COMPOUNDS FOR THE TREATMENT OF PROLIFERATIVE DISORDERS

RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application 60/653,890, filed February 17, 2005; U.S. Provisional Application 60/660,112, filed March 8, 2005; and U.S. Provisional Application 60/733,912, filed November 4, 2005, which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This invention relates to biologically active chemical compounds, namely isoxazole derivatives that may be used for treating or preventing proliferative disorders.

BACKGROUND OF THE INVENTION

Many chemotherapeutic methods are now available to be used in the treatment of cancer. One of the most successful methods is the use of anti-mitotic agents which interfere with the assembly or disassembly of microtubules. Since microtubule assemble and disassemble is necessary for mitosis, inhibition of either the assembly or disassembly of microtubules interferes with cell proliferation. Thus, compounds that inhibit the assembly of microtubule are useful in treating diseases or conditions which are caused or exasperated by rapid or abnormal cell proliferation, such as cancer.

Several anti-mitotic agents have had considerable clinical success. For example, the following vinca alkaloids which inhibit microtubule assembly have proved clinically successful: Vincristine has been successfully used to treat hematological malignancies and non-small-cell lung carcinoma; Vinblastine has been successfully used to treat hematological malignancies, testicular carcinomas and non-small-cell lung carcinoma; and Vinorelbine has been successfully used to treat hematological malignancies, breast carcinomas and non-small-cell lung carcinoma. In addition, taxanes which inhibit microtubule disassemble have also proved to be clinically successful. For example, Paclitaxel has been successful in treating breast, ovarian and non-small-cell lung carcinomas; and Docetaxel has been successful in treating breast and non-small-cell lung carcinomas.

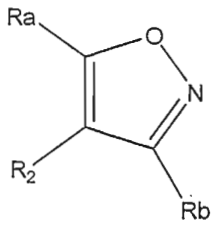
Despite these successes, available anti-mitotic agents are inadequate for a number of reasons. For example, paclitaxel, docetaxel and vincristine are associated with significant neuropathy which can limit their use in repeat courses of therapy. In addition, both the vinca alkaloids and taxanes are good substrates for the 170 kDa P-glycoprotein (Pgp) efflux pump found in most multi-drug resistant cells. This protein pumps a drug out of the tumor cells causing the tumor cells to become resistant to treatment. Once a patient's cancer has become multi-drug resistant, there is typically little that can be done to halt or retard further progression of the disease.

There is therefore still a need for new drugs which overcome one or more of the aforementioned shortcomings of drugs currently used in the treatment of cancer. Desirable properties of new anti-cancer drugs therefore include a good therapeutic index, efficacy against tumors that are currently untreatable or poorly treatable, efficacy against multi-drug resistant tumors and/or reduced side effects.

SUMMARY OF THE INVENTION

This invention meets the above-mentioned needs by providing certain isoxazole derivatives that inhibit tubulin polymerization. Compounds of the invention are also capable of vascular targeting, in particular, blocking, occluding, or otherwise disrupting blood flow in neovasculature. These compounds are particularly useful for treating or preventing proliferative disorders, such as cancer.

In one embodiment, the invention relates to compounds of formula (I):



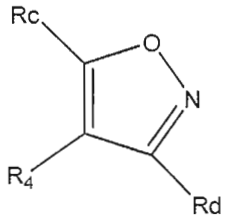
(I)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_a or R_b is –H and the other is an optionally substituted aryl, or an optionally substituted heteroaryl; and

R_2 is an optionally substituted phenyl, an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrrolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl.

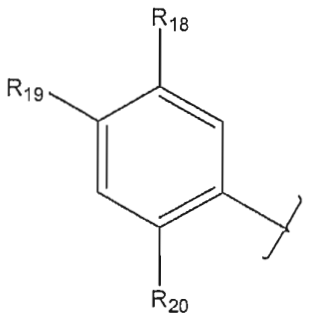
In another embodiment, the invention relates to compounds of formula (II):



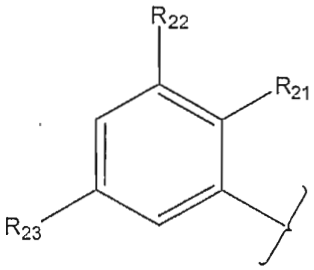
(II)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, or a substituted phenyl represented by one of the following formulas:



or



R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl,

a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2.

Compounds of the invention or pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof are potent antimitotic agents which inhibiting tubulin polymerization, and thus can inhibit microtubule growth. In order for cells to undergo mitosis, microtubules must be able to assemble and disassemble, in a process known as dynamic instability. Thus, in one embodiment, the compounds of the invention can be used to inhibit tubulin polymerization in a cell by contacting the cell with an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, compounds of the invention can be used to inhibit tubulin polymerization in a subject by administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

Compounds of the invention or pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof are vascular targeting agents which can be used to block, occlude, or otherwise disrupt blood flow in neovasculature, and thus lead to destruction of vasculature. Thus in one embodiment, compounds of the invention can be used to block, occlude, or otherwise disrupt blood flow in neovasculature by contacting the neovasculature with an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, compounds of the invention can be used to block, occlude, or otherwise disrupt blood flow in neovasculature of a subject by administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

Since the compounds of the invention disrupt mitosis by inhibiting tubulin polymerization, they are particularly useful in treating or preventing proliferative disorders, such as cancer. Therefore, in one embodiment, compounds of the invention or pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof can be used to treat or prevent a proliferative disorder in a subject by administering to the subject an effective amount of a compound of the invention or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof

All of the methods of this invention may be practice with a compound of the invention alone, or in combination with other agents, such as other anti-cancer agents.

As will be described in detail below, compounds of the invention overcome or ameliorated some of the limitation of known anti-mitotic agents. In particular,

compounds of the invention are cytotoxic in multidrug resistant cells, and thus may be useful for treating cancers that have become resistant to other therapies.

DESCRIPTION OF THE FIGURES

Figure 1 shows the cytotoxic effects of compounds of the invention on hepatocytes compared to untreated cells and to known cancer drugs Taxol and 17AAG.

Figure 2 shows the cytotoxic effects of compounds of the invention on hepatocytes compared to untreated cells and to known cancer drug 17AAG.

Figure 3 shows the microtubule network of Chinese Hamster Ovary (CHO) cells transfected with a vector encoding α-tubulin-YFP after they have been treated with DMSO.

Figure 4 shows the microtubule network of CHO cells transfected with a vector encoding α-tubulin-YFP after they have been treated with 0.1 μM Taxol.

Figure 5 shows the microtubule network of CHO cells transfected with a vector encoding α-tubulin-YFP after they have been treated with 0.1 μM Compound 1.

Figure 6 shows the microtubule network of CHO cells transfected with a vector encoding α-tubulin-YFP after they have been treated with 0.1 μM Compound 3.

Figure 7 shows the microtubule network of CHO cells transfected with a vector encoding α-tubulin-YFP after they have been treated with 0.1 μM Compound 6.

Figure 8A shows the microtubule network of CV-1 cells 24 hrs after treatment with DMSO. CV-1 cells are known to be resistant to the depolymerization effects of colchicines and vincristine.

Figure 8B shows the microtubule network of CV-1 cells 24 hrs after treatment with Compound 3.

Figure 8C shows the microtubule network of CV-1 cells 24 hrs after treatment with colchicine.

Figure 8D shows the microtubule network of CV-1 cells 24 hrs after treatment with vincristine.

Figure 8E shows a magnified view of the microtubule network of CV-1 cells 24 hrs after treatment with Compound 3.

Figure 9A shows the microtubule network of CV-1 cells 48 hrs after treatment with DMSO.

Figure 9B shows the microtubule network of CV-1 cells 48 hrs after treatment with Compound 3.

Figure 9C shows the microtubule network of CV-1 cells 48 hrs after treatment with colchicine.

Figure 9D shows the microtubule network of CV-1 cells 48 hrs after treatment with vincristine.

Figure 9E shows a magnified view of the microtubule network of CV-1 cells 48 hrs after treatment with Compound 3.

Figure 10A shows the microtubule network of CV-1 cells 72 hrs after treatment with DMSO.

Figure 10B shows the microtubule network of CV-1 cells 72 hrs after treatment with Compound 3.

Figure 10C shows the microtubule network of CV-1 cells 72 hrs after treatment with colchicine.

Figure 10D shows the microtubule network of CV-1 cells 72 hrs after treatment with vincristine.

Figure 10E shows a magnified view of the microtubule network of CV-1 cells 72 hrs after treatment with Compound 3.

Figure 11 shows the results of a *nude* mouse xenograft study to determine the effect of Compound 3 on the *in vivo* growth rate of the human tumor cell line MDA-MB-435S. Tumor bearing animals (10 mice/group) were i.v. injected 3 times per week for a total of 10 doses (hatched bar) and the average tumor volumes for each group (+/- SEM) were determined every 2-4 days. Treatment with doses of 12.5 and 25 mg/kg body weight of Compound 3 caused tumor regression, whereas a dose of 7.5 mg/kg body weight of paclitaxel did not.

Figure 12 shows percent change in body weight of animals during the study presented in Figure 11. Treatment with Compound 3 did not cause overt toxicity in a *nude* mouse xenograft model using the human tumor cell line MDA-MB-435S. Tumor bearing animals (10 mice/group) were i.v. injected 3 times per week for a total of 10 doses (hatched bar) and the cumulative average percent changes in body weights for each group relative to the start of dosing (+/- SEM) were determined every 1-3 days. Treatment with doses of 6.25, 12.5 and 25 mg/kg body weight of Compound 3 was not overtly toxic, as indicated by the minimal effects on the animal body weights in the test article-treated versus vehicle-treated groups.

Figure 13 shows the results of a *nude* mouse xenograft study to determine the effect of Compound 3 on the *in vivo* growth rate of the human tumor cell line RERF-LC-AI. Tumor bearing animals (8 mice/group) were i.v. injected 3 times per week for a total of 8 doses (hatched bar) and the average tumor volumes for each group (+/- SEM) were determined every 3-4 days. Treatment with 25 mg/kg body weight of Compound 3 inhibited tumor growth to a similar degree to what was observed with a dose of 12.5 mg/kg body weight of paclitaxel.

Figure 14 shows percent change in body weight of animals during the study presented in Figure 13. Treatment with Compound 3 did not cause overt toxicity in a *nude* mouse xenograft model using the human tumor cell line RERF-LC-AI. Tumor bearing animals (8 mice/group) were i.v. injected 3 times per week for a total of 9 doses (hatched bar) and the cumulative average percent changes in body weights for each group relative to the start of dosing (+/- SEM) were determined every 1-3 days. Treatment with doses of 25 mg/kg body weight of Compound 3 was not overtly toxic, as indicated by the minimal effects on the animal body weights in the test article-treated versus vehicle-treated groups.

Figure 15 shows the results of a *nude* mouse xenograft study to determine the effects of Compounds 169 and 174 on the *in vivo* growth rate of the human tumor cell line MDA-MB-435S. Tumor bearing animals (8 mice/group) were i.v. injected 1 time per week for a total of 3 doses (arrowheads) and the median tumor volumes for each group (error bars represent SEM) were determined every 3-4 days. Treatment with doses of 2 mg/kg body weight of Compound 169 and 4.55 mg/kg body weight of Compound 174 substantially inhibited tumor growth.

Figure 16 shows percent change in body weight of animals during the study presented in Figure 15. Treatment with Compounds 169 and 174 did not cause overt toxicity in a *nude* mouse xenograft model using the human tumor cell line MDA-MB-435S (data derived from the same study presented in Figure 15). Tumor bearing animals (8 mice/group) were i.v. injected 1 time per week for a total of 3 doses (arrowheads) and the cumulative average percent changes in body weights for each group relative to the start of dosing were determined every 1-4 days (error bars not shown for clarity). Treatment with doses of 2 and 1 mg/kg body weight of Compound 169 and 4.55 and 2.28 mg/kg body weight of Compound 174 were not overtly toxic, as indicated by the minimal effects on the animal body weights in the test article-treated versus vehicle-treated groups.

Figure 17 shows the results of a *nude* mouse xenograft study to determine the effect of Compound 178 on the *in vivo* growth rate of the human tumor cell line MDA-MB-435S. Tumor bearing animals (8 mice/group) were i.v. injected with

Compound 178 3 times per week for a total of 3 doses at 25 mg/kg body weight (closed arrowheads), followed by 3 times per week for a total of 3 doses at 37.5 mg/kg body weight (open arrowheads), followed by 3 times per week for a total of 3 doses at 50 mg/kg body weight (arrows). The median tumor volumes for each group (error bars represent SEM) were determined every 3-5 days. Compound 178 began to show moderate efficacy at doses of 37.5 and 50 mg/kg body weight.

Figure 18 shows percent change in body weight of animals during the study presented in Figure 17. Treatment with Compound 178 did not cause overt toxicity in a *nude* mouse xenograft model using the human tumor cell line MDA-MB-435S (data derived from the same study presented in Figure 17). Tumor bearing animals (8 mice/group) were i.v. injected with Compound 178 3 times per week for a total of 3 doses at 25 mg/kg body weight (closed arrowheads), followed by 3 times per week for a total of 3 doses at 37.5 mg/kg body weight (open arrowheads), followed by 3 times per week for a total of 3 doses at 50 mg/kg body weight (arrows). The cumulative average percent change in body weights for each group relative to the start of dosing (error bars represent SEM) were determined every 1-3 days. Treatment with doses of 25, 37.5 or 50 mg/kg body weight of Compound 178 were not overtly toxic, as indicated by the minimal effects on the animal body weights in the test article-treated versus vehicle-treated groups.

Figure 19 shows the effect of Compound 3 on the *in vivo* induction of tumor necrosis in an EMT6 mouse mammary carcinoma tumor model in *nude* mice. Tumor-bearing animals (5 mice/group) were given a single i.v. bolus injection of either vehicle or Compound 3, and at the indicated time points following dosing the tumors were excised and processed for histology. Light microscopy was used to quantitate the average area of necrosis as a percent of total area in tumor sections from each treatment group (error bars represent SEM). Treatment with a single dose of 25 mg/kg body weight of Compound 3 resulted in a near maximal 2.4 fold increase in tumor necrosis at 4 hours following drug treatment.

Figure 20A shows shows the microtubule network of CV-1 cells 24 hrs after treatment with DMSO.

Figure 20B shows the microtubule network of CV-1 cells 24 hrs after treatment with 1 nM of Compound 249.

Figure 20C shows the microtubule network of CV-1 cells 24 hrs after treatment with 10 nM of Compound 249.

Figure 20D shows the microtubule network of CV-1 cells 24 hrs after treatment with 100 nM of Compound 249.

Figure 20E shows the microtubule network of CV-1 cells 24 hrs after treatment with 1000 nM of Compound 249.

Figure 21A shows the microtubule network of HUVEC cells 24 hrs after treatment with DMSO.

Figure 21B shows the microtubule network of HUVEC cells 24 hrs after treatment with 1 nM of Compound 249.

Figure 21C shows the microtubule network of HUVEC cells 24 hrs after treatment with 5 nM of Compound 249.

Figure 21D shows the microtubule network of HUVEC cells 24 hrs after treatment with 10 nM of Compound 249.

Figure 21E shows the microtubule network of HUVEC cells 24 hrs after treatment with 50 nM of Compound 249.

Figure 21F shows the microtubule network of HUVEC cells 24 hrs after treatment with 100 nM of Compound 249.

Figure 22 shows a n*ude* mouse tumor study to determine the effect of Compound 174 on the *in vivo* growth rate of the allogeneic mouse mammary carcinoma cell line EMT6. Tumor-bearing animals (15 mice/group) were given a single i.v. bolus injection of either vehicle or Compound 174, and changes in median tumor volumes (error bars represent SEM) for each group were determined after 3 days. Treatment with doses of 4.55 and 3.22 mg/kg body weight of Compound 174 substantially inhibited tumor growth. The largest average percent change in body weight observed for any group in this study was -7.3% (+/- 0.9 SEM) one day after dosing Compound 174 at 4.55 mg/kg body weight. No individual animal lost > 11% body weight at any point over the course of the study.

Figure 23 shows a study examining the vascular disrupting activity of Compound 174 as measured by the Evans Blue dye assay in the EMT6 mouse mammary carcinoma tumor model conducted in *nude* mice. (*Top*) Tumor-bearing animals (8 mice/group) were given a single i.v. bolus injection of either vehicle or Compound 174 at time 0 hr, followed by a single i.v. bolus injection of Evan's Blue dye at time +1 hr. At +4 hrs, tumors were excised and tumor dye penetration was quantitated. Representations of black and white mice indicate animals that have been injected or not injected with Evan's Blue dye, respectively. (*Bottom*) Treatment with single doses of 4.55, 3.22 or 2.28 mg/kg body weight of Compound 174 resulted in substantial decreases in tumor dye uptake at + 4hr. A similar decrease was also observed after a single dose of 4.55 mg/kg body weight of Compound 174 at +2 hr (data not shown).

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

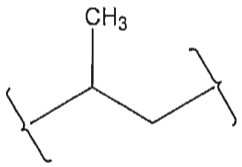
Unless otherwise specified, the below terms used herein are defined as follows:

As used herein, the term an "aromatic ring" or "aryl" means a monocyclic or polycyclic-aromatic ring or ring radical comprising carbon and hydrogen atoms. Typically, aryl groups have about 6 to about 14 carbon atom ring members. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused

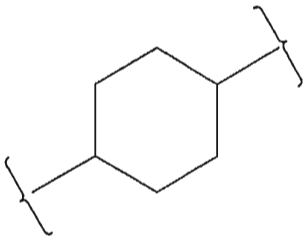
carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted with one or more substituents (including without limitation alkyl (preferably, lower alkyl or alkyl substituted with one or more halo), hydroxy, alkoxy (preferably, lower alkoxy), alkylsulfanyl, cyano, halo, amino, and nitro. In certain embodiments, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms.

As used herein, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon typically having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimtheylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. Alkyl groups included in compounds of this invention may be optionally substituted with one or more substituents. Examples of substituents include, but are not limited to, amino, alkylamino, alkoxy, alkylsulfanyl, oxo, halo, acyl, nitro, hydroxyl, cyano, aryl, alkylaryl, aryloxy, arylsulfanyl, arylamino, carbocyclyl, carbocyclyloxy, carbocyclylthio, carbocyclylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyclylthio, and the like. In addition, any carbon in the alkyl segment may be substituted with oxygen (=O), sulfur (=S), or nitrogen (=NR^{32}, wherein R^{32} is –H, an alkyl, acetyl, or aralkyl). Lower alkyls are typically preferred for the compounds of this invention.

The term alkylene refers to an alkyl group or a cycloalkyl group that has two points of attachment to two moieties (e.g., {-CH_2-}, -{CH_2CH_2-},



,



, etc., wherein the brackets indicate the points of attachment). Alkylene groups may be optionally substituted with one or more substituents.

An aralkyl group refers to an aryl group that is attached to another moiety via an alkylene linker. Aralkyl groups can be optionally substituted with one or more substituents.

The term "alkoxy," as used herein, refers to an alkyl group which is linked to another moiety though an oxygen atom. Alkoxy groups can be optionally substituted with one or more substituents.

The term "alkylsulfanyl," as used herein, refers to an alkyl group which is linked to another moiety though a divalent sulfur atom. Alkylsulfanyl groups can be optionally substituted with one or more substituents.

The term "arylsulfanyl," as used herein, refers to an aryl group which is linked to another moiety though a divalent sulfur atom. Arylsulfanyl groups can be optionally substituted with one or more substituents.

The term "alkyl ester" as used herein, refers to a group represented by the formula –C(O)OR_{32}, wherein R_{32} is an alkyl group. A lower alkyl ester is a group represented by the formula –C(O)OR_{32}, wherein R_{32} is a lower alkyl group.

The term "heteroalkyl," as used herein, refers to an alkyl group which has one or more carbons in the alkyl chain replaced with an –O-, -S- or -NR_{33}-, wherein R_{33} is

H or a lower alkyl. Heteroalkyl groups can be optionally substituted with one or more substituents.

The term "alkylamino," as used herein, refers to an amino group in which one hydrogen atom attached to the nitrogen has been replaced by an alkyl group. The term "dialkylamino," as used herein, refers to an amino group in which two hydrogen atoms attached to the nitrogen have been replaced by alkyl groups, in which the alkyl groups can be the same or different. Alkylamino groups and dialkylamino groups can be optionally substituted with one or more substituents.

As used herein, the term "alkenyl" means a straight chain or branched, hydrocarbon radical typically having from 2 to 10 carbon atoms and having at least one carbon-carbon double bond. Representative straight chain and branched alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 1-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl and the like. Alkenyl groups can be optionally substituted with one or more substituents.

As used herein, the term "alkynyl" means a straight chain or branched, hydrocarbon radical typically having from 2 to 10 carbon atoms and having at lease one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl,-1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonynyl, 2-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl, 9-decynyl and the like. Alkynyl groups can be optionally substituted with one or more substituents.

As used herein, the term "cycloalkyl" means a saturated, mono- or polycyclic alkyl radical typically having from 3 to 14 carbon atoms. Representative cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, adamantly, decahydronaphthyl, octahydropentalene,

bicycle[1.1.1]pentanyl, and the like. Cycloalkyl groups can be optionally substituted with one or more substituents.

As used herein, the term "cycloalkenyl" means a cyclic non-aromatic alkenyl radical having at least one carbon-carbon double bond in the cyclic system and typically having from 5 to 14 carbon atoms. Representative cycloalkenyls include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclodecenyl, cyclodecadienyl and the like. Cycloalkenyl groups can be optionally substituted with one or more substituents.

As used herein, the term "heterocycle" or "heterocyclyl" means a monocyclic or polycyclic heterocyclic ring (typically having 3- to 14-members) which is either a saturated ring or an unsaturated non-aromatic ring. A 3-membered heterocycle can contain from 1 to 3 heteroatoms, and a 4- to 14-membered heterocycle can contain from 1 to about 8 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 4H-pyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl may be optionally substituted with one or more substituents (including without limitation a halo, an alkyl, a haloalkyl, or aryl). Only stable isomers of such substituted heterocyclic groups are contemplated in this definition.

As used herein, the term "heteroaromatic" or "heteroaryl" means a monocyclic or polycyclic heteroaromatic ring (or radical thereof) comprising carbon atom ring members and one or more heteroatom ring members (such as, for example, oxygen,

sulfur or nitrogen). Typically, the heteroaromatic ring has from 5 to about 14 ring members in which at least 1 ring member is a heteroatom selected from oxygen, sulfur and nitrogen. In another embodiment, the heteroaromatic ring is a 5 or 6 membered ring and may contain from 1 to about 4 heteroatoms. In another embodiment, the heteroaromatic ring system has a 7 to 14 ring members and may contain from 1 to about 7 heteroatoms. Representative heteroaryls include pyridyl, furyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, indolizinyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, pyridinyl, thiadiazolyl, pyrazinyl, quinolyl, isoquniolyl, indazolyl, benzoxazolyl, benzofuryl, benzothiazolyl, indolizinyl, imidazopyridinyl, isothiazolyl, tetrazolyl, benzo[1,3]dioxolyl, 2,3-dihydro-benzo[1,4]dioxinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, qunizaolinyl, purinyl, pyrrolo[2,3]pyrimidyl, pyrazolo[3,4]pyrimidyl or benzo(b)thienyl and the like. Heteroaryl groups may be optionally substituted with one or more substituents

A heteroaralkyl group refers to a heteroaryl group that is attached to another moiety via an alkylene linker. Heteroaralkyl groups can be substituted or unsubstituted with one or more substituents.

As used herein, the term "halogen" or "halo" means -F, -Cl, -Br or -I.

As used herein, the term "haloalkyl" means an alkyl group in which one or more –H is replaced with a halo group. Examples of haloalkyl groups include $-CF_3$, $-CHF_2$, $-CCl_3$, $-CH_2CH_2Br$, $-CH_2CH(CH_2CH_2Br)CH_3$, $-CHICH_3$, and the like.

As used herein, the term "haloalkoxy" means an alkoxy group in which one or more –H is replaced with a halo group. Examples of haloalkoxy groups include $-OCF_3$ and $-OCHF_2$.

The terms "bioisostere" and "bioisosteric replacement" have the same meanings as those generally recognized in the art. Bioisosteres are atoms, ions, or molecules in which the peripheral layers of electrons can be considered substantially identical.

The term bioisostere is usually used to mean a portion of an overall molecule, as opposed to the entire molecule itself. Bioisosteric replacement involves using one bioisostere to replace another with the expectation of maintaining or slightly modifying the biological activity of the first bioisostere. The bioisosteres in this case are thus atoms or groups of atoms having similar size, shape and electron density. Preferred bioisosteres of esters, amides or carboxylic acids are compounds containing two sites for hydrogen bond acceptance. In one embodiment, the ester, amide or carboxylic acid bioisostere is a 5-membered monocyclic heteroaryl ring, such as an optionally substituted 1H-imidazolyl, an optionally substituted oxazolyl, 1H-tetrazolyl, [1,2,4]triazolyl, or an optionally substituted [1,2,4]oxadiazolyl.

As used herein, the terms "subject", "patient" and "animal", are used interchangeably and include, but are not limited to, a cow, monkey, horse, sheep, pig, mini pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human. The preferred subject, patient or animal is a human.

As used herein, the term "lower" refers to a group having up to four carbon atoms. For example, a "lower alkyl" refers to an alkyl radical having from 1 to 4 carbon atoms, and a "lower alkenyl" or "lower alkynyl" refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms, respectively. A lower alkoxy or a lower alkylsulfanyl refers to an alkoxy or an alkylsulfanyl having from 1 to 4 carbon atoms. Lower substituents are typically preferred.

Where a particular substituent, such as an alkyl substituent, occurs multiple times in a given structure or moeity, the identity of the substitutent is independent in each case and may be the same as or different from other occurrences of that substituent in the structure or moiety. Furthermore, individual substituents in the specific embodiments and exemplary compounds of this invention are preferred in combination with other such substituents in the compounds of this invention, even if such individual substituents are not expressly noted as being preferred or not expressly shown in combination with other substituents.

The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

Suitable substituents for an alkyl, alkoxy, alkylsulfanyl, alkylamino, dialkylamino, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl groups include any substituent which will form a stable compound of the invention. Examples of substituents for an alkyl, alkoxy, alkylsulfanyl, alkylamino, dialkylamino, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl include an alkyl, an alkoxy, an alkylsulfanyl, an alkylamino, a dialkylamino, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a heterocyclyl, an aryl, a heteroaryl, an aralkyl, a heteraralkyl, a haloalkyl, $-C(O)NR_{34}R_{35}$, $-NR_{36}C(O)R_{37}$, halo, $-OR_{36}$, cyano, nitro, haloalkoxy, $-C(O)R_{36}$, $-NR_{34}R_{35}$, $-SR_{36}$, $-C(O)OR_{36}$, $-OC(O)R_{36}$, $-NR_{36}C(O)NR_{34}R_{35}$, $-OC(O)NR_{34}R_{35}$, $-NR_{36}C(O)OR_{37}$, $-S(O)_pR_{36}$, or $-S(O)_pNR_{34}R_{35}$, wherein R_{34} and R_{35}, for each occurrence are, independently, H, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a heterocyclyl, an aryl, a heteroaryl, an aralkyl, or a heteraralkyl; or R_{34} and R_{35} taken together with the nitrogen to which they are attached is a heterocyclyl or a heteroaryl; and R_{36} and R_{37} for each occurrence are, independently, H, an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a heterocyclyl, an aryl, a heteroaryl, an aralkyl, or a heteraralkyl;

In addition, alkyl, cycloalkyl, alkylene, a heterocyclyl, and any saturated portion of a alkenyl, cycloalkenyl, alkynyl, aralkyl, and heteroaralkyl groups, may also be substituted with =O, =S, $=N-R_{32}$.

When a heterocyclyl, heteroaryl, or heteroaralkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic ring of a heteroaryl group has a substituent the nitrogen may be a quaternary nitrogen.

Choices and combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable",

as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (*e.g.*, therapeutic or prophylactic administration to a subject). Typically, such compounds are stable at a temperature of 40 °C or less, in the absence of excessive moisture, for at least one week. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

Unless indicated otherwise, the compounds of the invention containing reactive functional groups (such as, without limitation, carboxy, hydroxy, and amino moieties) also include protected derivatives thereof. "Protected derivatives" are those compounds in which a reactive site or sites are blocked with one ore more protecting groups. Suitable protecting groups for carboxy moieties include benzyl, tert-butyl, and the like. Suitable protecting groups for amino and amido groups include acetyl, tert-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for hydroxy include benzyl, trimethyl silyl (TMS) and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the entire teachings of which are incorporated herein by reference.

As used herein, the term "compound(s) of this invention" and similar terms refers to a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof and also include protected derivatives thereof.

As used herein, the term "amino acid residue" refers to what is left of an amino acid (losing a H^+ from the nitrogenous side, an OH^- from the carboxylic side, or a H^+ from the nitrogenous side and an OH^- from the carboxylic side) in the formation of a peptide bond(s). An "amino acid analog" includes D or L amino acids having the following formula: NH_2-CHR-C(O)OH, wherein R is an optionally substituted alkyl group, an optionally substituted heteroalkyl group, an optionally substituted aromatic group, or an optionally substituted heteroaromatic group, and wherein R does not correspond to the side chain of a naturally-occurring amino acid. An "amino acid

residue analog" refers to what is left of an amino acid analog (losing a H^+ from the nitrogenous side, an OH^- from the carboxylic side, or a H^+ from the nitrogenous side and an OH^- from the carboxylic side) in the formation of a peptide bond(s).

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide a compound of this invention. Prodrugs may only become active upon such reaction under biological conditions, but they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1 that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of compounds of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1 that comprise -NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed), the entire teachings of which are incorporated herein by reference.

As used herein and unless otherwise indicated, the terms "biohydrolyzable amide", "biohydrolyzable ester", "biohydrolyzable carbamate", "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable phosphate analogue" mean an amide, ester, carbamate, carbonate, ureide, or phosphate analogue, respectively, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties *in vivo*, such as uptake, duration of action, or onset of action; or 2) is itself biologically inactive but is converted *in vivo* to a biologically active compound. Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters. Examples of biohydrolyzable carbamates include, but are

not limited to, lower alkylamines, substituted ethylenediamines, aminoacids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from an acid and a basic group of one of the compounds of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1 having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)- amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)- amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1 having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. Suitable acids include, but are not limited to, hydrogen sulfate, citric acid, acetic acid, oxalic acid, hydrochloric acid, hydrogen bromide, hydrogen iodide, nitric acid, phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic

acid, succinic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid,and *p*-toluenesulfonic acid.

As used herein, the term "pharmaceutically acceptable solvate," is a solvate formed from the association of one or more solvent molecules to one or more molecules of a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1. The term solvate includes hydrates (*e.g.*, hemi-hydrate, mono-hydrate, dihydrate, trihydrate, tetrahydrate, and the like).

As used herein, the term "clathrate" means a compound of the present invention or a salt thereof in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

Inhibition of tubulin polymerization can be determined by any method known to those skilled in the art, such as the method described herein in Example 7. In addition the amount of a tubulin polymerization inhibitor that inhibits 50% of tubulin polymerization that occurs in the absence of the inhibitor (*i.e.*, the IC_{50}) can be determined by pre-incubating purified tubulin with various amounts of an inhibitor for 15 minutes at 37°C. The mixture is then cooled to room temperature and GTP is added to induce tubulin polymerization. The polymerization can be monitored in a spectrophotometer at 350 nm. A typical reaction mixtures (0.25 mL) contains 1.5 mg/mL tubulin, 0.6 mg/mL microtubule-associated proteins (MAPs), 0.5 mM GTP, 0.5 mIM MgCl.sub.2, 4% DMSO and 0.1M 4-morpholineethanesulfonate buffer (MES, pH 6.4).

As used herein, a "proliferative disorder" or a "hyperproliferative disorder," and other equivalent terms, means a disease or medical condition involving pathological growth of cells. Proliferative disorders include cancer, smooth muscle cell proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, retinopathy (*e.g.*, diabetic retinopathy or other retinopathies), choroidal neovascularisation (*e.g.*, macular degeneration), cardiac hyperplasia, reproductive system associated disorders such

as benign prostatic hyperplasia and ovarian cysts, pulmonary fibrosis, endometriosis, fibromatosis, harmatomas, lymphangiomatosis, sarcoidosis, and desmoid tumors.

Smooth muscle cell proliferation includes hyperproliferation of cells in the vasculature, for example, intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion, particularly stenosis following biologically- or mechanically-mediated vascular injury, *e.g.*, vascular injury associated with angioplasty. Moreover, intimal smooth muscle cell hyperplasia can include hyperplasia in smooth muscle other than the vasculature, *e.g.*, bile duct blockage, bronchial airways of the lung in patients with asthma, in the kidneys of patients with renal interstitial fibrosis, and the like.

Non-cancerous proliferative disorders also include hyperproliferation of cells in the skin such as psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, and hyperproliferative variants of disorders of keratinization (*e.g.*, actinic keratosis, senile keratosis), scleroderma, and the like.

In a preferred embodiment, the proliferative disorder is cancer. Cancers that can be treated or prevented by the methods of the present invention include, but are not limited to human sarcomas and carcinomas, *e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, *e.g.*, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic

myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease.

Other examples of leukemias include acute and/or chronic leukemias, *e.g.*, lymphocytic leukemia (*e.g.*, as exemplified by the p388 (murine) cell line), large granular lymphocytic leukemia, and lymphoblastic leukemia; T-cell leukemias, e.g., T-cell leukemia (*e.g.*, as exemplified by the CEM, Jurkat, and HSB-2 (acute), YAC-1(murine) cell lines), T-lymphocytic leukemia, and T-lymphoblastic leukemia; B cell leukemia (*e.g.*, as exemplified by the SB (acute) cell line) , and B-lymphocytic leukemia; mixed cell leukemias, *e.g.*, B and T cell leukemia and B and T lymphocytic leukemia; myeloid leukemias, *e.g.*, granulocytic leukemia, myelocytic leukemia (*e.g.*, as exemplified by the HL-60 (promyelocyte) cell line), and myelogenous leukemia (*e.g.*, as exemplified by the K562(chronic)cell line); neutrophilic leukemia; eosinophilic leukemia; monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); myelomonocytic leukemia; Naegeli-type myeloid leukemia; and nonlymphocytic leukemia. Other examples of leukemias are described in Chapter 60 of *The Chemotherapy Sourcebook*, Michael C. Perry Ed., Williams & Williams (1992) and Section 36 of *Holland Frie Cancer Medicine* 5th Ed., Bast et al. Eds., B.C. Decker Inc. (2000). The entire teachings of the preceding references are incorporated herein by reference.

In one embodiment, the compounds of the invention are believed to be particularly effective in treating subject with hematological malignancies (*e.g.*, Hodgkin's disease, Non-Hodgkin lymphoma, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and multiple myeloma). In another embodiment, the compounds of the invention are believed to be particularly useful in treating solid tumors.

In one embodiment, the compounds of the invention are particularly effective at treating subjects whose cancer has become "multi-drug resistant". A cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug when the anti-cancer drug is no longer effective in treating the subject with the

cancer. For example, many tumors will initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the drug. Drug resistant tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission, despite the administration of increased dosages of the anti-cancer drug. Cancers that have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

An "effective amount" is the quantity of compound in which a beneficial outcome is achieved when the compound is administered to a subject or alternatively, the quantity of compound that possess a desired activity in vivo or in vitro. In the case of proliferative disorders, a beneficial clinical outcome includes reduction in the extent or severity of the symptoms associated with the disease or disorder and/or an increase in the longevity and/or quality of life of the subject compared with the absence of the treatment. For example, for a subject with cancer, a "beneficial clinical outcome" includes a reduction in tumor mass, a reduction in the rate of tumor growth, a reduction in metastasis, a reduction in the severity of the symptoms associated with the cancer and/or an increase in the longevity of the subject compared with the absence of the treatment. The precise amount of compound administered to a subject will depend on the type and severity of the disease or condition and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to drugs. It will also depend on the degree, severity and type of proliferative disorder. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. Effective amounts of the disclosed compounds typically range between about 1 mg/mm^2 per day and about 10 $grams/mm^2$ per day, and preferably between 10 mg/mm^2 per day and about 1 $gram/mm^2$.

In one embodiment, compounds of the invention are vascular targeting agents. In one aspect, compounds of the invention are effective for blocking, occluding, or otherwise disrupting blood flow in "neovasculature." In one aspect, the invention

provides a novel treatment for diseases involving the growth of new blood vessels ("neovasculature"), including, but not limited to: cancer; infectious diseases; autoimmune disorders; benign tumors, *e.g.* hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, *e.g.*, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, persistent hyperplastic vitreous syndrome, choroidal neovascularization, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; warts; allergic dermatitis; blistering disease; Karposi sarcoma; delayed wound healing; endometriosis; uterine bleeding; ovarian cysts; ovarian hyperstimulation; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; vascular malformations; DiGeorge syndrome; HHT; transplant arteriopathy; restinosis; obesity; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; primary pulmonary hypertension; asthma; nasal polyps; inflammatory bowel disease; periodontal disease; ascites; peritoneal adhesions; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; synovitis; osteomyelitis; osteophyte formation; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

Vascular targeting can be demonstrated by any method known to those skilled in the art, such as the method described herein in Example 11.

The compounds of the invention may contain one or more chiral centers and/or double bonds and, therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers), enantiomers, or diastereomers. According to this invention, the chemical structures depicted herein, including the compounds of this invention, encompass all of the corresponding compounds' enantiomers and stereoisomers, that is, both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric, diastereomeric, and geometric isomeric mixtures. In some cases, one enantiomer, diastereomer, or geometric isomer will possess superior activity or an improved toxicity or kinetic

profile compared to others. In those cases, such enantiomers, diastereomers, and geometric isomers of a compound of this invention are preferred.

As used herein, a composition that "substantially" comprises a compound means that the composition contains more than about 80% by weight, more preferably more than about 90% by weight, even more preferably more than about 95% by weight, and most preferably more than about 97% by weight of the compound.

As used herein, a composition that is "substantially free" of a compound means that the composition contains less than about 20% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight, and most preferably less than about 3% by weight of the compound.

As used herein, a reaction that is "substantially complete" means that the reaction contains more than about 80% by weight of the desired product, more preferably more than about 90% by weight of the desired product, even more preferably more than about 95% by weight of the desired product, and most preferably more than about 97% by weight of the desired product.

As used herein, a racemic mixture means about 50% of one enantiomer and about 50% of is corresponding enantiomer relative to all chiral centers in the molecule. The invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically. pure, diastereomerically enriched, and racemic mixtures of the compounds of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1.

Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

When administered to a patient, *e.g.*, to a non-human animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are typically administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, via conventional techniques, the compounds of the invention are purified. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a single compound of the invention by weight of the isolate.

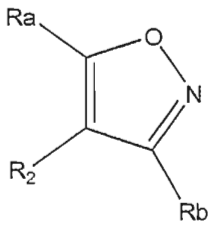
Only those choices and combinations of substituents that result in a stable structure are contemplated. Such choices and combinations will be apparent to those of ordinary skill in the art and may be determined without undue experimentation.

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

SPECIFIC EMBODIMENTS

The invention relates to compounds and pharmaceutical compositions that are useful for inhibiting tubulin polymerization and are particularly useful in treating or preventing proliferative disorders, such as cancer. The invention also relates to compounds and pharmaceutical compositions that are useful as vascular targeting agents, particularly, in blocking, occluding, or otherwise disrupting blood flow in neovasculature.

In one embodiment, the invention relates to compounds of formula (I):



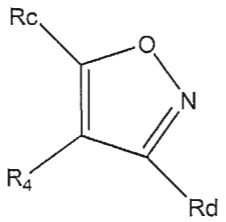
(I)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_a or R_b is –H and the other is an optionally substituted aryl, or an optionally substituted heteroaryl; and

R_2 is an optionally substituted phenyl, an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrrolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl.

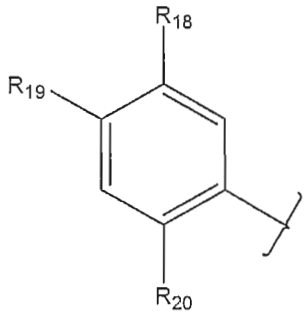
In another embodiment, the invention relates to compounds of formula (II):



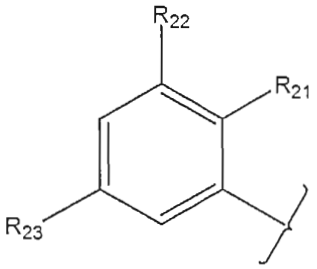
(II)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, or a substituted phenyl represented by one of the following formulas:



or



R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally

substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

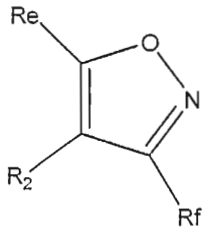
R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2.

In another embodiment, the invention relates to compounds of formula (III):



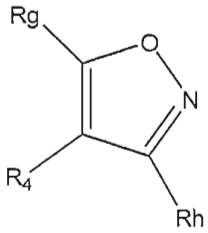
(III)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_e or R_f is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_2 is defined as for formula (I).

In another embodiment, the invention relates to compounds of formula (IV):

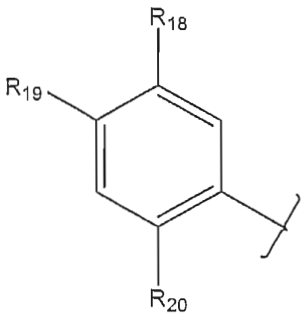


(IV)

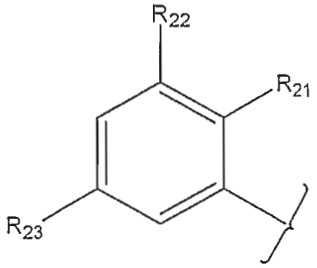
or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_g or R_h is –H and the other is:

i) an unsubstituted phenyl or a substituted phenyl represented by one of the following formulas:



or



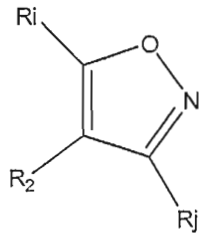
; or

ii) an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an

optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_4, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, and R_{23} are defined as for formula (II).

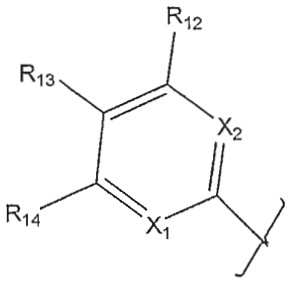
In another embodiment, the invention relates to compounds of formula (V):



(V)

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



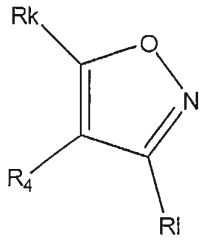
X_1 and X_2 are each, independently, CH or N;

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_2 is defined as for formula (I); and

R_7, R_8, R_{10}, R_{11}, and p are defined as for formula (II).

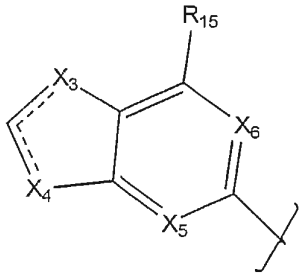
In another embodiment, the invention relates to compounds of formula (VI):



(VI)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_k or R_l is –H and the other is represented by the following formula:



the dashed line indicates that the bond is a single bond or a double bond;

X_3 and X_4 are each, independently, CH, N, CH_2, NR_{16}, O, or S;

X_5 and X_6 are each, independently, CR_{29} or N;

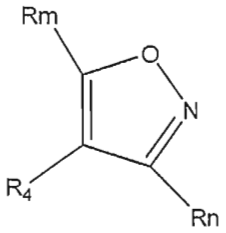
R_{15} is H, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{16} is H, an alkyl, a cycloalkyl, an aralkyl, -C(O)R, wherein R is an alkyl, a cycloalkyl, or an aralkyl;

R_{29}, for each occurrence, is independently, H or a substituent; and

R_7, R_8, R_{10}, R_{11}, R_{17}, and p are defined as for formula (II).

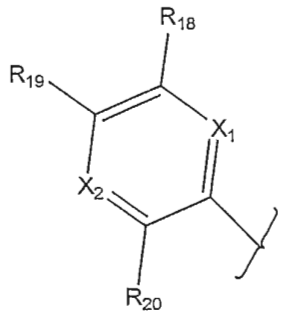
In another embodiment, the invention relates to compounds of formula (VII):



(VII)

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, wherein:

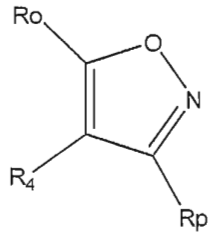
one of R_m or R_n is –H and the other is represented by the following formula:



R_4, R_{18}, R_{19}, and R_{20} are defined as for formula (II); and

X_1 and X_2 are defined as for formula (V).

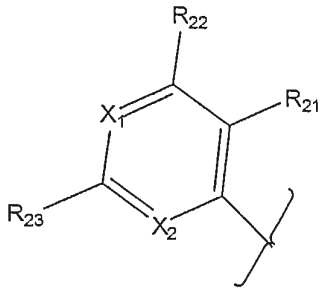
In another embodiment, the invention relates to compounds of formula (VIII):



(VIII)

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, wherein:

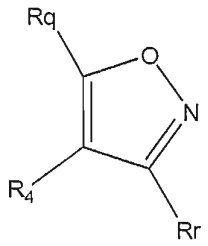
one of Ro or Rp is –H and the other is represented by the following formula:



R_4, R_{21}, R_{22}, and R_{23} are defined as for formula (II); and

X_1 and X_2 are defined as for formula (V).

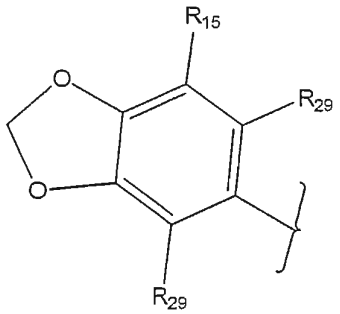
In another embodiment, the invention relates to compounds of formula (IX):



(IX)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

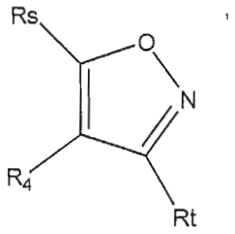
one of R_q or R_r is –H and the other is represented by the following formula:



R_4 is defined as for formula (II);and

R_{15} and R_{29} are defined as for formula (VI).

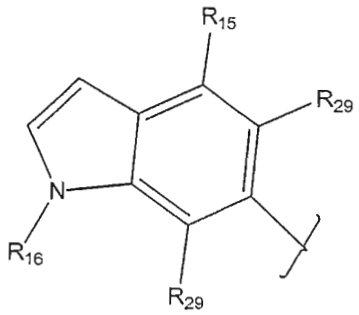
In another embodiment, the invention relates to compounds of formula (X):



(X)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

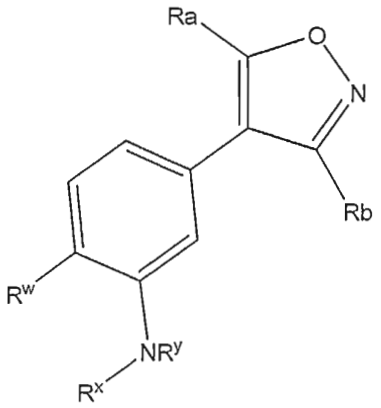
one of R_s or R_t is –H and the other is represented by the following formula:



R_4 is defined as for formula (II); and

R_{15}, R_{16}, and R_{29} are defined as for formula (VI).

In another embodiment, the invention relates to compounds of formula (IA):



(IA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_a or R_b is –H and the other is an optionally substituted aryl, or an optionally substituted heteroaryl; and

R^x is $(R^{aa})_m$, $-R^{aa}$-$C(O)(CH_2)_nC(O)OH$, $-C(O)(CH_2)_nC(O)OH$, $-C(O)YR^z$, $-C(O)NH$-R^{aa}, or $-(R^{aa})_qC(O)(Y_1)$;

R^y is –H or lower alkyl;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl;

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R^{aa} is an amino acid residue or an amino acid residue analog;

Y is CH_2, O, or NH;

R^z is Alk-NH_2, Alk-C(O)OH, Het, or Y_1;

Alk is an optionally substituted alkylene;

Het is an optionally substituted heteroalkyl;

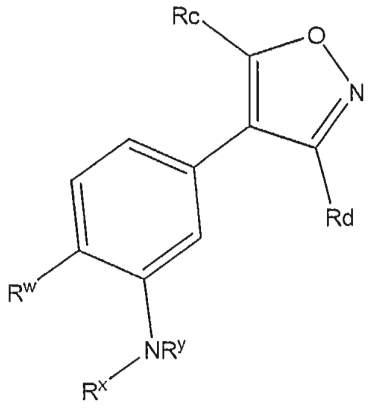
Y_1 is a water soluble polymer with a molecular weight less than 60,000 daltons;

n is 1, 2, 3, or 4;

m is an integer from 1 to 10; and

q is 0 or 1.

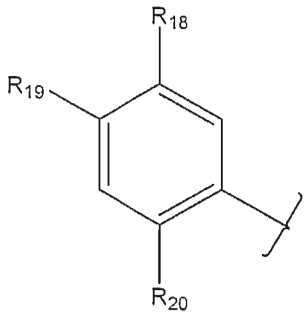
In another embodiment, the invention relates to compounds of formula (IIA):



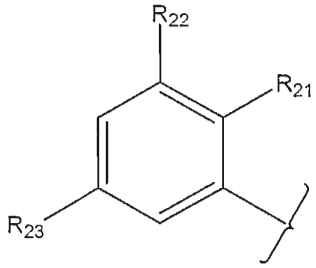
(IIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, a substituted phenyl represented by one of the following formulas:



or



R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$,

$-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

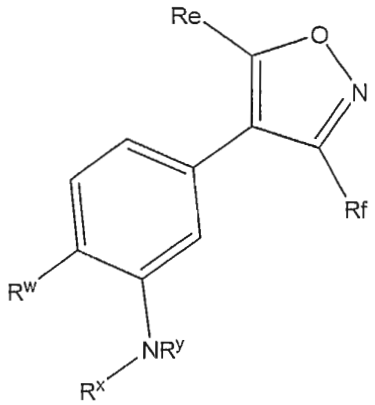
R_{17}, for each occurrence, is independently, an optionally substituted

alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

p is 1 or 2; and

R^x, R^y, and R^w are defined as for formula (IA).

In another embodiment, the invention relates to compounds of formula (IIIA):



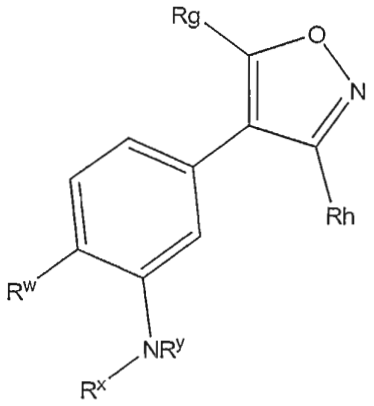
(IIIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_e or R_f is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-

benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and R^x, R^y, and R^w are defined as for formula (IA).

In another embodiment, the invention relates to compounds of formula (IVA):

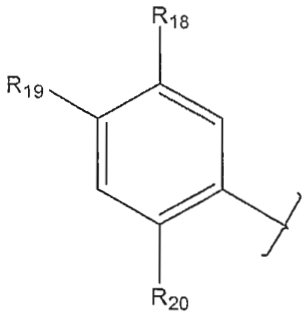


(IVA)

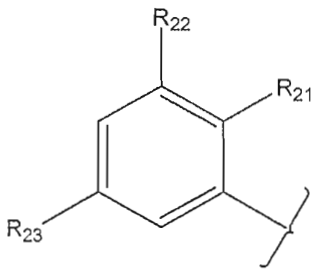
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_g or R_h is –H and the other is:

i) an unsubstituted phenyl or a substituted phenyl represented by one of the following formulas:



or



; or

ii) an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl,

an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

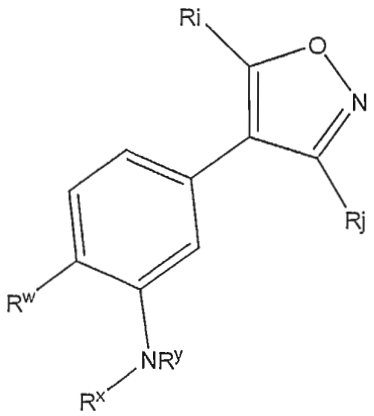
R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are defined as for formula (IIA);

p is 1 or 2; and

R^x, R^y, and R^w are defined as for formula (IA).

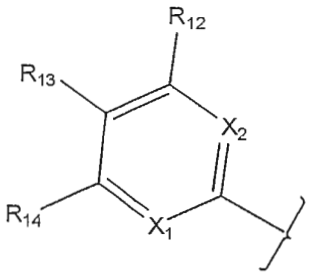
In another embodiment, the invention relates to compounds of formula (VA):



(VA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



X_1 and X_2 are each, independently, CH or N;

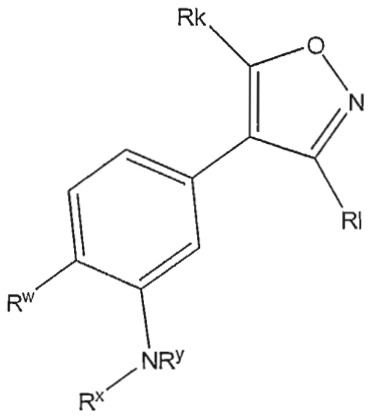
R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$,

$-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7, R_8, R_{10}, R_{11}, and p are defined as for formula (IIA); and

R^x, R^y, and R^w are defined as for formula (IA).

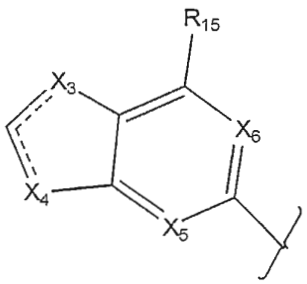
In another embodiment, this invention relates to compounds of formula (VIA):



(VIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_k or R_l is –H and the other is represented by the following formula:



the dashed line indicates that the bond is a single bond or a double bond;

X_3 and X_4 are each, independently, CH, N, CH_2, NR_{16}, O, or S;

X_5 and X_6 are each, independently, CR_{29} or N;

R_{15} is H, halo, an optionally substituted alkyl, an optionally substituted

alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

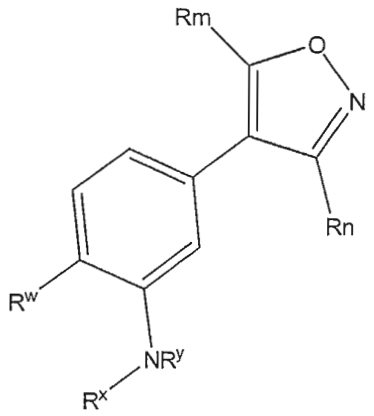
R_{16} is H, an alkyl, a cycloalkyl, an aralkyl, -C(O)R, wherein R is an alkyl, a cycloalkyl, or an aralkyl;

R_{29}, for each occurrence, is independently, H or a substituent

R_7, R_8, R_{10}, R_{11}, R_{17}, and p are defined as for formula (IIA); and

R^x, R^y, and R^w are defined as for formula (IA).

In another embodiment, the invention relates to compounds of formula (VIIA):

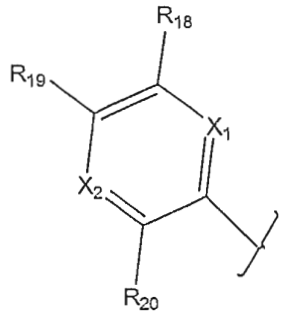


(VIIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof,

wherein:

one of R_m or R_n is –H and the other is represented by the following formula:

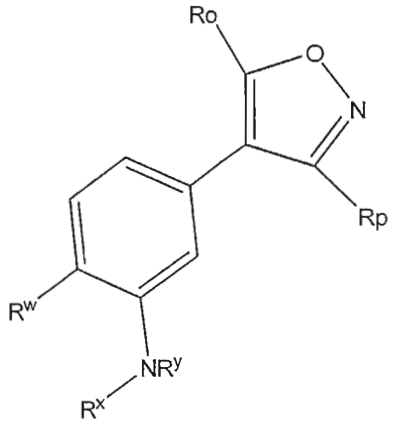


X_1 and X_2 are each, independently, CH or N;

R_{18}, R_{19}, and R_{20} are defined as for formula (IIA); and

R^x, R^y, and R^w are defined as for formula (IA).

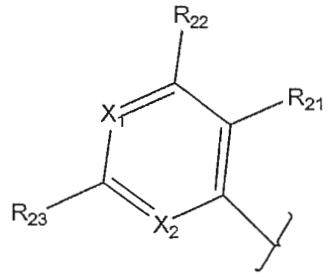
In another embodiment, the invention relates to compounds of formula (VIIIA):



(VIIIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_o or R_p is –H and the other is represented by the following formula:

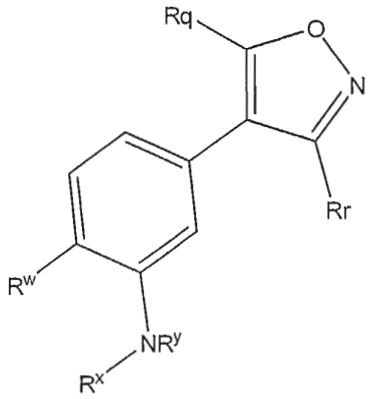


X_1 and X_2 are each, independently, CH or N;

R_{21}, R_{22}, and R_{23} are defined as for formula (IIA); and

R^x, R^y, and R^w are defined as for formula (IA).

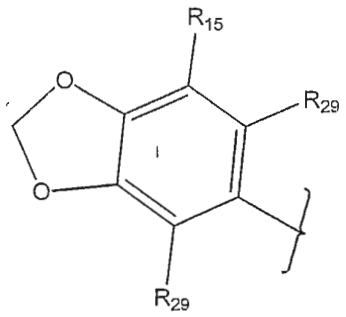
In another embodiment, the invention relates to compounds of formula (IXA):



(IXA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

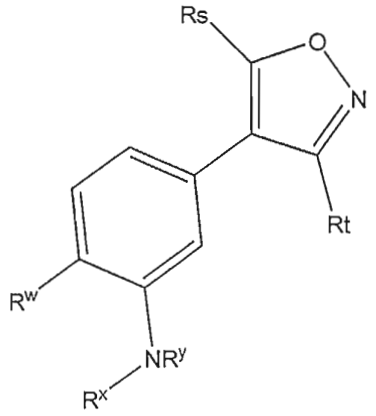
one of R_q or R_r is –H and the other is represented by the following formula:



R_{15} and R_{19} are defined as for formula (VIA); and

R^x, R^y, and R^w are defined as for formula (IA).

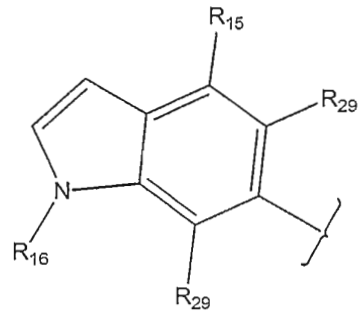
In another embodiment, the invention relates to compounds of formula (XA):



(XA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

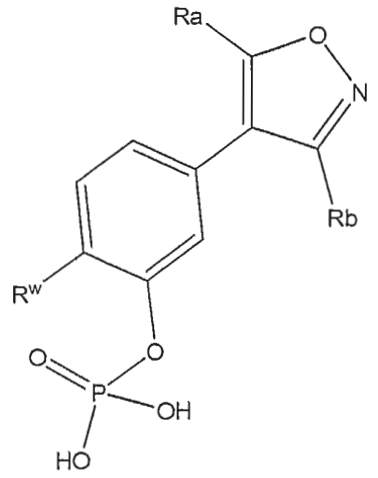
one of R_s or R_t is –H and the other is represented by the following formula:



R_{15}, R_{16}, and R_{29} are defined as for formula (VIA); and

R^x, R^y, and R^w are defined as for formula (IA).

In another embodiment, the invention relates to compounds of formula (IB):



(IB)

or a pharmaceutically acceptable salt, solvate, or clathrate, thereof,

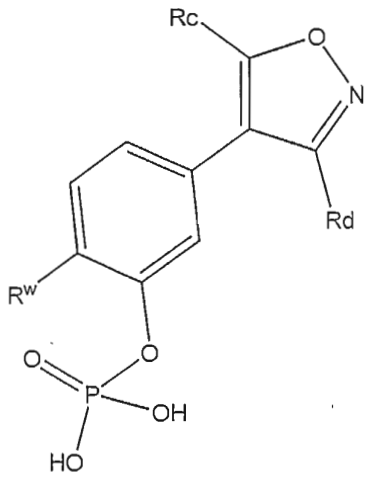
wherein:

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl;

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

one of R_a or R_b is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl.

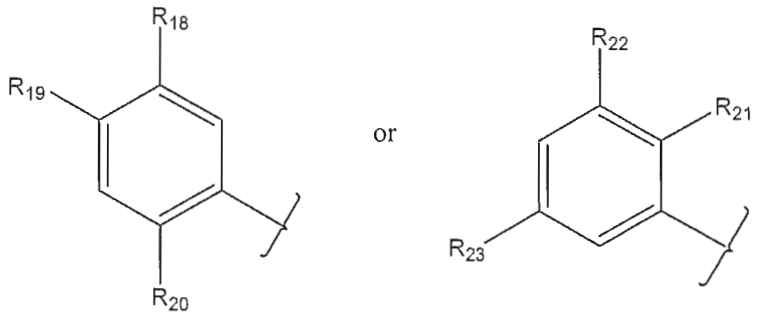
In another embodiment, the invention relates to compounds of formula (IIB):



(IIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, or a substituted phenyl represented by one of the following formulas:



R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl,

an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

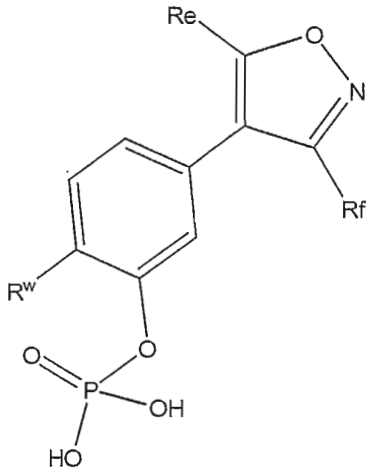
R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally

substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

p is 1 or 2; and

R^w is defined as for formula (IB).

In another embodiment, the invention relates to compounds of formula (IIIB):



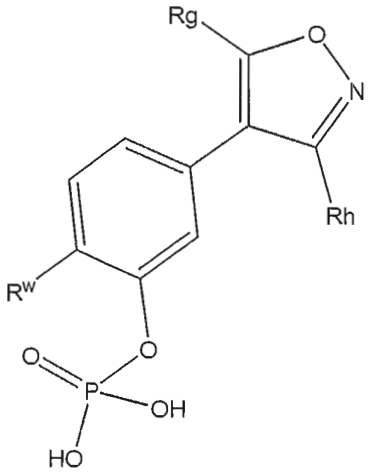
(IIIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_e or R_f is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-

benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and R^w is defined as for formula (IB).

In another embodiment, the invention relates to compounds of formula (IVB):

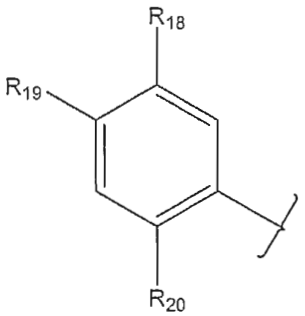


(IVB)

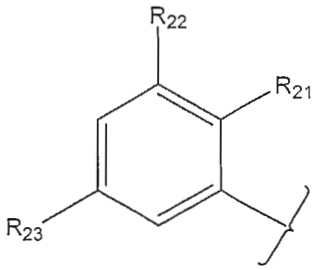
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_g or R_h is –H and the other is:

i) an unsubstituted phenyl or a substituted phenyl represented by one of the following formulas:



or



; or

ii) an optionally substituted heteroaryl selected from the group consisting of an optionally substituted

2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an

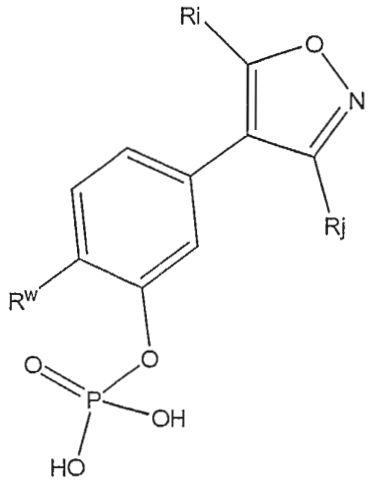
optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, and R_{23}, are defined as for formula (IIB);

R^w is defined as for formula (IB); and

p is 1 or 2.

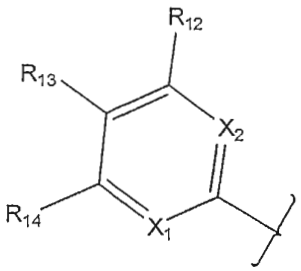
In another embodiment, the invention relates to compounds of formula (VB):



(VB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



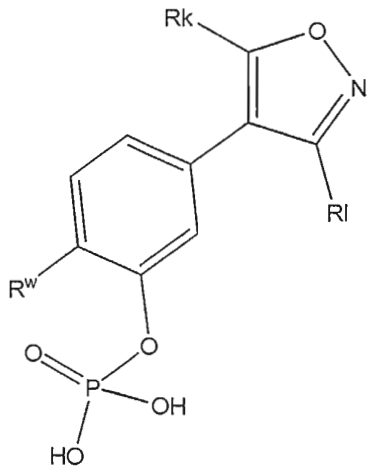
X_1 and X_2 are each, independently, CH or N;

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R^w is defined as for formula (IB); and

R_7, R_8, R_{10}, R_{11}, and p are defined as for formula (IIB).

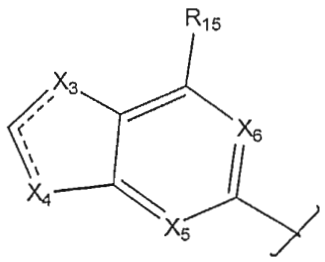
In another embodiment, the invention relates to compounds of formula (VIB):



(VIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_k or R_l is --H and the other is represented by the following formula:



the dashed line indicates that the bond is a single bond or a double bond;

X_3 and X_4 are each, independently, CH, N, CH_2, NR_{16}, O, or S;

X_5 and X_6 are each, independently, CR_{29} or N;

R_{15} is H, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

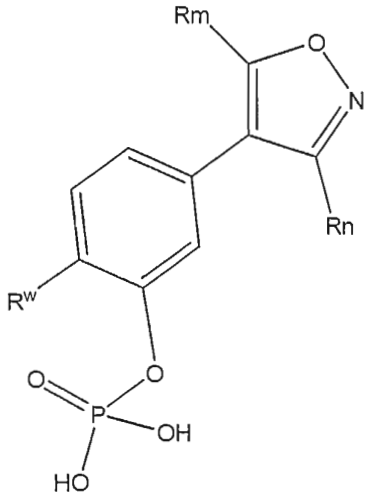
R_7, R_8, R_{10}, R_{11}, R_{17}, and p are defined as for formula (IIB);

R_{16} is H, an alkyl, a cycloalkyl, an aralkyl, -C(O)R, wherein R is an alkyl, a cycloalkyl, or an aralkyl;

R^w is defined as for formula (IB); and

R_{29}, for each occurrence, is independently, H or a substituent.

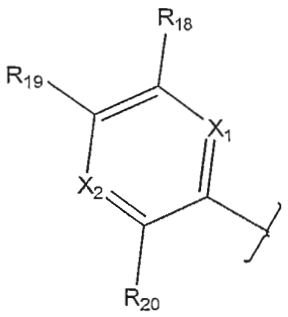
In another embodiment, the invention relates to compounds of formula (VIIB):



(VIIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_m or R_n is –H and the other is represented by the following formula:

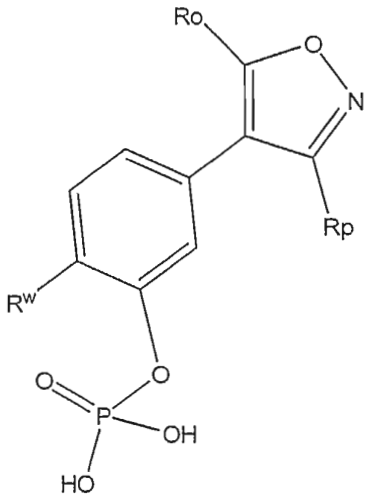


X_1 and X_2 are each, independently, CH or N;

R^w is defined as for formula (IB); and

R_{18}, R_{19}, and R_{20} are defined as for formula (IIB).

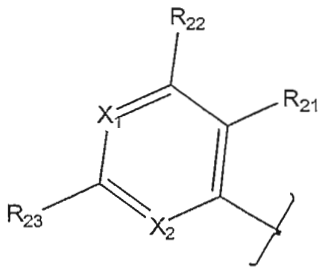
In another embodiment, the invention relates to compounds of formula (VIIIB):



(VIIIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_o or R_p is –H and the other is represented by the following formula:

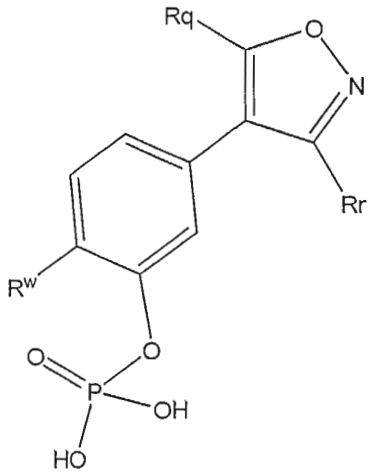


X_1 and X_2 are each, independently, CH or N;

R^w is defined as for formula (IB); and

R_{21}, R_{22}, and R_{23} are defined as for formula (IIB).

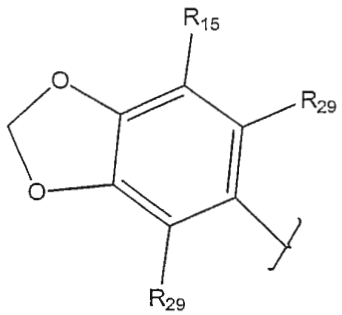
In another embodiment, the invention relates to compounds of formula (IXB):



(IXB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

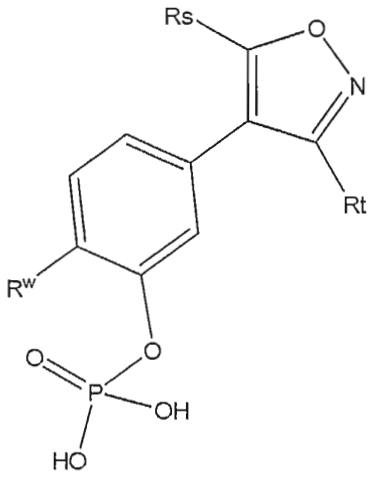
one of R_q or R_r is –H and the other is represented by the following formula:



R^w is defined as for formula (IB); and

R_{15} and R_{19} are defined as for formula (VIB).

In another embodiment, the invention relates to compounds of formula (XB):

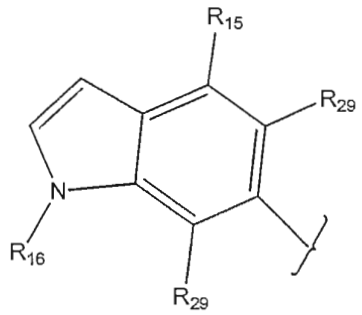


(XB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof,,

wherein:

one of R_s or R_t is –H and the other is represented by the following formula:



R^w is defined as for formula (IB); and

R_{15}, R_{16}, and R_{29} are defined as for formula (VIB).

In some embodiments, in the compounds represented by formula (I), (IA), or (IB), one of R_a or R_b is –H and the other is an optionally substituted phenyl. In one aspect of this embodiment, the phenyl group represented by R_a or R_b is unsubstituted. In another aspect of this embodiment, the phenyl group represented by R_a or R_b is substituted with from one to five substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an

optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the phenyl group represented by R_a or R_b is substituted with from one to five substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the phenyl group represented by R_a or R_b is substituted with from one to three substituents. More preferably, the phenyl group represented by R_a or R_b is substituted with three substituents.

In some embodiments, in the compounds represented by formula (I), (IA), (IB), one of R_a or R_b is –H and the other is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_a or R_b is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_a or R_b is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the pyridinyl group represented by R_a or R_b is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the pyridinyl group represented by R_a or R_b is

substituted with from one to three substituents. More preferably, the pyridinyl group represented by R_a or R_b is substituted with three substituents.

In some embodiments, in the compounds represented by formula (I), (IA), or (IB), one of R_a or R_b is –H and the other is an optionally substituted benzo[1,3]dioxolyl. In one aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_a or R_b is unsubstituted. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_a or R_b is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_a or R_b is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the benzo[1,3]dioxolyl group represented by R_a or R_b is substituted with from one to three substituents. More preferably, the benzo[1,3]dioxolyl group represented by R_a or R_b is substituted with one substituent.

In some embodiments, in the compounds represented by formula (I), (IA), or (IB), R_a or R_b is –H and the other is an optionally substituted 1*H*-indolyl. In one aspect of this embodiment, the 1*H*-indolyl group represented by R_a or R_b is unsubstituted. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_a or R_b is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally

substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_a or R_b is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the 1*H*-indolyl group represented by R_a or R_b is substituted with from one to three substituents. More preferably, the 1*H*-indolyl group represented by R_a or R_b is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (II), (IIA), or (IIB), R_c or R_d is –H and the other is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_c or R_d is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_c or R_d is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the pyridinyl group represented by R_c or R_d is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the pyridinyl group represented by R_c or R_d is substituted with from one to three substituents. More preferably, the pyridinyl group represented by R_c or R_d is substituted with three substituents.

In some embodiments, in the compounds represented by formulas (II), (IIA), or (IIB), R_c or R_d is –H and the other is an optionally substituted benzo[1,3]dioxolyl. In one aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_c or R_d is unsubstituted. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_c or R_d is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_c or R_d is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the benzo[1,3]dioxolyl group represented by R_c or R_d is substituted with from one to three substituents. More preferably, the benzo[1,3]dioxolyl group represented by R_c or R_d is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (II), (IIA), or (IIB), R_c or R_d is –H and the other is an optionally substituted 1*H*-indolyl. In one aspect of this embodiment, the 1*H*-indolyl group represented by R_c or R_d is unsubstituted. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_c or R_d is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$,

$-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_c or R_d is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the 1*H*-indolyl group represented by R_c or R_d is substituted with from one to three substituents. More preferably, the 1*H*-indolyl group represented by R_c or R_d is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (III), (IIIA), or (IIIB), R_e or R_f is –H and the other is an optionally substituted phenyl. In one aspect of this embodiment, the phenyl group represented by R_e or R_f is unsubstituted. In another aspect of this embodiment, the phenyl group represented by R_e or R_f is substituted with from one to five substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the phenyl group represented by R_e or R_f is substituted with from one to five substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the phenyl group represented by R_e or R_f is substituted with from one to three substituents. More preferably, the phenyl group represented by R_e or R_f is substituted with three substituents.

In some embodiments, in the compounds represented by formulas (III), (IIIA), or (IIIB), R_e or R_f is –H and the other is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_e or R_f is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_e or R_f is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the pyridinyl group represented by R_e or R_f is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the pyridinyl group represented by R_e or R_f is substituted with from one to three substituents. More preferably, the pyridinyl group represented by R_e or R_f is substituted with three substituents.

In some embodiments, in the compounds represented by formulas (III), (IIIA), or (IIIB), R_e or R_f is –H and the other is an optionally substituted benzo[1,3]dioxolyl. In one aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_e or R_f is unsubstituted. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_e or R_f is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$,

$-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_e or R_f is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the benzo[1,3]dioxolyl group represented by R_e or R_f is substituted with from one to three substituents. More preferably, the benzo[1,3]dioxolyl group represented by R_e or R_f is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (III), (IIIA), or (IIIB), R_e or R_f is –H and the other is an optionally substituted 1*H*-indolyl. In one aspect of this embodiment, the 1*H*-indolyl group represented by R_e or R_f is unsubstituted. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_e or R_f is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_e or R_f is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the 1*H*-indolyl group represented by R_e or R_f is substituted with from one to three substituents. More preferably, the 1*H*-indolyl group represented by R_e or R_f is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (IV), (IVA), or (IVB), R_g or R_h is –H and the other is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_g or R_h is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_g or R_h is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the pyridinyl group represented by R_g or R_h is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the pyridinyl group represented by R_g or R_h is substituted with from one to three substituents. More preferably, the pyridinyl group represented by R_g or R_h is substituted with three substituents.

In some embodiments, in the compounds represented by formulas (IV), (IVA), or (IVB), R_g or R_h is –H and the other is an optionally substituted benzo[1,3]dioxolyl. In one aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_g or R_h is unsubstituted. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_g or R_h is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$,

$-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the benzo[1,3]dioxolyl group represented by R_g or R_h is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the benzo[1,3]dioxolyl group represented by R_g or R_h is substituted with from one to three substituents. More preferably, the benzo[1,3]dioxolyl group represented by R_g or R_h is substituted with one substituent.

In some embodiments, in the cornpounds represented by formulas (IV), (IVA), or (IVB), R_g or R_h is –H and the other is an optionally substituted 1*H*-indolyl. In one aspect of this embodiment, the 1*H*-indolyl group represented by R_g or R_h is unsubstituted. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_g or R_h is substituted with one or more substituents independently selected from a halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$, wherein R_7, R_8, R_{10}, R_{11}, and p are defined as above. In another aspect of this embodiment, the 1*H*-indolyl group represented by R_g or R_h is substituted with one or more substituents, independently, selected from an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. Preferably, the 1*H*-indolyl group represented by R_g or R_h is substituted with from one to three substituents. More preferably, the 1*H*-indolyl group represented by R_g or R_h is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (I), (III), or (V), R_2 is an optionally substituted phenyl. In one aspect of this embodiment, the phenyl group represented by R_2 is unsubstituted. In another aspect of this embodiment, the phenyl group represented by R_2 is substituted with from one to five groups independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein:

p is defined as above;

R_{24} and R_{27}, for each occurrence are, independently, H, an alkyl, or a cycloalkyl;

R_{25} and R_{26}, for each occurrence are, independently, H, an alkyl, or a cycloalkyl; or R_{25} and R_{26}, together with the nitrogen to which they are attached are a heterocyclyl or a heteroaryl; and

R_{28}, for each occurrence, is an alkyl or a cycloalkyl.

In one aspect of this embodiment, the phenyl group represented by R_2 is substituted with from one to three substituents. In one aspect of this embodiment, the phenyl group represented by R_2 is substituted with two substituents. In one aspect, the phenyl is substituted with one amino group and one alkoxy group. In one aspect of this embodiment, the phenyl represented by R_2 is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (I), (III), or (V), R_2 is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_2 is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_2 is substituted with one or more substituents independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and p are defined as above. In one aspect of this embodiment, the pyridinyl

group represented by R_2 is substituted with from one to three substituents. Preferably, the pyridinyl represented by R_2 is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (I), (III), or (V), R_2 is an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted pyridinyl-phenyl, an optionally substituted pyridinyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted oxazolyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, or an optionally substituted benzofuranyl. In one aspect of this embodiment, R_2 is unsubstituted. In another aspect of this embodiment, R_2 is substituted with one or more substituents independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and p are defined as above. In one aspect of this embodiment, R_2 is substituted with from one to three substituents. Preferably, R_2 is substituted with one substituent.

In some embodiments, in the compounds represented by formula (II), (IV), (VI), (VII), (VIII), (IX), or (X), R_4 is an optionally substituted phenyl. In one aspect of this embodiment, the phenyl group represented by R_4 is unsubstituted. In another aspect of this embodiment, the phenyl group represented by R_4 is substituted with from one to five groups independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and p are defined as above. In one aspect of this embodiment, the phenyl group represented by R_4 is substituted with from one to three substituents. In one aspect of this embodiment, the phenyl group represented by R_4 is substituted with two substituents. In one aspect, the phenyl is

substituted with one amino group and one alkoxy group. In one aspect, the phenyl represented by R_4 is substituted with one substituent.

In some embodiments, in the compounds represented by formula (II), (IV), (VI), (VII), (VIII), (IX), or (X), R_4 is an optionally substituted pyridinyl. In one aspect of this embodiment, the pyridinyl group represented by R_4 is unsubstituted. In another aspect of this embodiment, the pyridinyl group represented by R_4 is substituted with one or more substituents independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and p are defined as above. In one aspect of this embodiment, the pyridinyl group represented by R_4 is substituted with from one to three substituents. Preferably, the pyridinyl represented by R_4 is substituted with one substituent.

In some embodiments, in the compounds represented by formula (II), (IV), (VI), (VII), (VIII), (IX), or (X), R_4 is an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted pyridinyl-phenyl, an optionally substituted pyridinyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted oxazolyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, or an optionally substituted benzofuranyl. In one aspect of this embodiment, R_4 is unsubstituted. In another aspect of this embodiment, R_4 is substituted with one or more substituents independently selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and p are defined as above. In one aspect of this embodiment, R_4 is

substituted with from one to three substituents. Preferably, R_4 is substituted with one substituent.

In some embodiments, in the compounds represented by formulas (V), (VA), or (VB), R_{12}, R_{13}, and R_{14} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl. In one aspect of this embodiment, R_{12}, R_{13}, and R_{14} are each, independently, an alkoxy. In another aspect of this embodiment, R_{12}, R_{13}, and R_{14} are each methoxy.

In some embodiments, in the compounds represented by formulas (V), (VA), (VB), (VII), (VIIA), (VIIB), (VIII), (VIIIA), or (VIIIB), X_1 and X_2 are CH.

In some embodiments, in the compounds represented by formulas (V), (VA), (VB), (VII), (VIIA), (VIIB), (VIII), (VIIIA), or (VIIIB), X_1 and X_2 are N.

In some embodiments, in the compounds represented by formulas (V), (VA), (VB), (VII), (VIIA), (VIIB), (VIII), (VIIIA), or (VIIIB), X_1 is N and X_2 is CH.

In some embodiments, in the compounds represented by formulas (V), (VA), (VB), (VII), (VIIA), (VIIB), (VIII), (VIIIA), or (VIIIB), X_1 is CH and X_2 is N.

In some embodiments, in the compounds represented by formulas (VI), (VIA), or (VIB), X_3 and X_4 are O and X_5 and X_6 are CH. In one aspect of this embodiment, X_3 and X_4 are O; X_5 and X_6 are CH; and R_{15} is an alkoxy, such as methoxy.

In some embodiments, in the compounds represented by formulas (VI), (VIA), or (VIB), X_3 is CH; X_4 are NR_{16}; and X_5 and X_6 are CH. In one aspect of this embodiment, X_3 is CH; X_4 are NR_{16}; X_5 and X_6 are CH; and R_{16} is H. In one aspect of this embodiment, X_3 is CH; X_4 are NR_{16}; X_5 and X_6 are CH; and R_{16} is a lower alkyl.

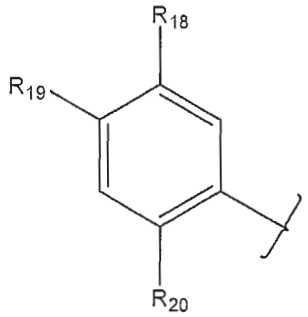
In some embodiments, in the compounds represented by formulas (VI), (VIA), (VIB), (IX), (IXA), (IXB), (X), (XA), or (XB), R_{15} is H, alkoxy, halo, alkyl, haloalkyl, haloalkoxy,

nitro, cyano, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkylamino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$; wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and p are defined as above.

In some embodiments, in the compounds represented by formulas (IX), (IXA), (IXB), (X), (XA) or (XB), R_{15} is H, alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkylamino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$; and R_{29}, for each occurrence, is independently, H, alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino, dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$; wherein R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, and p are defined as above.

In some embodiments, in the compounds represented by formulas (VII), (VIIA), or (VIIB), R_{18} and R_{19} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{20} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester; wherein R_7 is defined as above.

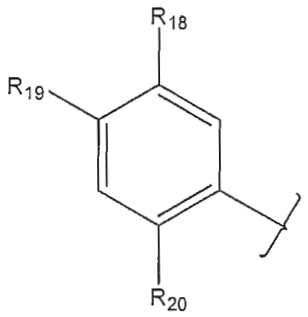
In some embodiments, in the compounds represented by formulas (II), (IIA) or (IIB), R_c or R_d is –H and the other is a substituted phenyl represented by the following structural formula:



; and

R_{18} and R_{19} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{20} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester; wherein R_7 is defined as above and "}" represents the point of attachment of the phenyl ring to the isoxazole ring.

In some embodiments, in the compounds represented by formulas (IV), (IVA), or (IVB), R_g or R_h is –H and the other is a substituted phenyl represented by the following structural formula:

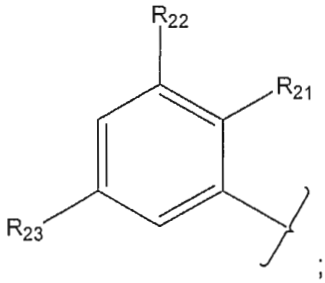


; and

R_{18} and R_{19} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{20} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester; wherein R_7 is defined as above and "}" represents the point of attachment of the phenyl ring to the isoxazole ring.

In some embodiments, in the compounds represented by formulas (VIII), (VIIIA), or (VIIIB), R_{22} and R_{23} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{21} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester, wherein R_7 is defined as above.

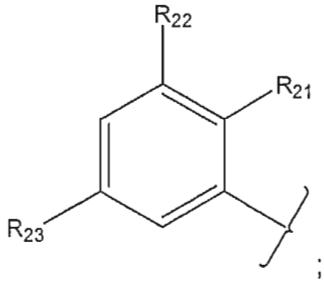
In some embodiments, in the compounds represented by formulas (II), (IIA), or (IIB), R_c or R_d is –H and the other is a substituted phenyl represented by the following structural formula:



; and

R_{22} and R_{23} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{21} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester, wherein R_7 is defined as above and "}" represents the point of attachment of the phenyl ring to the isoxazole ring.

In some embodiments, in the compounds represented by formulas (IV), (IVA), or (IVB), R_g or R_h is –H and the other is a substituted phenyl represented by the following structural formula:



; and

R_{22} and R_{23} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and R_{21} is an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, or an alkyl ester, wherein R_7 is defined as above and "}" represents the point of attachment of the phenyl ring to the isoxazole ring.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is R^{aa}, $-C(O)YR^z$, or $-C(O)NH-R^{aa}$. In one aspect, R^x is R^{aa}. In another aspect, R^x is $-C(O)YR^z$. R^{aa}, R^z, and Y are defined as for formula (IA).

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is $(R^{aa})_m$. In one aspect, m is 3.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is R^{aa} and R^{aa} is defined as for formula (IA). In one aspect, R^{aa} is glycine, serine, alanine, phenylalanine, leucine, or methionine.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is R^{aa} and R^{aa} is a D-amino acid residue or a D-amino acid residue analog. In one aspect, R^{aa} is D-alanine, D-valine, D-leucine, D-isoleucine, D-serine, D-threonine, D-cysteine, D-methionine, D-phenylalanine, D-tyrosine, D-tryptophan, D-aspartic acid, D-asparagine, D-glutamic acid, D-glutamine, D-arginine, D-histidine, D-lysine, or D-proline.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is R^{aa} and R^{aa} is an L-amino acid residue or an L-amino acid residue analog. In one aspect, R^{aa} is L-alanine, L-valine, L-leucine, L-isoleucine, L-serine, L-threonine, L-cysteine, L-methionine, L-phenylalanine, L-tyrosine, L-tryptophan, L-aspartic acid, L-asparagine, L-glutamic acid, L-glutamine, L-arginine, L-histidine, L-lysine, or L-proline.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is R^{aa} and R^y is –H, wherein R^{aa} is defined as for formula (IA). In one aspect, R^{aa} is glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, phenylalanine, tyrosine, tryptophan, aspartic acid, asparagine, glutamic acid, glutamine, arginine, histidine, lysine, or proline. In another aspect, R^{aa} is glycine, serine, alanine, phenylalanine, leucine, or methionine.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^x is -C(O)YR^z and Y and R^z are defined as for formula (IA). In one aspect, Y is CH_2. In another aspect, Y is O. In another aspect, Y is NH. In one aspect, R^z is Y_1 and Y_1 is defined as for formula (IA). In another aspect, R^z is Alk-NH_2. In another aspect, R^z is Alk-C(O)OH. In another aspect, R^z is Het. Alk and Het and defined as for formula (IA).

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), m is 1, 2 or 3.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), Y_1 is PEG, HPMA copolymer-methacryloyl-Gly-Phe-Leu-Gly-ethylenediamine, or HPMA copolymer-methacryloyl-Gly-Phe-Leu-Gly-OH. In one aspect, Y_1 is PEG.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^y is –H.

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In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), R^y is a lower alkyl.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), Y_1 has a molecular weight greater than 20,000 daltons. In one aspect, Y_1 has a molecular weight of less than 40,000 daltons, but greater than 25,000 daltons.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), Alk is an optionally substituted lower alkylene.

In some embodiments, in the compounds represented by formula (IA), (IIA), (IIIA), (IVA), (VA), (VIA), (VIIA), or (VIIIA), Het is an optionally substituted lower heteroalkyl.

In some embodiments, in the compounds represented by formula (VA), X_1 and X_2 are CH and R_{12}, R_{13}, and R_{14} are each methoxy. In one aspect, R^x is R^{aa}. In another aspect, R^x is $(R^{aa})_m$. In another aspect, R^x is $-R^{aa}-C(O)(CH_2)_nC(O)OH$. In another aspect, R^x is $-C(O)(CH_2)_nC(O)OH$. In another aspect, R^x is $-C(O)YR^z$. In another aspect, R^x is $-C(O)NH-R^{aa}$. In another aspect, R^x is $-(R^{aa})_qC(O)(Y_1)$. R^{aa}, Y, R^z, Y_1, m, n, and q are defined as for formula (IA).

In some embodiments, in the compounds represented by formula (VA), X_1 and X_2 are CH and R_{12}, R_{13}, and R_{14} are each methoxy. In one aspect, R^x is R^{aa} and R^w is alkoxy. In another aspect, R^x is R^{aa} and R^y is –H. In another aspect, R^x is R^{aa}, R^w is alkoxy, and R^y is –H. In another aspect, R^x is R^{aa}, R^w is alkoxy, and R^y is –H. In another aspect, R^x is R^{aa}, R^w is methoxy, and R^y is –H. R^{aa} is defined as for formula (IA).

In some embodiments, in the compounds represented by formula (VA), X_1 and X_2 are CH; R_{12}, R_{13} and R_{14} are methoxy; R_j is –H; R^w is methoxy; R^y is –H; and R^x is R^{aa}. R^{aa} is defined as for formula (IA).

In some embodiments, in the compounds represented by formula (VB), X_1 and X_2 are CH; R_{12}, R_{13}, and R_{14} are each methoxy; and R^w is alkoxy. In one aspect, R^w is methoxy.

In some embodiments, in the compounds represented by formula (IA or B), (IIA or B), (IIIA or B), (IVA or B), (VA or B), (VIA or B), (VIIA or B), (VIIIA or B), (IXA or B), or (XA or B), R^w is alkoxy. In one aspect, R^w is methoxy.

In some embodiments represented by formula (I), (IA), or (IB), R_a is –H. In some embodiments represented by formula (I), (IA), or (IB), R_b is –H. In some embodiments represented by formula (V), (VA), or (VB), R_i is –H. In some embodiments represented by formula (V), (VA), or (VB), R_j is –H.

In another embodiment, the invention relates to compounds selected from the group consisting of:

4-(4-Bromo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(Naphthalen-2-yl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(4-Methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Iodo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-Phenyl-5-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole;
4-(4-Bromo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(2,3-Dihydro-benzo[1,4]di-oxin-6-yl)-5-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole;
4-(4-hydroxy-phenyl)-5-(3,4,5-trihydroxy-phenyl)-isoxazole;
4-(4-Iodo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Nitro-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Amino-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4'-Methoxy-biphenyl-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-3-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-4-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(Quinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Isoquinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-6-yl)-isoxazole;

4-(4-Carboxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxycarbonyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(Oxazol-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Iodo-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-N,N-dimethylamino-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,4,5-trimethyl-phenyl)-isoxazole;

4-[4-(Pyridin-3-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-[4-(Pyridin-4-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-[4-(Pyridin-2-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Quinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Pyridin-4-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Isoquinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(1*H*-Indol-5-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-[1-isopropyl-1*H*-indol-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[3-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Isopropyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-pyridin-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,5-dimethoxy-4-methoxycarbonyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,5-diacetoxy-phenyl)-isoxazole;

4-(2-Methoxy-pyridin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-methyl-5-methoxy-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-4-yl)-isoxazole;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy)-isoxazole;

4-[2-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyrimidin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridin-3-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Acetylamino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2-Methoxy-pyridine-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridine-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(2-Amino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Hydroxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyrimidin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyridin-3-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Acetylamino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(2-Methoxy-pyridin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-Hydroxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(1-methyl-1*H*-indol-5-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(3-phosphonooxy-4-methoxy-phenyl)-isoxazole, disodium salt;

4-(3,4,5-Trimethoxy-phenyl)-5-(N,N-dimethylamino-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(3-amino-4-methoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3,4,5-Trimethoxy-phenyl)-5-[3-(3-hydroxy-2S-amino-propionamido)-4-methoxy-phenyl]-isoxazole, hydrochloric acid salt;

4-(4-Methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2,4,5- trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-bromo-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-chloro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-fluoro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-nitro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-[4-(N,N,-dimethylamino)-phenyl]-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4-dimethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3-hydroxy-4-methoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4-dimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethy-phenyl)-5-(2-Hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Amino-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Trifluoromethyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Naphthalen-2-yl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Iodo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-hydroxy-phenyl)-5-(3,4,5-trihydroxy-phenyl)-isoxazole;

4-(4-Iodo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Amino-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4'-Methoxy-biphenyl-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(pyridine-3-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(pyridine-4-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(pyridine-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Quinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Isoquinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-6-yl)-isoxazole;

4-(4-Carboxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxycarbonyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(Oxazol-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Iodo-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-N,N-dimethylamino-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,4,5-trimethyl-phenyl)-isoxazole;

4-[4-(Pyridin-3-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-[4-(Pyridin-4-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-[4-(Pyridin-2-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Quinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Pyridin-4-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Isoquinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(1*H*-Indol-5-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-[1-isopropyl-1*H*-indol-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[3-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Isopropyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-pyridin-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,5-dimethoxy-4-methoxycarbonyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(3,5-diacetoxy-phenyl)-isoxazole;

4-(2-Methoxy-pyridin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-methyl-5-methoxy-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-4-yl)-isoxazole;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy)-isoxazole;

4-[2-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyrimidin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridin-3-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Acetylamino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2-Methoxy-pyridine-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridine-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(2-Amino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Hydroxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyrimidin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyridin-3-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Acetylamino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(2-Methoxy-pyridin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-Hydroxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(1-methyl-1*H*-indol-5-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(3-phosphonooxy-4-methoxy-phenyl)-isoxazole, disodium salt;

4-(3,4,5-Trimethoxy-phenyl)-5-(N,N-dimethylamino-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(3-amino-4-methoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3,4,5-Trimethoxy-phenyl)-5-[3-(3-hydroxy-2S-amino-propionamido)-4-methoxy-phenyl]-isoxazole, hydrochloric acid salt;

4-(4-Methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2,4,5- trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-bromo-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-chloro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-fluoro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-nitro-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-[4-(N,N,-dimethylamino)-phenyl]-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4-dimethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3-hydroxy-4-methoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4-dimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethy-phenyl)-5-(2-Hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Amino-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole; and

4-(4-Trifluoromethyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole; or

pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

In another embodiment, the invention relates to compounds selected from the group consisting of:

4-(4-Bromo-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Naphthalen-2-yl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Iodo-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl- henyl)-isoxazole;
4-Phenyl-3-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole;
4-(4-Bromo-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(2,3-Dihydro-benzo[1,4]di-oxin-6-yl)-3-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole;
4-(4-hydroxy-phenyl)-3-(3,4,5-trihydroxy-phenyl)-isoxazole;
4-(4-Iodo-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(3-Fluoro-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Nitro-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Amino-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4'-Methoxy-biphenyl-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-3-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-4-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(pyridine-2-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(Quinolin-7-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(Pyridin-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(Isoquinolin-7-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(1-Methyl-1*H*-indol-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-5-yl)-isoxazole;
4-(4-Methoxy-phenyl)-3-(1-ethyl-1*H*-indol-6-yl)-isoxazole;
4-(4-Carboxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Methoxycarbonyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-[4-(Oxazol-2-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(4-Methoxy-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(4-Iodo-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(3-Fluoro-4-methoxy-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(4-Nitro-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(4-N,N-dimethylamino-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(4-Methoxy-phenyl)-3-(3,4,5-trimethyl-phenyl)-isoxazole;
4-[4-(Pyridin-3-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-[4-(Pyridin-4-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-[4-(Pyridin-2-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole;
4-(Quinolin-7-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Pyridin-4-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole;

4-(Isoquinolin-7-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole;

4-(1*H*-Indol-5-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-5-yl)-isoxazole;

4-(4-Methoxy-phenyl)-3-[1-isopropyl-1*H*-indol-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(2,3,4-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-[3-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;

4-(4-Isopropyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro- benzo[1,4]dioxin-6-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-3- (3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(2,3,4-trimethoxy-pyridin-6-yl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(3,5-dimethoxy-4-methoxycarbonyl-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(3,5-diacetoxy-phenyl)- isoxazole;

4-(2-Methoxy-pyridin-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(1-methyl-5-methoxy-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(1-ethyl-1*H*-indol-7-yl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-4-yl)-isoxazole;

4-(2-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy)-isoxazole;

4-[2-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyrimidin-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridin-3-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Acetylamino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2-Methoxy-pyridine-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(5-Methoxy-pyridine-2-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(2-Amino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Hydroxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;

4-(Pyridazin-4-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyrimidin-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(Pyridin-3-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(3-Mercapto-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Acetylamino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Amino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt;

4-(2-Hydroxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(2-Methoxy-pyridin-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(5-Methoxy-pyridin-2-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Carboxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Methoxycarbonyl-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Sulfooxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(3-Amino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(2-Phosphonooxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(4-Methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt;

4-(3-Amino-4-methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)- isoxazole;

4-(2,3-Dihydro-benzofuran-6-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-Hydroxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt;

4-(4-Phosphonooxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(4-1*H*-Tetrazol-5-yl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(1-Methyl-1*H*-indol-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-3-(1-methyl-1*H*-indol-5-yl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-3-(3-phosphonooxy-4-methoxy-phenyl)-isoxazole, disodium salt;

4-(3,4,5-Trimethoxy-phenyl)-3-(N,N-dimethylamino-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-3-(3-amino-4-methoxy-phenyl)-isoxazole, hydrochloric acid salt;

4-(3,4,5-Trimethoxy-phenyl)-3-[3-(3-hydroxy-2S-amino-propionamido)-4-methoxy-phenyl]-isoxazole, hydrochloric acid salt;

4-(4-Methoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-3-(2,4,5- trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Methyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Ethyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Propyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Butyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Bromo-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Chloro-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Fluoro-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(4-Nitro-phenyl)-3- (2,3,5-trimethoxy-phenyl)-isoxazole;

4-[4-(N,N-Dimethylamino)-phenyl]-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4-Dimethoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3-Hydroxy-4-methoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(3,4,5-Trimethoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-methoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-methyl-phenyl)-isoxazole

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-ethoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-ethyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-propoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-propyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-butoxy-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-butyl-phenyl)-isoxazole;

4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-bromo-phenyl)-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-chloro-phenyl)-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-fluoro-phenyl)-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-nitro-phenyl)-isoxazole
4-(2,3,4,5-Tetramethoxy-phenyl)-3-[4-(N,N,-dimethylamino)-phenyl]-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3,4-dimethoxy-phenyl)-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3-hydroxy-4-methoxy-phenyl)-isoxazole;
4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole;
4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-3-(3,4-dimethoxy-phenyl)-isoxazole;
4-(3,4-Dimethy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(4-Chloro-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl- phenyl)-isoxazole;
4-(4-Methyl-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(4-Amino-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(4-Trifluoromethyl-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
4-(4-Methoxy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole; and
4-(3,4,5-Trimethoxy-phenyl)-3-(4-bromo-phenyl)-isoxazole; or
pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof.

In another embodiment, the invention relates to compounds selected from the group consisting of:

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride;

2-amino-3-hydroxy-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) butanamide;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenyl propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methyl pentanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride;

1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride;

1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-butyl-ammonium chloride;

2-hydroxy-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

C-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride;

2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-benzofuran-2-yl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

3-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

3-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

2-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-(3*H*-imidazol-4-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

5-amino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride;

4-guanidino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid;

4-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid;

2-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride;

3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;

3-(2-PEG)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide;

3-PEG-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid

{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester;

2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenylcarbamate-PEG;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride;

2-amino-3-hydroxy-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)butanamide;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenyl propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methyl pentanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride;

1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride;

1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-butyl-ammonium chloride;

2-hydroxy-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

C-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride;

2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-benzofuran-2-yl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

3-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

3-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;
3-carbamoyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;
2-carbamoyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
2-(3*H*-imidazol-4-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]phenyl carbomoyl}-ethyl-ammonium chloride;
5-amino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride;
4-guanidino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride;
N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid;
4-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid;
2-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride;
3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;
3-(2-PEG)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;
N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide;
3-PEG-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide;
N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid;
{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester;
2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylcarbamate-PEG;
3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;
2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide hydrochloride;
methyl-2-(2-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate;
4-amino-5-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride;
3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl) propanamide hydrochloride;
3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride;
methyl-2-(2-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate;
4-amino-5-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride;
3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl) propanamide hydrochloride; and
3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride; or

a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

All of the features, specific embodiments and particular substituents disclosed herein may be combined in any combination. Each feature, embodiment or substituent disclosed in this specification may be replaced by an alternative feature, embodiment or substituent serving the same, equivalent, or similar purpose. In the case of chemical compounds, specific values for variables (*e.g.*, values shown in the exemplary compounds disclosed herein) in any chemical formula disclosed herein can be combined in any combination resulting in a stable structure. Furthermore, specific values (whether preferred or not) for substituents in one type of chemical structure may be combined with values for other substituents (whether preferred or not) in the same or different type of chemical structure. Thus, unless expressly stated otherwise, each feature, embodiment or substituent disclosed is only an

example of a generic series of equivalent or similar features, embodiments or substituents.

In another embodiment, the invention relates to pharmaceutical compositions that comprise a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, as an active ingredient, and a pharmaceutically acceptable carrier or vehicle. The compositions are useful for treating or preventing proliferative disorders such as cancer or macular degeneration.

In another embodiment, the invention relates to methods for inhibiting tubulin polymerization in a cell comprising contacting the cell with an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, the invention relates to methods for promoting microtubule depolymerization in a cell comprising contacting the cell with an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, the invention relates to methods for promoting microtubule depolymerization in a subject comprising administering to the subject an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, the invention relates to methods for treating or preventing a proliferative disorder in a subject in need thereof comprising administering an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

In another embodiment, the invention relates to methods for treating cancer in a subject in need thereof comprising administering an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof. In one aspect of this embodiment, the method involves treating a subject with multidrug resistant cancer. In another aspect of this embodiment, the method involves treating a subject having a solid tumor. In another aspect of this embodiment, the method involves treating a subject having a hematological malignancy.

In another embodiment, the invention relates to methods for treating cancer in a subject in need thereof comprising administering an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, and an additional therapeutic agent. In one aspect of this embodiment, the additional therapeutic agent is another anti-cancer agent.

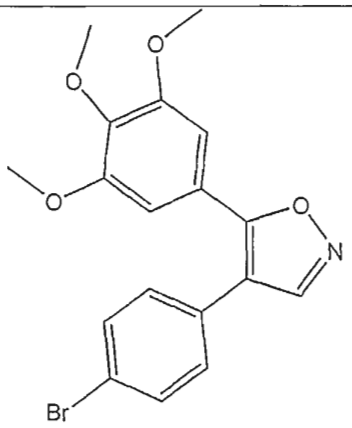
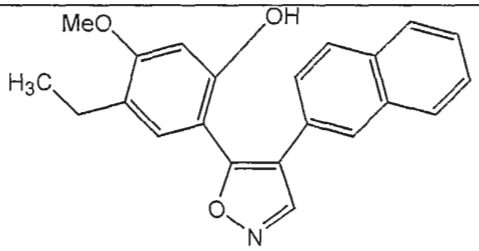
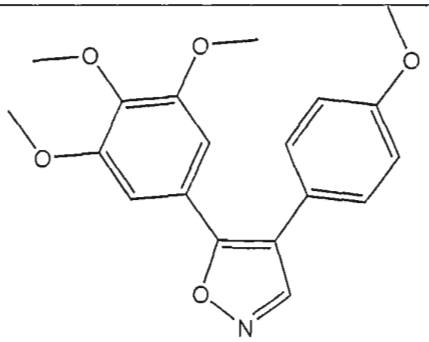
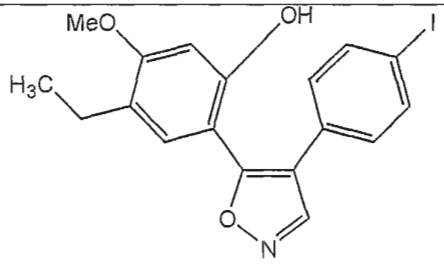
In another embodiment, the invention relates to methods for blocking, occluding, or otherwise disrupting blood flow in neovasculature, comprising contacting the neovasculature with an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, and an additional therapeutic agent.

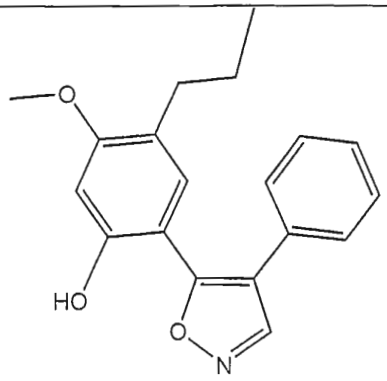
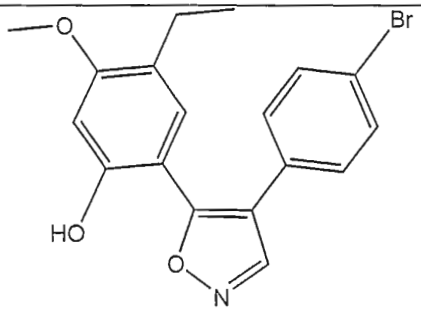
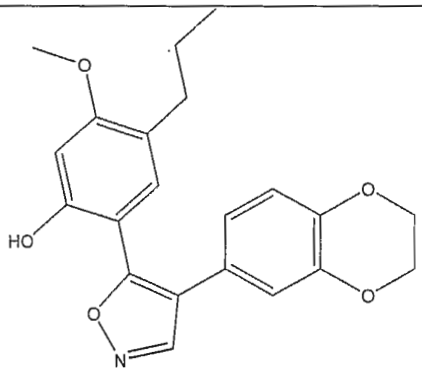
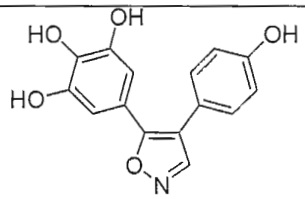
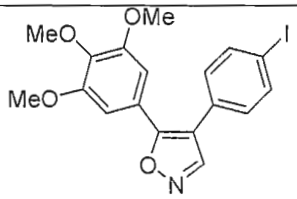
In another embodiment, the invention relates to methods blocking, occluding, or otherwise disrupting blood flow in neovasculature in a subject, comprising administering to the subject an effective amount of a compound represented by any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, and an additional therapeutic agent.

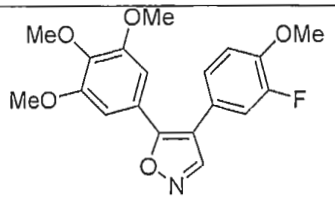
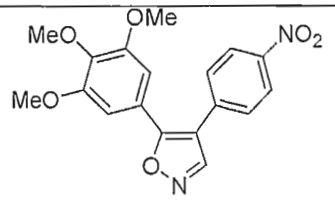
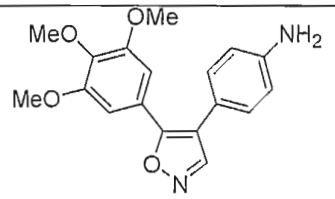
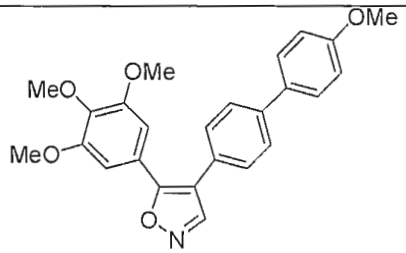
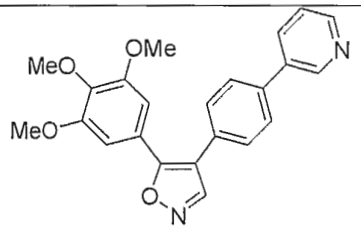
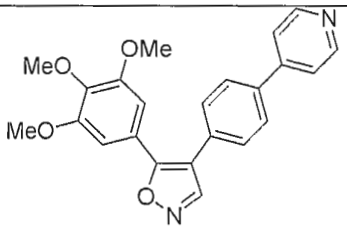
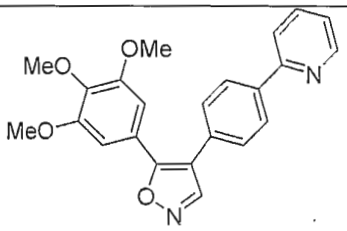
EXEMPLARY COMPOUNDS OF THE INVENTION

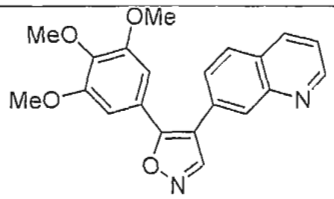
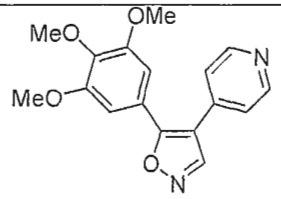
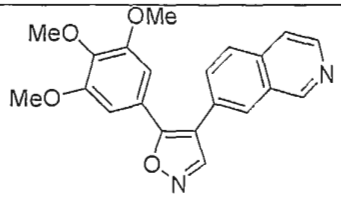
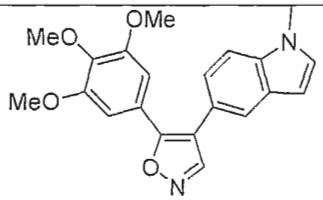
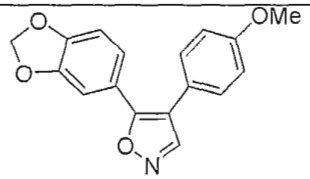
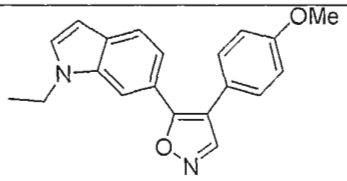
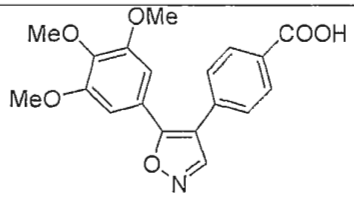
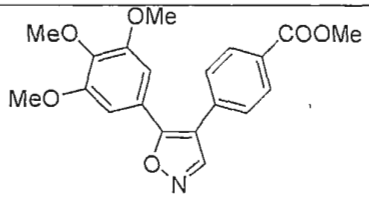
Exemplary compounds of the invention are depicted in Table 1 below.

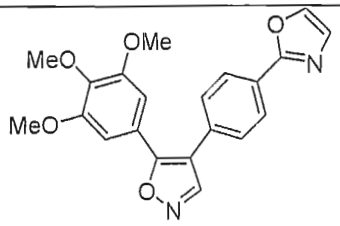
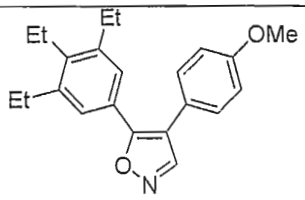
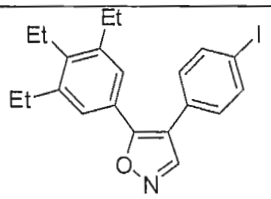
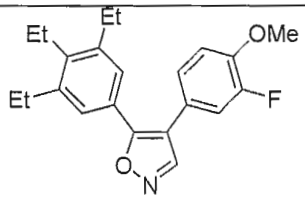
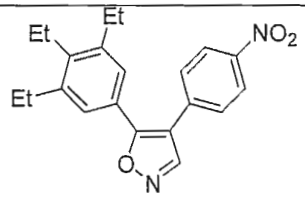
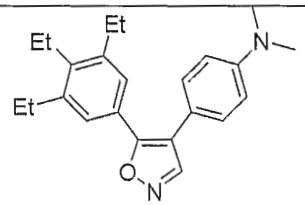
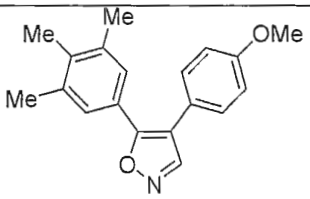
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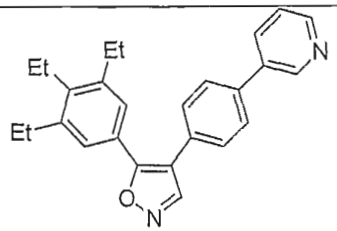
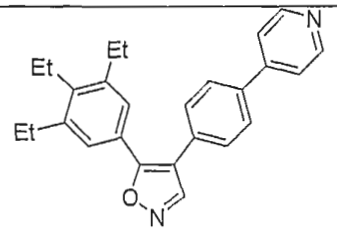
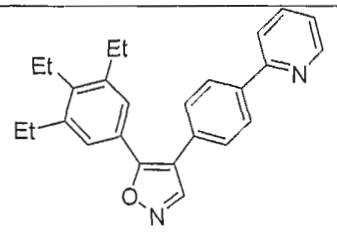
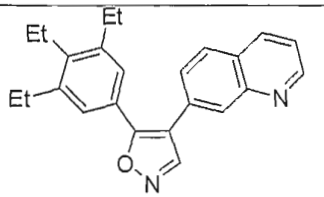
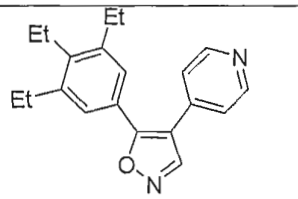
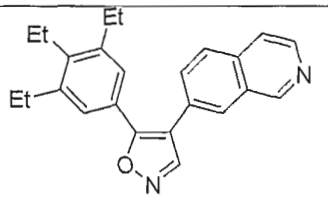
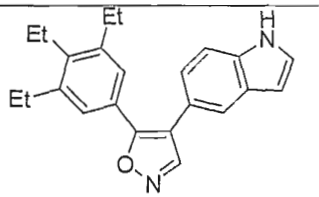
Compound No.	Structure	Chemical Name
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2		4-(4-Bromo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
3		4-(4-Methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
4		4-(4-Iodo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)- isoxazole

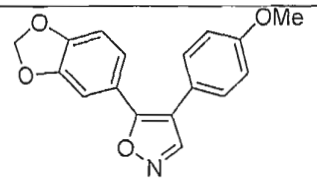
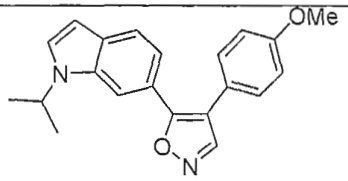
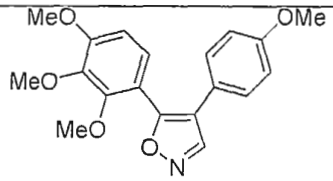
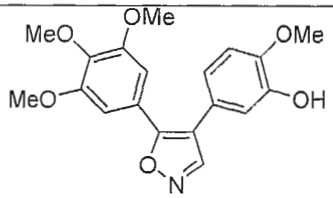
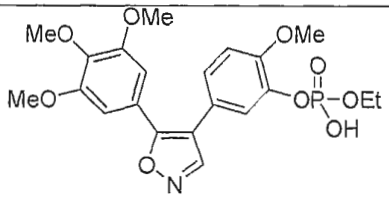
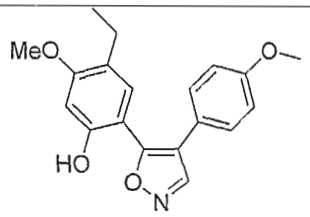
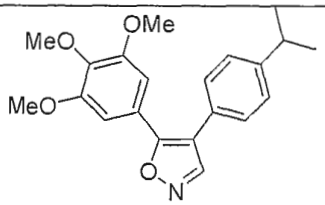
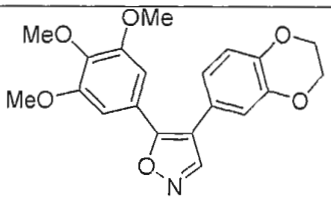
5		4-Phenyl-5-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole
6		4-(4-Bromo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)- isoxazole
7		4-(2,3-Dihydro-benzo[1,4]di-oxin-6-yl)-5-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole
8		4-(4-hydroxy-phenyl)-5-(3,4,5-trihydroxy-phenyl)-isoxazole
9		4-(4-Iodo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

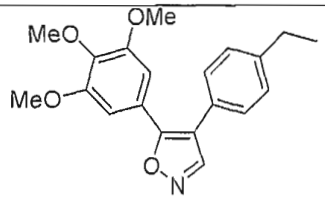
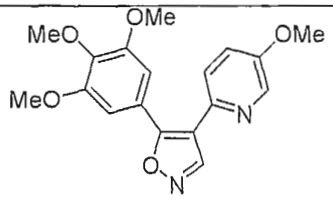
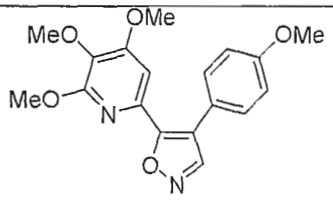
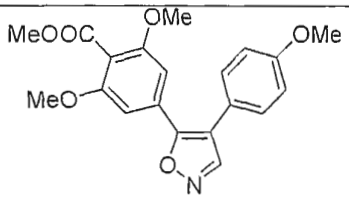
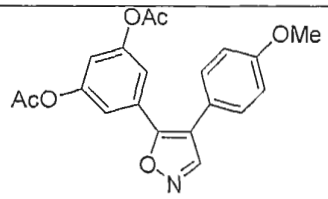
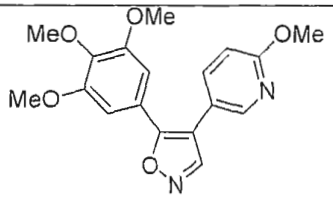
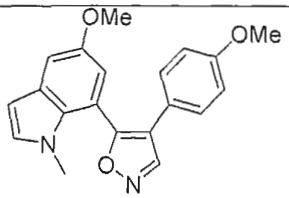
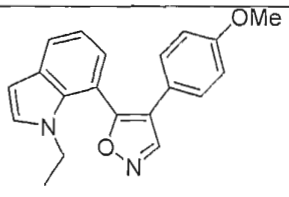
10		4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
11		4-(4-Nitro-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
12		4-(4-Amino-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
13		4-(4'-Methoxy-biphenyl-4-yl)-5- (3,4,5-trimethoxy-phenyl)-isoxazole
14		4-[4-(pyridine-3-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole
15		4-[4-(pyridine-4-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole
16		4-[4-(pyridine-2-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole

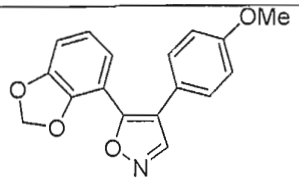
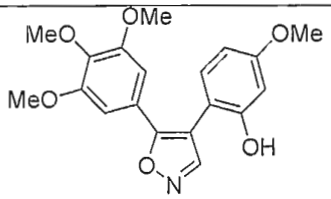
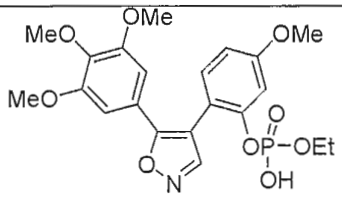
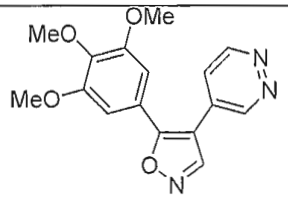
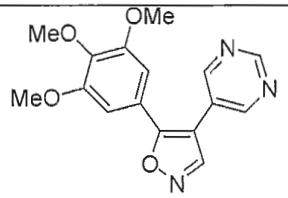
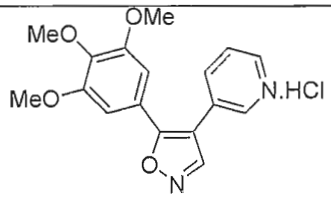
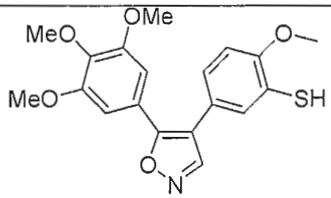
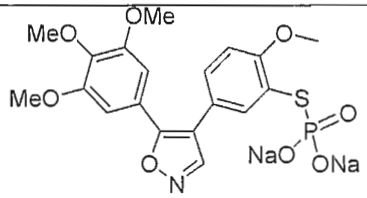
17		4-(Quinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
18		4-(Pyridin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
19		4-(Isoquinolin-7-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
20		4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
21		4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole
22		4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-6-yl)-isoxazole
23		4-(4-Carboxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
24		4-(4-Methoxycarbonyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

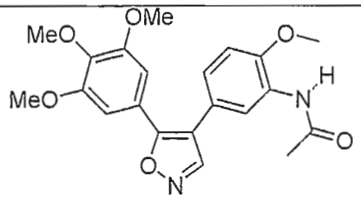
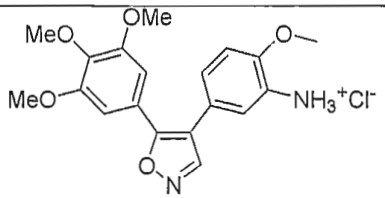
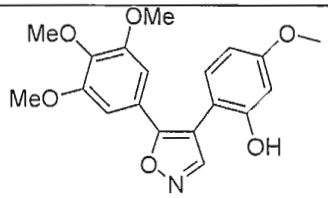
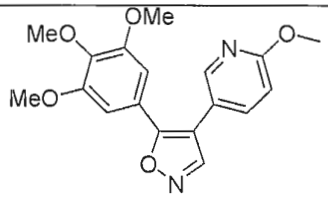
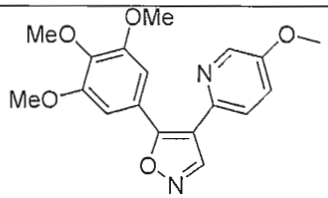
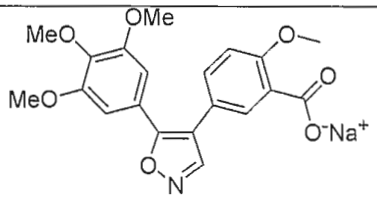
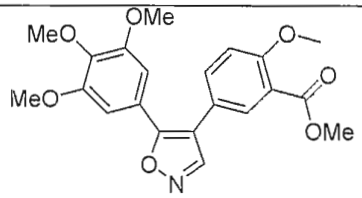
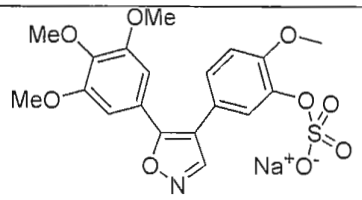
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26		4-(4-Methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole
27		4-(4-Iodo-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole
28		4-(3-Fluoro-4-methoxy-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole
29		4-(4-Nitro-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole
30		4-(4-N,N-dimethylamino-phenyl)-5-(3,4,5-triethyl-phenyl)-isoxazole
31		4-(4-Methoxy-phenyl)-5-(3,4,5-trimethyl-phenyl)-isoxazole

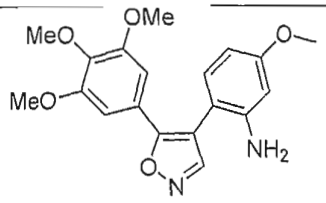
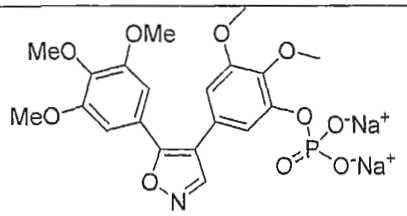
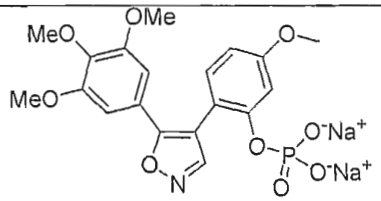
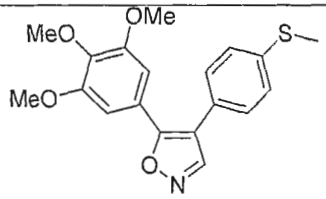
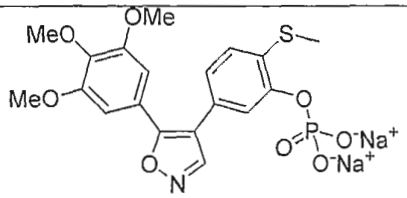
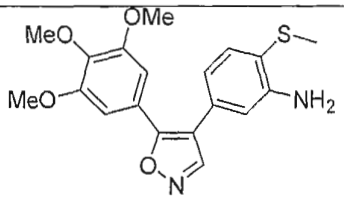
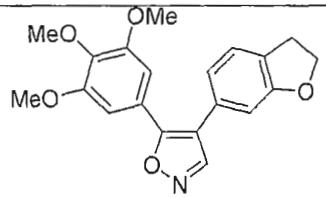
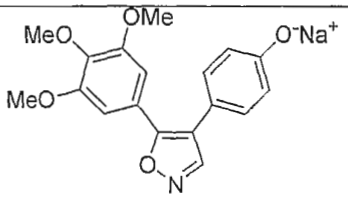
32		4-[4-(Pyridin-3-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole
33		4-[4-(Pyridin-4-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole
34		4-[4-(Pyridin-2-yl)-phenyl]-5-(3,4,5-triethyl-phenyl)-isoxazole
35		4-(Quinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole
36		4-(Pyridin-4-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole
37		4-(Isoquinolin-7-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole
38		4-(1*H*-Indol-5-yl)-5-(3,4,5-triethyl-phenyl)-isoxazole

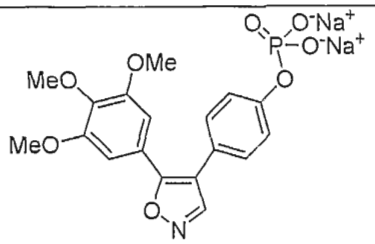
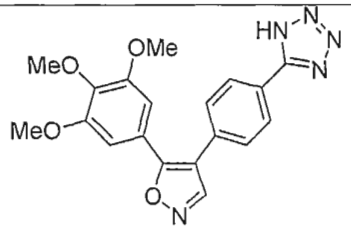
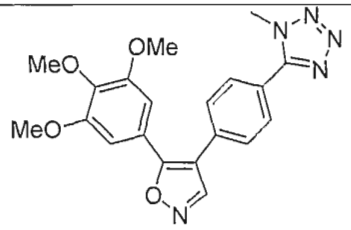
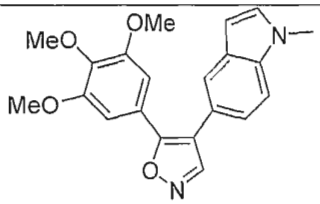
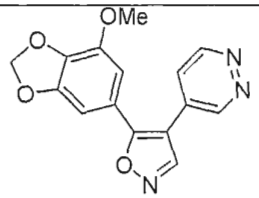
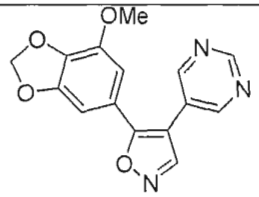
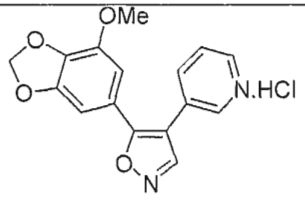
39		4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-5-yl)-isoxazole
40		4-(4-Methoxy-phenyl)-5-[1-isopropyl-1*H*-indol-6-yl)-isoxazole
41		4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-phenyl)-isoxazole
42		4-(3-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
43		4-[3-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole
44		4-(4-Methoxy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
45		4-(4-Isopropyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
46		4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

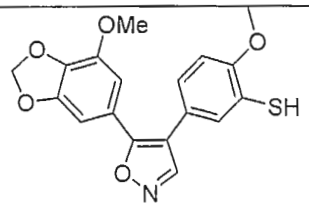
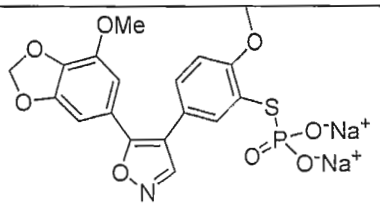
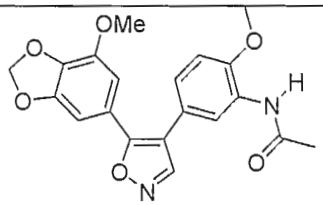
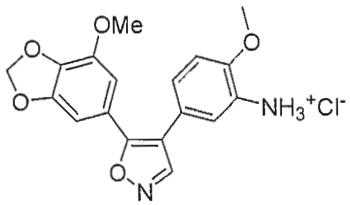
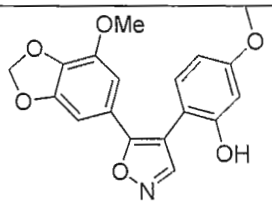
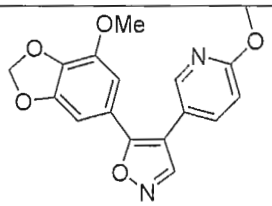
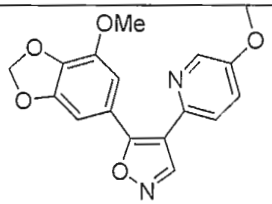
47		4-(4-Ethyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
48		4-(5-Methoxy-pyridin-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
49		4-(4-Methoxy-phenyl)-5-(2,3,4-trimethoxy-pyridin-6-yl)-isoxazole
50		4-(4-Methoxy-phenyl)-5-(3,5-dimethoxy-4-methoxycarbonyl-phenyl)-isoxazole
51		4-(4-Methoxy-phenyl)-5-(3,5-diacetoxy-phenyl)-isoxazole
52		4-(2-Methoxy-pyridin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
53		4-(4-Methoxy-phenyl)-5-(1-methyl-5-methoxy-1*H*-indol-7-yl)-isoxazole
54		4-(4-Methoxy-phenyl)-5-(1-ethyl-1*H*-indol-7-yl)-isoxazole

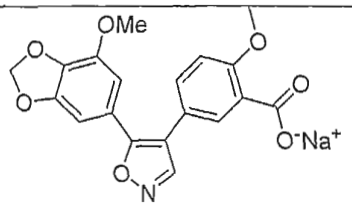
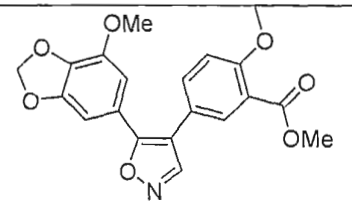
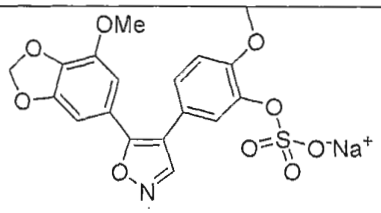
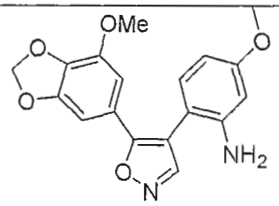
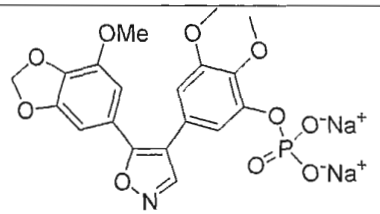
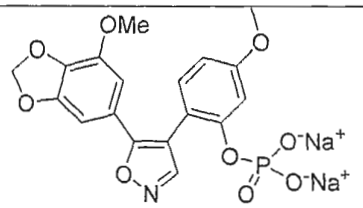
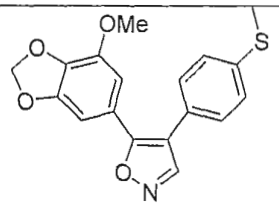
55		4-(4-Methoxy-phenyl)-5-(benzo[1,3]dioxol-4-yl)-isoxazole
56		4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy)-isoxazole
57		4-[2-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole
58		4-(Pyridazin-4-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
59		4-(Pyrimidin-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
60		4-(Pyridin-3-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt
61		4-(3-Mercapto-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
62		4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt

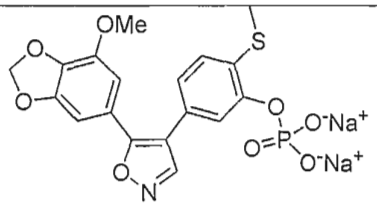
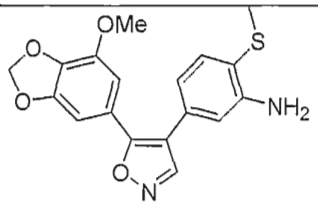
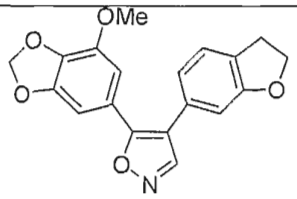
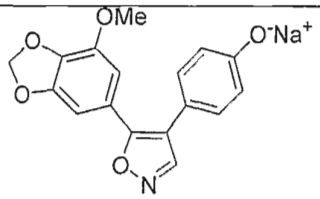
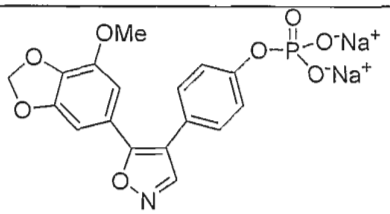
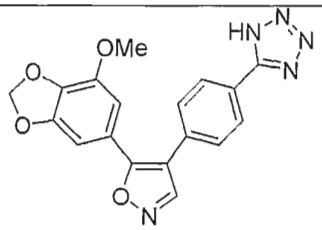
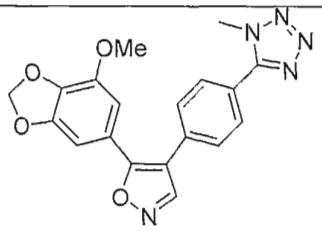
63		4-(3-Acetylamino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
64		2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenylamine hydrochloride
65		4-(2-Hydroxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
66		4-(2-Methoxy-pyridine-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
67		4-(5-Methoxy-pyridine-2-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
68		4-(3-Carboxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt
69		4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
70		4-(3-Sulfooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt

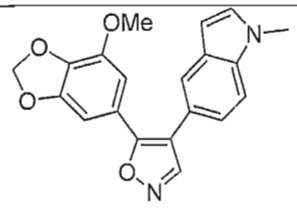
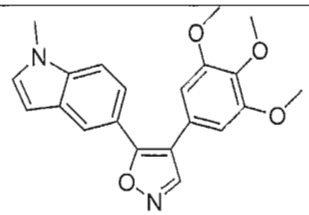
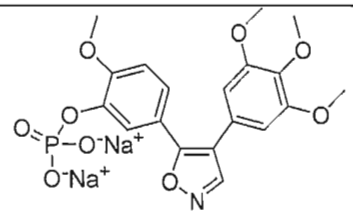
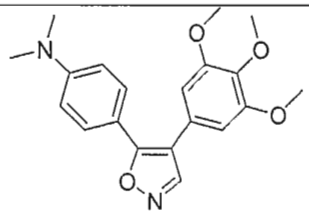
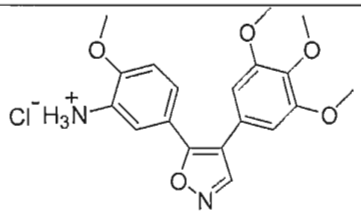
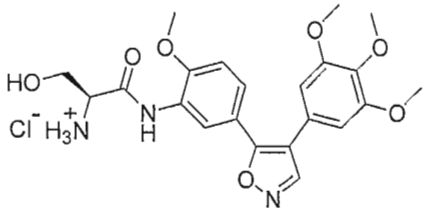
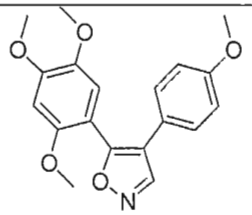
71		4-(2-Amino-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
72		4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
73		4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
74		4-(4-Methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
75		4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
76		4-(3-Amino-4-methylsulfanyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)- isoxazole
77		4-(2,3-Dihydro-benzofuran-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
78		4-(4-Hydroxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt

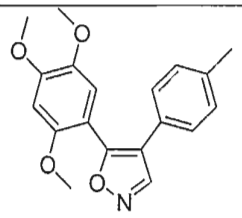
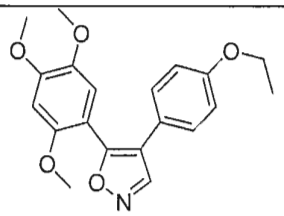
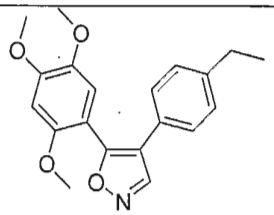
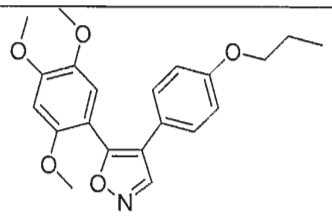
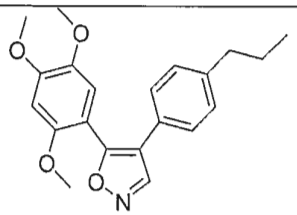
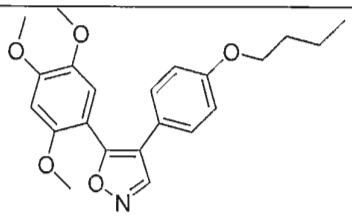
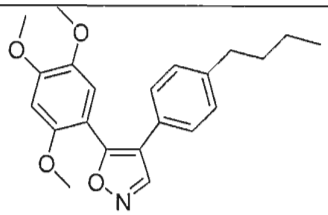
79		4-(4-Phosphonooxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
80		4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
81		4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(3,4,5-trimethoxy-phenyl)-isoxazole
82		4-(1-Methyl-1*H*-indol-5-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole
83		4-(Pyridazin-4-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
84		4-(Pyrimidin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
85		4-(Pyridin-3-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt

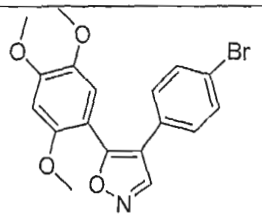
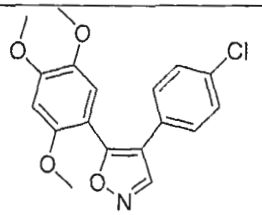
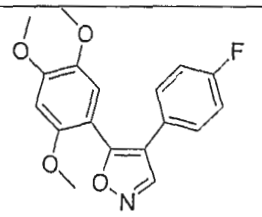
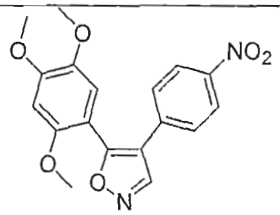
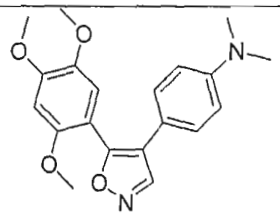
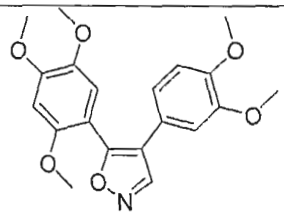
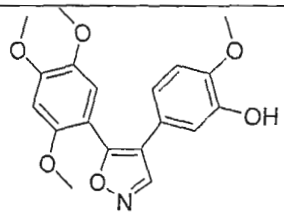
86		4-(3-Mercapto-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
87		4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
88		4-(3-Acetylamino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
89		4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt
90		4-(2-Hydroxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
91		4-(2-Methoxy-pyridin-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
92		4-(5-Methoxy-pyridin-2-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole

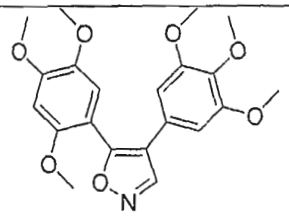
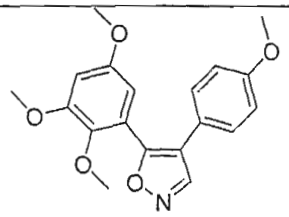
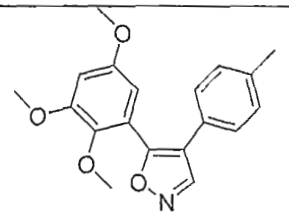
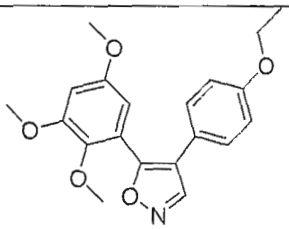
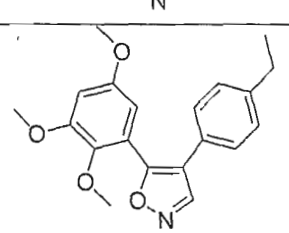
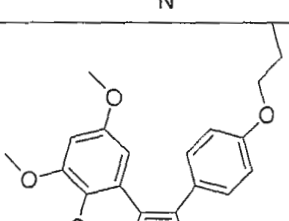
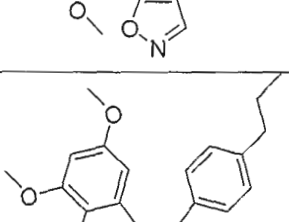
93		4-(3-Carboxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt
94		4-(3-Methoxycarbonyl-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
95		4-(3-Sulfooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt
96		4-(3-Amino-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
97		4-(3,4-Dimethoxy-5 phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt
98		4-(2-Phosphonooxy-4-methoxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt
99		4-(4-Methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole

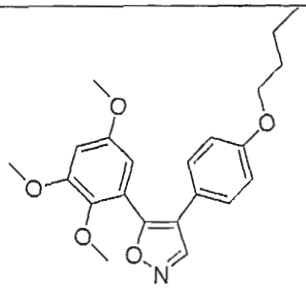
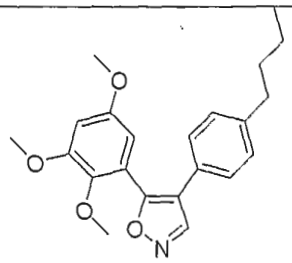
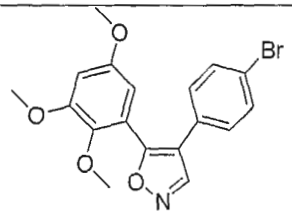
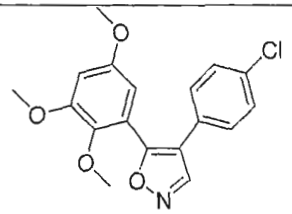
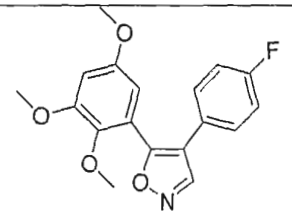
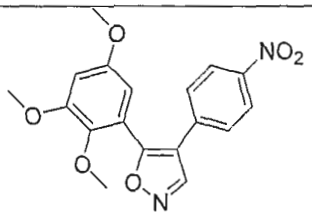
100		4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt
101		4-(3-Amino-4-methylsulfanyl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
102		4-(2,3-Dihydro-benzofuran-6-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
103		4-(4-Hydroxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt
104		4-(4-Phosphonooxy-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
105		4-(4-1*H*-Tetrazol-5-yl-phenyl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
106		4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole

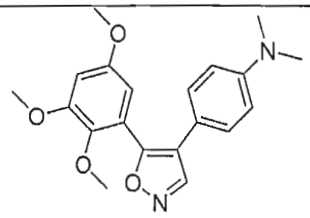
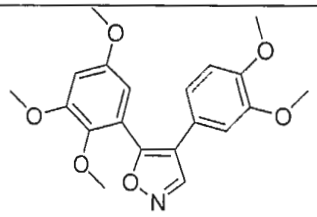
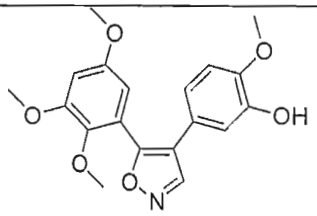
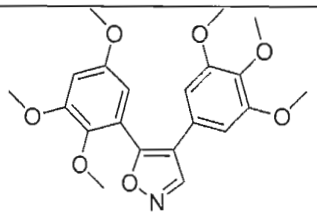
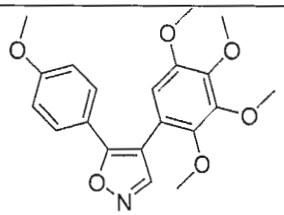
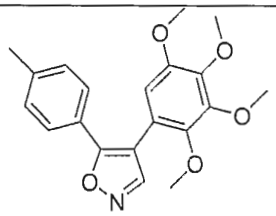
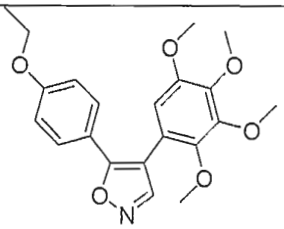
107		4-(1-Methyl-1*H*-indol-5-yl)-5-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
108		4-(3,4,5-Trimethoxy-phenyl)-5-(1-methyl-1*H*-indol-5-yl)-isoxazole
109		4-(3,4,5-Trimethoxy-phenyl)-5-(3-phosphonooxy-4-methoxy-phenyl)-isoxazole, disodium salt
110		4-(3,4,5-Trimethoxy-phenyl)-5-(N,N-dimethylamino-phenyl)-isoxazole
111		4-(3,4,5-Trimethoxy-phenyl)-5-(3-amino-4-methoxy-phenyl)-isoxazole, hydrochloric acid salt
112		4-(3,4,5-Trimethoxy-phenyl)-5-[3-(3-hydroxy-2S-amino-propionamido)-4-methoxy-phenyl]-isoxazole, hydrochloric acid salt
113		4-(4-Methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole

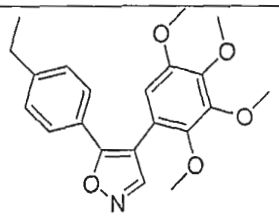
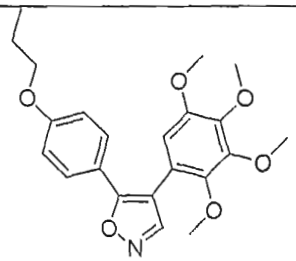
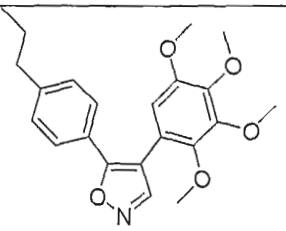
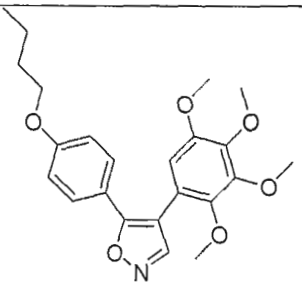
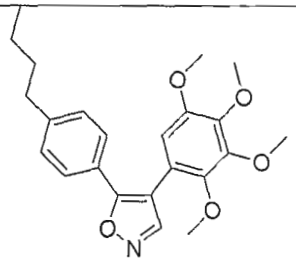
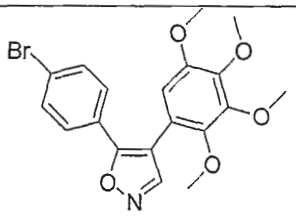
114		4-(4-Methyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
115		4-(4-Ethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
116		4-(4-Ethyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
117		4-(4-Propoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
118		4-(4-Propyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
119		4-(4-Butoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
120		4-(4-Butyl-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole

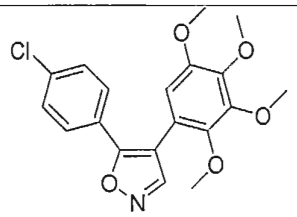
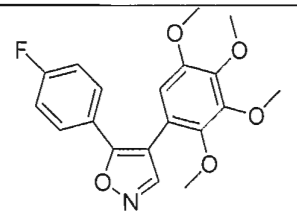
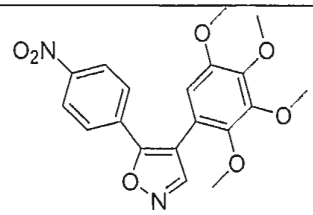
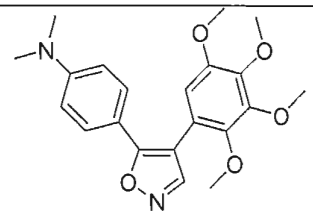
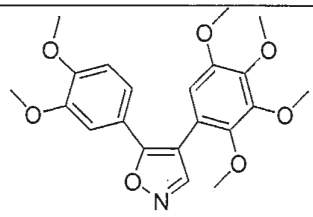
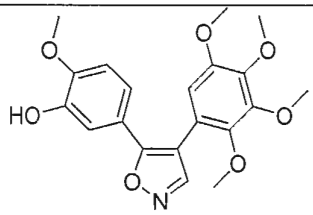
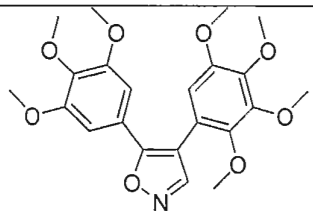
121		4-(4-Bromo-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
122		4-(4-Chloro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
123		4-(4-Fluoro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
124		4-(4-Nitro-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
125		4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,4,5-trimethoxy-phenyl)-isoxazole
126		4-(3,4-Dimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
127		4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole

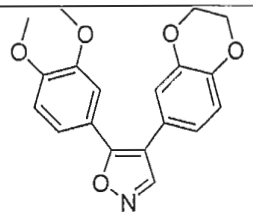
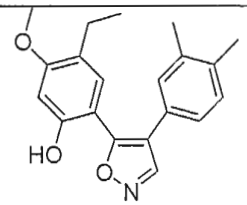
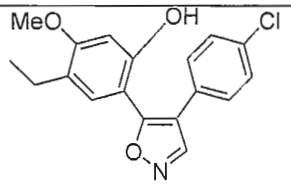
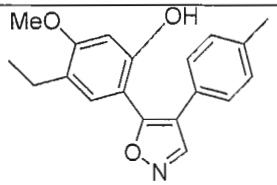
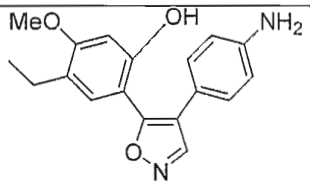
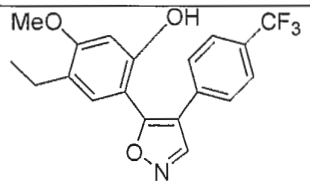
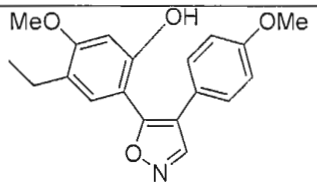
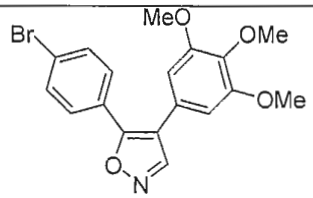
128		4-(3,4,5-Trimethoxy-phenyl)-5-(2,4,5-trimethoxy-phenyl)-isoxazole
129		4-(4-Methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
130		4-(4-Methyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
131		4-(4-Ethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
132		4-(4-Ethyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
133		4-(4-Propoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
134		4-(4-Propyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole

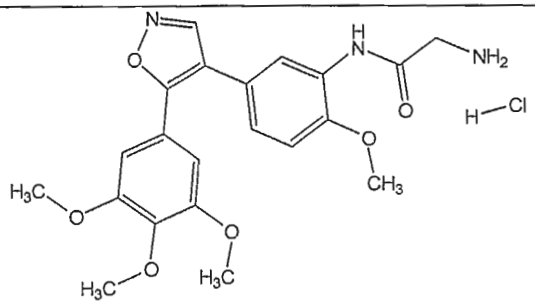
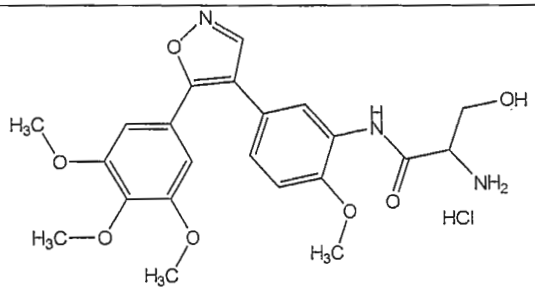
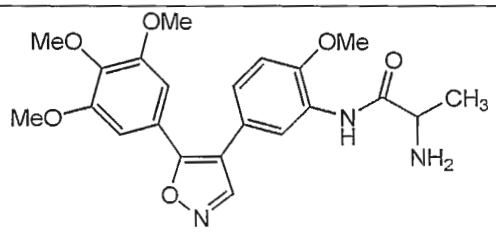
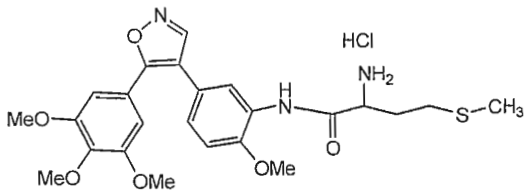
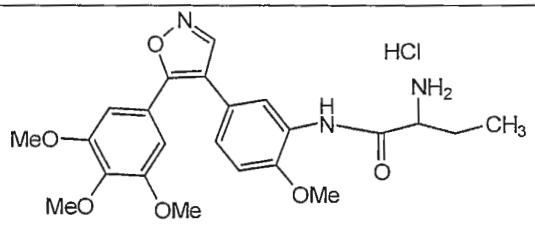
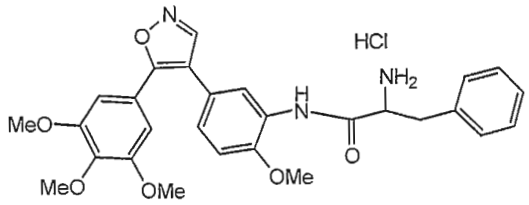
135		4-(4-Butoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
136		4-(4-Butyl-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
137		4-(4-Bromo-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
138		4-(4-Chloro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
139		4-(4-Fluoro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
140		4-(4-Nitro-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole

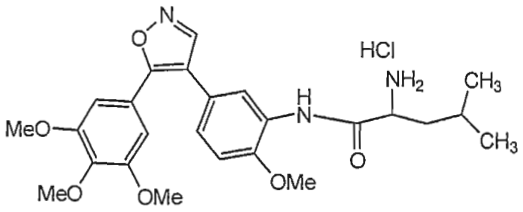
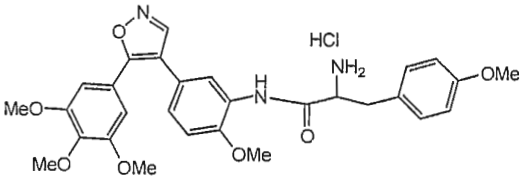
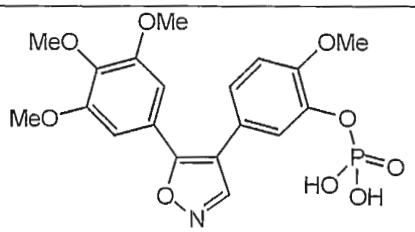
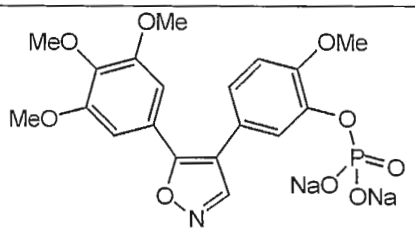
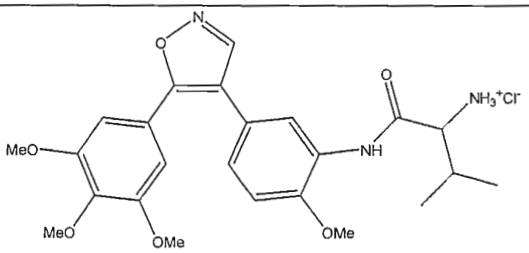
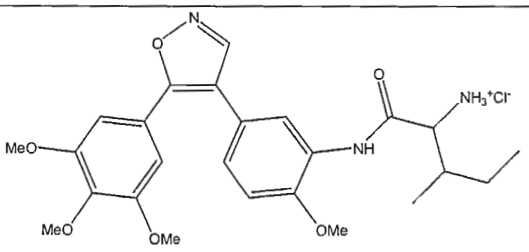
141		4-[4-(N,N-Dimethylamino)-phenyl]-5-(2,3,5-trimethoxy-phenyl)-isoxazole
142		4-(3,4-Dimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
143		4-(3-Hydroxy-4-methoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
144		4-(3,4,5-Trimethoxy-phenyl)-5-(2,3,5-trimethoxy-phenyl)-isoxazole
145		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methoxy-phenyl)-isoxazole
146		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-methyl-phenyl)-isoxazole
147		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethoxy-phenyl)-isoxazole

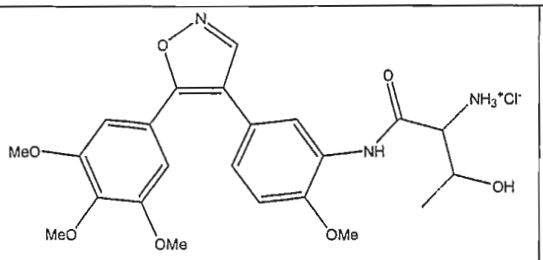
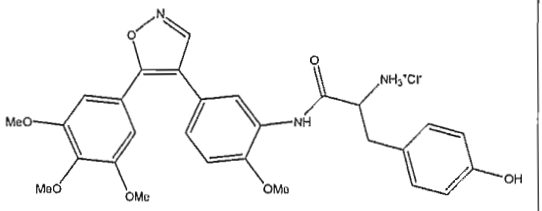
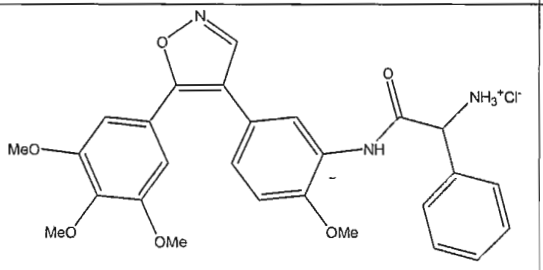
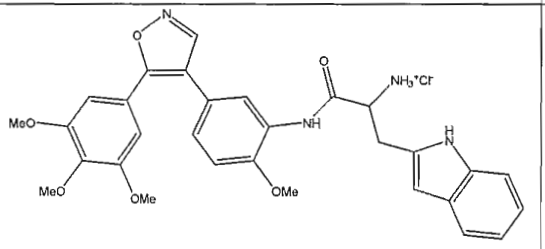
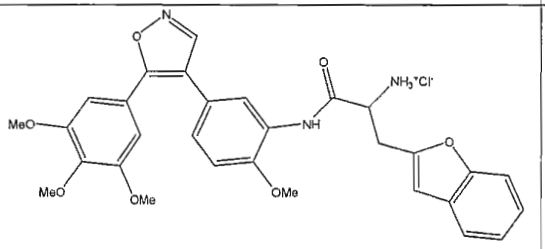
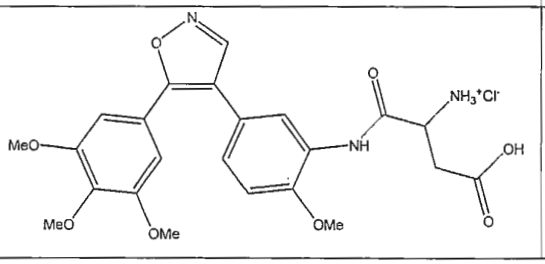
148		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-ethyl-phenyl)-isoxazole
149		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propoxy-phenyl)-isoxazole
150		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-propyl-phenyl)-isoxazole
151		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butoxy-phenyl)-isoxazole
152		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-butyl-phenyl)-isoxazole
153		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-bromo-phenyl)-isoxazole

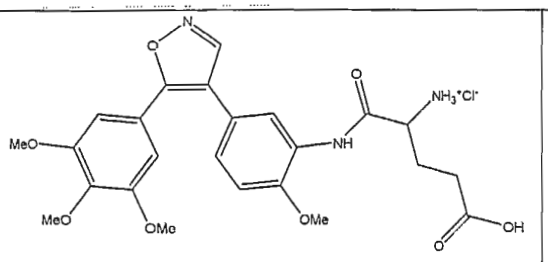
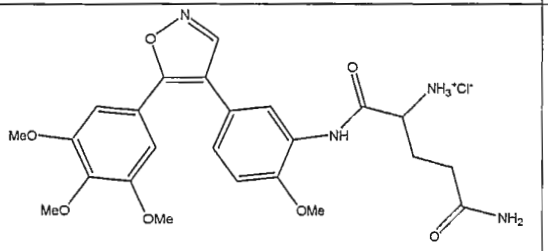
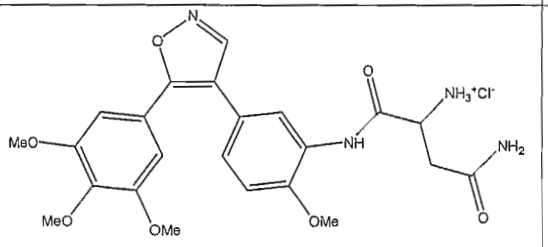
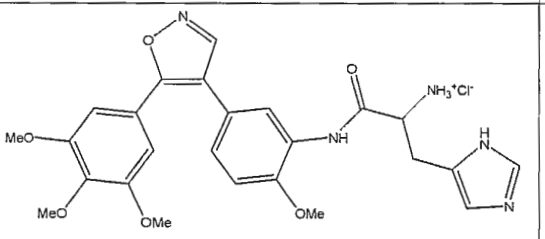
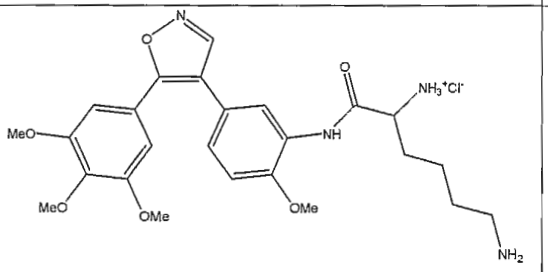
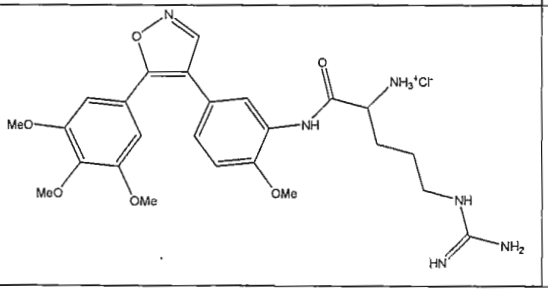
154		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-chloro-phenyl)-isoxazole
155		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-fluoro-phenyl)-isoxazole
156		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(4-nitro-phenyl)-isoxazole
157		4-(2,3,4,5-Tetramethoxy-phenyl)-5-[4-(N,N,-dimethylamino)-phenyl]-isoxazole
158		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4-dimethoxy-phenyl)-isoxazole
159		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3-hydroxy-4-methoxy-phenyl)-isoxazole
160		4-(2,3,4,5-Tetramethoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

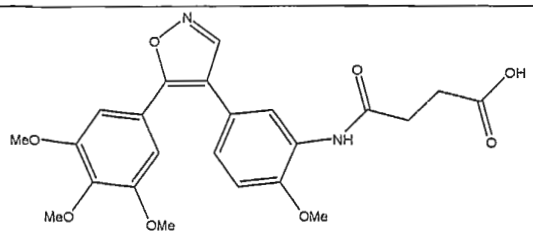
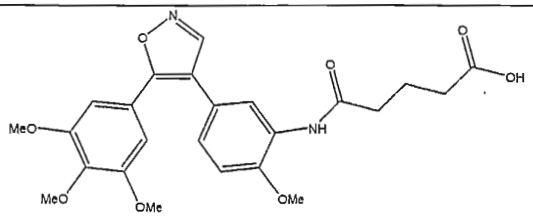
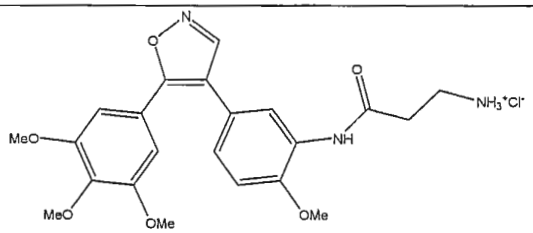
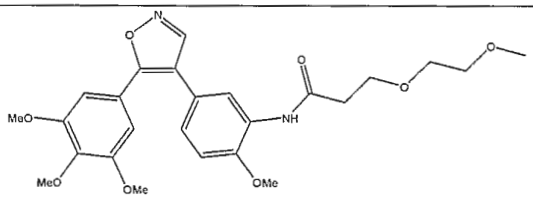
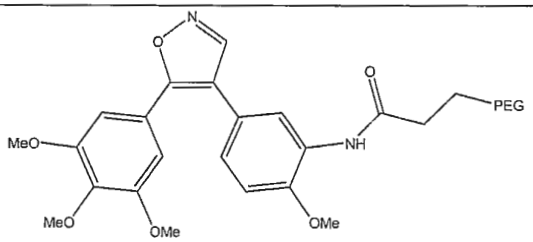
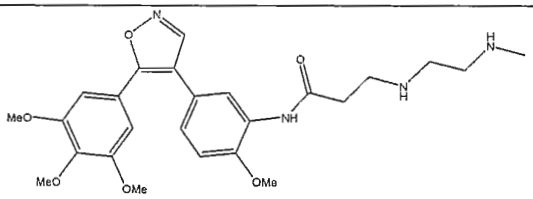
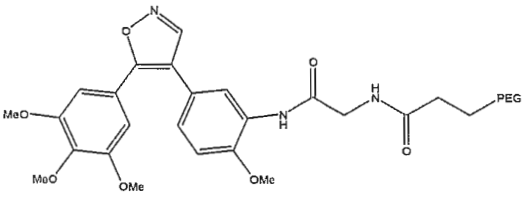
161		4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4-dimethoxy-phenyl)-isoxazole
162		4-(3,4-Dimethy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
163		4-(4-Chloro-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
164		4-(4-Methyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
165		4-(4-Amino-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
166		4-(4-Trifluoromethyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
167		4-(4-Methoxy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
168		4-(3,4,5-Trimethoxy-phenyl)-5-(4-bromo-phenyl)-isoxazole

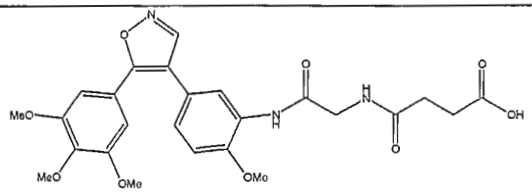
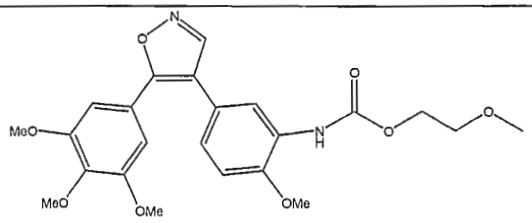
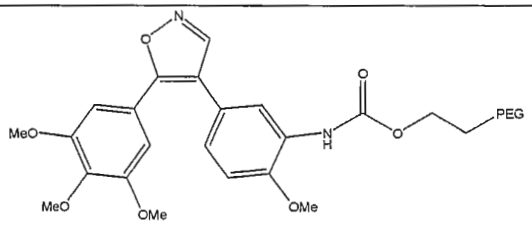
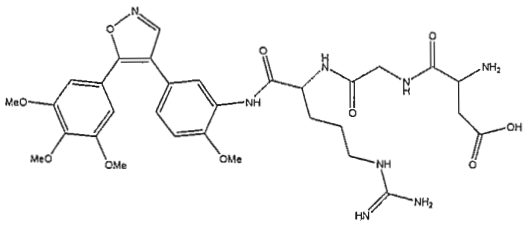
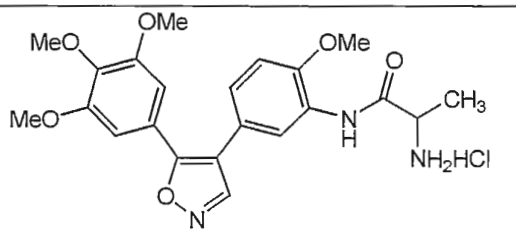
169		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride
170		2-amino-3-hydroxy-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride
171		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide
172		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride
173		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) butanamide
174		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenylpropanamide hydrochloride

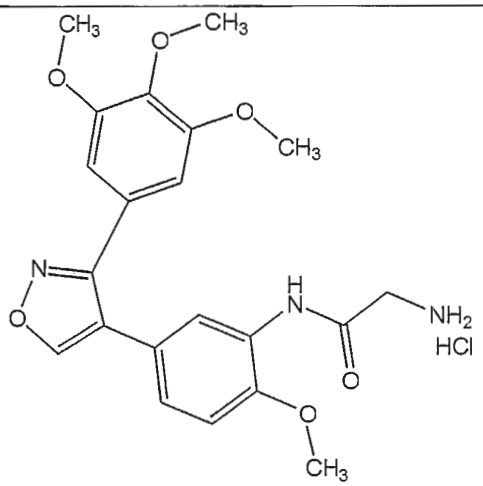
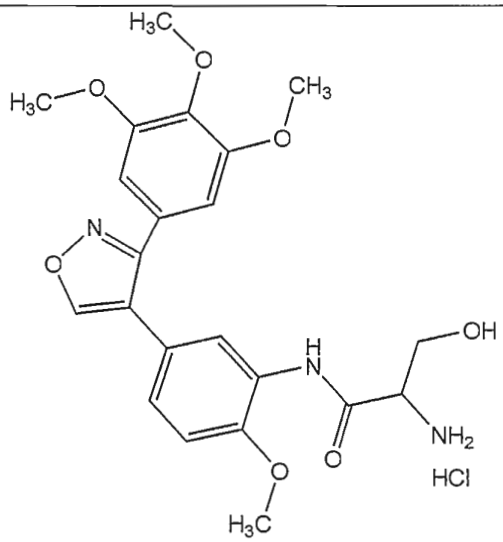
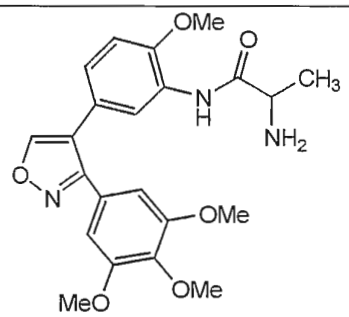
175		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methylpentanamide hydrochloride
176		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride
177		2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl dihydrogen phosphate
178		Sodium 2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl phosphate
179		1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride
180		1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-butyl-ammonium chloride

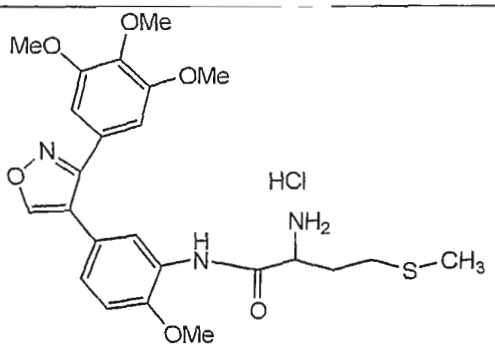
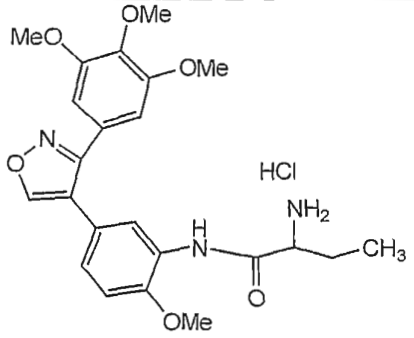
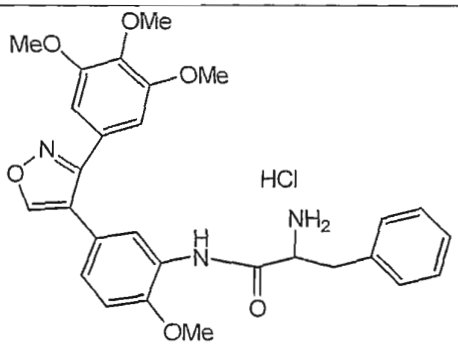
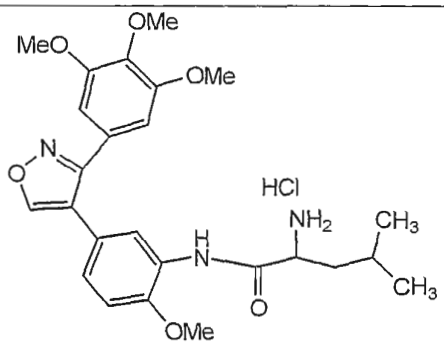
181		2-hydroxy-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
182		2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
183		C-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride
184		2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
185		2-benzofuran-2-yl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
186		2-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride

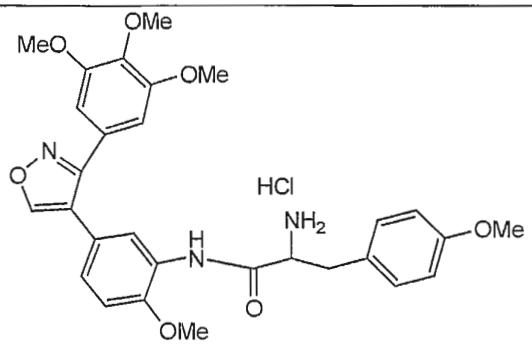
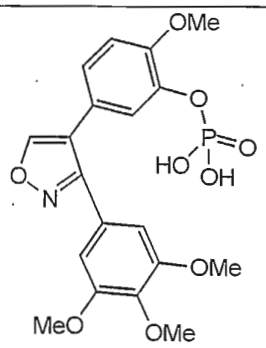
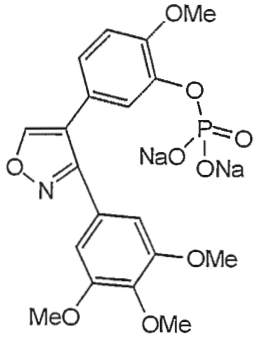
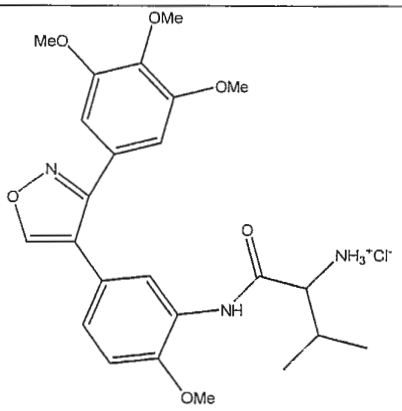
187		3-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
188		3-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
189		2-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
190		2-(3*H*-imidazol-4-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
191		5-amino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride
192		4-guanidino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride

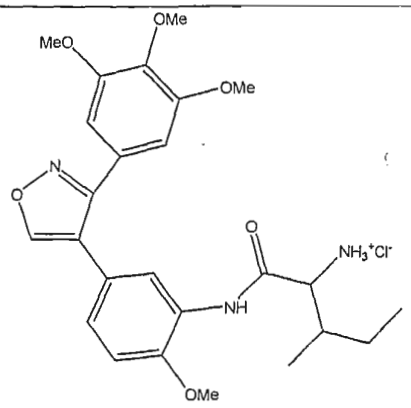
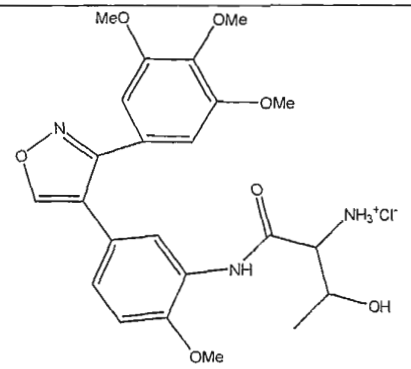
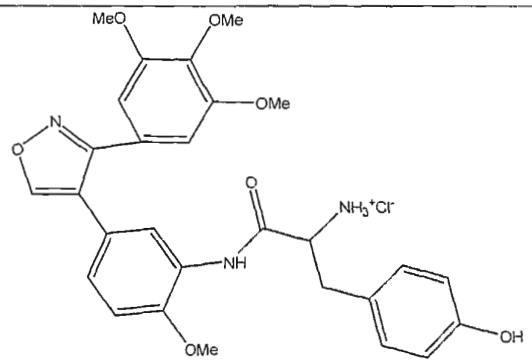
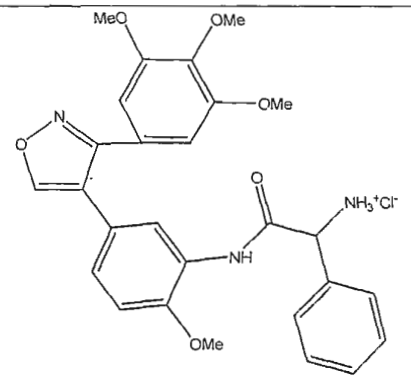
193		*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid
194		4-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid
195		2-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride
196		3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide
197		3-(2-PEG)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide
198		*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide
199		3-PEG-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide

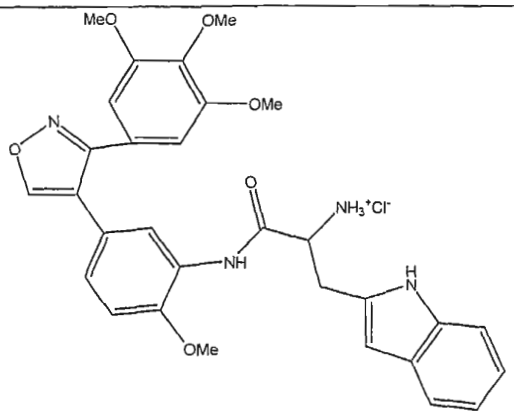
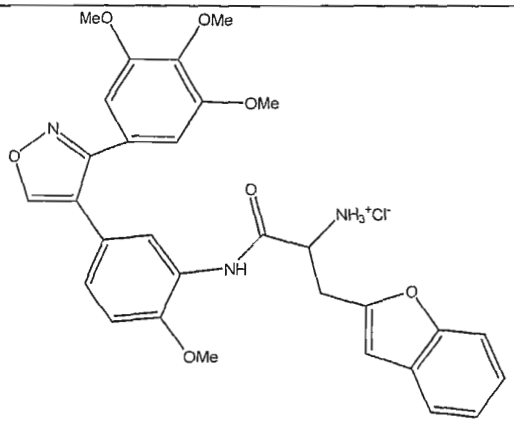
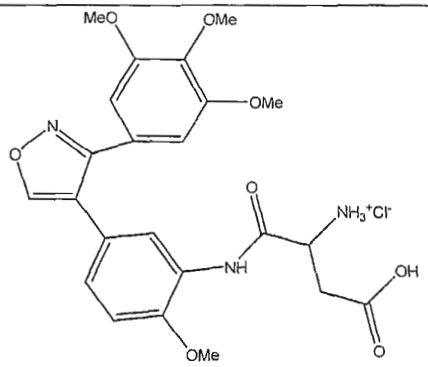
200		*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid
201		{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester
202		2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylcarbamate-PEG
203		3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyl carbamoyl)-methyl]-succinamic acid
204		2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide hydrochloride

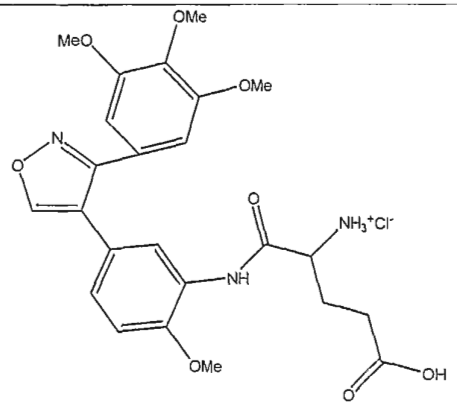
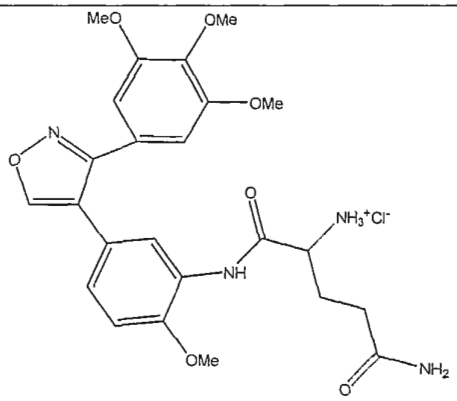
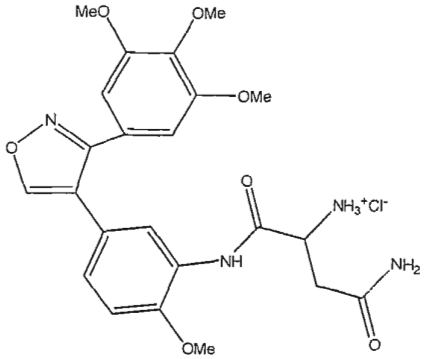
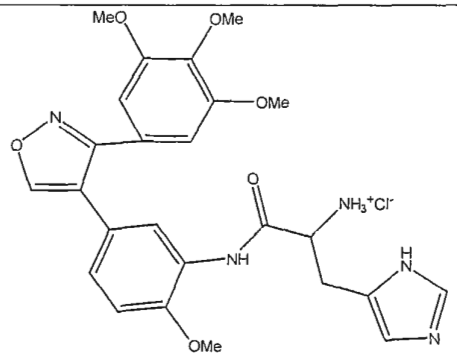
205		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride
206		2-amino-3-hydroxy-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride
207		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide

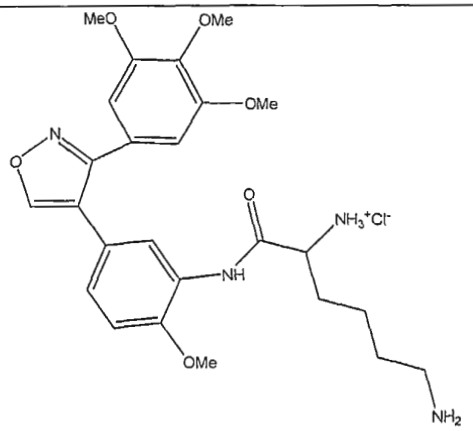
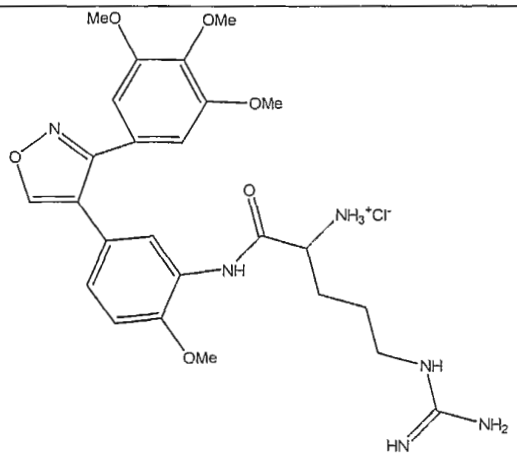
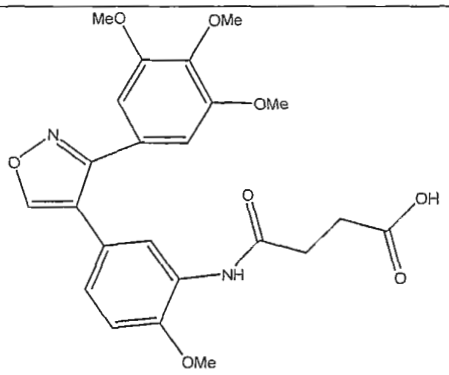
208		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride
209		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) butanamide
210		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenylpropanamide hydrochloride
211		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methylpentanamide hydrochloride

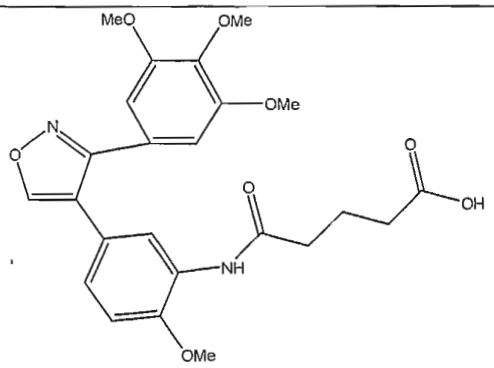
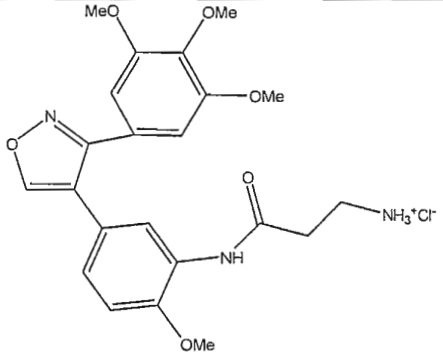
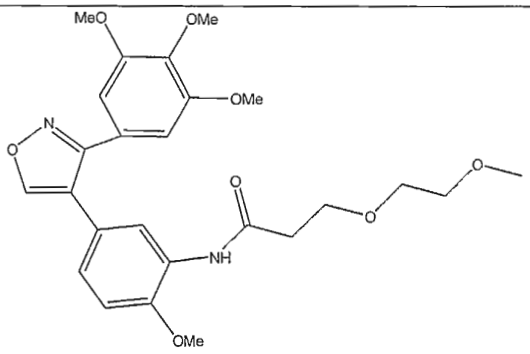
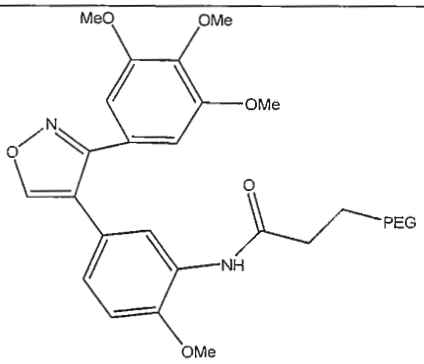
212		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride
213		2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl dihydrogen phosphate
214		Sodium 2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl phosphate
215		1-{2-methoxy-3-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride

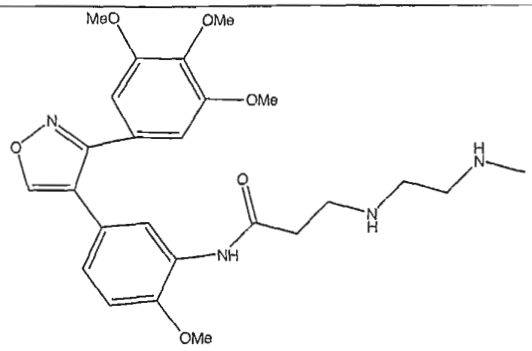
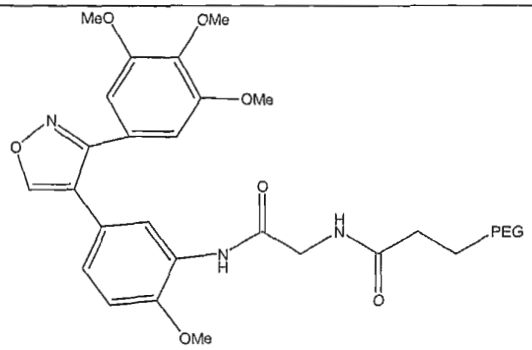
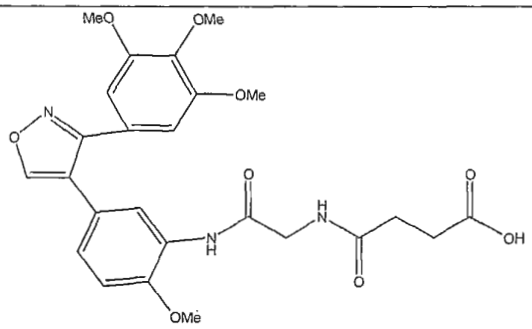
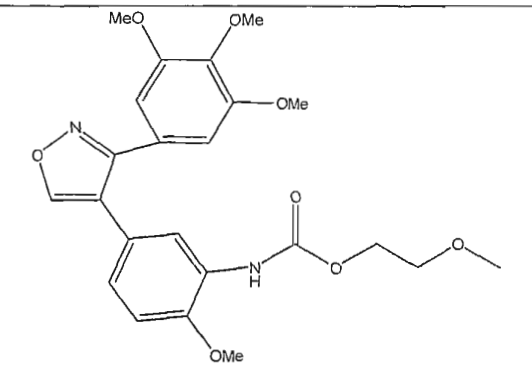
216		1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-butyl-ammonium chloride
217		2-hydroxy-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
218		2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
219		C-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride

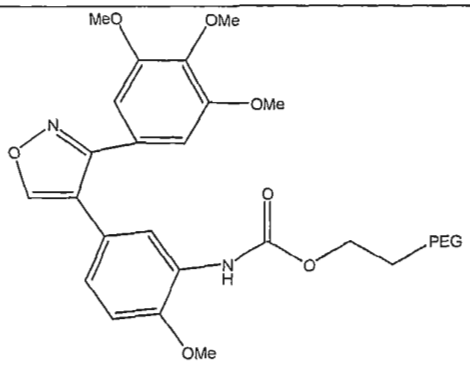
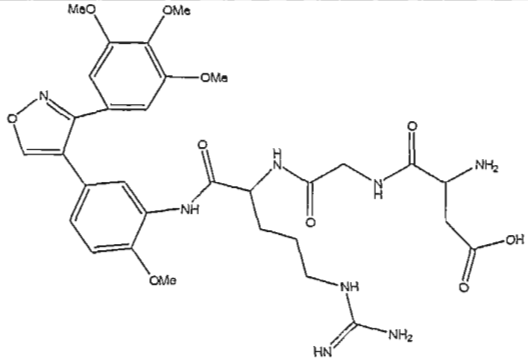
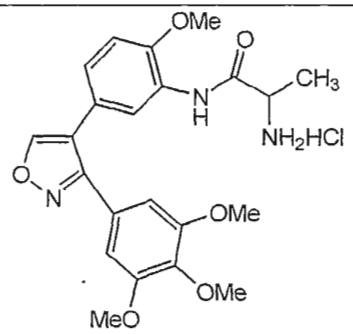
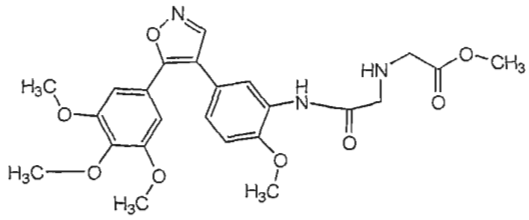
220		2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
221		2-benzofuran-2-yl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
222		2-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride

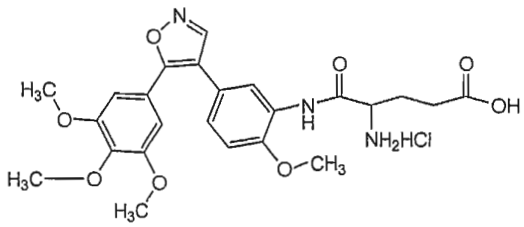
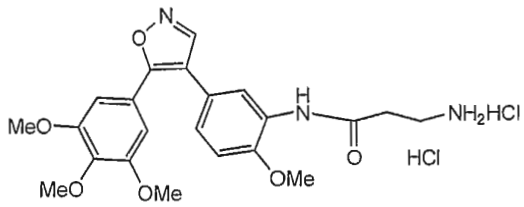
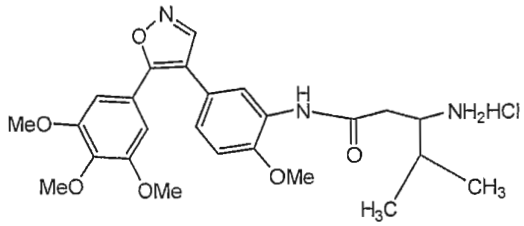
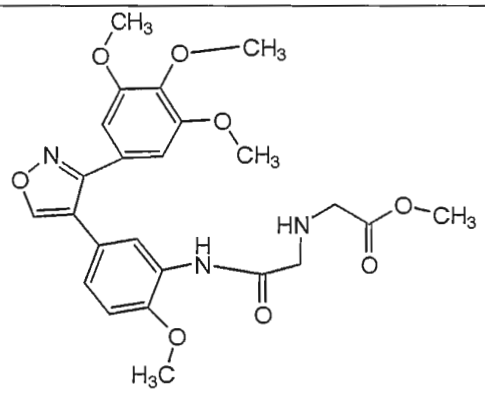
223		3-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
224		3-carbamoyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride
225		2-carbamoyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride
226		2-(3*H*-imidazol-4-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride

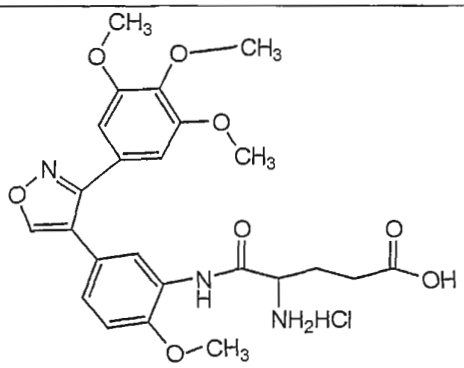
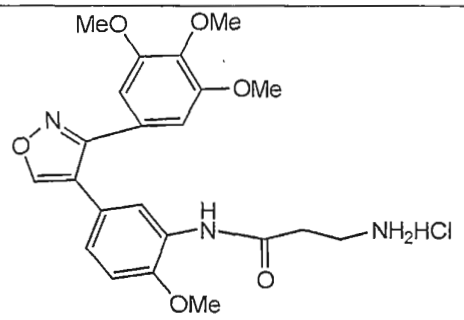
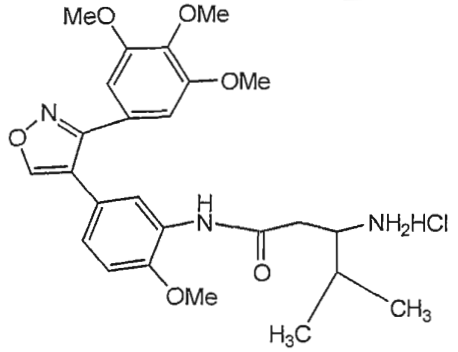
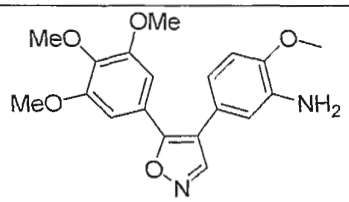
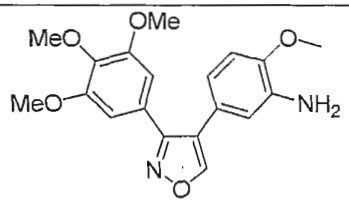
227		5-amino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride
228		4-guanidino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride
229		*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid

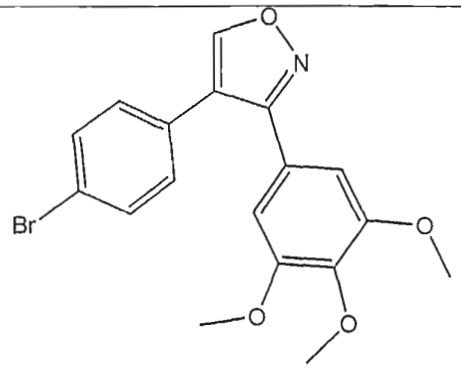
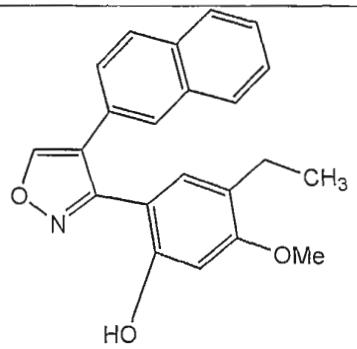
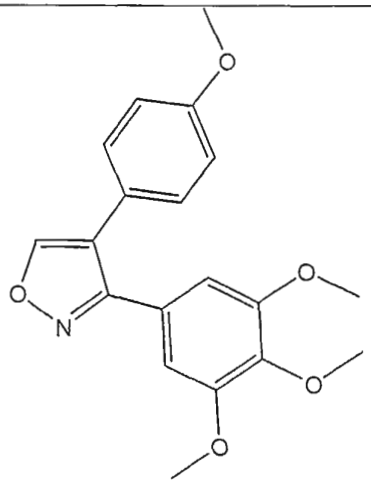
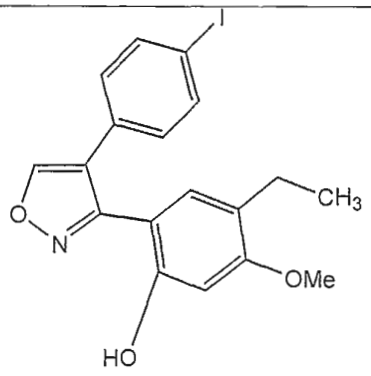
230		4-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid
231		2-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride
232		3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide
233		3-(2-PEG)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide

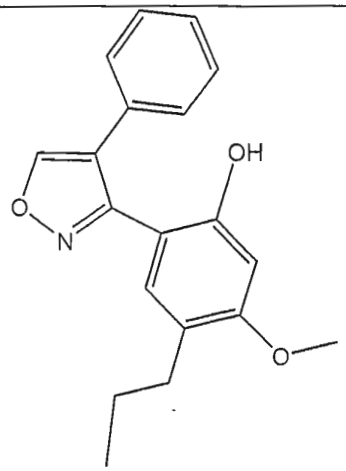
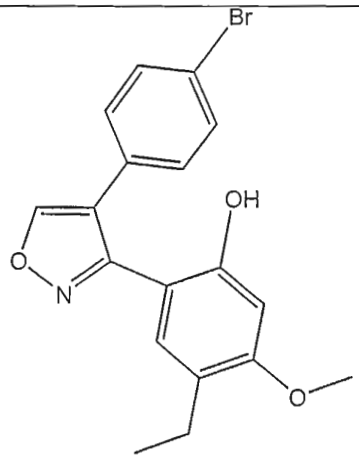
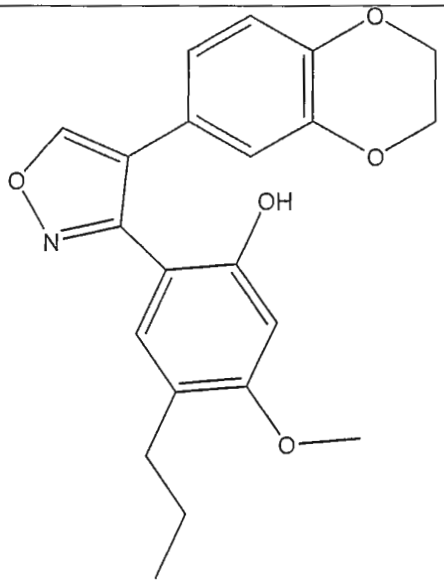
234		*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide
235		3-PEG-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide
236		*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid
237		{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester

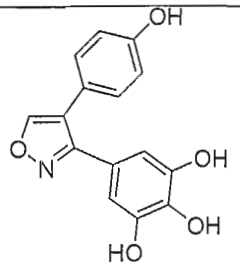
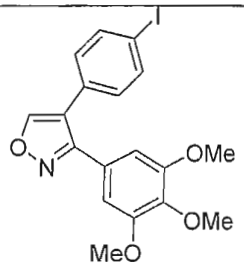
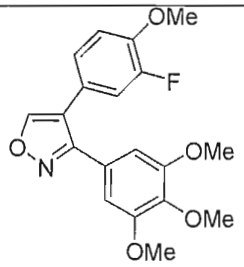
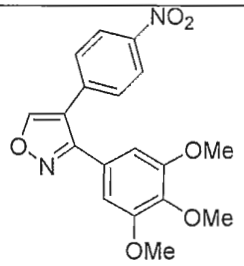
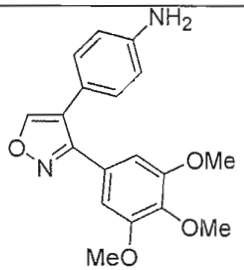
238		2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylcarbamate-PEG
239		3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyl carbamoyl)-methyl]-succinamic acid
240		2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide hydrochloride
241		methyl2-(2-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate

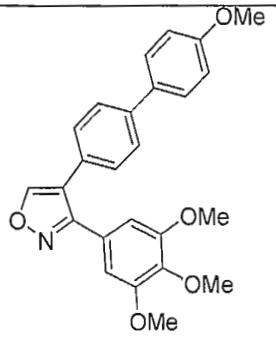
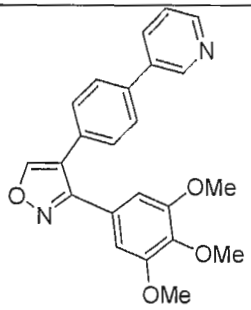
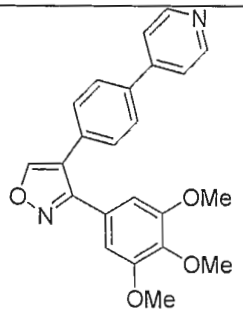
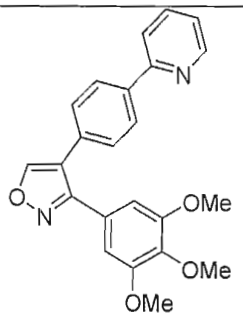
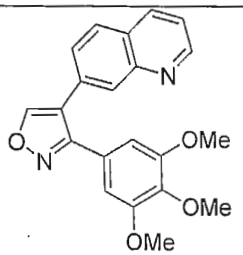
242		4-amino-5-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride
243		3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenyl) propanamide hydrochloride
244		3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride
245		methyl2-(2-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate

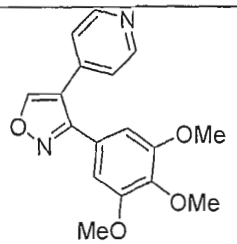
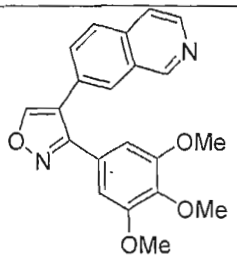
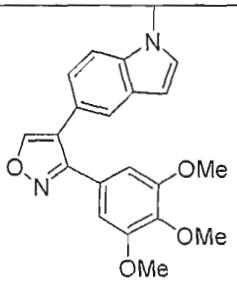
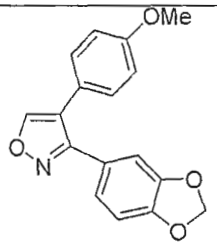
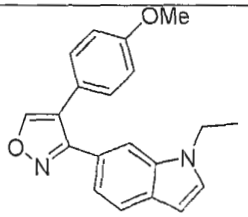
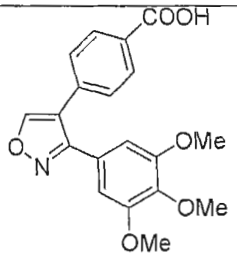
246		4-amino-5-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride
247		3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenyl) propanamide hydrochloride
248		3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl) isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride
249		2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline
250		2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline

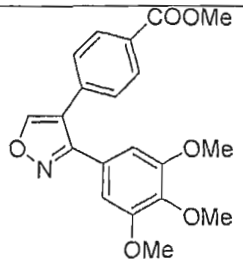
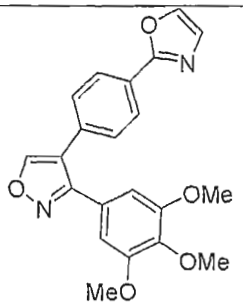
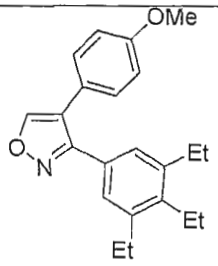
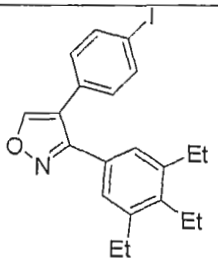
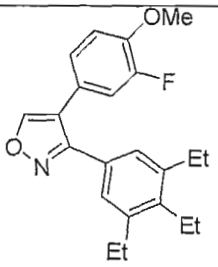
1b		4-(4-Bromo-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
2b		4-(Naphthalen-2-yl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
3b		4-(4-Methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
4b		4-(4-Iodo-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)- isoxazole

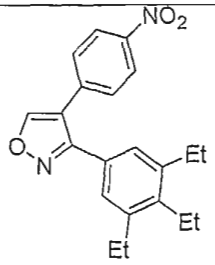
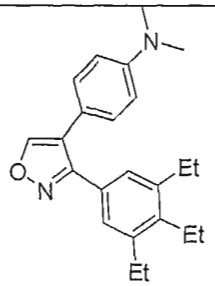
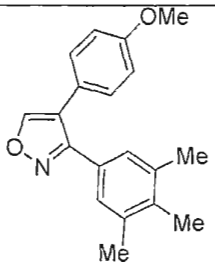
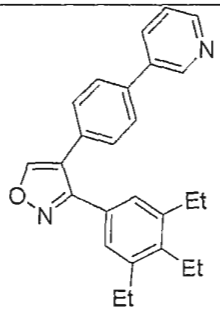
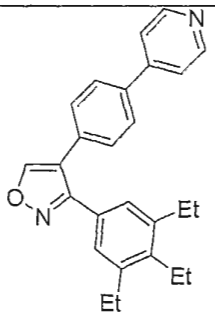
5b		4-Phenyl-3-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole
6b		4-(4-Bromo-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)- isoxazole
7b		4-(2,3-Dihydro-benzo[1,4]di-oxin-6-yl)-3-(2-hydroxy-4-methoxy-5-propyl-phenyl)-isoxazole

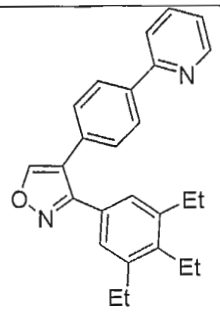
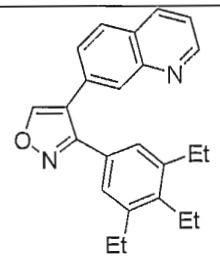
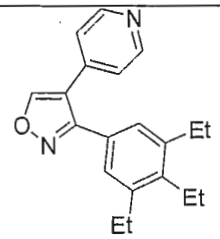
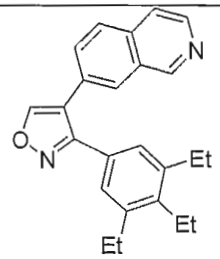
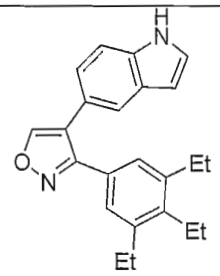
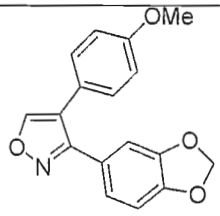
8b		4-(4-hydroxy-phenyl)-3-(3,4,5-trihydroxy-phenyl)-isoxazole
9b		4-(4-Iodo-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
10b		4-(3-Fluoro-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
11b		4-(4-Nitro-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
12b		4-(4-Amino-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

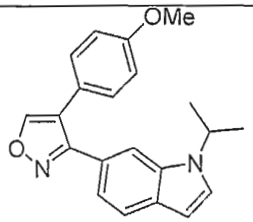
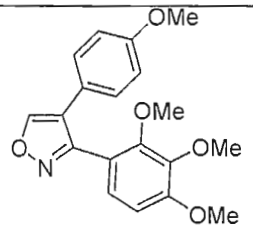
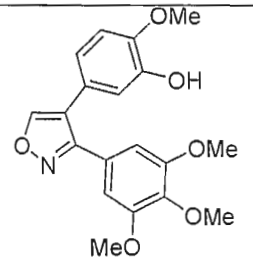
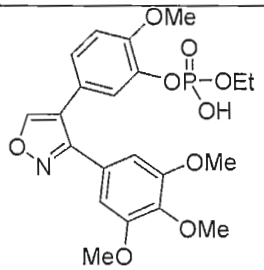
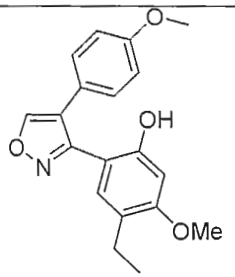
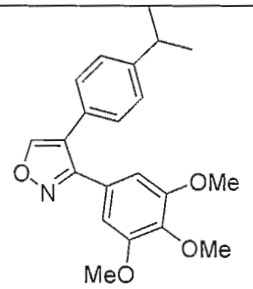
13b		4-(4'-Methoxy-biphenyl-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
14b		4-[4-(pyridine-3-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
15b		4-[4-(pyridine-4-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
16b		4-[4-(pyridine-2-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
17b		4-(Quinolin-7-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

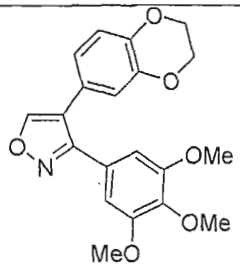
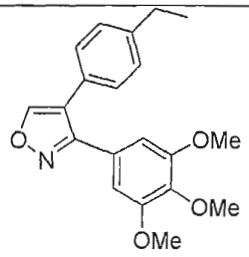
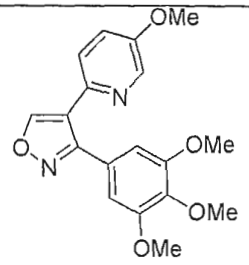
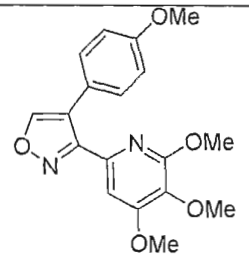
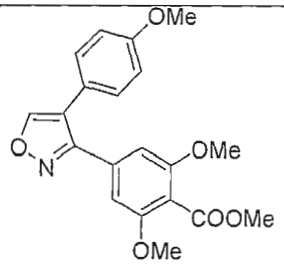
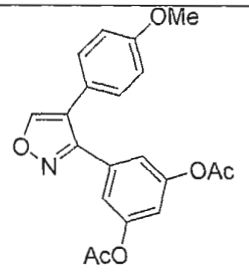
18b		4-(Pyridin-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
19b		4-(Isoquinolin-7-yl)-3 -(3,4,5-trimethoxy-phenyl)-isoxazole
20b		4-(1-Methyl-1*H*-indol-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
21b		4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-5-yl)-isoxazole
22b		4-(4-Methoxy-phenyl)-3-(1-ethyl-1*H*-indol-6-yl)-isoxazole
23b		4-(4-Carboxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

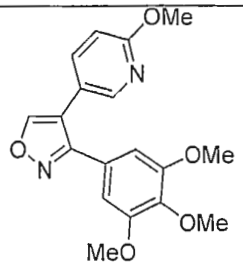
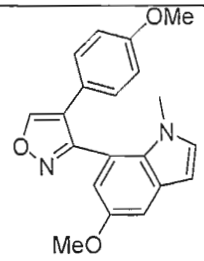
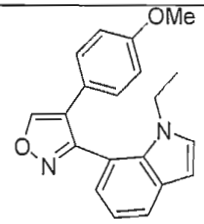
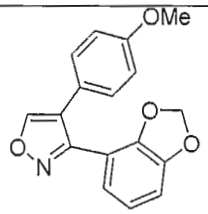
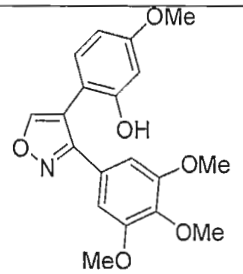
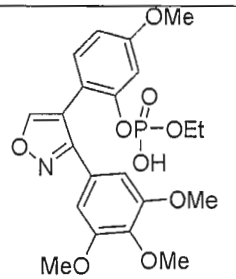
24b		4-(4-Methoxycarbonyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
25b		4-[4-(Oxazol-2-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
26b		4-(4-Methoxy-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole
27b		4-(4-Iodo-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole
28b		4-(3-Fluoro-4-methoxy-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole

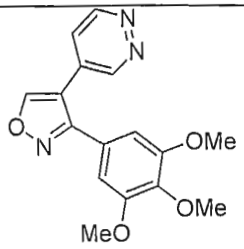
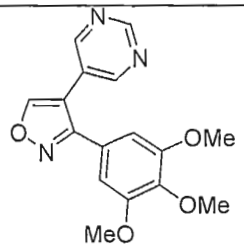
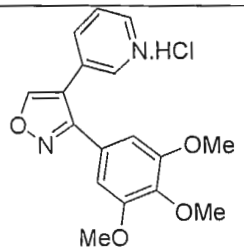
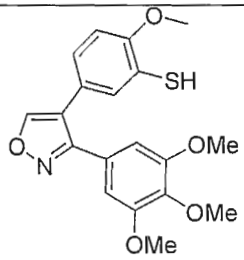
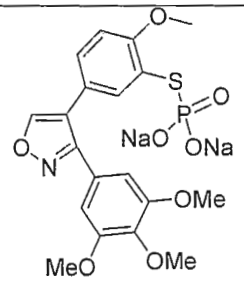
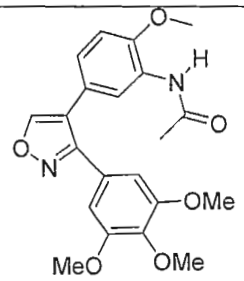
29b		4-(4-Nitro-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole
30b		4-(4-N,N-dimethylamino-phenyl)-3-(3,4,5-triethyl-phenyl)-isoxazole
31b		4-(4-Methoxy-phenyl)-3-(3,4,5-trimethyl-phenyl)-isoxazole
32b		4-[4-(Pyridin-3-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole
33b		4-[4-(Pyridin-4-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole

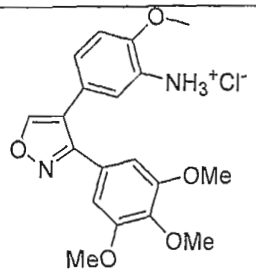
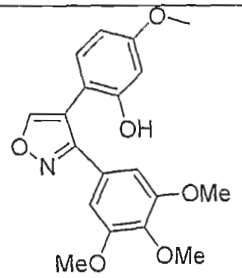
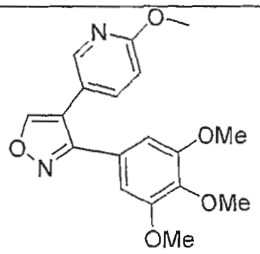
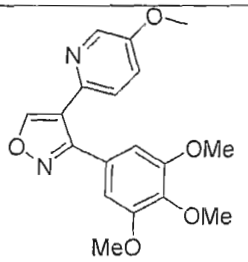
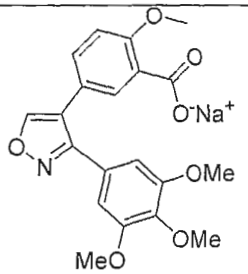
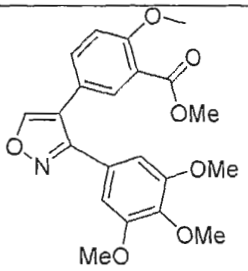
34b		4-[4-(Pyridin-2-yl)-phenyl]-3-(3,4,5-triethyl-phenyl)-isoxazole
35b		4-(Quinolin-7-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole
36b		4-(Pyridin-4-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole
37b		4-(Isoquinolin-7-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole
38b		4-(1*H*-Indol-5-yl)-3-(3,4,5-triethyl-phenyl)-isoxazole
39b		4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-5-yl)-isoxazole

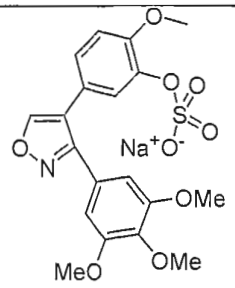
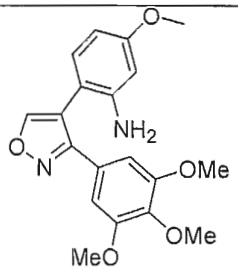
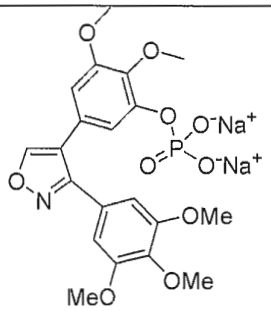
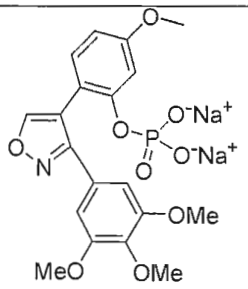
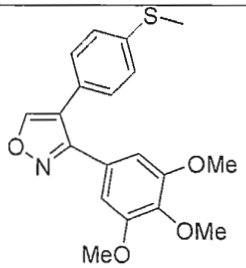
40b		4-(4-Methoxy-phenyl)-3-[1-isopropyl-1*H*-indol-6-yl)-isoxazole
41b		4-(4-Methoxy-phenyl)-3-(2,3,4-trimethoxy-phenyl)-isoxazole
42b		4-(3-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
43b		4-[3-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
44b		4-(4-Methoxy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole;
45b		4-(4-Isopropyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

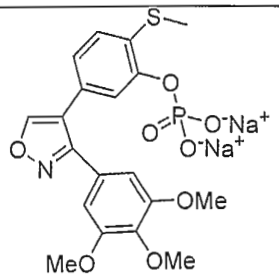
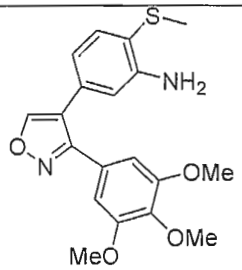
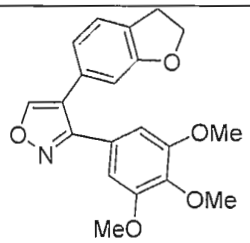
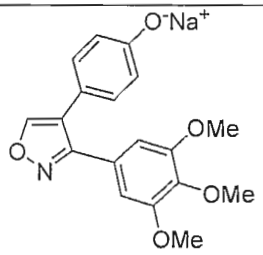
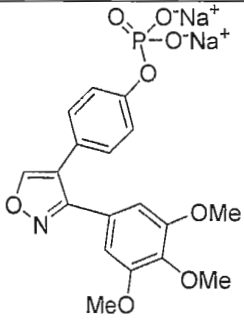
46b		4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
47b		4-(4-Ethyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
48b		4-(5-Methoxy-pyridin-2-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
49b		4-(4-Methoxy-phenyl)-3-(2,3,4-trimethoxy-pyridin-6-yl)-isoxazole
50b		4-(4-Methoxy-phenyl)-3-(3,5-dimethoxy-4-methoxycarbonyl-phenyl)-isoxazole
51b		4-(4-Methoxy-phenyl)-3-(3,5-diacetoxy-phenyl)-isoxazole

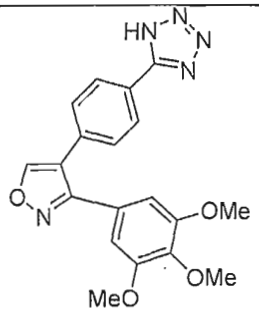
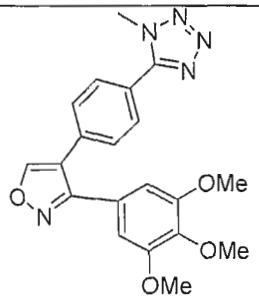
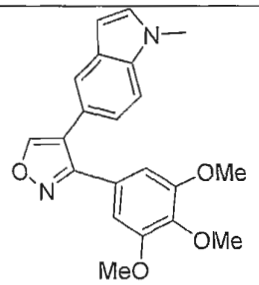
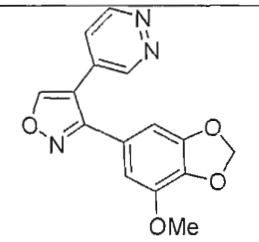
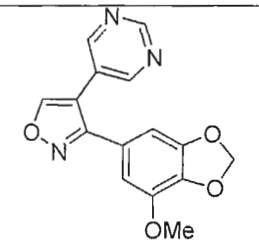
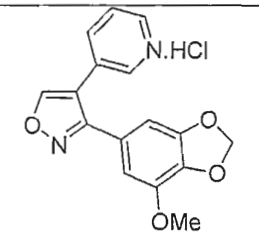
52b		4-(2-Methoxy-pyridin-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
53b		4-(4-Methoxy-phenyl)-3-(1-methyl-5-methoxy-1*H*-indol-7-yl)-isoxazole
54b		4-(4-Methoxy-phenyl)-3-(1-ethyl-1*H*-indol-7-yl)-isoxazole
55b		4-(4-Methoxy-phenyl)-3-(benzo[1,3]dioxol-4-yl)-isoxazole
56b		4-(2-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy)-isoxazole
57b		4-[2-(Ethyl-hydroxy-phosphoryloxy)-4-methoxy-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole

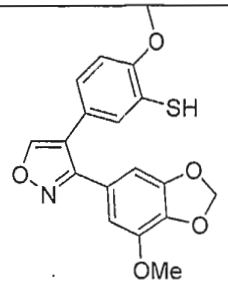
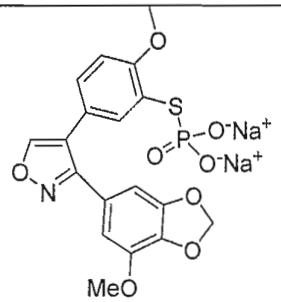
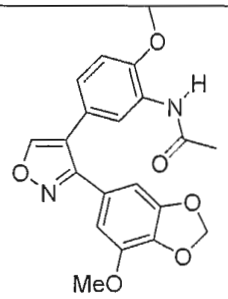
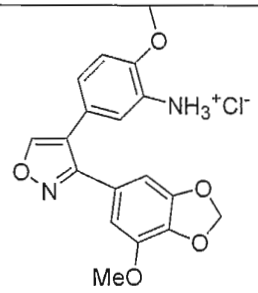
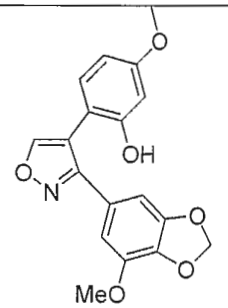
58b		4-(Pyridazin-4-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
59b		4-(Pyrimidin-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
60b		4-(Pyridin-3-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt
61b		4-(3-Mercapto-4-methoxy-phenyl)-3 -(3,4,5-trimethoxy-phenyl)-isoxazole
62b		4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
63b		4-(3-Acetylamino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

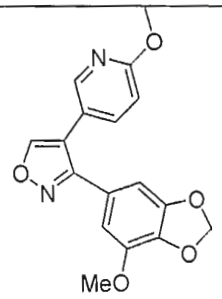
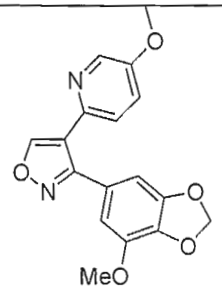
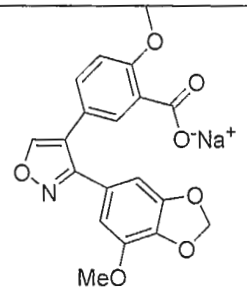
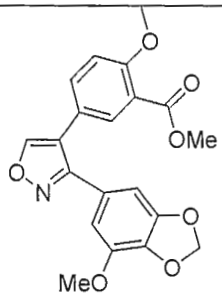
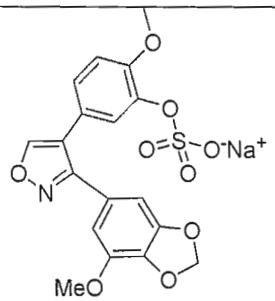
64b		4-(3-Amino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, hydrochloric acid salt
65b		4-(2-Hydroxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
66b		4-(2-Methoxy-pyridine-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
67b		4-(5-Methoxy-pyridine-2-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
68b		4-(3-Carboxy-4-methoxy-phenyl)-3 -(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt
69b		4-(3-Methoxycarbonyl-4-methoxy-phenyl)-3 -(3,4,5-trimethoxy-phenyl)-isoxazole

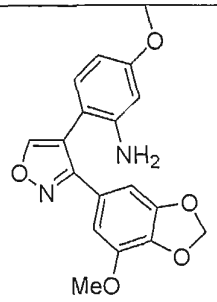
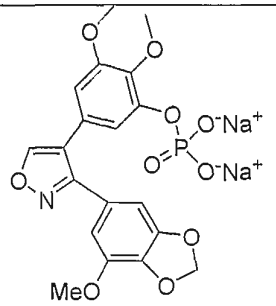
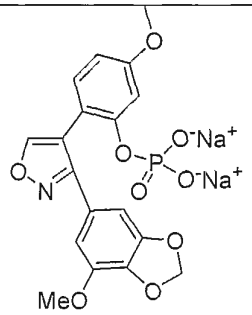
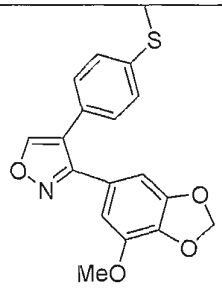
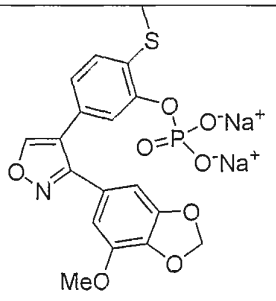
70b		4-(3-Sulfooxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt
71b		4-(2-Amino-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
72b		4-(3,4-Dimethoxy-5-phosphonooxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
73b		4-(2-Phosphonooxy-4-methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
74b		4-(4-Methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole

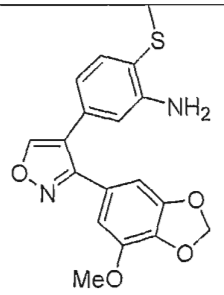
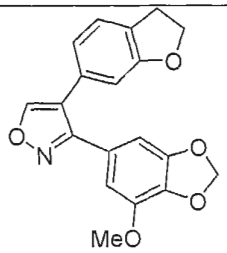
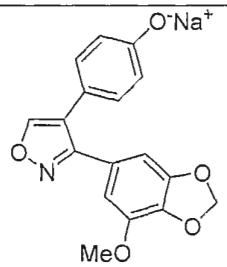
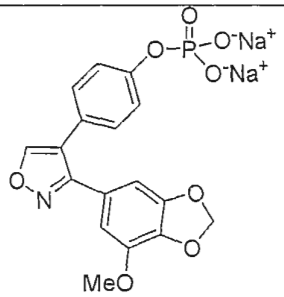
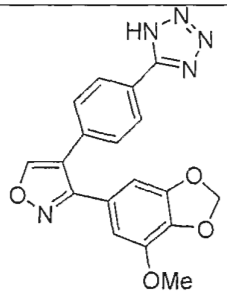
75b		4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt
76b		4-(3-Amino-4-methylsulfanyl-phenyl)-3-(3,4,5-trimethoxy-phenyl)- isoxazole
77b		4-(2,3-Dihydro-benzofuran-6-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
78b		4-(4-Hydroxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, sodium salt
79b		4-(4-Phosphonooxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole, disodium salt

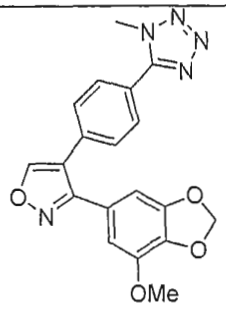
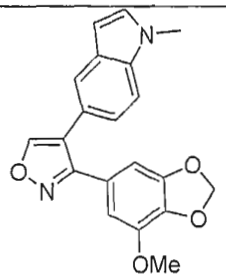
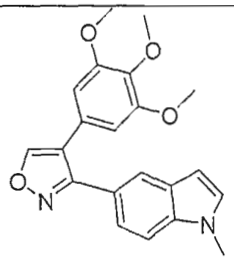
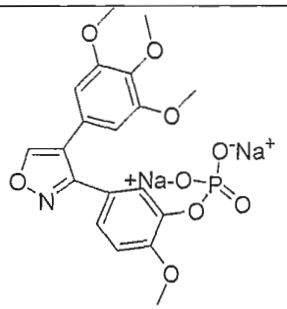
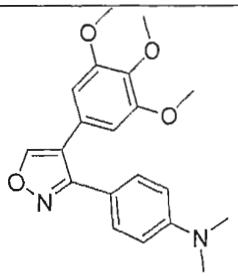
80b		4-(4-1*H*-Tetrazol-5-yl-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
81b		4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-3-(3,4,5-trimethoxy-phenyl)-isoxazole
82b		4-(1-Methyl-1*H*-indol-5-yl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
83b		4-(Pyridazin-4-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
84b		4-(Pyrimidin-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
85b		4-(Pyridin-3-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt

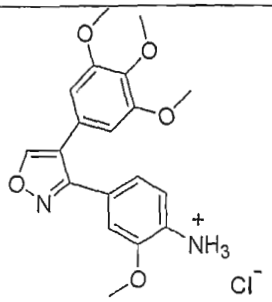
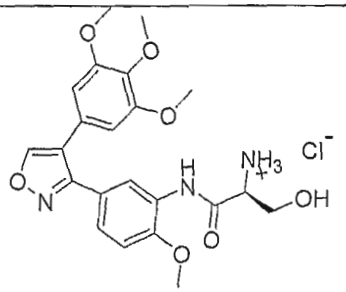
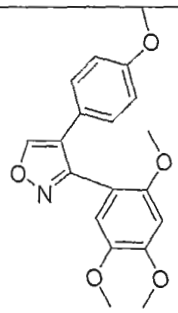
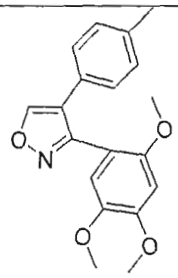
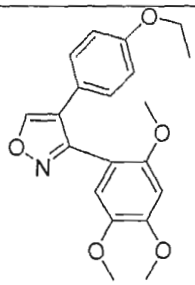
86b		4-(3-Mercapto-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
87b		4-(3-Phosphonosulfanyl-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
88b		4-(3-Acetylamino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
89b		4-(3-Amino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, hydrochloric acid salt
90b		4-(2-Hydroxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole

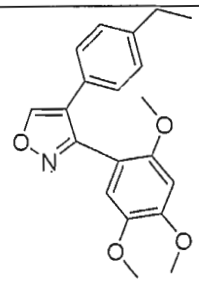
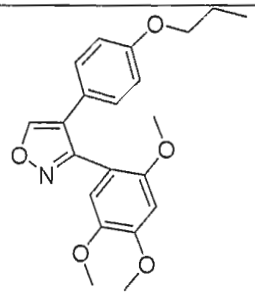
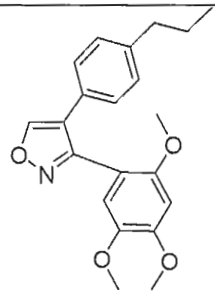
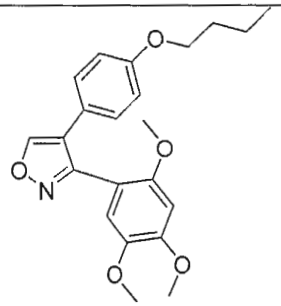
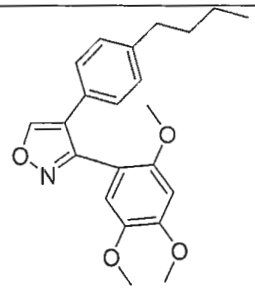
91b		4-(2-Methoxy-pyridin-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
92b		4-(5-Methoxy-pyridin-2-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
93b		4-(3-Carboxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt
94b		4-(3-Methoxycarbonyl-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
95b		4-(3-Sulfooxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt

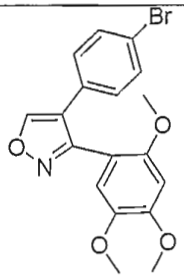
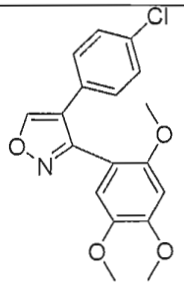
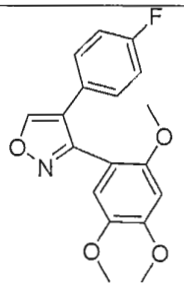
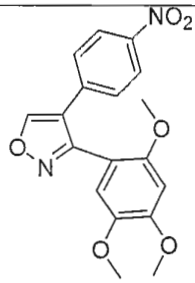
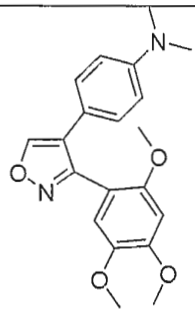
96b		4-(3-Amino-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
97b		4-(3,4-Dimethoxy-5 phosphonooxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt
98b		4-(2-Phosphonooxy-4-methoxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt
99b		4-(4-Methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
100b		4-(3-Phosphonooxy-4-methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, disodium salt

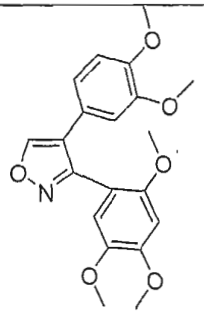
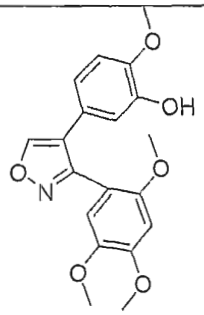
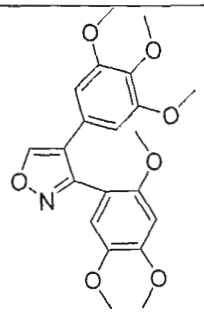
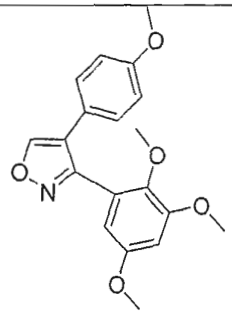
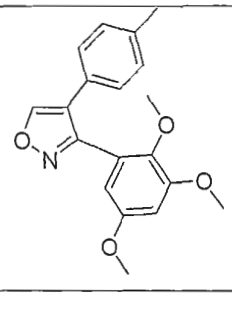
101b		4-(3-Amino-4-methylsulfanyl-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
102b		4-(2,3-Dihydro-benzofuran-6-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
103b		4-(4-Hydroxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole, sodium salt
104b		4-(4-Phosphonooxy-phenyl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
105b		4-(4-1*H*-Tetrazol-5-yl-phenyl) -3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole

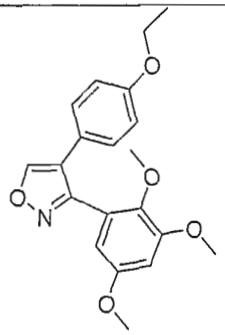
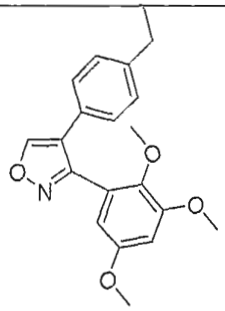
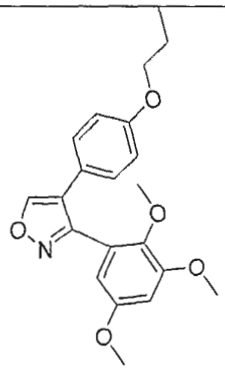
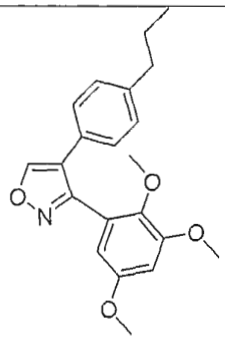
106b		4-[4-(1-Methyl-1*H*-tetrazol-5-yl)-phenyl]-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
107b		4-(1-Methyl-1*H*-indol-5-yl)-3-(4-methoxy-benzo[1,3]dioxol-6-yl)-isoxazole
108b		4-(3,4,5-Trimethoxy-phenyl)-3-(1-methyl-1*H*-indol-5-yl)-isoxazole
109b		4-(3,4,5-Trimethoxy-phenyl)-3-(3-phosphonooxy-4-methoxy-phenyl)-isoxazole, disodium salt
110b		4-(3,4,5-Trimethoxy-phenyl)-3-(N,N-dimethylamino-phenyl)-isoxazole

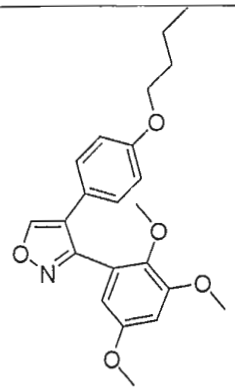
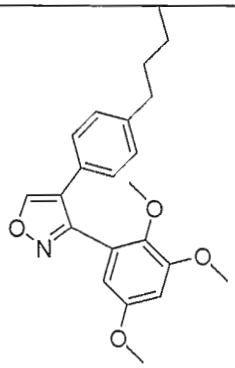
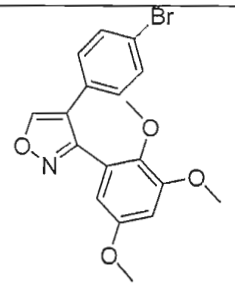
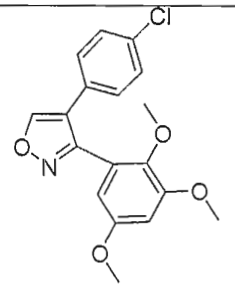
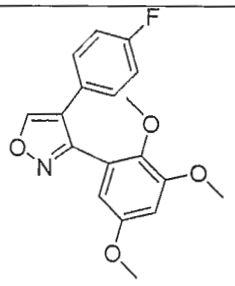
111b		4-(3,4,5-Trimethoxy-phenyl)-3-(3-amino-4-methoxy-phenyl)-isoxazole, hydrochloric acid salt
112b		4-(3,4,5-Trimethoxy-phenyl)-3-[3-(3-hydroxy-2S-amino-propionamido)-4-methoxy-phenyl]-isoxazole, hydrochloric acid salt
113b		4-(4-Methoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
114b		4-(4-Methyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
115b		4-(4-Ethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole

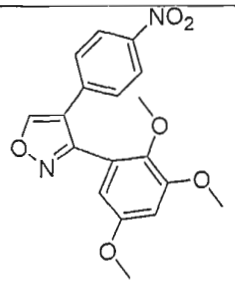
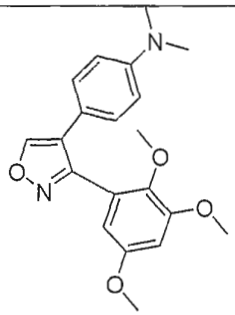
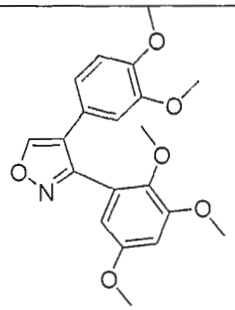
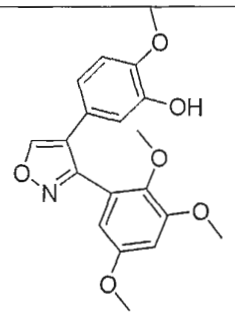
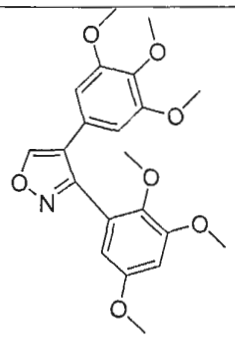
116b		4-(4-Ethyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
117b		4-(4-Propoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
118b		4-(4-Propyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
119b		4-(4-Butoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
120b		4-(4-Butyl-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole

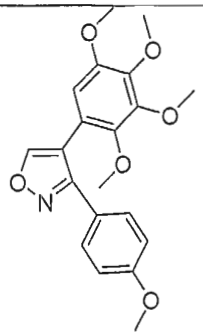
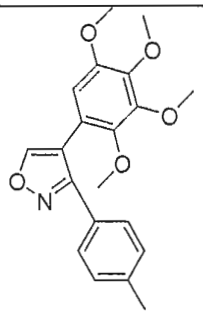
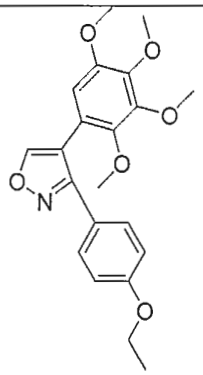
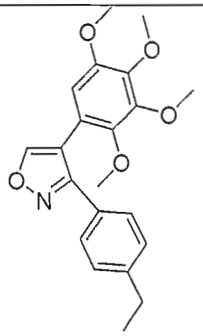
121b		4-(4-Bromo-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
122b		4-(4-Chloro-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
123b		4-(4-Fluoro-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
124b		4-(4-Nitro-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
125b		4-[4-(N,N-Dimethylamino)-phenyl]-3-(2,4,5-trimethoxy-phenyl)-isoxazole

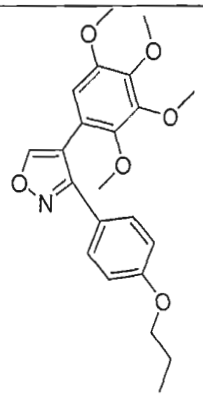
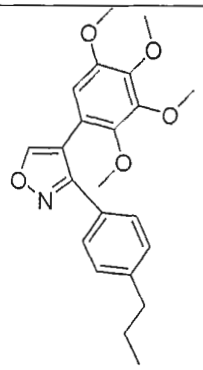
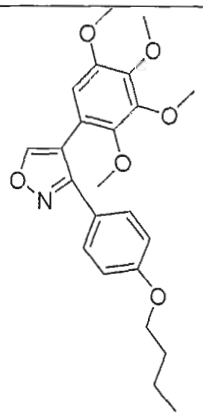
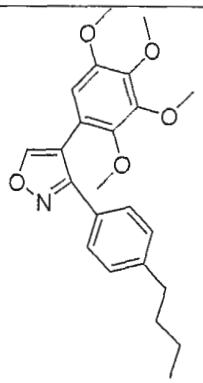
126b		4-(3,4-Dimethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
127b		4-(3-Hydroxy-4-methoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
128b		4-(3,4,5-Trimethoxy-phenyl)-3-(2,4,5-trimethoxy-phenyl)-isoxazole
129b		4-(4-Methoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
130b		4-(4-Methyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole

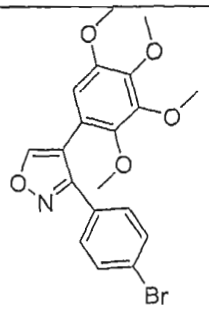
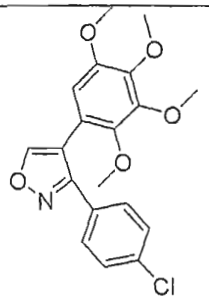
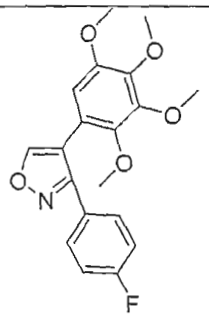
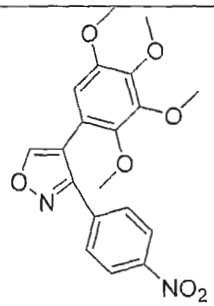
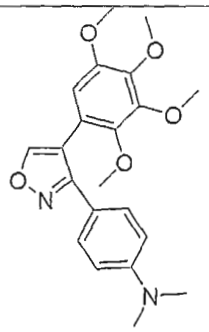
131b		4-(4-Ethoxy-phenyl)-3 -(2,3,5-trimethoxy-phenyl)-isoxazole
132b		4-(4-Ethyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
133b		4-(4-Propoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
134b		4-(4-Propyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole

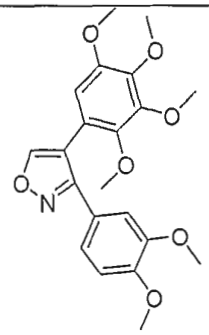
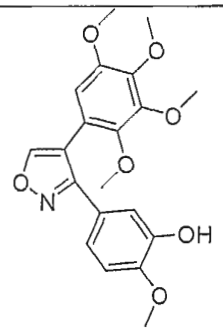
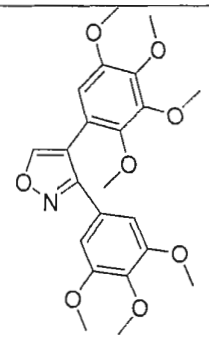
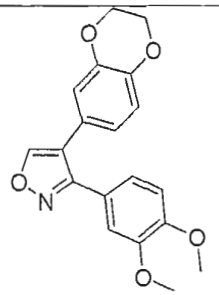
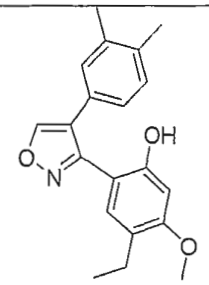
135b		4-(4-Butoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
136b		4-(4-Butyl-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
137b		4-(4-Bromo-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
138b		4-(4-Chloro-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
139b		4-(4-Fluoro-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole

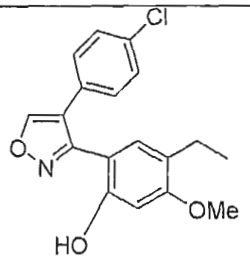
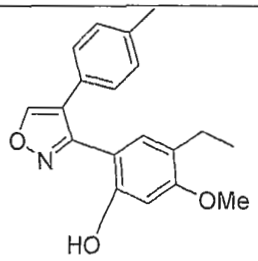
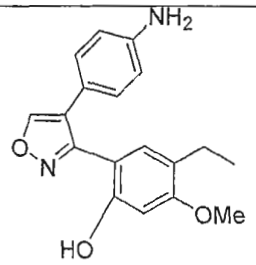
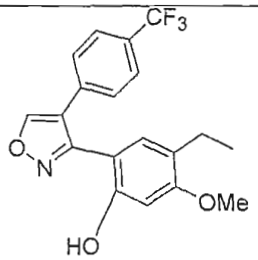
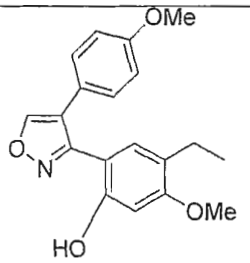
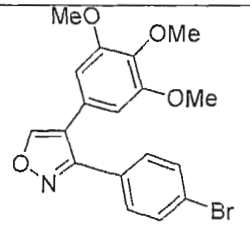
140b		4-(4-Nitro-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
141b		4-[4-(N,N-Dimethylamino)-phenyl]-3-(2,3,5-trimethoxy-phenyl)-isoxazole
142b		4-(3,4-Dimethoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
143b		4-(3-Hydroxy-4-methoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole
144b		4-(3,4,5-Trimethoxy-phenyl)-3-(2,3,5-trimethoxy-phenyl)-isoxazole

145b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-methoxy-phenyl)-isoxazole
146b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-methyl-phenyl)-isoxazole
147b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-ethoxy-phenyl)-isoxazole
148b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-ethyl-phenyl)-isoxazole

149b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-propoxy-phenyl)-isoxazole
150b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-propyl-phenyl)-isoxazole
151b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-butoxy-phenyl)-isoxazole
152b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-butyl-phenyl)-isoxazole

153b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-bromo-phenyl)-isoxazole
154b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-chloro-phenyl)-isoxazole
155b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-fluoro-phenyl)-isoxazole
156b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(4-nitro-phenyl)-isoxazole
157b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-[4-(N,N,-dimethylamino)-phenyl]-isoxazole

158b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3,4-dimethoxy-phenyl)-isoxazole
159b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3-hydroxy-4-methoxy-phenyl)-isoxazole
160b		4-(2,3,4,5-Tetramethoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole
161b		4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-3-(3,4-dimethoxy-phenyl)-isoxazole
162b		4-(3,4-Dimethy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

163b		4-(4-Chloro-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
164b		4-(4-Methyl-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
165b		4-(4-Amino-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
166b		4-(4-Trifluoromethyl-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
167b		4-(4-Methoxy-phenyl)-3-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole
168b		4-(3,4,5-Trimethoxy-phenyl)-3-(4-bromo-phenyl)-isoxazole

METHODS OF MAKING THE COMPOUNDS OF THE INVENTION

The compounds of the invention can be made by the methods described herein in Example 1. In addition, the compounds of the invention can be prepared using the methods described in Olivera, *et al.*, *J. Org. Chem.* (2000), *65*:6398-6411; Olivera, *et al.*, *Tetrahedron* (2002), *58*:3021-3037; Dominguez, *et al.*, *J. Org. Chem.* (1996), *61*:5435-5439; Olivera, *et al.*, *Tet. Let.* (1999), *40*:3479-3480; Khilya, *et al. Ukrainskii Khimicheskii Zhurnal* (Russian Edition) (1990), *56*(3);280-286. The entire teachings of these references are incorporated herein by reference.

METHODS OF TREATMENT AND PREVENTION

In one embodiment, the invention provides a method of inhibiting tubulin polymerization in a cell, comprising contacting the cell with an effective amount of a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, or a pharmaceutical composition comprising a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof. Inhibition of tubulin polymerization can be determined by determining the IC_{50} for tubulin polymerization inhibition for a compound as described above, or by using the methods described in Examples 7 and 8, herein.

In another embodiment, the invention provides a method of treating a proliferative disorder, such as cancer, in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, or a pharmaceutical composition comprising a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof. Such patients may be treatment naïve or may experience partial or no response to conventional therapies.

In another embodiment, the invention provides a method of blocking, occluding, or otherwise disrupting blood flow in neovasculature, in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any

one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, or a pharmaceutical composition comprising a compound of any one of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof.

Responsiveness to treatment with the compounds of the invention in the case of proliferative disorders can be measured by reduction in the extent or severity of the symptoms associated with the disease or disorder and/or an increase in the longevity and/or quality of life of the subject compared with the absence of the treatment. Responsiveness to treatment with the compounds of the invention in the case of cancer, can be measured by a reduction in tumor mass, a reduction in the rate of tumor growth, a reduction in metastasis, a reduction in the severity of the symptoms associated with the cancer and/or an increase in the longevity of the subject compared with the absence of the treatment.

COMBINATION THERAPIES

The invention also provides methods of preventing, treating, managing, or ameliorating a proliferative disorder, such as cancer, or one or more symptoms thereof, said methods comprising administering to a subject in need thereof one or more compounds of the invention and one or more other therapies (*e.g.*, one or more prophylactic or therapeutic agents that are currently being used, have been used, are known to be useful or in development for use in the prevention, treatment or amelioration of a proliferative disorder, such as cancer, or one or more symptoms associated with said proliferative disorder).

The prophylactic or therapeutic agents of the combination therapies of the invention can be administered sequentially or concurrently. In a specific embodiment, the combination therapies of the invention comprise one or more compounds and at least one other therapy (*e.g.*, another prophylactic or therapeutic agent) which has the same mechanism of action as said compounds (*e.g.*, a therapeutic agent that inhibits tubulin polymerization). In another specific embodiment, the combination therapies of the invention comprise one or more compounds of the invention and at

least one other therapy (*e.g.*, another prophylactic or therapeutic agent) which has a different mechanism of action than said compounds. In certain embodiments, the combination therapies of the present invention improve the prophylactic or therapeutic effect of one or more compounds of the invention by functioning together with the compounds to have an additive or synergistic effect. In certain embodiments, the combination therapies of the present invention reduce the side effects associated with the therapies (*e.g.*, prophylactic or therapeutic agents). In certain embodiments, the combination therapies of the present invention reduce the effective dosage of one or more of the therapies.

The prophylactic or therapeutic agents of the combination therapies can be administered to a subject, preferably a human subject, in the same pharmaceutical composition. In alternative embodiments, the prophylactic or therapeutic agents of the combination therapies can be administered concurrently to a subject in separate pharmaceutical compositions. The prophylactic or therapeutic agents may be administered to a subject by the same or different routes of administration.

In a specific embodiment, a pharmaceutical composition comprising one or more compounds of the invention is administered to a subject, preferably a human, to prevent, treat, manage, or ameliorate a proliferative disorder, such as cancer, or one or more symptoms thereof. In accordance with the invention, pharmaceutical compositions of the invention may also comprise one or more other agents (*e.g.*, prophylactic or therapeutic agents which are currently being used, have been used, or are known to be useful in the prevention, treatment or amelioration of a proliferative disorder or a symptom thereof).

The invention provides methods for preventing, managing, treating or ameliorating a proliferative disorder, such as cancer, or one or more symptoms thereof in a subject refractory (either completely or partially) to existing agent therapies for such a proliferative disorder, said methods comprising administering to said subject a dose of an effective amount of one or more compounds of the invention and a dose of an effective amount of one or more therapies (*e.g.*, one or more prophylactic or therapeutic agents useful for the prevention, treatment, management, or amelioration

of a proliferative disorder or a symptom thereof). The invention also provides methods for preventing, treating, managing, or ameliorating a proliferative disorder or a symptom thereof by administering one or more compounds of the invention in combination with any other therapy(ies) to patients who have proven refractory to other therapies but are no longer on these therapies.

The compounds of the invention and/or other therapies can be administered to a subject by any route known to one of skill in the art. Examples of routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), intranasal, transdermal (topical), transmucosal, and rectal administration.

Agents Useful In Combination With Compounds of the Invention

Anticancer agents that can be co-administered with the compounds of the invention include Taxol™, also referred to as "paclitaxel", which is a well-known anti-cancer drug which acts by enhancing and stabilizing microtubule formation, and analogs of Taxol™, such as Taxotere™. Compounds that have the basic taxane skeleton as a common structure feature, have also been shown to have the ability to arrest cells in the G2-M phases due to stabilized microtubules and may be useful for treating cancer in combination with the compounds of the invention.

Other anti-cancer agents that can be employed in combination with the compounds of the invention include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate;

dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

Other anti-cancer drugs that can be employed in combination with the compounds of the invention include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone;

aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene;

idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine

phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred anti-cancer drugs are 5-fluorouracil and leucovorin.

Other chemotherapeutic agents that can be employed in combination with the compounds of the invention include but are not limited to alkylating agents, antimetabolites, natural products, or hormones. Examples of alkylating agents useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to, nitrogen mustards (*e.g.*, mechloroethamine, cyclophosphamide, chlorambucil, *etc.*), alkyl sulfonates (*e.g.*,

busulfan), nitrosoureas (*e.g.*, carmustine, lomusitne, *etc.*), or triazenes (decarbazine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, Cytarabine), purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin). Examples of natural products useful for the treatment or prevention of T-cell malignancies in the methods and compositions of the invention include but are not limited to vinca alkaloids (*e.g.*, vinblastin, vincristine), epipodophyllotoxins (*e.g.*, etoposide), antibiotics (*e.g.*, daunorubicin, doxorubicin, bleomycin), enzymes (*e.g.*, L-asparaginase), or biological response modifiers (*e.g.*, interferon alpha).

Examples of alkylating agents that can be employed in combination with the compounds of the invention include but are not limited to, nitrogen mustards (*e.g.*, mechloroethamine, cyclophosphamide, chlorambucil, melphalan, *etc.*), ethylenimine and methylmelamines (*e.g.*, hexamethlymelamine, thiotepa), alkyl sulfonates (*e.g.*, busulfan), nitrosoureas (*e.g.*, carmustine, lomusitne, semustine, streptozocin, *etc.*), or triazenes (decarbazine, *etc.*). Examples of antimetabolites useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to folic acid analog (*e.g.*, methotrexate), or pyrimidine analogs (*e.g.*, fluorouracil, floxouridine, Cytarabine), purine analogs (*e.g.*, mercaptopurine, thioguanine, pentostatin). Examples of natural products useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to vinca alkaloids (*e.g.*, vinblastin, vincristine), epipodophyllotoxins (*e.g.*, etoposide, teniposide), antibiotics (*e.g.*, actinomycin D, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin), enzymes (*e.g.*, L-asparaginase), or biological response modifiers (*e.g.*, interferon alpha). Examples of hormones and antagonists useful for the treatment or prevention of cancer in the methods and compositions of the invention include but are not limited to adrenocorticosteroids (*e.g.*, prednisone), progestins (*e.g.*, hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (*e.g.*, diethlystilbestrol, ethinyl estradiol), antiestrogen (*e.g.*, tamoxifen), androgens (*e.g.*, testosterone propionate, fluoxymesterone), antiandrogen (*e.g.*, flutamide), gonadotropin releasing hormone analog (*e.g.*, leuprolide). Other agents that can be

used in the methods and compositions of the invention for the treatment or prevention of cancer include platinum coordination complexes (*e.g.*, cisplatin, carboblatin), anthracenedione (*e.g.*, mitoxantrone), substituted urea (*e.g.*, hydroxyurea), methyl hydrazine derivative (*e.g.*, procarbazine), adrenocortical suppressant (*e.g.*, mitotane, aminoglutethimide).

Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules and which can be used in combination with the compounds of the invention include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known

as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-0Y-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

PHARMACEUTICAL COMPOSITIONS

The present invention provides compositions for the treatment, prophylaxis, and amelioration of proliferative disorders, such as cancer. In a specific embodiment, a composition comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof. In another embodiment, a composition of the invention comprises one or more prophylactic or therapeutic agents other than a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, prodrug thereof. In another embodiment, a composition of the invention comprises one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate or prodrug thereof, and one or more other prophylactic or therapeutic agents.

In another embodiment, the composition comprises a compound of the invention, or a pharmaceutically acceptable salt, solvate, clathrate, hydrate, or prodrug thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

In a preferred embodiment, a composition of the invention is a pharmaceutical composition or a single unit dosage form. Pharmaceutical compositions and dosage forms of the invention comprise one or more active ingredients in relative amounts and formulated in such a way that a given pharmaceutical composition or dosage form can be used to treat or prevent proliferative disorders, such as cancer. Preferred pharmaceutical compositions and dosage forms comprise a compound of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable prodrug, salt, solvate, clathrate, hydrate, or prodrug thereof, optionally in combination with one or more additional active agents.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include, but are not limited to, parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), intranasal, transdermal (topical), transmucosal, and rectal administration. In a specific embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal or topical administration to human beings. In a preferred embodiment, a pharmaceutical composition is formulated in accordance with routine procedures for subcutaneous administration to human beings.

Single unit dosage forms of the invention are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid

dosage forms suitable for parenteral administration to a patient; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form suitable for mucosal administration may contain a smaller amount of active ingredient(s) than an oral dosage form used to treat the same indication. This aspect of the invention will be readily apparent to those skilled in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms.

The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients can be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines (*e.g.*, N-desmethylvenlafaxine and N,N-didesmethylvenlafaxine) are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the U.S. Pharmocopia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage

forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. *See*, *e.g.*, Jens T. Carstensen (1995) Drug Stability: Principles & Practice, 2d. Ed., Marcel Dekker, NY, NY, 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizer" include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally*, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (*e.g.*, Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. One specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103J and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation,

and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Controlled Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a

combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

A particular extended release formulation of this invention comprises a therapeutically or prophylactically effective amount of a compound of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, in spheroids which further comprise microcrystalline cellulose and, optionally, hydroxypropylmethyl-cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Such extended release formulations can be prepared according to U.S. Patent No. 6,274,171, the entirely of which is incorporated herein by reference.

A specific controlled-release formulation of this invention comprises from about 6% to about 40% a compound of formulas (I) through (X), (IA) through (XA), (IB) through (XB), or of Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, clathrate, or prodrug thereof, by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

Transdermal, Topical, and Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels,

solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA and Introduction to Pharmaceutical Dosage Forms (1985) 4th ed., Lea & Febiger, Philadelphia. Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. *See, e.g.*, Remington's Pharmaceutical Sciences (1980 & 1990) 16th and 18th eds., Mack Publishing, Easton PA.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Dosage & Frequency of Administration

The amount of the compound or composition of the invention which will be effective in the prevention, treatment, management, or amelioration of a proliferative disorders, such as cancer, or one or more symptoms thereof, will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dosage will also vary according to factors specific for each patient depending on the specific therapy (*e.g.*, therapeutic or prophylactic agents) administered, the severity of the disorder, disease, or condition, the route of administration, as well as age, body, weight, response, and the past medical history of the patient. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Suitable regiments can be selected by one skilled in the art by considering such factors and by following, for example, dosages reported in the literature and recommended in the *Physician's Desk Reference* (57th ed., 2003).

Exemplary doses of a small molecule include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram).

In general, the recommended daily dose range of a compound of the invention for the conditions described herein lie within the range of from about 0.01 mg to about 1000 mg per day, given as a single once-a-day dose or preferably as divided doses throughout a day. In one embodiment, the daily dose is administered twice daily in equally divided doses. Specifically, a daily dose range should be from about 5 mg to about 500 mg per day, more specifically, between about 10 mg and about 200 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response. It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

Different therapeutically effective amounts may be applicable for different proliferative disorders, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to prevent, manage, treat or ameliorate such proliferative disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with the compounds of the invention are also encompassed by the above described dosage amounts and dose frequency schedules. Further, when a patient is administered multiple dosages of a compound of the invention, not all of the dosages need be the same. For example, the dosage administered to the patient may be increased to improve the prophylactic or therapeutic effect of the compound or it may be decreased to reduce one or more side effects that a particular patient is experiencing.

In a specific embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or ameliorate a proliferative disorders, such as cancer, or one or more symptoms thereof in a patient is 150 µg/kg, preferably 250 µg/kg, 500 µg/kg, 1 mg/kg, 5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg, 75 mg/kg, 100 mg/kg, 125 mg/kg, 150 mg/kg, or 200 mg/kg or more of a patient's body weight. In another embodiment, the dosage of the composition of the invention or a compound of the invention administered to prevent, treat, manage, or

ameliorate a proliferative disorders, such as cancer, or one or more symptoms thereof in a patient is a unit dose of 0.1 mg to 20 mg, 0.1 mg to 15 mg, 0.1 mg to 12 mg, 0.1 mg to 10 mg, 0.1 mg to 8 mg, 0.1 mg to 7 mg, 0.1 mg to 5 mg, 0.1 to 2.5 mg, 0.25 mg to 20 mg, 0.25 to 15 mg, 0.25 to 12 mg, 0.25 to 10 mg, 0.25 to 8 mg, 0.25 mg to 7m g, 0.25 mg to 5 mg, 0.5 mg to 2.5 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 12 mg, 1 mg to 10 mg, 1 mg to 8 mg, 1 mg to 7 mg, 1 mg to 5 mg, or 1 mg to 2.5 mg.

The dosages of prophylactic or therapeutic agents other than compounds of the invention, which have been or are currently being used to prevent, treat, manage, or proliferative disorders, such as cancer, or one or more symptoms thereof can be used in the combination therapies of the invention. Preferably, dosages lower than those which have been or are currently being used to prevent, treat, manage, or ameliorate a proliferative disorders, or one or more symptoms thereof, are used in the combination therapies of the invention. The recommended dosages of agents currently used for the prevention, treatment, management, or amelioration of a proliferative disorders, such as cancer, or one or more symptoms thereof, can obtained from any reference in the art including, but not limited to, Hardman *et al.*, eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ, which are incorporated herein by reference in its entirety.

In certain embodiments, when the compounds of the invention are administered in combination with another therapy, the therapies (*e.g.*, prophylactic or therapeutic agents) are administered less than 5 minutes apart, less than 30 minutes apart, 1 hour apart, at about 1 hour apart, at about 1 to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, at about 12 hours to 18 hours apart, 18 hours to 24 hours apart, 24 hours to 36 hours apart, 36 hours to 48 hours apart, 48 hours to 52 hours apart, 52 hours to 60 hours apart, 60 hours to 72 hours apart, 72 hours to 84 hours apart, 84 hours to 96 hours apart, or 96 hours to 120 hours part. In

one embodiment, two or more therapies (*e.g.*, prophylactic or therapeutic agents) are administered within the same patient visit.

In certain embodiments, one or more compounds of the invention and one or more other the therapies (*e.g.*, prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agents) for a period of time, followed by the administration of a third therapy (*e.g.*, a third prophylactic or therapeutic agents) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

In certain embodiments, administration of the same compound of the invention may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months. In other embodiments, administration of the same prophylactic or therapeutic agent may be repeated and the administration may be separated by at least at least 1 day, 2 days, 3 days, 5 days, 10 days, 15 days, 30 days, 45 days, 2 months, 75 days, 3 months, or 6 months.

In a specific embodiment, the invention provides a method of preventing, treating, managing, or ameliorating a proliferative disorders, such as cancer, or one or more symptoms thereof, said methods comprising administering to a subject in need thereof a dose of at least 150 µg/kg, preferably at least 250 µg/kg, at least 500 µg/kg, at least 1 mg/kg, at least 5 mg/kg, at least 10 mg/kg, at least 25 mg/kg, at least 50 mg/kg, at least 75 mg/kg, at least 100 mg/kg, at least 125 mg/kg, at least 150 mg/kg, or at least 200 mg/kg or more of one or more compounds of the invention once every day, preferably, once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every 7 days, once every 8 days, once every 10 days, once every two weeks, once every three weeks, or once a month.

Other Embodiments

The compounds of the invention may be used as research tools (for example, to evaluate the mechanism of action of new drug agents, to isolate new drug discovery targets using affinity chromatography, as antigens in an ELISA or ELISA-like assay, or as standards in *in vitro* or *in vivo* assays). These and other uses and embodiments of the compounds and compositions of this invention will be apparent to those of ordinary skill in the art.

The invention is further defined by reference to the following examples describing in detail the preparation of compounds of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention. The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

EXAMPLES

EXPERIMENTAL RATIONALE

Without wishing to be bound by theory, it is believed that the compounds of this invention inhibit tubulin polymerization and/or target vasculature and, therefore, can be used to inhibit undesirable cellular proliferation in disorders such as cancer. The examples that follow demonstrate these properties.

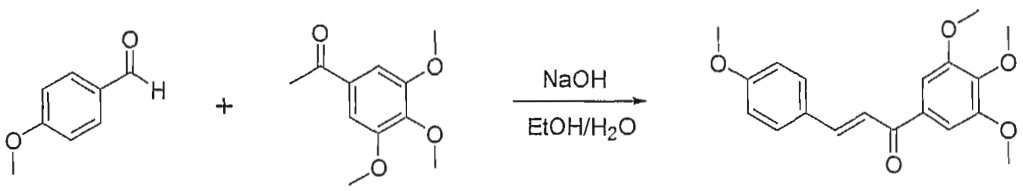
MATERIALS AND GENERAL METHODS

Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 300MHz NMR spectrometer. Significant peaks are tabulated in the order: δ (ppm): chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet), coupling constant(s) in Hertz (Hz) and number of protons.

EXAMPLE 1: SYNTHESIS OF REPRESENTATIVE EXEMPLARY COMPOUNDS OF THIS INVENTION

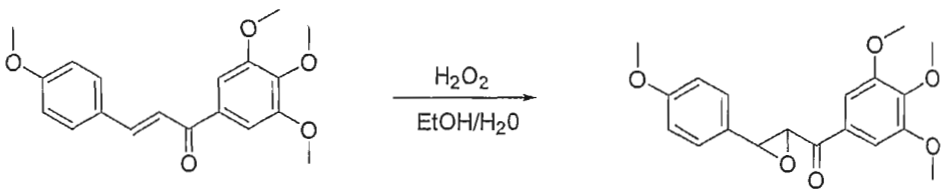
Compound 3: 4-(4-Methoxy-phenyl)-5- (3,4,5-trimethoxy-phenyl)- isoxazole

(1) Synthesis of 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone.



To a stirred solution of p-anislaldehyde (1.36g, 10 mmol) and 1-(3,4,5-trimethoxy-phenyl)-ethanone (2.1g, 10 mmol) in ethyl alcohol (EtOH) (10 mL) was added a 50% solution of NaOH in H_2O (1 mL). After the reaction had proceeded to completion, volatile components were removed under reduced pressure and the residue was taken up with ethyl acetate (EtOAc) (50 mL). The EtOAc layer was washed with H_2O (2 x 30 mL) and then dried with Na_2SO_4. After removal of EtOAc, the product was precipitated out from EtOH/H_2O. Solid material collected by filtration and was washed by H_2O (20 mL) and 95% ethyl alcohol (10 mL). The product, 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (2.8g, 85% yield) , was obtained as a yellow solid. ^{1}H-NMR δ 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 6H), 6.95 (d, 2H, J = 8), 7.28(s, 2H), 7.39 (d, 1H, J = 15), 7.65 (d, 2H, J=8), 7.85 (d, 1H, J=15)ppm.

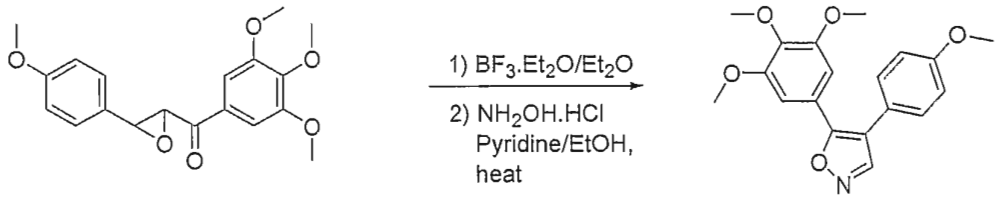
(2) Synthesis of [3-(4-Methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone



To a stirred solution of 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (1.64g, 5 mmol) and 1N NaOH (2.52 mL) in 95% EtOH (22mL) was added a cold solution of 30% H_2O_2 (0.77 mL) at room temperature. After 72 h stirring, the precipitated material was collected by filtration and washed with 95% EtOH to afford

[3-(4-methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone as a white solid (1.38g, yield 80%). ^{1}H-NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.92 (s, 6H), 3.95 (s, 3H), 4.05 (d, 1H, J =2), 4.20 (1H, J=2), 6.95 (d, 2H, J =7), 7.25-7.35 (m, 4H)ppm.

(3) Synthesis of 4-(4-Methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole



To a stirred solution of [3-(4-methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone (0.5g, 1.45 mmol) in dry ether (15 mL) was added $BF_3.Et_2O$ (2.52 mL) slowly. After the addition, it was heated to reflux for 1 h. After the reaction mixture had cooled to room temperature, it was poured into ice-H_2O (100 mL). The etheral layer was separated and the aquous layer was extracted with ether (10 mL x 3). The combined ether layers were washed with H_2O (20 mL x 2) and concentrated to dryness. The residue was then transferred with EtOH (3mL) to a flask suited for a microwave reactor, and hydroxylamine hydrochloride (0.32g, 4.6 mmol) and pyridine (1mL) were added. The mixture was heated and stirred in a microwave reactor at 130 °C for 30 min. The reaction mixture was then cooled to room temperature and poured into ice-H_2O (20 mL). The solid material was collected and washed with H_2O. After preparative HPLC or repeated solvating gas chromatography (SGC) (hexane to 14% Hexane/EtOAc), the product 4-(4-Methoxy-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole was obtained as a light yellow solid. ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 6.85 (s, 2H), 6.94 (d, 2H, J = 8), 7.33 (d, 2H, J = 8), 8.30 (s, 1H) ppm; ESMS calcd for $C_{19}H_{19}NO_5$: 341.0; found: 342.0 ($M + H^+$).

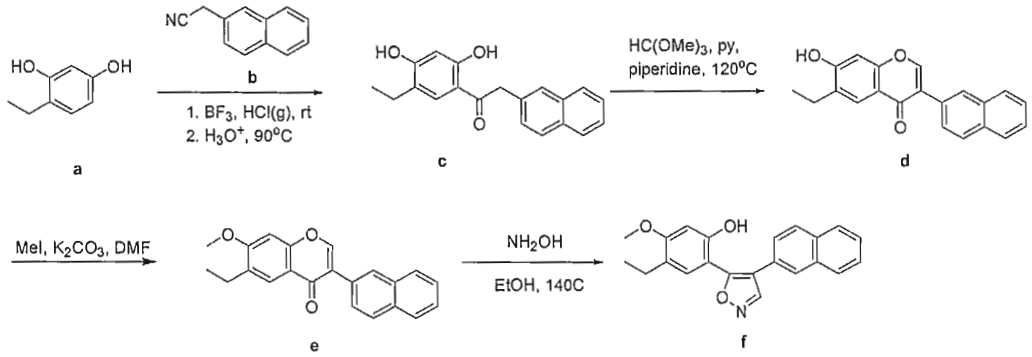
Compound 1: 4-(4-Bromo-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

Compound 1 was synthesized in a similar way as described for Compound 3. ^{1}H-NMR ($CDCl_3$) δ 3.75 (s, 6H), 3.88 (s, 3H), 6.85 (s, 2H), 7.25 (d, 2H, J = 8), 7.58 (d, 2H, J = 8), 8.35 (s, 1H)ppm; ESMS calcd for $C_{18}H_{16}BrNO_4$: 389.0; found: 390.0 ($M + H^+$).

Compound 46: 4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole

Compound 46 was synthesized in a similar way as described for Compound 3. ^{1}H-NMR ($CDCl_3$) δ 3.75 (s, 6H), 3.85 (s, 3H), 4.28 9S, 4h), 6.80-7.30 (m, 5H), 8.28 (s, 1H)ppm; ESMS calcd for $C_{20}H_{19}NO_6$: 369.1; found: 370.1 ($M + H^+$).

Compound 2: 4-(Naphthalen-2-yl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole



To a mixture of 4-ethyl-benzene-1,3-diol (**a**, 10 mmol) and naphthalen-2-yl-acetonitrile (**b**, 10 mmol) in boron trifluoride etherate (20 mL) was bubbled gaseous HCl for 12 h. The solids that formed were collected by filtration and heated in 6N HCl (100 mL) and EtOH (20 mL) for 6 h. The mixture was diluted with water and extracted with CH_2Cl_2. The organic extract was washed with water and dried. The oil obtained on concentration of the organic layer was crystallized in EtOAc/hexanes to give 1-(5-ethyl-2,4-dihydroxy-phenyl)-2-naphthalen-2-yl-ethanone (**c**, 0.74g).

To 1-(5-ethyl-2,4-dihydroxy-phenyl)-2-naphthalen-2-yl-ethanone (**c**, 0.50 g) was added a mixture of pyridine (2 mL), trimethyl orthoformate (2 mL) and piperidine (2 drops), and the mixture was heated at 120 °C for 12 h. The mixture was cooled to room temperature, diluted with EtOAc (100 mL) then washed with 1 N HCl (100 mL). The organic layer was washed with water and dried. The oil obtained on concentration of the organic layer was crystallized in EtOAc/hexanes to give 6-ethyl-7-hydroxy-3-naphthalen-2-yl-chromen-4-one (**d**, 0.36 g).

6-Ethyl-7-hydroxy-3-naphthalen-2-yl-chromen-4-one (**d**, 0.36 g) was dissolved in dry dimethyl formamide (DMF) (5 mL) and treated with iodomethane (MeI) (0.5 mL) and potassium carbonate (1 g) at room temperature for 2 h. The mixture was diluted with water (50 mL) and the precipitate was collected by filtration, washed with water and dried under vacuum to give 6-ethyl-7-methoxy- 3-naphthalen-2-yl-chromen-4-one (**e**, 0.36 g).

A mixture of 6-ethyl-7-methoxy- 3-naphthalen-2-yl-chromen-4-one (**e**, 0.36 g), hydroxylamine hydrochloride (0.6 g), triethylamine (0.5 mL) in EtOH (10 mL) was heated at 140 °C in microwave reactor for 4 h. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with water and dried using a drying agent. The oil obtained on concentration was flash chromatograghed on silica gel to give 4-(naphthalen-2-yl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)- isoxazole as white powder (**f**, 0.19 g). ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.57 (s, 1H), 7.8 (m, 4H), 7.5 (m, 3H), 7.10 (s, 1H), 6.52 (s, 2H), 3.92 (s, 3H), 2.4 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{22}H_{19}NO_3$: 345.1; Found: 346.0 $(M+H)^+$.

Compound 163: 4-(4-Chloro-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 163 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.40 (s, 1H), 7.6 (d, 2H, J = 8), 7.3 (m, 2H), 7.02 (s, 2H), 6.52 (s, 1H), 3.86 (s, 3H), 2.4 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{18}H_{16}ClNO_3$: 329.1; Found: 330.0 $(M+H)^+$.

Compound 164: 4-(4-Methyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 164 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.40 (s, 1H), 7.3 (d, 2H, J = 8), 7.2 (d, 2H, J = 8), 7.10 (s, 1H), 6.52 (s, 1H), 6.42 (s, 1H), 3.84 (s, 3H), 2.4 (q, 2H, J = 7), 2.18 (s, 3H), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{19}H_{19}NO_3$: 309.1; Found: 310.0 $(M+H)^+$.

Compound 165: 4-(4-Amino-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 165 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.28 (s, 1H), 7.2 (d, 2H, J = 8), 7.0 (m, 2H), 6.88 (s, 2H), 6.32 (s, 1H), 4.0 (br, 2H), 3.85 (s, 3H), 2.4 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{18}H_{18}N_2O_3$: 310.1; Found: 311.0 $(M+H)^+$.

Compound 166: 4-(4-Trifluoromethyl-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 166 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.47 (s, 1H), 7.7 (d, 2H, J = 8), 7.5 (d, 2H, J = 8), 6.98 (s, 1H), 6.53 (s, 1H), 6.38 (s, 1H), 3.86 (s, 3H), 2.5 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{19}H_{16}F_3NO_3$: 363.1; Found: 364.0 $(M+H)^+$.

Compound 167: 4-(4-Methoxy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 167 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.39 (s, 1H), 7.3 (d, 2H, J = 8), 7.09 (s, 1H), 6.9 (d, 2H, J = 8), 6.51 (s, 1H), 6.37 (s, 1H), 3.84 (s, 6H), 2.4 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{19}H_{19}NO_4$: 325.1; Found: 326.0 $(M+H)^+$.

Compound 4: 4-(4-Iodo-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl- phenyl)-isoxazole

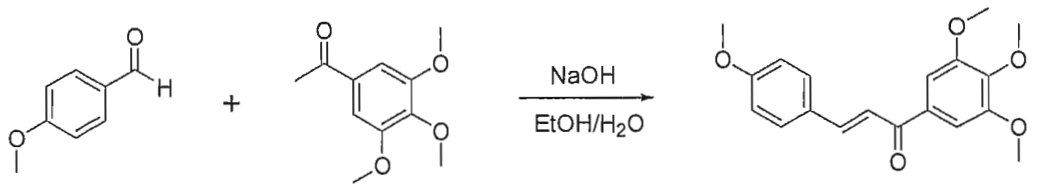
Compound 4 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.42 (s, 1H), 7.6 (d, 2H, J = 8), 7.3 (m, 2H), 7.00 (s, 2H), 6.50 (s, 1H), 3.84 (s, 3H), 2.4 (q, 2H, J = 7), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{18}H_{16}INO_3$: 421.0; Found: 421.9 $(M+H)^+$.

Compound 162: 4-(3,4-Dimethy-phenyl)-5-(2-hydroxy-4-methoxy-5-ethyl-phenyl)-isoxazole

Compound 162 was synthesized in a similar manner as described for Compound 2. ^{1}H-NMR ($CDCl_3$) δ (ppm) 8.41 (s, 1H), 7.1 (m, 4H), 6.51 (s, 1H), 6.42 (s, 1h), 3.84 (s, 3H), 2.4 (q, 2H, J = 7), 2.29 (s, 3H), 2.26 (s, 3H), 1.0 (t, 3H, J = 7); ESMS clcd for $C_{20}H_{21}NO_3$: 323.1; Found: 324.0 $(M+H)^+$.

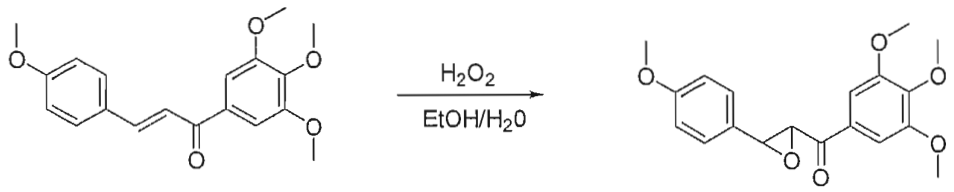
Compound 3b: 4-(4-Methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)- isoxazole

(1) Synthesis of 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone.



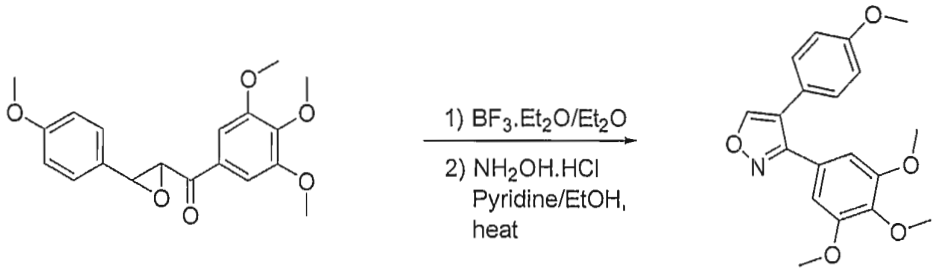
To a stirred solution of p-anislaldehyde (1.36g, 10 mmol) and 1-(3,4,5-trimethoxy-phenyl)-ethanone (2.1g, 10 mmol) in ethyl alcohol (EtOH) (10 mL) was added a 50% solution of NaOH in H_2O (1 mL). After the reaction had proceeded to completion, volatile components were removed under reduced pressure and the residue was taken up with ethyl acetate (EtOAc) (50 mL). The EtOAc layer was washed with H_2O (2 x 30 mL) and then dried with Na_2SO_4. After removal of EtOAc, the product was precipitated out from EtOH/H_2O. Solid material collected by filtration and was washed by H_2O (20 mL) and 95% ethyl alcohol (10 mL). The product, 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (2.8g, 85% yield) , was obtained as a yellow solid. ^{1}H-NMR δ 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 6H), 6.95 (d, 2H, J = 8), 7.28(s, 2H), 7.39 (d, 1H, J = 15), 7.65 (d, 2H, J=8), 7.85 (d, 1H, J=15)ppm.

(2) Synthesis of [3-(4-Methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone



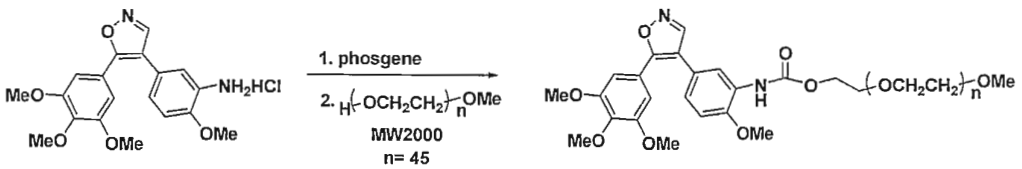
To a stirred solution of 3-(4-Methoxy-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (1.64g, 5 mmol) and 1N NaOH (2.52 mL) in 95% EtOH (22mL) was added a cold solution of 30% H_2O_2 (0.77 mL) at room temperature. After 72 h stirring, the precipitated material was collected by filtration and washed with 95% EtOH to afford [3-(4-methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone as a white solid (1.38g, yield 80%). ^{1}H-NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.92 (s, 6H), 3.95 (s, 3H), 4.05 (d, 1H, J =2), 4.20 (1H, J=2), 6.95 (d, 2H, J =7), 7.25-7.35 (m, 4H)ppm.

(3) Synthesis of 4-(4-Methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole



To a stirred solution of [3-(4-methoxy-phenyl)-oxiranyl]-(3,4,5-trimethoxy-phenyl)-methanone (0.5g, 1.45 mmol) in dry ether (15 mL) was added $BF_3.Et_2O$ (2.52 mL) slowly. After the addition, it was heated to reflux for 1 h. After the reaction mixture had cooled to room temperature, it was poured into ice-H_2O (100 mL). The etheral layer was separated and the aquous layer was extracted with ether (10 mL x 3). The combined ether layers were washed with H_2O (20 mL x 2) and concentrated to dryness. The residue was then transferred with EtOH (3mL) to a flask suited for a microwave reactor, and hydroxylamine hydrochloride (0.32g, 4.6 mmol) and pyridine (1mL) were added. The mixture was heated and stirred in a microwave reactor at 130 °C for 30 min. The reaction mixture was then cooled to room temperature and poured into ice-H_2O (20 mL). The solid material was collected and washed with H_2O. After preparative HPLC or repeated solvating gas chromatography (SGC) (hexane to 14% Hexane/EtOAc), the product 4-(4-Methoxy-phenyl)-3-(3,4,5-trimethoxy-phenyl)-isoxazole was obtained as a light yellow solid. ^{1}H-NMR ($CDCl_3$) δ 3.70 (s, 6H), 3.82 (s, 3H), 3.85 (s, 3H), 6.85 (s, 2H), 6.94 (d, 2H, J = 8), 7.33 (d, 2H, J = 8), 8.30 (s, 1H) ppm; ESMS calcd for $C_{19}H_{19}NO_5$: 341.0; found: 342.0 ($M + H^+$).

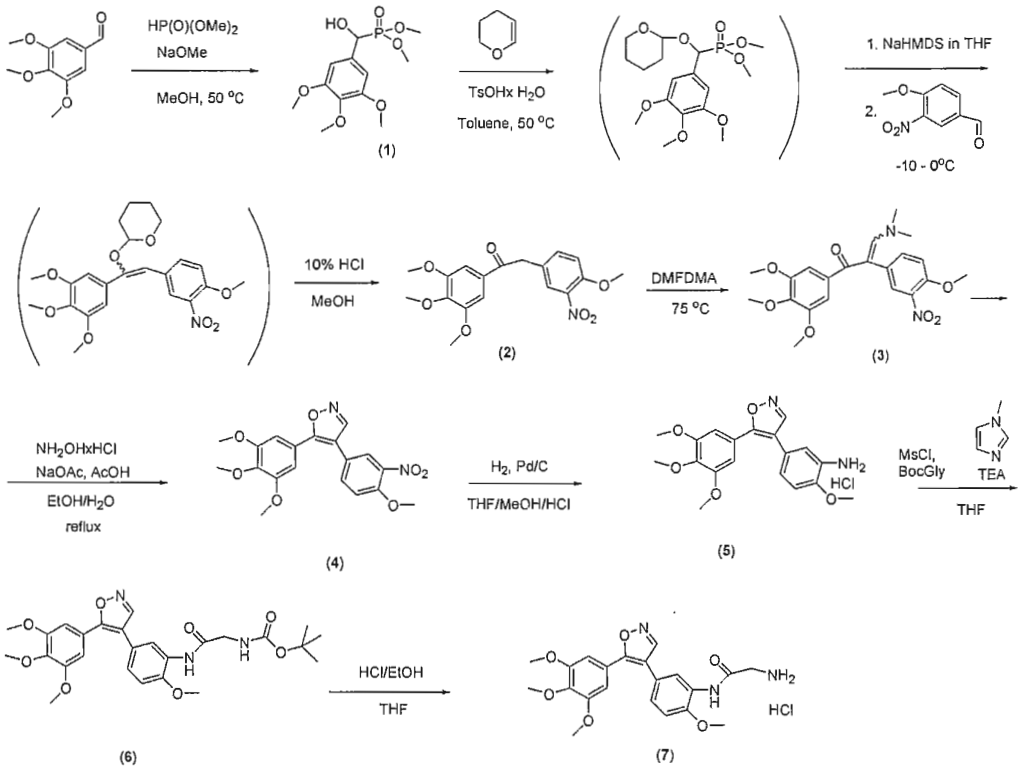
Compound 202: 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenylcarbamate-PEG



A solution of 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline hydrochloride (300 mg, 0.76 mmol) and triethylamine (0.22 mL, 1.60 mmol) in

dichloromethane (3 mL) was added slowly to a solution of triphosgene (77 mg, 0.26 mmol) in dichloromethane (5 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min at room temperature, and then cooled to 0 °C before the addition of PEG (1.53 g, 0.76 mmol) and triethylamine (0.12 mL, 0.77mmol) in 2 ml of dichloromethane. The resulting reaction mixture was stirred for 3 h. and washed with $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (2X), and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel column chromatography (20% MeOH in EA) to give desired product 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylcarbamate-PEG (130 mg). ^1H NMR ($CDCl_3$): δ (ppm) 8.31 (s, 1H); 8.22 (s, 1H); 7.40 (s, 1H); 7.02 (d, *J*=9.0 Hz, 2H); 6.91 (s, 2H); 6.88 (d, *J*=9.0 Hz, 1H); 4.31 (m, 2H); 3.86 (m, 9H); 3.72 - 3.37 (m, ~ 178H).

Synthesis of amino-acid derivatives



[Hydroxy-(3,4,5-trimethoxy-phenyl)-methyl]-phosphonic acid dimethyl ester (**1**)

A round-bottom flask equipped with thermometer, condenser and gas inlet was charged with methanol (150 mL) and sodium methoxide (1.074g, 20 mmol) and cooled to 0 ºC under nitrogen protection. To a stirred solution were added subsequently dimethyl phosphate (19.52 g, 0.177 mol) and 3,4,5-trimethoxybenzaldehyde (30 g, 0.153 mol). A resulted solution was heated at 50 ºC for 1 hour, cooled down to r.t. and treated with trifluoroacetic acid (4.6 ml). The mixture was concentrated under reduced pressure, the residue dissolved in EtOAc (300mL), washed once with 18% brine, then once with saturated brine, dried over sodium sulfate. The filtered solution was concentrated until precipitation started. To the resulted suspension 1:1 mixture of t-butylmethyl ether and heptane was added (50 mL). Solid was filtered out, washed with two portions (20 mL) of the same solvent mixture and vacuum-dried to give 41.2 g (88%) of **1**, LC purity 99.4% (AUC), m.p. 103-104 ºC.

2-(4-Methoxy-3-nitro-phenyl)-1-(3,4,5-trimethoxy-phenyl)-ethanone (**2**)

A round-bottom flask equipped with thermometer, condenser and gas inlet was purged and maintained under nitrogen and charged with hydroxy-(3,4,5-trimethoxy-phenyl)-methyl]-phosphonic acid dimethyl ester (10g, 32.6 mmol), 3,4-dihydro-2H-pyran (3.57g, 42.4 mmol), toluene (100 mL) and p-toluenesolfonic acid hydrate (62.1 mg, 0.01eq). Resulted solution was stirred at 55 ºC for 1.5 hours. TLC (EtOAc) showed full conversion of starting material into a less polar compound. Reaction mixture was cooled to -10 ºC and a solution of sodium bis(trimethylsilyl)amide in THF (1M, 33.3 mL) was added drop-wise, followed by a solution of 4-methoxy-3-nitrobenzaldehyde (5.91 g, 32.6 mmol) in THF (20 mL). Reaction mixture was stirred at 0 ºC for 1 hour before allowed to warm to room temperature. TLC (Hx:EtOAc, 2:1) showed formation of Z/E isomers of 2-[2-(4-methoxy-3-nitro-phenyl)-1-(3,4,5-trimethoxy-phenyl)-vinyloxy]-tetrahydro-pyr an and traces of starting materials remaining. Reaction was quenched with water (140 mL), diluted with EtOAc (60 mL) and transferred into separatory funnel. Organic layer was separated, washed with water (2x50 mL), brine, and concentrated. A residue was dissolved in methanol (100 mL) with energetic mechanical stirring, and 1M aqueous solution of HCl (10 mL) was added. Precipitation of product started soon, and a resulted suspension was stirred for 1 hour. Solid was filtered out, washed

with methanol (50 mL), then with water (3x30 mL) and dried on filter followed by vacuum-drying at 60 °C until constant weight. Crude deoxybenzoin **2**, 6.81 g (58%) showed LC purity of ≥ 97% and was used in the next step without further purification.

3-Dimethylamino-2-(4-methoxy-3-nitro-phenyl)-1-(3,4,5-trimethoxy-phenyl)-propenone (**3**)

200 mL round-bottom flask was charged with 2-(4-methoxy-3-nitro-phenyl)-1-(3,4,5-trimethoxy-phenyl)-ethanone (6.81g, 18.8 mmol) and *N,N*-dimethylformamide dimethyl acetal (52 mL) and heated to 75 °C. After all substrate dissolved, heating continued for 15 min, and TLC indicated completion of reaction. Excess of DMF-DMA was removed under reduced pressure to give crude enamine **3** as an oily residue still containing some of the reagent (caution! product foams and clogs adaptors). It was used in the next step without purification.

4-(4-Methoxy-3-nitro-phenyl)-5-(3,4,5-trimethoxy-phenyl)-isoxazole (**4**)

Method A.

A flask containing crude enamine **3** (~ 18.8 mmol) was charged with hydroxylamine hydrochloride 1.44g, 20.7 mmol), sodium acetate (1.93g, 23.6 mmol), ethanol (58 mL) and water (29 mL). A resulted clear solution was acidified with acetic acid to pH 4-5 (~11.2 mL) and refluxed for 4 hours. Reaction was monitored by TLC (Hexane/EtOAc, 1:1) for the conversion of open-chain intermediate into less polar isoxazole derivative. Ice-water (59 mL) was added to the cooled reaction mixture, and stirring was continued for 1 hour to complete precipitation. A solid was filtered out, washed with water (2x20 mL), with ethanol (15 mL) and dried to give crude isoxazole, 5.24g (72%). Re-crystallization from EtOAc/2-ProOH afforded 4.95g (68%) of **4**, purity >99.2% (AUC).

Method B.

A flask containing crude enamine **3** (~ 10 mmol) was charged with methanol (23 mL), hydroxylamine hydrochloride (1.39g, 20mmol) and triethylamine (2.02g, 20mmol) and refluxed for one hour. TLC showed traces of starting material remained. Reaction mixture was concentrated using vacuum pump to remove triethylamine.

The residue was triturated with water, water decanted from an oil, and that operation was repeated two more times. The oil was then dissolved in ethanol with heating, ethanol was partly removed from the solution and a solid precipitated. Crude product was isolated by filtration and re-crystallized from EtOAc/2-propanol to give **4**, 2.67g (69%).

Compound 64: 2-Methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylamine hydrochloride (**5**)

A 200-mL round-bottom flask equipped with T-bore stopcock connected to a balloon with hydrogen was charged with **4** (4.44g, 11.5 mmol) and THF (40 mL), and a mixture was stirred to dissolve a substrate. Methanol (22 mL), solution of HCl in methanol (1M, 22mL) and palladium, 10 wt% on activated carbon (532 mg, 12 wt %) were added to the flask, the system was evacuated and stirred under atmosphere of hydrogen for 2 hours. TLC indicated completion of reaction (Hexane/EtOAc, 2:1, developed two times). Catalyst was filtered out and washed with methanol (15 mL x 3). Filtrate was diluted with 2-propanol (20 mL) and concentrated under reduced pressure to ~ 20 mL volume. A resulted suspension was diluted with EtOAc (20 mL), a solid was filtered out, washed with EtOAc (20x2) and dried to give crude amine hydrochloride **5** as a yellow solid, 3.3 g (80%), LC purity 97.1%. The solid was refluxed in ethanol (50 mL) for 15 min to dissolve colored impurities. A cooled suspension was filtered out, washed with EtOAc (20x2) and vacuum-dried to obtain a creamy-colored solid, 2.9 g (70%), LC purity 99.1%.

{[2-Methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-carbamic acid tert-butyl ester (**6**)

To a solution of N-t-Boc-glycine (357mg, 2mmol) and N-methyl-imidazole (0.162mL, 2mmol) in THF (16mL) cooled with ice methanesulfonyl chloride (0.158mL, 2mmol) was added. Ice batch was removed, compound 5 (0.4g, 1 mmol) was added as a solid, followed by thriethylamine (0.144mL, 2.02mmol), and the reaction mixture was stirred at 40-50 °C overnight. A resulted solution was decanted from a solid, a flask rinsed with EtOAc, and a combined organic solution was washed with saturated ammonium chloride solution, then twice with water, brine and dried over anhydrous

sodium sulfate. The solution was filtered out through a celite pad, concentrated and the residue was dissolved in 2-propanol (3 mL) with heating, and hexane (1-2mL) was added drop-wise to start precipitation. In 1 hour a solid was filtered out, washed with 1:1 Hexane: ether mixture (10ml x2) and vacuum-dried to give compound **6**, 0.49 g (93.7%), LC purity 99 %. ^{1}H NMR (DMSO-d_6): δ 9.11 (s, 1H), 8.81 (s, 1H), 8.22 (s, 1H), 7.24 (m, 1H), 7.20-7.15 (m, 2H), 6.91 (s, 2H), 3.87 (s, 3H), 3.73 (m, 2H), 3.70 (s, 3H), 3.66 (s, 6H). 1.40 (s, 9H).

Compound 169: 2-Amino-N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-acetamide (**7**)

To a solution of **6** in THF (6 mL) a 1M solution of HCl in ethanol (17mL) was added, and a resulted solution was stirred overnight at room temperature to form a suspension with product partly precipitated out. The reaction mixture was concentrated under reduced pressure keeping temperature below 45 °C to ~ 10mL volume. A solid was filtered out, washed with ether (5ml x 2), hexane (5 mL) and vacuum-dried to give a title compound **7**, 353mg (84%), LC purity 99%. ^{1}H NMR (DMSO-d_6): δ 9.86 (s, 1H), 8.80 (s, 1H), 8.12 (brs, 3H), 8.07 (d, J = 1.8 Hz, 1H), 7.25 (td, J = 8.4 and 1.8 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 6.90 (s, 2H), 3.89 (s, 3H), 3.83 (m, 2H), 3.70 (s, 3H), 3.67 (s, 6H).

Compound 173: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)butanamide hydrochloride

Compound 173 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.78 – 8.22 (m, 5H); 7.15 (s, 1H); 6.84 – 6.72 (m, 3H); 3.84 – 3.70 (m, 12H); 3.48 (m, 2H); 1.23 (m, 3H); 0.98 (m, 2H). ESMS calcd ($C_{23}H_{28}ClN_3O_6$): 477.17; found: 477.2 $(M+H)^+$

Compound 174: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)-3-phenylpropanamide hydrochloride

Compound 174 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.82 (s, 1H); 8.22 (m, 2H); 7.15 – 6.66 (m, 8H); 3.82 – 3.58 (m, 14H). ESMS calcd ($C_{28}H_{30}ClN_3O_6$): 539.18; found: 539.2 $(M+H)^+$

Compound 172: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)-4-(methylthio)butanamide hydrochloride

Compound 172 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.79 (m, 2H); 8.36 (m, 1H); 7.08 (m, 1H); 6.84 (m, 2H); 3.86-3.72 (m, 9H); 2.75 – 2.15 (m, 4H); 2.07 (m, 3H), ESMS calcd ($C_{24}H_{30}ClN_3O_6S$): 523.15; found: 523.1 $(M+H)^+$

Compound 176: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)-3-(4-methoxyphenyl)propanamide

Compound 176 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 8.90 – 8.78 (m, 2H); 8.27 (m, 2H), 7.23 – 6.68 (m, 5H); 3.83-3.68 (m, 12H); 2.10 (m, 2H). ESMS calcd ($C_{29}H_{32}ClN_3O_7$): 569.19; found: 569.1 $(M+H)^+$

Compound 175: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)-4-methylpentanamide hydrochloride

Compound 175 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR (D_2O): δ (ppm) 8.15 (s, 1H); 7.37 (s, 1H); 6.78 (m. 2H); 6.31 (m, 2H); 4.02 (m, 1H); 3.62 (m, 8H); 3.31 (m, 8H); 1.56 (m, 3H); 0.71 (m, 6H). ESMS calcd ($C_{25}H_{32}ClN_3O_6$): 505.20; found: 505.2 $(M+H)^+$

Compound 241: methyl 2-(2-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenylamino)-2-oxoethylamino)acetate

Compound 274 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.88 (s, 1H), 9.24 (s, 1H), 8.30 (m, 2H), 7.94 (m, 1H), 7.56 (m, 1H), 7.03 – 6.77 (m, 4H), 4.42 – 3.44 (m, 18H). ESMS calcd ($C_{24}H_{28}ClN_3O_8$): 521.16; found: 521.1 $(M+H)^+$

Cornpound 242: 4-amino-5-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenylamino)-5-oxopentanoic acid hydrochloride

Cornpound 275 was synthesized in a similar manner as described for Compound 169. ^{1}H NMR ($CDCl_3$): δ (ppm) 9.38 (s, 1H); 8.34 – 8.04 (m, 3H); 6.82 -6.66 (m, 4H);

3.62 (m, 16H); 2.7 – 2.4 (m, 4H). ESMS calcd ($C_{24}H_{28}ClN_3O_6$): 521.16; found: 521.1 $(M+H)^+$

Compound 243: 3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)propanamide hydrochloride

Compound 276 was synthesized in a similar manner as described for Compound 169. ^1H NMR (D_2O): δ (ppm) 8.23 (s, 1H); 7.47 (m, 1H); 6.82 (m, 2H); 6.45 (m, 2H); 3.68 (m, 4H); 3.56 (m, 6H); 3.39 (m, 6H); 2.65 (m, 4H). ESMS calcd ($C_{22}H_{26}ClN_3O_6$): 463.15; found: 463.1 $(M+H)^+$

Compound 244: 3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)-4-methylpentanamide hydrochloride

Compound 277 was synthesized in a similar manner as described for Compound 169. ^1H NMR (D_2O): δ (ppm) 8.27 (s, 1H); 7.44 (m, 1H); 6.89 (m, 2H); 6.52 (m, 2H); 3.69 (m, 5H); 3.56 (m, 4H); 3.42 (m, 7H); 3.31 (m, 3H); 2.65 (m, 4H); 1.78 (m, 2H). ESMS calcd ($C_{25}H_{32}ClN_3O_6$): 505.20; found: 505.2 $(M+H)^+$

Compound 204: 2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenyl)propanamide hydrochloride

Compound 219 was synthesized in a similar manner as described for Compound 169. ^1H NMR ($CDCl_3$): δ (ppm) 8.32 (s, 1H); 8.22 (s, 1H). 7.16 (m, 2H), 6.90 (m, 3H); 3.90 – 3.70 (m, 15H); 1.90 (m, 4H). ESMS calcd ($C_{22}H_{26}ClN_3O_6$): 463.15; found: 463.1 $(M+H)^+$

Compound 249: 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline

^1H NMR (DMSO-d_6): δ 8.72 (s, 1H), 6.95 (s, 2H), 6.86 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 1.8 Hz, 1H), 6.64-6.61 (m, 1H), 4.87 (s, 2H), 3.78 (s, 3H), 3.70-3.68 (m, 9H).

EXAMPLE 2: Cytotoxicity of Compounds of the Invention

Tumor cell line, MDA-435, was seeded in 96-well plates at $1X10^4$ cells/well in DMEM medium and treated with compounds at different concentrations. Taxol was used as a positive control. The cells were incubated at 37 °C for 70 h. Viability of the cells was measured with Cell Counting Kit 8 (Dojindo, Cat # CK04). IC_{50} of the

compounds was determined by Five-Parameter Logistic equation. As can be seen from Table 2 several compounds of the invention have IC_{50} values comparable to Taxol.

compound	IC_{50} (nM)
Taxol	16
1	132
2	79
3	16
4	232
6	461
44	200
45	219
46	21
47	47
161	591
162	842
168	>1000

Table 2

EXAMPLE 3: Cytotoxicity of Compounds of the Invention in Multidrug Resistant Cell Lines

The *in vitro* cytotoxicity of the compounds of the invention was determined in the following human cell lines: HL-60 (T-cell leukemia), MDA-435 and MCF-7 (human breast carcinoma), NCI-H460 and H29 (colon carcinoma), DU145 (prostate carcinoma), and MES-SA and MES-SA/DX5 (uterine sarcoma). MES-SA is a model of uterine sarcoma, and the cell are sensitive to a number of chemotherapeutic agents including doxorubicin, dactinomycin, mitomycin C, taxol and bleomycin, but resistant to vinblastine and cisplatin. MES-SA /Dx5 was established in the presence of increasing concentrations of doxorubicin. The cells express high levels of mdr-1 mRNA and p-glycoprotein and exhibit cross resistance to more than fifteen chemotherapeutic agents including taxol, etoposide, mitomycin C, colchicine, vinblastine, dactinomycin, 5-fluorouracil, methotrexate and so on. All cells were purchased from ATCC.

The cell lines were maintained in RPMI1640 (GIBCO) supplemented with 10% FCS, 100 units/mL penicillin, 100 ug/ml streptomycin, and 2 mM L-glutamine. Cells were

split every third day and diluted to a concentration of 2 x 105 cells/mL one day before the experiment was performed. All experiments were performed on exponentially growing cell cultures. Cell densities were 2.5 x 10^4 cells/mL in all experiments.

Compounds of the invention were prepared by dissolving the compound at a concentration of 10 mM in 100% DMSO. Final concentrations 10, 1, 0.1, 0.01 and 0.001 μM were obtained by diluting the stock solution directly into the tissue culture medium. Cells were incubated with varying concentrations of compounds for 72 hours and the IC_{50} was determined by MTS (i.e. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay. IC_{50} in this context stands for the concentration of compound required to inhibit 50% tumor cell growth. As can be seen from Tables 3 and 4, compounds of the invention showed much greater activity than Taxol against multidrug resistant cell line MES/DX5.

Cell Line	Cell Type	Comp. 3 IC_{50} in μM	Comp. 46 IC_{50} in μM	Comp. 4 IC_{50} in μM	Taxol IC_{50} in μM
HL60	Leukemia	0.005	0.05	0.05	0.005
MDA-435	Breast Cancer	0.005	0.05	0.05	0.002
MCF-7	Breast Cancer	0.01	0.05	0.05	0.005
NCI-H460	Colon Carcinoma	0.005	0.05	0.05	0.005
MES-SA	Uterine Carcinoma	0.01	0.05	0.05	0.005
MES/DX5	MDR-1	0.005	0.05	0.05	10
DU145	Prostate Carcinoma	0.005	0.1	0.05	0.005
H29	Colon Carcinoma	0.005	0.05	0.05	0.01

Table 3

Cell Line:	**HL60**	**MES-SA**	**MES/DX5**
Cell Type:	**Leukemia**	**Uterine Carcinoma**	**MDR-1**
Compound No.	IC_{50} in μM	IC_{50} in μM	IC_{50} in μM
169	0.007	0.003	0.003
170	0.002	0.009	0.003
171	0.005	0.002	0.004
172	0.005	0.0001	0.0001
173	0.002	0.0001	0.0001
174	0.002	0.0001	0.0001
175	0.005	0.0001	0.0001
176	0.064	0.0001	0.0001
177	0.052	0.008	0.004
178	0.022	0.004	0.004
202	> 1.0	> 1.0	> 1.0
204	0.500	0.106	0.120
241	0.600	0.136	0.063
243	0.063	0.050	0.038
249	0.001	0.001	0.001

Table 4

5

EXAMPLE 4: Induction of Apoptosis by Compounds of the Invention

SB cells ($2X10^5$ cells/mL) were cultured in 12-well plates (2 mL/well) and were left untreated (negative control), treated with Taxol (positive control), or treated with a compound of the invention for 24 h at 37 °C. After treatment, the cells were washed one time with 1X PBS and stained with FITC labeled anti-Annexin V and PI (10 µg/ml) for 15 min at room temperature. The cells were analyzed by FACSCalibur (Becton Dickinson). As can be seen from Table 5, many compounds of the invention were more potent apoptosis inducers in SB cells than Taxol.

Compound # (1 µM)	% Live Cells Gated	% Apoptotic Cells Gated	% Dead Cells Gated
Untreated Cells	68.75	10.85	11.88
Taxol	63.74	17.84	12.50
1	60.15	18.36	14.41
2	45.72	22.73	22.67
3	46.43	22.99	21.79
4	52.82	19.05	20.15
6	59.17	14.17	17.31
44	64.77	16.05	12.27
45	62.05	17.74	15.37
46	51.04	19.04	17.33
47	61.85	13.83	14.76
161	66.80	14.61	10.49
162	64.62	17.74	11.52
168	60.37	15.49	14.38

Table 5

EXAMPLE 5: Hepatocyte Toxicity

Hepatocytes isolated from normal rats were seeded in 96-well plates coated with extracellular matrix at $1.5X10^4$ cells/well. The cells were untreated (negative control), treated with 17AAG (positive control) or Taxol (positive control), or treated with a compound of the invention at different concentrations at 37 °C for 48 h. Viability of the cells was measured with Cell Counting Kit 8. Figures 1 and 2 show that the compounds of the invention had similar cytotoxic effects on normal hepatocytes compared to Taxol and had less cytotoxic activity than 17AAG at 1 to 20 uM.

EXAMPLE 6: Cell Cycle Analysis

MDA-435 cells were cultured in 6-well plates at $1X10^6$ cells/well and were untreated (negative control), treated with Taxol (positive control), or treated with a compound of the invention at 37°C for 20 h. The cells were detached with 1X trypsin and washed one time with PBS. Cycle TEST PLUS kit (BD PharMingen, Cat # 340242) was used to stain the cells. Cell cycle was analyzed with FACScomp program (BS PharMingen). As can be seen from Table 6, compounds of the invention decrease the percentage of cells entering mitosis (G2/M phase) and increase the apoptotic population compared to untreated cells.

Treatment	G0/G1 Phase (%)	S Phase (%)	G2/M Phase (%)	Apoptotic Population (%)
Untreated	34.60	26.58	36.09	3.26
Taxol (30 nM)	19.12	32.93	32.32	16.17
Comp. 1 (100 nM)	19.15	37.60	32.60	11.35
Comp. 2 (500 nM)	21.25	37.67	30.53	11.17
Comp. 3 (10 nM)	17.72	37.96	29.92	14.99
Comp. 6 (800 mM)	18.45	35.55	35.96	10.59
Comp. 46 (50 nM)	19.67	37.98	28.18	9.88

Table 6

EXAMPLE 7: Inhibition of Tubulin Polymerization by Compounds of the Invention

Material and Methods: Wild-type Chinese Hamster Ovary cells (WT CHO) cells were maintained in Ham's F-12 medium supplemented with 10% fetal bovine serum (FBS; HyClone, Logan, UT). Cells of low density (~20%) growing on 2-well chambered cover-slips (Labtek (Campbell, CA) or Fisher Scientific) were transfected with a mammalian expression vector encoding α-tubulin-YFP (Clontech, Palo Alto, CA) with the use of FuGENE 6 (Roche Molecular Biochemicals, Indianapolis, IN), according to the manufacturer's instructions. Twenty-four hours after transfection, the cells were cultured in 400 μg/ml G418 (Invitrogen, Carlsbad, CA)-containing selection medium for 2 weeks. Living cells were examined using a fluorescent microscope for α-tubulin-YFP expression. Cells in single colonies containing microtubules labeled with α-tubulin-YFP were lifted and expanded in G418-containing medium. Expression of α-tubulin-YFP was confirmed by the presence of the tubulin-YFP labeled microtubule pattern identical to immunostained microtubule pattern of non-transfected cells, as well as by subjecting the cells to Western blot analysis using an anti-GFP antibody (Roche Molecular Biochemicals, Basel, Switzerland) and confirming the correct mass of the α-tubulin-YFP chimeric protein. Expressed tubulin-YFP was detected as a single band in Western blots. The tubulin-YFP expressing cell lines (referred as CHO-α-tubulin-YFP cells) were used in the studies described below. Similar methods were used to generate MCF-7 cell lines stably expressing α-tubulin-YFP (referred as MCF7-α-tubulin-YFP cells).

CHO-α-tubulin-YFP or MCF7-α-tubulin-YFP cells were cultured in 2-well chambered cover-slips (Labtek (Campbell, CA) or Fisher Scientific) for 24 hours before treatment with a compound of the invention. For comparison of the effects of treatment on α-tubulin-YFP labeled microtubules with the compounds of the invention, CHO-α-tubulin-YFP or MCF7-α-tubulin-YFP cells were treated with the a compound of the invention, Taxol or equivalent concentrations of DMSO-containing media for

various time periods before imaging. Tubulin-YFP fluorescence in living cells or fixed cells was captured using a standard filter for FITC and objectives of 20x or 60x magnification on a Nikon TE300 microscope with a Leica DC50 color digital camera (Leica, Bannockburn, IL) or a CoolSnap HQ monochrome CCD camera (Photonetrics, Tucson, AZ). The Leica DC50 and CoolSnapHQ cameras were controlled with Leica DC50 software and MetaVue/MetaMorph software, respectively (Universal Imaging Corp, Downingtown, PA). Tubulin-YFP signal in live cells is present as typical microtubule network (normal condition, see Fig. 3 which shows DMSO treated MCF7-α-tubulin-YFP cells), microtubule bundle formation (stabilized microtubules, see Fig. 4 which shows MCF7-α-tubulin-YFP cells treated with 0.1 μM Taxol), or cytoplasmic pattern (depolymerized tubulin-YFP, see Figs. 5, 6 and 7 which show MCF7-α-tubulin-YFP cells treated with 1.0 μM Compounds 1, 3, and 6 of the invention, respectively). As can be seen from the Figures, the compounds of the invention inhibit tubulin polymerization.

EXAMPLE 8: Compounds of the Invention Disrupt Microtubules in Cells Resistant to the Depolymerization Effects of Colchicine and Vincristine

The effects of compounds of the invention on microtubules were studied in CV-1 cells. The microtubules of CV-1 cells are known to be resistant to the depolymerizing effects of colchicine and vincristine. CV-1 cells were treated with 500nM of either Compound 3, vincristine, or colchicines, and their microtubules were examined at 24, 48 and 72 hr (Figs. 8, 9 and 10). Cells were then fixed and stained to examine microtubule structure. In cells treated with Compound 3 for 24 hrs, no microtubule structure was found (Figs. 8B and 8E). However, disorganized but clear microtubule structures were found in cells treated with either vincristine (Fig. 8D) or colchicines (Fig. 8C). At 48 hr treatment, cells with Compound 3 still contained no microtubule structures (Figs. 9B and 9E), while microtubule structures were still found in vincristine (Fig. 9D), colchicines (Fig. 9C) and DMSO (Fig. 9A) treated cells. Most interestingly, at 72 hr of treatment with Compound 3 (Figs. 10B and 10E), most cells contained fragmented, short, and strongly stained tubular structures in the cytoplasm. These data suggest that Compound 3 is a more potent disrupter of microtubule function that either vincristine or colchicine.

EXAMPLE 9: Compound 3 Displays Anti-Tumor Activity Against Human Tumor Cells Line in Nude Mouse Xenograft Models

The human tumor cell line, MDA-MB-435S (ATCC #HTB-129; G. Ellison, et al., *Mol. Pathol.* 55:294-299, 2002), was obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The human tumor cell line, RERF-LC-AI (RCB0444; S. Kyoizumi, et al., *Cancer. Res.* 45:3274-3281, 1985), was obtained from the Riken Cell Bank (RCB; Tsukuba, Ibaraki, Japan). The cell lines were cultured in growth media prepared from 50% Dulbecco's Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS was obtained from ATCC and all other reagents were obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately 4-5 x 10(6) cells that had been cryopreserved in liquid nitrogen were rapidly thawed at 37°C and transferred to a 175 cm^2 tissue culture flask containing 50 ml of growth media and then incubated at 37 °C in a 5% CO_2 incubator. The growth media was replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask was washed with 10 mL of room temperature phosphate buffered saline (PBS) and the cells were disassociated by adding 5 mL 1X Trypsin-EDTA (Invitrogen) and incubating at 37°C until the cells detached from the surface of the flask. To inactivate the trypsin, 5 mL of growth media was added and then the contents of the flask were centrifuged to pellet the cells. The supernatant was aspirated and the cell pellet was resuspended in 10 mL of growth media and the cell number determined using a hemocytometer. Approximately 1-3 x 10(6) cells per flask were seeded into 175 cm^2 flasks containing 50 mL of growth media and incubated at 37°C in a 5% CO_2 incubator. When the flasks reached 90% confluence, the above passaging

process was repeated until sufficient cells had been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice were obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals were housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies were conducted on animals between 7 and 19 weeks of age at implantation. To implant MDA-MB-435S tumor cells into *nude* mice, the cells were trypsinized as above, washed in PBS and resusupended at a concentration of 50 x 10(6) cells/mL in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 mL of the cell suspension was injected into the corpus adiposum of *nude* mice. The corpus adiposum is a fat body located in the ventral abdominal vicera in the right quadrant of the abdomen at the juncture of the os coxae (pelvic bone) and the os femoris (femur). To implant RERF-LC-AI tumor cells into nude mice, the cells were trypsinized as above, washed in PBS and resuspended at a concentration of 50 x 10(6) cells/mL in 50% non-supplemented RPMI Media 1640 and 50% Matrigel Basement Membrane Matrix (#354234; BD Biosciences; Bedford, Massachusetts, USA). Using a 27 gauge needle and 1 cc syringe, 0.1 mL of the cell suspension was injected subcutaneously into the flank of *nude* mice.

Tumors were then permitted to develop *in vivo* until they reached approximately 100-200 mm^3 in volume, which typically required 2-3 weeks following implantation. Tumor volumes (V) were calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5326 \times (L \times W \times T)$. Animals were randomized into treatment groups so that the average tumor volumes of each group were similar at the start of dosing.

Stock solutions of test articles were prepared by dissolving the appropriate amounts of each compound in dimethyl sulfoxide (DMSO) by sonication in an ultrasonic water bath. Stock solutions were prepared at the start of the study, stored at -20°C and diluted fresh each day for dosing. A solution of 20% Cremophore RH40 (polyoxyl 40 hydrogenated castor oil; BASF Corp., Aktiengesellschaft, Ludwigshafen, Germany)

in 80% D5W (5% dextrose in water; Abbott Laboratories, North Chicago, Illinois, USA) was also prepared by first heating 100% Cremophore RH40 at 50-60°C until liquefied and clear, diluting 1:5 with 100% D5W, reheating again until clear and then mixing well. This solution was stored at room temperature for up to 3 months prior to use. To prepare formulations for daily dosing, DMSO stock solutions were diluted 1:10 with 20% Cremophore RH40. The final formulation for dosing contained 10% DMSO, 18% Cremophore RH40, 3.6% dextrose, 68.4% water and the appropriate amount of test article (Compound 3 or paclitaxel). Animals were intravenously (i.v.) injected with this solution at 10 ml per kg body weight on a schedule of 3 days per week (Monday, Wednesday, Friday, with no dosing on Saturday and Sunday) for a total of 9-10 doses.

As shown in Figure 11, treatment with 6.25, 12.5 and 25 mg/kg body weight of Compound 3 decreased the growth rate of MDA-MB-435S melanoma cells in *nude* mice. Tumor regression was observed at the two highest dose levels of Compound 3. Treatment with 6.25 mg/kg of Compound 3 or with 7.5 mg/kg of paclitaxel (an unrelated drug that is used to treat cancer in humans) resulted in decreased tumor growth compared to animals treated with vehicle alone. This effect was not associated with overt toxicity of Compound 3, as shown by the minimal effect on body weights (Figure 12).

As shown in Figure 13, treatment with 25 mg/kg body weight of Compound 3 also decreased the growth rate of RERF-LC-AI lung tumor cells in *nude* mice. This effect was not associated with overt toxicity, as shown by the minimal effect on body weights (Figure 14).

EXAMPLE 10: Compounds 169, 174, and 178 Display Anti-Tumor Activity Against Human Tumor Cells Line in a *nude* Mouse Xenograft Model

The human tumor cell line, MDA-MB-435S (ATCC #HTB-129; G. Ellison, et al., *Mol. Pathol.* 55:294-299, 2002), was obtained and cultured as described in Example 9 above.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice were obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals were housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies were conducted on animals between 8 and 10 weeks of age at implantation. To implant MDA-MB-435S tumor cells into *nude* mice, the cells were trypsinized as above, washed in PBS and resusupended at a concentration of 50 x 10(6) cells/ml in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 ml of the cell suspension was injected into the corpus adiposum of *nude* mice. The corpus adiposum is a fat body located in the ventral abdominal vicera in the right quadrant of the abdomen at the juncture of the os coxae (pelvic bone) and the os femoris (femur).

Tumors were then permitted to develop *in vivo* until the majority reached an average of 100-200 mm^3 in tumor volume, which typically required 2-3 weeks following implantation. Animals with oblong, very small or large tumors were discarded, and only animals carrying tumors that displayed consistent growth rates were selected for studies. Tumor volumes (V) were calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: V = 0.5236 x (L x W x T). Animals were randomized into treatment groups so that the median tumor volumes of each group were similar at the start of dosing. %T/C values, as a measure of efficacy, were determined as follows:

(i) If $\Delta T > 0$: $\%T/C = (\Delta T/\Box C) \times 100$

(ii) If $\Delta T < 0$: $\%T/C = (\Delta T/T_0) \times 100$

(iii) ΔT = Change in median tumor volume between start of dosing and the end of study.

(iv) ΔC = Change in median tumor volume between start of dosing and the end of study.

(v) T_0 = Median tumor volume at start of dosing.

Compounds were formulated in either D5W (Compounds 169 and 174) or DRD (Compound 178). For formulations in D5W, solutions of test articles were prepared

by dissolving the appropriate amounts of each compound in 5% dextrose in water (Abbott Laboratories, North Chicago, Illinois, USA) by sonication in an ultrasonic water bath. For formulations in DRD, stock solutions of test articles were prepared by dissolving the appropriate amounts of each compound in dimethyl sulfoxide (DMSO) by sonication in an ultrasonic water bath. Stock solutions were prepared weekly, stored at -20°C and diluted fresh each day for dosing. A solution of 20% Cremophore RH40 (polyoxyl 40 hydrogenated castor oil; BASF Corp., Aktiengesellschaft, Ludwigshafen, Germany) in 5% dextrose in water (Abbott Laboratories, North Chicago, Illinois, USA) was also prepared by first heating 100% Cremophore RH40 at 50-60°C until liquefied and clear, diluting 1:5 with 100% D5W, reheating again until clear and then mixing well. This solution was stored at room temperature for up to 3 months prior to use. To prepare DRD formulations for daily dosing, DMSO stock solutions were diluted 1:10 with 20% Cremophore RH40. The final DRD formulation for dosing contained 10% DMSO, 18% Cremophore RH40, 3.6% dextrose, 68.4% water and the appropriate amount of test article. Animals were intravenously (i.v.) injected with these formulations at 10 ml per kg body weight on schedules of either 1 day per week for a total of 3 doses, or 3 days per week (Monday, Wednesday, Friday, with no dosing on Saturday and Sunday) for a total of 9 doses.

As shown in Figure 15, treatment 1 time/week with doses of 2 mg/kg body weight of Compound 169 and 4.55 mg/kg body weight of Compound 174 substantially decreased the growth rate of MDA-MB-435S cells in *nude* mice, with %T/C values of 38 and 25, respectively. This effect was not associated with overt toxicity, as shown by the minimal effect on body weights (Figure 16).

As shown in Figure 17, treatment with Compound 178 3 times per week for a total of 3 doses at 25 mg/kg body weight, followed by 3 times per week for a total of 3 doses at 37.5 mg/kg body weight, followed by 3 times per week for a total of 3 doses at 50 mg/kg body weight (arrows) began to show modest efficacy after the dose escalation reached 37.5 mg/kg. This effect was not associated with overt toxicity, as shown by the minimal effect on body weights (Figure 18).

Example 11: Compound 3 Rapidly Induces Necrosis in a *nude* Mouse Tumor Model

The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), was obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line was cultured in growth media prepared from 50% Dulbecco's Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS was obtained from ATCC and all other reagents were obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately 4-5 x 10(6) cells that had been cryopreserved in liquid nitrogen were rapidly thawed at 37 °C and transferred to a 175 cm^2 tissue culture flask containing 50 ml of growth media and then incubated at 37°C in a 5% CO_2 incubator. The growth media was replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask was washed with 10 ml of room temperature phosphate buffered saline (PBS) and the cells were disassociated by adding 5 ml 1X Trypsin-EDTA (Invitrogen) and incubating at 37 °C until the cells detached from the surface of the flask. To inactivate the trypsin, 5 ml of growth media was added and then the contents of the flask were centrifuged to pellet the cells. The supernatant was aspirated and the cell pellet was resuspended in 10 ml of growth media and the cell number determined using a hemocytometer. Approximately 1-3 x 10(6) cells per flask were seeded into 175 cm^2 flasks containing 50 ml of growth media and incubated at 37 °C in a 5% CO_2 incubator. When the flasks reached 90% confluence, the above passaging process was repeated until sufficient cells had been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice were obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals were housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies were conducted on animals between 8 and 10 weeks of age at implantation. To implant EMT6 tumor cells into *nude* mice, the cells were trypsinized as above, washed in

PBS and resusupended at a concentration of 10 x 10(6) cells/ml in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 ml of the cell suspension was injected subcutaneously into the flank of each *nude* mouse.

Tumors were then permitted to develop *in vivo* until the majority reached 75-125 mm^3 in tumor volume, which typically required 1 week following implantation. Animals with oblong, very small or large tumors were discarded, and only animals carrying tumors that displayed consistent growth rates were selected for studies. Tumor volumes (V) were calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals were randomized into treatment groups so that each group had median tumor volumes of ~100 mm^3 at the start of dosing.

To formulate Compound 3 in DRD, a stock solution of the test article were prepared by dissolving an appropriate amount of the compound in dimethyl sulfoxide (DMSO) by sonication in an ultrasonic water bath. A solution of 20% Cremophore RH40 (polyoxyl 40 hydrogenated castor oil; BASF Corp., Aktiengesellschaft, Ludwigshafen, Germany) in 5% dextrose in water (Abbott Laboratories, North Chicago, Illinois, USA) was also prepared by first heating 100% Cremophore RH40 at 50-60°C until liquefied and clear, diluting 1:5 with 100% D5W, reheating again until clear and then mixing well. This solution was stored at room temperature for up to 3 months prior to use. To prepare a DRD formulation for dosing, the DMSO stock solution was diluted 1:10 with 20% Cremophore RH40. The final DRD formulation for dosing contained 10% DMSO, 18% Cremophore RH40, 3.6% dextrose, 68.4% water and the appropriate amount of test article.

Tumor-bearing animals were given a single intravenous (i.v.) bolus injections of either DRD vehicle or Compound 3 formulated in DRD, both at 10 mL per kg body weight. Then, 4-24 hr after drug treatment, tumors were excised, cut in half and fixed overnight in 10% neutral-buffered formalin. Each tumor was embedded in paraffin with the cut surfaces placed downwards in the block, and rough cut until a complete section was obtained. From each tumor, 5 µM serial sections were prepared and stained with hematoxylin and eosin. Slides were evaluated manually

using light microscopy with a 10 x 10 square gridded reticle. The percentage of necrosis in a tumor was quantified at 200X magnification by scoring the total number of grid squares containing necrosis and the total number of grid squares containing viable tumor cells.

As shown in Figure 19, a dramatic increase in necrotic tissue in the center of EMT6 tumors was observed after a single bolus injection of 25 mg/kg body weight of Compound 3 relative to the baseline necrosis observed in vehicle treated tumors. A near maximal 2.4 fold increase in necrosis was observed 4 hr after drug treatment. As would be expected for a vascular targeting mechanism of action, such rapid onset of necrosis is consistent with there being a loss of blood flow to tumors resulting in hypoxia and tumor cell death.

EXAMPLE 12: COMPOUND 249 DEPOLYMERIZES MICROTUBULES IN CV-1 AND HUVEC CELLS

Depolymerizing microtubules not only kills dividing tumor cells but also induces disruption of newly generated blood vessels in tumor. The potency of Compound 249 in depolymerizing microtubules was examined in Africa green monkey kidney fibroblasts (CV1 cells) and primary human umbilical vein endothelium cells (HUVEC cells). The cells were treated with drugs (1, 10, 100, and 1000nM for CV-1 and 1, 5, 10, 50, 100 nM for HUVEC) for 24 hr and fixed with 3% paraformaldehyde followed by cold methanol treatment to preserve both microtubule structures and depolymerized tubulin in the cytoplasm. The cells were stained with anti-tubulin antibody and subsequently fluorescent conjugated secondary antibody to visualize microtubule networks or cytoplasmic tubulin with fluorescent microscopy. As shown in Fig. 20 and Fig. 21, Compound 249 completely depolymerizes MT in a considerable proportion of CV1 cells at 10nM and HUVEC cells at 1nM (about 10% for both cell lines; data not shown). At 100nM for CV1 and 5nM for HUVEC cells, microtubules were completely depolymerized in nearly 100% cells. Tubulin staining in these cells was shown as cytoplasmic location and no microtubule structures were found in those cells. Fragmented microtubules were found in HUVEC cells treated with 1nM Compound 249 (Fig. 21). Compound 249 is a potent microtubule

depolymerizing drug and HUVEC cells are extremely sensitive to Compound 249's anti-microtubule effect.

EXAMPLE 13: Compound 174 Displays Anti-tumor and Vascular Disrupting Activities in a *nude* Mouse Tumor Model

The mouse mammary carcinoma cell line, EMT6 (ATCC #CRL-2755), was obtained from the American Type Culture Collection (ATCC; Manassas, Virginia, USA). The cell line was cultured in growth media prepared from 50% Dulbecco's Modified Eagle Medium (high glucose), 50% RPMI Media 1640, 10% fetal bovine serum (FBS), 1% 100X L-glutamine, 1% 100X Penicillin-Streptomycin, 1% 100X sodium pyruvate and 1% 100X MEM non-essential amino acids. FBS was obtained from ATCC and all other reagents were obtained from Invitrogen Corp. (Carlsbad, California, USA). Approximately 4-5 x 10^6 cells that had been cryopreserved in liquid nitrogen were rapidly thawed at 37°C and transferred to a 175 cm^2 tissue culture flask containing 50 mL of growth media and then incubated at 37°C in a 5% CO_2 incubator. The growth media was replaced every 2-3 days until the flask became 90% confluent, typically in 5-7 days. To passage and expand the cell line, a 90% confluent flask was washed with 10 mL of room temperature phosphate buffered saline (PBS) and the cells were disassociated by adding 5 mL 1X Trypsin-EDTA (Invitrogen) and incubating at 37°C until the cells detached from the surface of the flask. To inactivate the trypsin, 5 mL of growth media was added and then the contents of the flask were centrifuged to pellet the cells. The supernatant was aspirated and the cell pellet was resuspended in 10 mL of growth media and the cell number determined using a hemocytometer. Approximately 1-3 x 10^6 cells per flask were seeded into 175 cm^2 flasks containing 50 mL of growth media and incubated at 37°C in a 5% CO_2 incubator. When the flasks reached 90% confluence, the above passaging process was repeated until sufficient cells had been obtained for implantation into mice.

Seven to eight week old, female Crl:CD-1-*nu*BR (*nude*) mice were obtained from Charles River Laboratories (Wilmington, Massachusetts, USA). Animals were housed 4-5/cage in micro-isolators, with a 12hr/12hr light/dark cycle, acclimated for at least 1 week prior to use and fed normal laboratory chow *ad libitum*. Studies were conducted on animals between 8 and 10 weeks of age at implantation. To implant

EMT6 tumor cells into *nude* mice, the cells were trypsinized as above, washed in PBS and resusupended at a concentration of 10 x 10^6 cells/mL in PBS. Using a 27 gauge needle and 1 cc syringe, 0.1 mL of the cell suspension was injected subcutaneously into the flank of each *nude* mouse.

For the tumor growth delay assay, tumors were permitted to develop *in vivo* until the majority reached 90-200 mm^3 in tumor volume, which typically required 1 week following implantation. Alternatively, for the Evans Blue dye assay, tumors were permitted to develop *in vivo* until the majority reached 40-90 mm^3 in tumor volume (to minimize the extent of tumor necrosis), which typically required 4-6 days following implantation. Animals with visibly necrotic, oblong, very small or very large tumors were discarded and only animals carrying tumors that displayed consistent growth rates were selected for use. Tumor volumes (V) were calculated by caliper measurement of the width (W), length (L) and thickness (T) of tumors using the following formula: $V = 0.5236 \times (L \times W \times T)$. Animals were randomized into treatment groups so that at the start of dosing each group had median tumor volumes of ~125 mm^3 or ~55 mm^3 for the tumor growth delay or Evans Blue dye assays, respectively.

To formulate Compound 174 for dosing, the appropriate amount of compound was dissolved in 5% dextrose in water (D5W; Abbott Laboratories, North Chicago, Illinois, USA). Vehicle-treated animals were dosed with D5W.

Tumor-bearing animals were given single intravenous (i.v.) bolus injections of either vehicle or Compound 174 at 10 mL per kg body weight. To measure the effect of the drug treatment on tumor growth rates, tumor volumes were measured 3 days after dosing (Figure 22).

To conduct the Evans Blue dye assay (Figure 23), tumor-bearing animals were dosed with vehicle or test article at 0 hr, and then i.v. injected with 100 µL of a 1% (w/v) Evan's Blue dye (Sigma #E-2129; St. Louis, Missouri, USA) solution in 0.9% NaCl at +1 hr. Tumors were excised at + 4 hr, weighed and the tissue disassociated by incubation in 50 µL 1 N KOH at 60 °C for 16 hr. To extract the dye, 125 µL of a

0.6 N phosphoric acid and 325□L acetone were added, and the samples vigorously vortexed and then microcentrifuged at 3000 RPM for 15 min to pellet cell debris. The optical absorbance of 200 µL of supernatant was then measured at 620 nM in a Triad spectrophotometer (Dynex Technologies, Chantilly, Virginia, USA). Background OD_{620} values from similarly sized groups of vehicle or test article-treated animals that had not been injected with dye were subtracted as background. OD_{620} values were then normalized for tumor weight and dye uptake was calculated relative to vehicle-treated tumors.

The EMT6 mouse mammary carcinoma tumor model in *nude* mice is highly sensitive to treatment with Compound 174. As shown in Figure 22, a single i.v. bolus injection of 4.55 or 3.22 mg/kg body weight of Compound 174 resulted in substantially decreased tumor growth over the subsequent 3 days relative to vehicle-treated animals.

To examine the vascular disrupting activity of Compound 174, the Evans Blue dye assay was employed as a measurement of tumor blood volume (Graff *et al.,* Eur J Cancer 36:1433-1440, 2000). Evans Blue dye makes a complex with serum albumin by electrostatic interaction between the sulphonic acid group of the dye and the terminal cationic nitrogens of the lysine residues in albumin. The dye leaves the circulation very slowly, principally by diffusion into extravascular tissues while still bound to albumin. Albumin-dye complex taken up by tumors is located in the extracellular space of non-necrotic tissue, and intracellular uptake and uptake in necrotic regions is negligible. The amount of dye present in a tumor is a measurement of the tumor blood volume and microvessel permeability. As shown in Figure 23, a single i.v. bolus injection of 4.55, 3.22 or 2.28 mg/kg body weight of Compound 174 resulted in substantially decreased tumor dye uptake relative to vehicle-treated animals. Such a decrease in dye penetration into the tumor is consistent with there being a loss of blood flow to tumors due to blockage of tumor vasculature, consistent with a vascular disrupting mechanism of action.

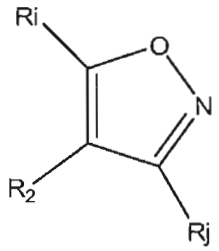
All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present

specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting in any way.

CLAIMS

WE CLAIM:

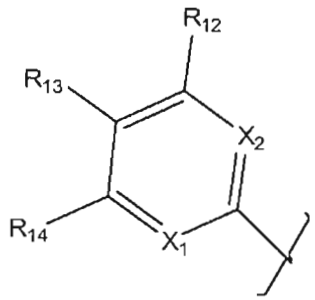
1. A compound represented by structural formula (V):



(V)

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



X_1 and X_2 are CH;

R_2 is an optionally substituted phenyl, an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrrolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally

substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an

optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl; and

p is 1 or 2.

2. The compound of Claim 1, wherein R_{12}, R_{13} and R_{14} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl.

3. The compound of Claim 2, wherein R_{12}, R_{13} and R_{14} are methoxy.

4. The compound of Claim 2, wherein R_2 is an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted pyridinyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted oxazolyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, or an optionally substituted benzofuranyl.

5. The compound of Claim 2, wherein R_2 is an optionally substituted phenyl.

6. The compound of Claim 5, wherein R_2 is substituted with one to five groups selected from alkoxy, halo, alkyl, haloalkyl, haloalkoxy, nitro, cyano, oxazolyl, 1*H*-tetrazolyl, 1-methyl-1*H*-tetrazolyl, $-OR_{24}$, $-SR_{24}$, $-C(O)R_{24}$, $-C(O)OR_{24}$, $-OC(O)R_{24}$, $-C(O)NR_{25}R_{26}$, $-NR_{24}C(O)R_{27}$, $-NR_{24}C(O)OR_{27}$, $-OC(O)NR_{25}R_{26}$, guanidino, amino, alkyl amino,

dialkylamino, $-NR_{24}S(O)_pR_{28}$, $-S(O)_pR_{28}$, $-S(O)_pOR_{27}$, $-OS(O)_pR_{28}$, $-OS(O)_pOR_{27}$, $-OP(O)(OR_{27})_2$, or $-SP(O)(OR_{27})_2$, wherein:

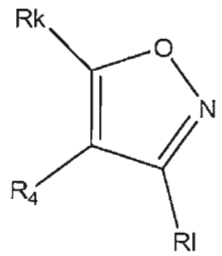
R_{24} and R_{27}, for each occurrence are, independently, H, an alkyl, or a cycloalkyl;

R_{25} and R_{26}, for each occurrence are, independently, H, an alkyl, or a cycloalkyl; or R_{25} and R_{26}, together with the nitrogen to which they are attached are a heterocyclyl or a heteroaryl; and

R_{28}, for each occurrence, is an alkyl or a cycloalkyl.

7. The compound of Claim 6, wherein R_2 is substituted with one alkoxy group and one amino group.

8. A compound represented by structural formula (VI):

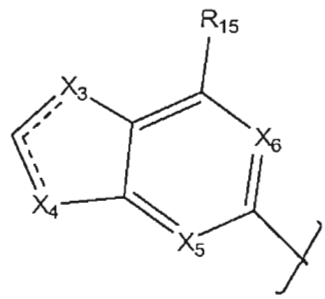


(VI)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

one of R_k or R_l is –H and the other is represented by the following formula:



the dashed line indicates that the bond is a single bond or a double bond;

X_3 and X_4 are each, independently, CH, N, CH_2, NR_{16}, O, or S;

X_5 and X_6 are each, independently, CR_{29} or N;

R_{15} is H, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{16} is H, an alkyl, a cycloalkyl, an aralkyl, -C(O)R, wherein R is an alkyl, a cycloalkyl, or an aralkyl;

R_{29}, for each occurrence, is independently, H or a substituent;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

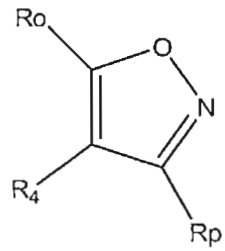
or

R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2.

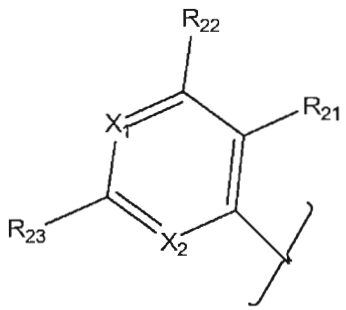
9. A compound represented by structural formula (VIII):



(VIII)

and pharmaceutically acceptable salts, solvates, clathrates, or prodrugs thereof, wherein:

one of R_o or R_p is –H and the other is represented by the following formula:



X_1 is N and X_2 is CH or N;

R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{22}, and R_{23} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted

heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

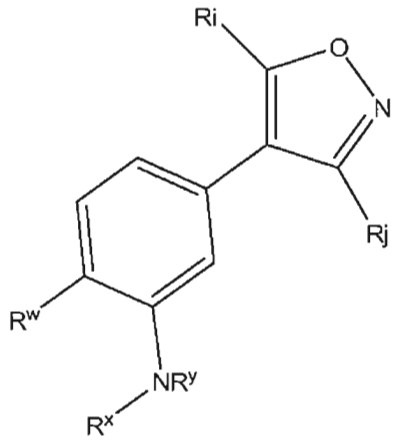
R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2.

10. The compound of Claim 9, wherein R_4 is an optionally substituted phenyl.

11. The compound of Claim 10, wherein R_4 is an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted pyridinyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted oxazolyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, or an optionally substituted benzofuranyl.

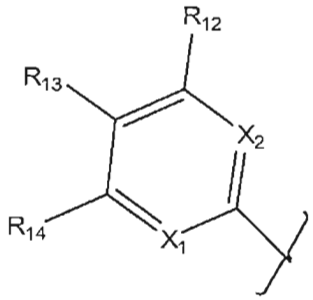
12. A compound represented by formula (VA):



(VA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



X_1 and X_2 are each, independently, CH or N;

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$,

$-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl; and

p is 1 or 2;

R^x is $(R^{aa})_m$, $-R^{aa}-C(O)(CH_2)_nC(O)OH$, $-C(O)(CH_2)_nC(O)OH$, $-C(O)YR^z$, $-C(O)NH-R^{aa}$, or $-(R^{aa})_qC(O)(Y_1)$;

R^y is –H or lower alkyl;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl;

R^{aa} is an amino acid residue or an amino acid residue analog;

Y is CH_2, O, or NH;

R^z is Alk-NH_2, Alk-C(O)OH, Het, or Y_1;

Alk is an optionally substituted alkylene;

Het is an optionally substituted heteroalkyl;

Y_1 is a water soluble polymer with a molecular weight less than 60,000 daltons;

n is 1, 2, 3, or 4;

m is an integer from 1 to 10; and

q is 0 or 1.

13. The compound of Claim 12, wherein R_i is –H.

14. The compound of Claim 12, wherein R_j is –H.

15. The compound of Claim 12, wherein X_1 and X_2 are CH.

16. The compound of Claim 15, wherein R_{12}, R_{13} and R_{14} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl.

17. The compound of Claim 16, wherein R_{12}, R_{13} and R_{14} are methoxy.

18. The compound of Claim 16, wherein R^y is –H.

19. The compound of Claim 16, wherein R^w is alkoxy.

20. The compound of Claim 19, wherein R^w is methoxy.

21. The compound of Claim 16, wherein R^x is R^{aa}, $-C(O)YR^z$, or $-C(O)NH-R^{aa}$.

22. The compound of Claim 21, wherein R^x is R^{aa}.

23. The compound of Claim 22, wherein R^{aa} is glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, phenylalanine, tyrosine, tryptophan, aspartic acid, asparagine, glutamic acid, glutamine, arginine, histidine, lysine, or proline.

24. The compound of Claim 21, wherein R^x is $-C(O)YR^z$.

25. The compound of Claim 24, wherein R^z is Y_1.

26. The compound of Claim 25, wherein Y_1 is PEG, HPMA copolymer-methacryloyl-Gly-Phe-Leu-Gly-ethylenediamine, or HPMA copolymer-methacryloyl-Gly-Phe-Leu-Gly-OH.

27. The compound of Claim 12, wherein

X_1 and X_2 are CH;

R_{12}, R_{13} and R_{14} are methoxy;

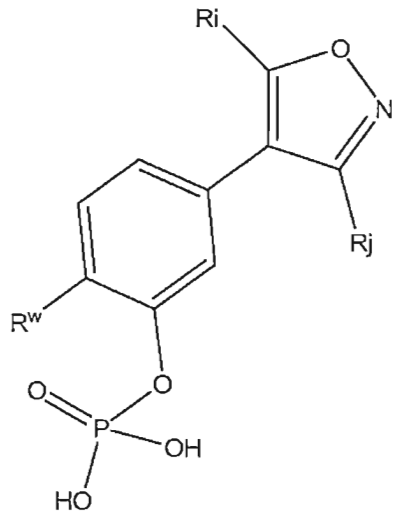
R_j is –H;

R^w is methoxy;

R^y is –H; and

R^x is R^{aa}.

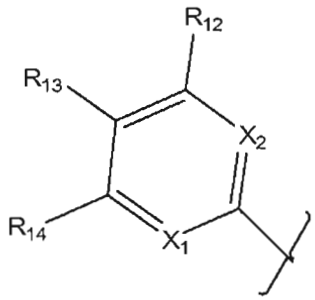
28. A compound represented by formula (VB):



(VB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



X_1 and X_2 are each, independently, CH or N;

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl; and

p is 1 or 2;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl.

29. The compound of Claim 28, wherein R_i is –H.

30. The compound of Claim 28, wherein R_j is –H.

31. The compound of Claim 28, wherein X_1 and X_2 are CH.

32. The compound of Claim 31, wherein R_{12}, R_{13} and R_{14} are each, independently, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl.

33. The compound of Claim 32, wherein R_{12}, R_{13} and R_{14} are methoxy.

34. The compound of Claim 33, wherein R^w is alkoxy.

35. The compound of Claim 34, wherein R^w is methoxy.

36. The compound of Claim 12, wherein the compound is selected from the group consisting of:

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride;

2-amino-3-hydroxy-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) butanamide;
2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenylpropanamide hydrochloride;
2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methylpentanamide hydrochloride;
2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride;
1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride;
1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-butyl-ammonium chloride;
2-hydroxy-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;
2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
C-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride;
2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
2-benzofuran-2-yl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
2-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
3-carboxyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;
3-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;
2-carbamoyl-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;
2-(3*H*-irnidazol-4-yl)-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

5-amino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride;

4-guanidino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid;

4-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid;

2-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride;

3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;

3-(2-PEG)-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide;

3-PEG-*N*-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide;

N-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid

{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester;

2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenylcarbamate-PEG;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid; or

2-amino-*N*-(2-methoxy-5-[5-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl) acetamide hydrochloride;

2-amino-3-hydroxy-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)propanamide;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-(methylthio)butanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)butanamide;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-phenylpropanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-4-methylpentanamide hydrochloride;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl)-3-(4-methoxyphenyl) propanamide hydrochloride;

1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2-methyl-propyl-ammonium chloride;

1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-2methyl-butyl-ammonium chloride;

2-hydroxy-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

2-(4-hydroxy-phenyl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

C-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-C-phenyl-methyl-ammonium chloride;

2-(1*H*-indol-2-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-benzofuran-2-yl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

3-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

3-carboxyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-propyl-ammonium chloride;

2-carbamoyl-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-ethyl-ammonium chloride;

2-(3*H*-imidazol-4-yl)-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]phenylcarbomoyl}-ethyl-ammonium chloride;

5-amino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-pentyl-ammonium chloride;

4-guanidino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbomoyl}-butyl-ammonium chloride

N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl} succinamic acid;

4-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butyric acid;

2-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-ethyl-ammonium chloride;

3-(2-methoxy-ethoxy)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionarnide;

3-(2-PEG)-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-propionamide;

N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-3-(2-methylamino-ethylamino)-propionamide;

3-PEG-*N*-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-propionamide;

N-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-methyl)-succinamic acid;

{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenyl}-carbamic acid 2-methoxy-ethyl ester;

2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylcarbamate-PEG;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

3-amino-*N*-[4-guanadino-1-{2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl]-phenylcarbamoyl}-butylcarbamoyl)-methyl]-succinamic acid;

2-amino-*N*-(2-methoxy-5-[3-(3,4,5-trimethoxy-phenyl)-isoxazol-4-yl)-phenyl); propanamide hydrochloride;

methyl-2-(2-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate;
4-amino-5-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride;
3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl) propanamide hydrochloride;
3-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride;
methyl-2-(2-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-2-oxoethylamino)acetate;
4-amino-5-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenylamino)-5-oxopentanoic acid hydrochloride;
3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl) propanamide hydrochloride; and
3-amino-N-(2-methoxy-5-(3-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-4-methylpentanamide hydrochloride;

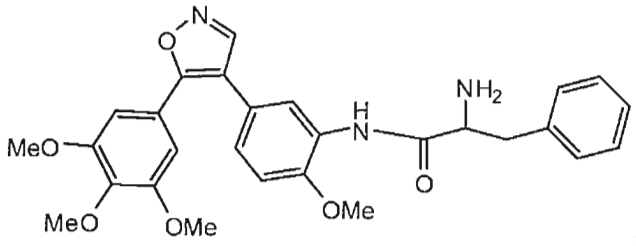
or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof.

37. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

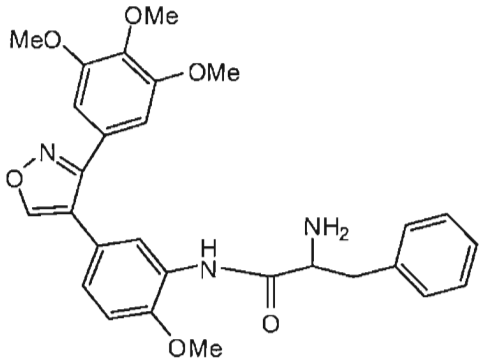
38. The pharmaceutical composition of Claim 37, further comprising one or more additional therapeutic agents.

39. The pharmaceutical composition according to Claim 38, wherein the additional therapeutic agent is an anti-cancer agent.

40. The compound of Claim 1, wherein the compound is selected from:

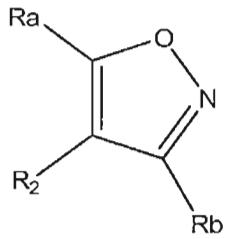


; and



or a pharmaceutically acceptable salt, solvate, or clathrate thereof.

41. Use of a compound represented by formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, clathrate, prodrug thereof, wherein:

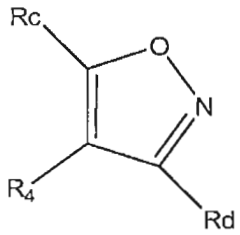
one of R_a or R_b is –H and the other is an optionally substituted phenyl; and

R_2 is an optionally substituted phenyl, an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an

optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrrolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl,

in the manufacture of a medicament for inhibiting tubulin polymerization in a cell.

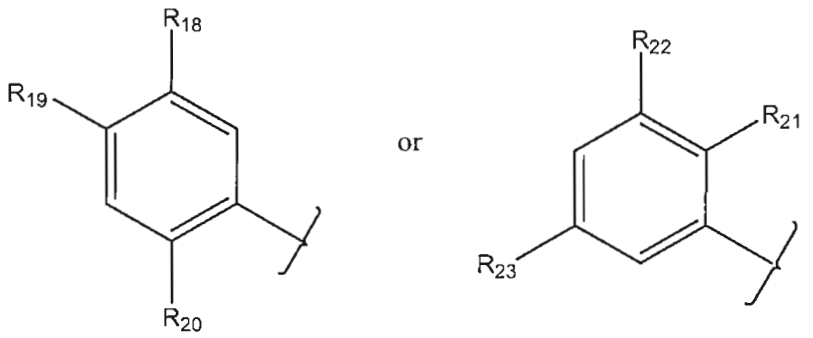
42. Use of a compound represented by formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, or a substituted phenyl represented by one of the following formulas:



R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an

optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

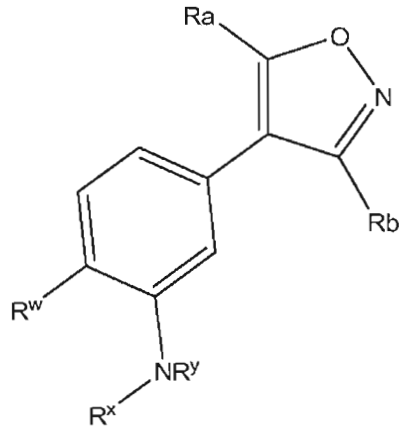
R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2,

in the manufacture of a medicament for inhibiting tubulin polymerization in a cell.

43. Use of a compound represented by formula (IA):



(IA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_a or R_b is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl;

R^x is $(R^{aa})_m$, $-R^{aa}-C(O)(CH_2)_nC(O)OH$, $-C(O)(CH_2)_nC(O)OH$, $-C(O)YR^z$, $-C(O)NH-R^{aa}$, or $-(R^{aa})_qC(O)(Y_1)$;

R^y is –H or lower alkyl;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl;

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R^{aa} is an amino acid residue or an amino acid residue analog;

Y is CH_2, O, or NH;

R^z is Alk-NH_2, Alk-C(O)OH, Het, or Y_1;

Alk is an optionally substituted alkylene;

Het is an optionally substituted heteroalkyl;

Y_1 is a water soluble polymer with a molecular weight less than 60,000 daltons;

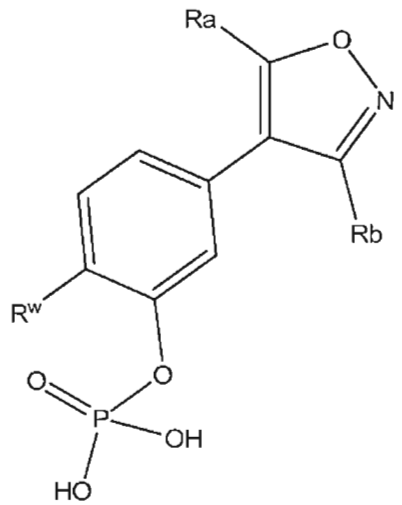
n is 1, 2, 3, or 4;

m is an integer from 1 to 10; and

q is 0 or 1,

in the manufacture of a medicament for inhibiting tubulin polymerization in a cell.

44. Use of a compound represented by formula (IB):



(IB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

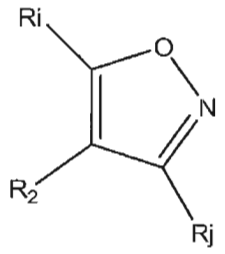
one of R_a or R_b is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl,

in the manufacture of a medicament for inhibiting tubulin polymerization in a cell.

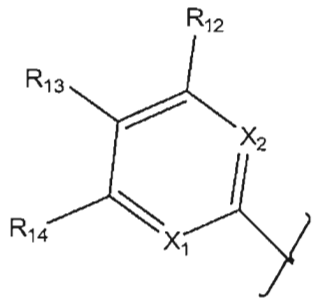
45. Use of a compound represented by formula (V):



(V)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_i or R_j is –H and the other is represented by the following formula:



X_1 and X_2 are CH;

R_{12}, R_{13} and R_{14} are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an

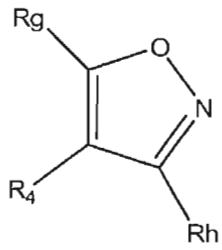
optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl; and

R_2 is an optionally substituted phenyl, an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted biphenyl, an optionally substituted 4-pyridinyl-phenyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrrolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro-benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted

pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl,
in the manufacture of a medicament for treating or preventing a proliferative disorder in a subject.

46. Use of a compound represented by formula (IV):

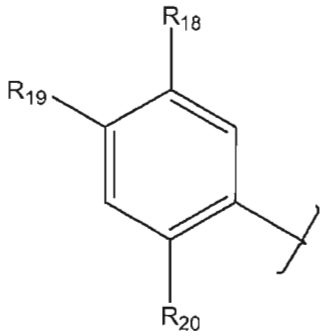


(IV)

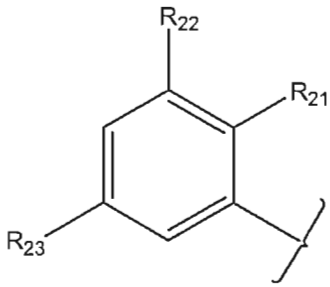
or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_g or R_h is –H and the other is:

i) an unsubstituted phenyl or a substituted phenyl represented by one of the following formulas:



or



; or

ii) an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl,

an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9*H*-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl; and

R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted

heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$,

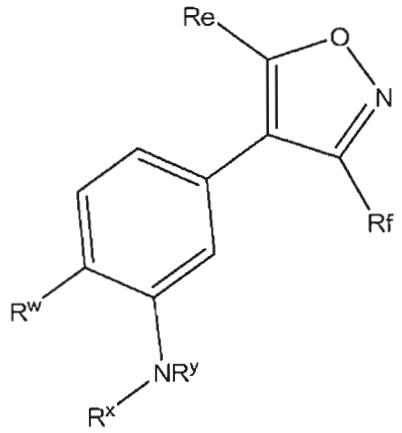
$-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2,

in the manufacture of a medicament for treating or preventing a proliferative disorder in a subject.

47. Use of a compound represented by formula (IIIA):



(IIIA)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_e or R_f is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally

substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl;

R^x is $(R^{aa})_m$, $-R^{aa}$-$C(O)(CH_2)_nC(O)OH$, $-C(O)(CH_2)_nC(O)OH$, $-C(O)YR^z$, $-C(O)NH-R^{aa}$, or $-(R^{aa})_qC(O)(Y_1)$;

R^y is –H or lower alkyl;

R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl;

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R^{aa} is an amino acid residue or an amino acid residue analog;

Y is CH_2, O, or NH;

R^z is Alk-NH_2, Alk-C(O)OH, Het, or Y_1;

Alk is an optionally substituted alkylene;

Het is an optionally substituted heteroalkyl;

Y_1 is a water soluble polymer with a molecular weight less than 60,000 daltons;

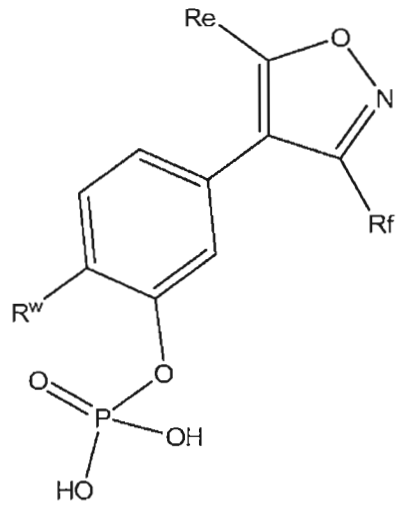
n is 1, 2, 3, or 4;

m is an integer from 1 to 10; and

q is 0 or 1,

in the manufacture of a medicament for treating or preventing a proliferative disorder in a subject.

48. Use of a compound represented by formula (IIIB):



(IIIB)

or a pharmaceutically acceptable salt, solvate, clathrate, or prodrug thereof, wherein:

one of R_e or R_f is –H and the other is an optionally substituted aryl or an optionally substituted heteroaryl selected from the group consisting of an optionally substituted 2,3-dihydro-benzo[1,4]dioxinyl, an optionally substituted benzo[1,3]dioxolyl, an optionally substituted quinolinyl, an optionally substituted isoquinolinyl, an optionally substituted 1H-indolyl, an optionally substituted pyridinyl, an optionally substituted oxazolyl, an optionally substituted isoxazolyl, an optionally substituted thiazolyl, an optionally substituted isothiazolyl, an optionally substituted imidazolyl, an optionally substituted pyrazolyl, an optionally substituted furanyl, an optionally substituted thiophenyl, an optionally substituted thiadiazolyl, an optionally substituted oxadiazolyl, an optionally substituted chromanyl, an optionally substituted

isochromanyl, an optionally substituted pyridazinyl, an optionally substituted pyrimidinyl, an optionally substituted pyrazinyl, an optionally substituted benzothiophenyl, an optionally substituted 2,3-dihydro-benzothiophenyl, an optionally substituted benzofuranyl, an optionally substituted 2,3-dihydro- benzofuranyl, an optionally substituted 1*H*-benzoimidazolyl, an optionally substituted benzothiazolyl, an optionally substituted benzooxazolyl, an optionally substituted 1*H*-benzotriazolyl, an optionally substituted 1*H*-indazolyl, an optionally substituted 9H-purinyl, an optionally substituted pyrrolopyrimidinyl, an optionally substituted pyrrolopyrazinyl, an optionally substituted pyrrolopyridazinyl, an optionally substituted imidazopyrazinyl, or an optionally substituted imidazolpyridazinyl;

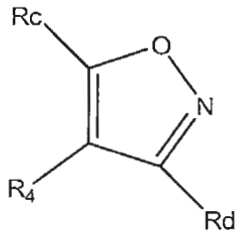
R^w is –H, an alkyl, an alkenyl, an alkynyl, cyano, a haloalkyl, an alkoxy, a haloalkoxy, a halo, an amino, an alkylamino, a dialkylamino, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, nitro, an alkyl ester, or hydroxyl; and

R_7 is -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl,

in the manufacture of a medicament for treating or preventing a proliferative disorder in a subject.

49. Use of of a compound according to any one of claims 1 to 36 and 40 in the manufacture of a medicament for blocking, occluding, or otherwise disrupting blood flow in neovasculature.

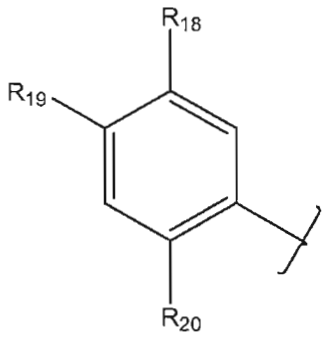
50. Use of a compound represented by formula (II):



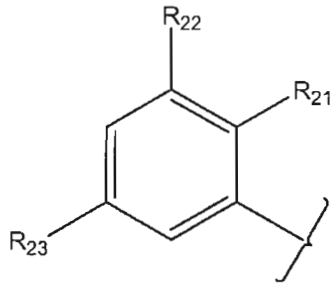
(II)

or a pharmaceutically acceptable salt, solvate, clathrate, and prodrug thereof, wherein:

one of R_c or R_d is –H and the other is an optionally substituted heteroaryl, an unsubstituted phenyl, or a substituted phenyl represented by one of the following formulas:



or



R_4 is an optionally substituted aryl or an optionally substituted heteroaryl;

R_{18}, R_{19}, R_{22}, and R_{23}, are each, independently, halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_7$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{20} is an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$,

$-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_{21} is halo, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, cyano, nitro, guanadino, a haloalkyl, a haloalkoxy, a heteroalkyl, $-OR_{17}$, $-NR_{10}R_{11}$, $-C(O)R_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-C(O)NR_{10}R_{11}$, $-NR_8C(O)R_7$, $-OP(O)(OR_7)_2$, $-SP(O)(OR_7)_2$, $-SR_7$, $-S(O)_pR_7$, $-OS(O)_pR_7$, $-S(O)_pOR_7$, $-NR_8S(O)_pR_7$, or $-S(O)_pNR_{10}R_{11}$;

R_7 and R_8, for each occurrence, are, independently, -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl;

R_{10} and R_{11}, for each occurrence, are independently -H, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, or an optionally substituted heteraralkyl; or R_{10} and R_{11}, taken together with the nitrogen to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

R_{17}, for each occurrence, is independently, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an

optionally substituted aralkyl, or an optionally substituted heteraralkyl; and

p is 1 or 2,

in the manufacture of a medicament for blocking, occluding, or otherwise disrupting blood flow in neovasculature.