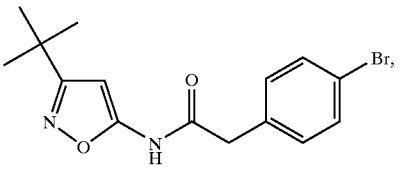
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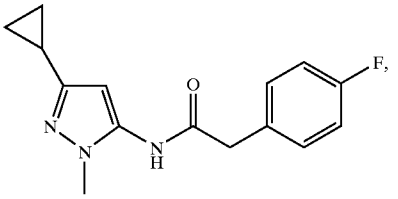
88. The method of claim 1, wherein said compound is selected from the group consisting of:

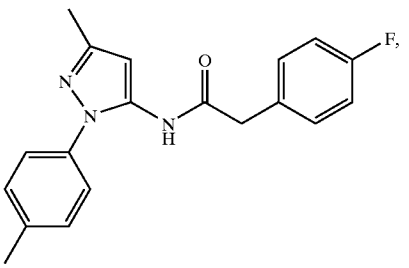




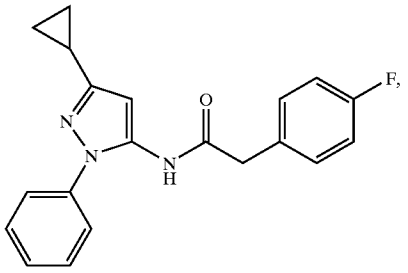


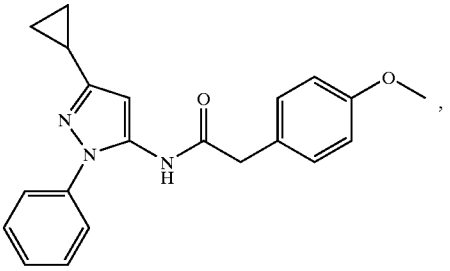


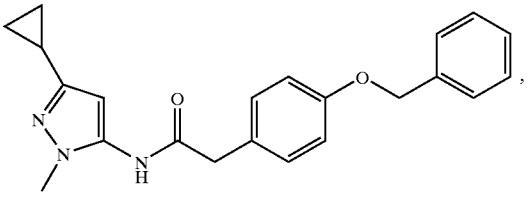


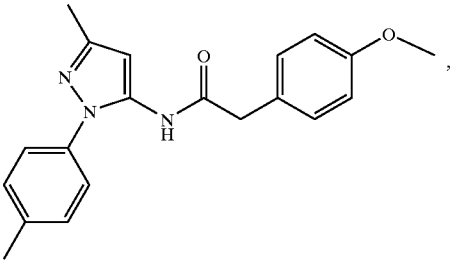


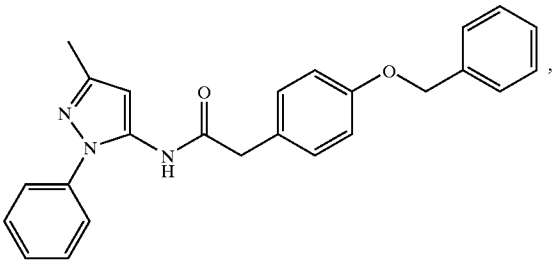
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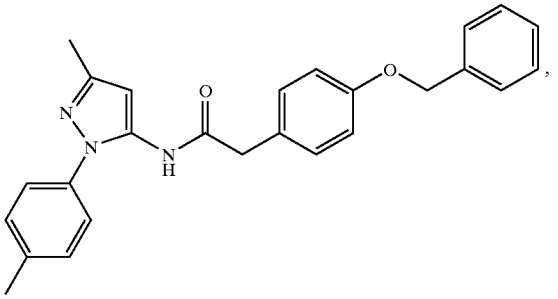




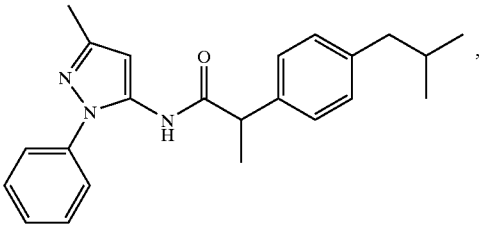


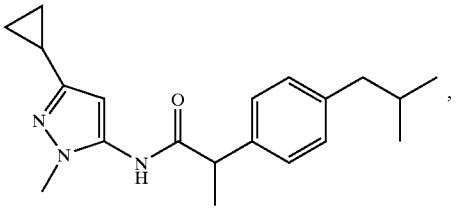


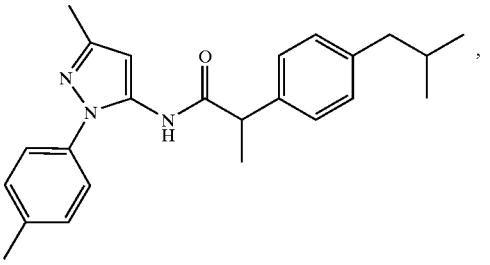


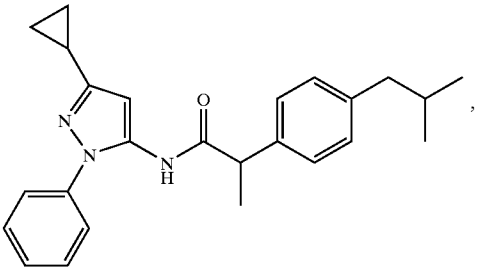


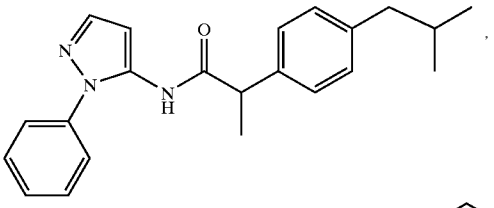
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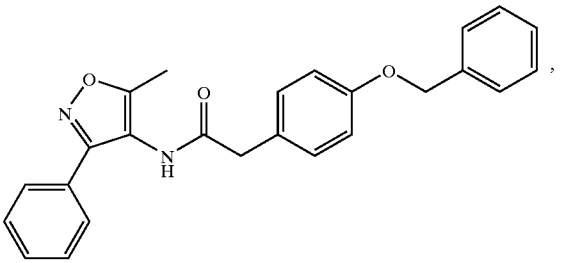


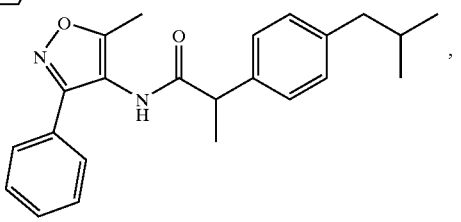




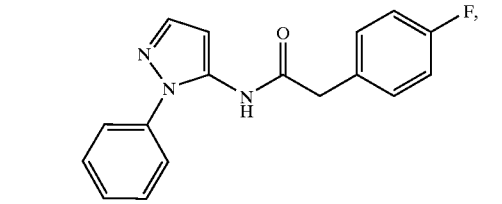


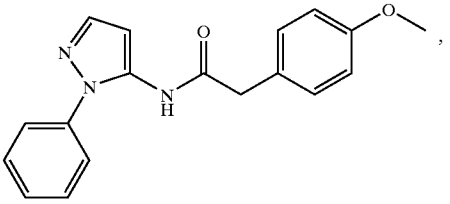


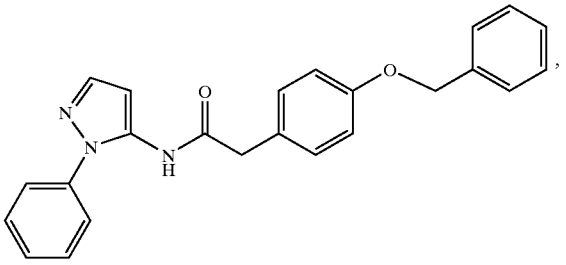


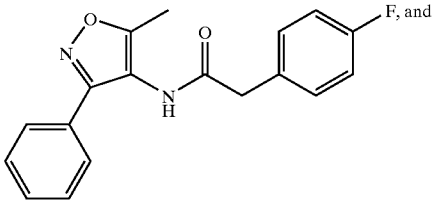


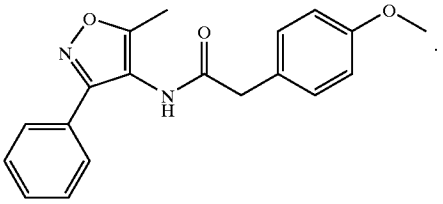
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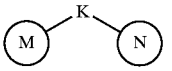








89. A method of treating a flt-3. mediated disease, said method comprising administering a therapeutically effective amount of a compound corresponding to Formula (IA):



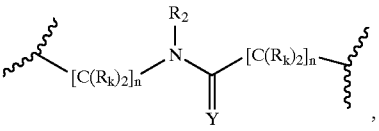
(IA)

wherein:

M is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

N is a substituted or unsubstituted aryl, or substituted or unsubstituted hetroaryl; and

K is



, where

Y is O or S;

each R_k is independently H, halogen, substituted or unsubstituted alkyl, —OH, substituted or unsubstituted alkoxy, —$OC(O)R_2$, —NO_2, —$N(R_2)_2$, —SR_2, —$C(O)R_2$, —$C(O)_2R_2$, —$C(O)N(R_2)_2$, or —$N(R_2)C(O)R_2$,

each R_2 is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or wherein two R_2 groups are linked together by an optionally substituted alkylene; and

each n is independently 0, 1, 2, 3 or 4;

or an active metabolite, or a pharmaceutically acceptable prodrug, isomer, pharmaceutically acceptable salt or solvate thereof.

* * * * *