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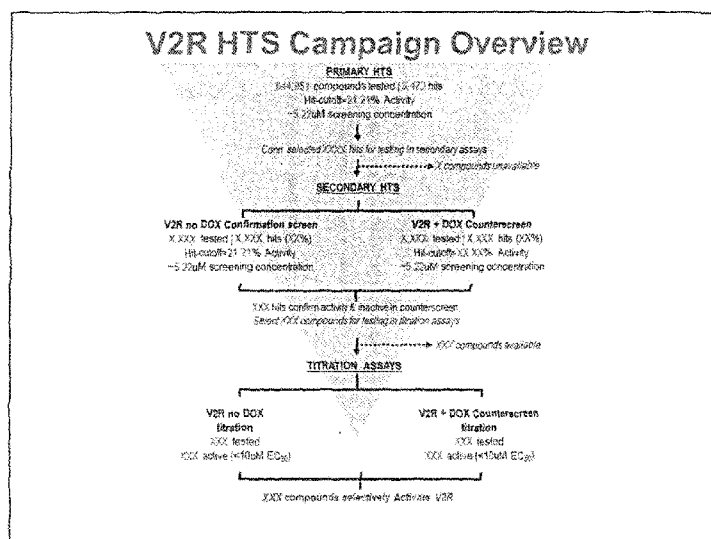


FIG. 1

(57) Abstract: The present invention includes compositions and methods for treating a subject with a G protein coupled receptors (GPCRs) misfolded, misrouted, or both misfolded and misrouted protein comprising: obtaining a sample from the subject suspected of having a G protein coupled receptor (GPCR) that is misfolded, misrouted, or both misfolded and misrouted; and providing the subject with an effective amount of a pharmacoperone that prevents misfolding, misrouting, or both misfolding and misrouting of the GPCR protein.

PHARMACOPERONES OF THE V2 RECEPTOR

Technical Field

The present invention relates in general to the field of compositions that aid in protein folding and promote correct trafficking in the cell, and more particularly, to novel pharmacoperones.

5 Background Art

Without limiting the scope of the invention, its background is described in connection with pharmacoperones.

One such invention is taught in U.S. Patent No. United States Patent 7,842,470, entitled “Method for pharmacoperones correction of GnRHR mutant protein misfolding”, by the present
10 inventor. Briefly, the application is directed to methods of identifying pharmacoperone agents that can restore function to a misfolded GnRHR mutant protein that causes a disease. Also disclosed are methods of using such pharmacoperone agents to treat a disease or disorder that results from the misfolded GnRHR mutant protein.

Another such invention is taught in U.S. Patent Publication No. 20110065661, filed by the
15 present inventor entitled, “Pharmacoperones for correcting disease states involving protein misfolding”. Briefly, the application is said to relate to methods for identifying pharmacoperone agents that can restore function to a misfolded protein, such as a misfolded protein that causes disease. Also disclosed are methods of using such pharmacoperone agents to treat a disease or disorder that results from the misfolded protein.

20 Another such invention is taught in U.S. Patent Publication No. 20110237538, filed by De Moor, et al., entitled “Treatment of lysosomal storage disorders and other proteostatic diseases”. These applicants are said to describe various compounds, in particular iminosugars, and methods for the treatment of proteostatic diseases, in particular lysosomal storage disorders. The compound may be a pharmacoperone of an enzyme selected from: (a) Acid alpha-glucosidase; (b) Acid
25 beta-glucosidase; (c) glucocerebrosidase; (d) alpha-Galactosidase A; (e) Acid beta-galactosidase; (f) beta-Hexosaminidase A; (g) beta-Hexosaminidase B; (h) Acid sphingomyelinase; (i) Galactocerebrosidase; (j) Acid ceramidase; (k) Arylsulfatase A; (l) alpha-L-Iduronidase; (m) Iduronate-2-sulfatase; (n) Heparin N-sulfatase; (o) alpha-N-Acetylglucosaminidase; (p) Acetyl-CoA: alpha-glucosaminide N-acetyltransferase; (q) N-
30 Acetylglucosamine-6-sulfate sulfatase; (r) N-Acetylgalactosamine-6-sulfate sulfatase; (s) Acid beta-galactosidase; (t) Arylsulfatase B; (u) beta-Glucuronidase; (v) Acid alpha-mannosidase; (w)

Acid beta-mannosidase; (x) Acid alpha-L-fucosidase; (y) Sialidase; and (z) alpha-N-acetylgalactosaminidase.

Disclosure of Invention

The present invention includes compounds and methods of treating a subject with a G protein coupled receptors (GPCRs) misfolded, misrouted, or both misfolded and misrouted protein comprising: obtaining a sample from the subject suspected of having a G protein coupled receptor (GPCR) that is misfolded, misrouted, or both misfolded and misrouted; and providing the subject with an effective amount of a pharmacoperone that prevents misfolding, misrouting, or both misfolding and misrouting of the GPCR protein. In one aspect, the misfolded, misrouted, or both misfolded and misrouted protein causes nephrogenic diabetes insipidus. In another aspect, the misfolded, misrouted, or both misfolded and misrouted protein is a vasopressin 2 receptor. In another aspect, the disease is caused by a misfolding and misrouting of the vasopressin type 2 receptor. In another aspect, the pharmacoperone is selected from at least one of a aminobenzothiazole amide, aminobenzothiazole benzamide, aminothiazole benzamide, aryl aminothiazole amide, aryl aminothiazole benzamide, a heteroaryl amide or other compounds as described in detail herein.

The present invention also includes method of evaluating a candidate drug believed to be useful in treating a disease caused by a misfolded and misdirected protein, the method comprising: a) obtaining a cell or tissue suspected of having a disease or condition caused by the misfolded and misdirected protein from a set of patients suspected of having a disease or condition; b) administering the candidate drug a cell or tissue of the patients, and a placebo to a second subset of cells or tissues that do not have the disease or disease condition; and c) determining if the candidate drug causes the protein to fold correctly and be directed to the correct cellular location that is statistically significant as compared to any change occurring in the second subset of cells or tissues, wherein a statistically significant reduction in misfolding and misdirecting of the protein indicates that the candidate drug is useful in treating said disease or condition. In one aspect, the candidate drug is selected from at least one of a aminobenzothiazole amide, aminobenzothiazole benzamide, aminothiazole benzamide, aryl aminothiazole amide, aryl aminothiazole benzamide, a heteroaryl amide or other compounds as described in detail herein.

Brief Description of Drawings

For a more complete understanding of the features and advantages of the present invention, reference is now made to the detailed description of the invention along with the accompanying figures and in which:

FIG. 1 shows the overview of the screen for vasopressin 2 receptor pharmacoperones.

5 FIG. 2 shows the overall results obtained from the initial screen.

FIG. 3 shows the Venn and Cluster ranking for the compounds screened.

FIG. 4 shows the detailed results for the final vasopressin 2 receptor pharmacoperones.

FIG. 5 begins on the page following FIG. 4 and lists the sample ID, the compound, and a graph with the dose response curve for each compound.

10 Description Of Invention

While the making and using of various embodiments of the present invention are discussed in detail below, it should be appreciated that the present invention provides many applicable inventive concepts that can be embodied in a wide variety of specific contexts. The specific embodiments discussed herein are merely illustrative of specific ways to make and use the
15 invention and do not delimit the scope of the invention.

To facilitate the understanding of this invention, a number of terms are defined below. Terms defined herein have meanings as commonly understood by a person of ordinary skill in the areas relevant to the present invention. Terms such as “a”, “an” and “the” are not intended to refer to only a singular entity, but include the general class of which a specific example may be used for
20 illustration. The terminology herein is used to describe specific embodiments of the invention, but their usage does not delimit the invention, except as outlined in the claims.

A number of definitions are provided herein to facilitate an understanding of the present invention. As used herein, the term “enveloped pharmaceutical” means a capsule, a suppository, a gel cap, a softgel, a lozenge, a sachet or even a fast dissolving wafer. As used herein the term
25 “carrier” is used to describe a substance, whether biodegradable or not, that is physiologically acceptable for human or animal use and may be pharmacologically active or inactive.

The term "immediate release" as used herein is used to describe a release profile to effect delivery of an active as soon as possible, that is, as soon as practically made available to an animal, whether in active form, as a precursor and/or as a metabolite. Immediate release may
30 also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient within about 60, 90, 100 or 120 minutes or less. Immediate release as used herein may also be

defined as making the active ingredient available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Immediate release formulations of the active on a carrier, such as rolled or compressed beads, may be formulated such that the surface area is maximized on beads and the active is exposed immediately. The immediate release formulations may also include effervescing agents that cause the disintegration of the structure integrity of the active and carrier such that release of the active is maximized. Various immediate release dosage forms may be designed readily by one of skill in art to achieve drug delivery to the stomach and small intestine, depending upon the choice of compression, adhesive materials and/or beading.

The immediate release actives of the present invention may be processed by agglomeration, air suspension chilling, air suspension drying, balling, coacervation, coating, comminution, compression, cryopelletization, encapsulation, extrusion, wet granulation, dry granulation, homogenization, inclusion complexation, lyophilization, melting, microencapsulation, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art. The extended release actives may be provided in the form of a minicapsule, a capsule, a tablet, an implant, a troche, a lozenge (minitab), a temporary or permanent suspension, a pellet, a bead, a pill, a strip or a sachet.

As used herein, the terms “extended release,” “sustained release,” and “delayed release” are used to define a release profile to effect delivery of an active over an extended period of time, defined herein as being between about 60 minutes and about 2, 4, 6, 8, 12 or even 24 hours. Extended release may also be defined functionally as the release of over 80 to 90 percent (%) of the active ingredient after about 60 minutes and about 2, 4, 6 or even 8 hours. Extended release as used herein may also be defined as making the active ingredient available to the patient or subject regardless of uptake, as some actives may never be absorbed by the animal. Various extended release dosage forms may be designed readily by one of skill in art as disclosed herein to achieve delivery to both the small and large intestines, to only the small intestine, or to only the large intestine, depending upon the choice of coating materials and/or coating thickness.

“Extended release” and “delayed release” formulations may be prepared and delivered so that release is accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. A method for delay of release is, e.g., a coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic

polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. Polymers and compatible mixtures thereof may be used to provide the coating for the delayed or the extended release of active ingredients, and some of their properties, include, but are not limited to: shellac, cellulose acetate, phthalate, resin, a purified lac (a refined product obtained from the resinous secretion of an insect). Generally, the coating dissolves in media of pH >7.

The pharmaceutical composition and/or the solid carrier particles can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings. Multiple coatings may be applied for desired performance. Further, one or more of the actives may be provided for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. In fact, the formulation may include combinations of typical pharmaceutical actives (e.g., pseudoephedrine) and vitamins (e.g., Vitamin C), minerals (Ca, Mg, Zn, K) or other supplements (e.g., St. John's Wort, echinaceae, amino acids). For release/absorption control, solid carriers can be made of various component types and levels or thicknesses of coats, with or without an active ingredient. Such diverse solid carriers can be blended in a dosage form to achieve a desired performance. The liquid formulations may be delivered to, and adapted for, oral, nasal, buccal, ocular, urethral, transmucosal, vaginal, topical or rectal delivery, although oral delivery is used mostly.

When formulated with microparticles or nanoparticles, the one or more actives the release profile can easily be adapted by adding, e.g., a hard or soft gelatin coating, a starch coating, a resin or polymer coating and/or a cellulosic coating. Although not limited to microparticles or nanoparticles (as in, e.g., microcapsules or nanocapsules), such dosage forms may be further coated with, for example, a seal coating, an enteric coating, an extended release coating, or a targeted delayed release coating. The term "enteric coating" as used herein relates to a mixture of pharmaceutically acceptable excipients that is applied to, combined with, mixed with or otherwise added to the carrier or composition. The coating may be applied to an active that is compressed, molded or extruded and may also include: gelatin, and/or pellets, beads, granules or particles of the carrier or composition. The coating may be applied through an aqueous dispersion or after dissolving in appropriate solvent. The carrier may or may not be fully or partially biodegradable.

Carriers for use with the present invention include permeable and semipermeable matrices or polymers that control the release characteristics of the formulation. Such polymers include, for

example, cellulose acrylates, acetates, and other semi-permeable polymers such as those described in U.S. Pat. No. 4,285,987 (hereby incorporated by reference), as well as the selectively permeable polymers formed by the coprecipitation of a polycation and a polyanion as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142 (relevant portions incorporated herein by reference).

Other carriers for use with the present invention include, e.g., starch, modified starch, and starch derivatives, gums, including but not limited to xanthan gum, alginic acid, other alginates, bentonite, veegum, agar, guar, locust bean gum, gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, potassium polymethacrylate, carrageenan (and derivatives), gum karaya and biosynthetic gum. Other examples of useful polymers include: polycarbonates (linear polyesters of carbonic acid); microporous materials (bisphenol, a microporous poly(vinylchloride), micro-porous polyamides, microporous modacrylic copolymers, microporous styrene-acrylic and its copolymers); porous polysulfones, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolics, polyesters, asymmetric porous polymers, cross-linked olefin polymers, hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and other similar materials, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone).

Additional additives and their levels, and selection of a primary coating material or materials will depend on the following properties: resistance to dissolution and disintegration in the stomach; impermeability to gastric fluids and drug/carrier/enzyme while in the stomach; ability to dissolve or disintegrate rapidly at the target intestine site; physical and chemical stability during storage; non-toxicity; easy application as a coating (substrate friendly); and economical practicality.

Dosage forms of the compositions of the present invention can also be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein that uses an enteric coating to effect release in the lower gastrointestinal tract. The enteric coated dosage form will generally include microparticles, microgranules, micropellets or microbeads of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form

may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

A dosage unit for use of the compound for preventing the misfolding of a vasopressin type 2 receptor (V2R) mutant protein of the present invention, also called a V2R pharmacological
5 chaperone, or pharmacoperone, may be a single compound or mixtures thereof with other compounds. The compounds may be mixed together, form ionic or even covalent bonds. The composition(s) of the present invention may be administered in oral, intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. Depending on the particular location
10 or method of delivery, different dosage forms, e.g., tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions may be used to provide the V2R pharmacoperone of the present invention to a patient in need of therapy that includes the V2R pharmacoperone in an amount effective to treat, e.g., nephrogenic diabetes insipidus, a disease caused by misfolding and misrouting of the vasopressin type 2 receptor. The V2R
15 pharmacoperone may also be administered as any one of known salt forms.

The V2R pharmacoperone is typically administered in admixture with suitable pharmaceutical salts, buffers, diluents, extenders, excipients and/or carriers (collectively referred to herein as a pharmaceutically acceptable carrier or carrier materials) selected based on the intended form of administration and as consistent with conventional pharmaceutical practices. Depending on the
20 best location for administration, the V2R pharmacoperone may be formulated to provide, e.g., maximum and/or consistent dosing for the particular form for oral, rectal, topical, intravenous injection or parenteral administration. While the V2R pharmacoperone may be administered alone, it will generally be provided in a stable salt form mixed with a pharmaceutically acceptable carrier. The carrier may be solid or liquid, depending on the type and/or location of
25 administration selected.

Techniques and compositions for making useful dosage forms using the present invention are described in one or more of the following references: Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill,
30 New York, 1990; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remington's Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The

Pharmaceutical Press, London, 1999); all of which are incorporated by reference, and the like, relevant portions incorporated herein by reference.

For example, the V2R pharmacoperone may be included in a tablet. Tablets may contain, e.g., suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents and/or melting agents. For example, oral administration may be in a dosage unit form of a tablet, gelcap, caplet or capsule, the active drug component being combined with an non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol, mixtures thereof, and the like. Suitable binders for use with the present invention include: starch, gelatin, natural sugars (e.g., glucose or beta-lactose), corn sweeteners, natural and synthetic gums (e.g., acacia, tragacanth or sodium alginate), carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants for use with the invention may include: sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, mixtures thereof, and the like. Disintegrators may include: starch, methyl cellulose, agar, bentonite, xanthan gum, mixtures thereof, and the like.

The V2R pharmacoperone may be administered in the form of liposome delivery systems, e.g., small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles, whether charged or uncharged. Liposomes may include one or more: phospholipids (e.g., cholesterol), stearylamine and/or phosphatidylcholines, mixtures thereof, and the like.

The V2R pharmacoperone may also be coupled to one or more soluble, biodegradable, bioacceptable polymers as drug carriers or as a prodrug. Such polymers may include: polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues, mixtures thereof, and the like. Furthermore, the V2R pharmacoperone may be coupled one or more biodegradable polymers to achieve controlled release of the V2R pharmacoperone, biodegradable polymers for use with the present invention include: polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels, mixtures thereof, and the like.

In one embodiment, gelatin capsules (gelcaps) may include the V2R pharmacoperone and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Like diluents may be used to make compressed tablets. Both tablets and

capsules may be manufactured as immediate-release, mixed-release or sustained-release formulations to provide for a range of release of medication over a period of minutes to hours. Compressed tablets may be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere. An enteric coating may be used to provide selective
5 disintegration in, e.g., the gastrointestinal tract.

For oral administration in a liquid dosage form, the oral drug components may be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in
10 water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents, mixtures thereof, and the like.

15 Liquid dosage forms for oral administration may also include coloring and flavoring agents that increase patient acceptance and therefore compliance with a dosing regimen. In general, water, a suitable oil, saline, aqueous dextrose (e.g., glucose, lactose and related sugar solutions) and glycols (e.g., propylene glycol or polyethylene glycols) may be used as suitable carriers for parenteral solutions. Solutions for parenteral administration include generally, a water soluble
20 salt of the active ingredient, suitable stabilizing agents, and if necessary, buffering salts. Antioxidizing agents such as sodium bisulfite, sodium sulfite and/or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Citric acid and its salts and sodium EDTA may also be included to increase stability. In addition, parenteral solutions may include pharmaceutically acceptable preservatives, e.g., benzalkonium chloride, methyl- or propyl-
25 paraben, and/or chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field, relevant portions incorporated herein by reference.

For direct delivery to the nasal passages, sinuses, mouth, throat, esophagous, trachea, lungs and alveoli, the V2R pharmacoperone may also be delivered as an intranasal form via use of a
30 suitable intranasal vehicle. For dermal and transdermal delivery, the V2R pharmacoperone may be delivered using lotions, creams, oils, elixirs, serums, transdermal skin patches and the like, as are well known to those of ordinary skill in that art. Parenteral and intravenous forms may also include pharmaceutically acceptable salts and/or minerals and other materials to make them

compatible with the type of injection or delivery system chosen, e.g., a buffered, isotonic solution. Examples of useful pharmaceutical dosage forms for administration of V2R pharmacoperone may include the following forms.

5 Capsules. Capsules may be prepared by filling standard two-piece hard gelatin capsules each with 10 to 500 milligrams of powdered active ingredient, 5 to 150 milligrams of lactose, 5 to 50 milligrams of cellulose and 6 milligrams magnesium stearate.

Soft Gelatin Capsules. A mixture of active ingredient is dissolved in a digestible oil such as soybean oil, cottonseed oil or olive oil. The active ingredient is prepared and injected by using a positive displacement pump into gelatin to form soft gelatin capsules containing, e.g., 100-500
10 milligrams of the active ingredient. The capsules are washed and dried.

Tablets. A large number of tablets are prepared by conventional procedures so that the dosage unit was 100-500 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 50-275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to
15 increase palatability or delay absorption.

To provide an effervescent tablet appropriate amounts of, e.g., monosodium citrate and sodium bicarbonate, are blended together and then roller compacted, in the absence of water, to form flakes that are then crushed to give granulates. The granulates are then combined with the active ingredient, drug and/or salt thereof, conventional beading or filling agents and, optionally,
20 sweeteners, flavors and lubricants.

Injectable solution. A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in deionized water and mixed with, e.g., up to 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized using, e.g., ultrafiltration.

25 Suspension. An aqueous suspension is prepared for oral administration so that each 5 ml contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 ml of vanillin.

For mini-tablets, the active ingredient is compressed into a hardness in the range 6 to 12 Kp. The hardness of the final tablets is influenced by the linear roller compaction strength used in
30 preparing the granulates, which are influenced by the particle size of, e.g., the monosodium hydrogen carbonate and sodium hydrogen carbonate. For smaller particle sizes, a linear roller compaction strength of about 15 to 20 KN/cm may be used.

Kits. The present invention also includes pharmaceutical kits useful, for example, for the treatment of cancer, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of V2R pharmacoperone. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Printed instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit. It should be understood that although the specified materials and conditions are important in practicing the invention, unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

The chemotherapeutic agents, V2R pharmacoperone is typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

The disclosed invention encompasses over 140 pharmacoperones for the treatment of nephrogenic diabetes insipidus (NDI) that were discovered/tested using an HTS assay already published by this inventor. The drugs are pharmacoperones of the V2 receptor, a protein whose mutation/misplacement causes NDI.

The present inventors have identified small molecules with a significant degree of novelty in therapeutic approach, relying on cellular mechanisms that are not currently represented in the Molecular Libraries assay pipeline; this offers an untapped opportunity for use of the HTS approach. Development of such assays is important and novel since the extensive use of agonist/antagonist screens alone means that useful chemical structures with the ability to control trafficking (without receptor agonism or antagonism) may be present in existing libraries, but have not been identified using existing methods. G protein coupled receptors (GPCRs) are frequently targeted in library screening, yet this approach generally relies on screens that identify agonists or antagonists and would have missed many of the drugs that will be identified in the proposed screens. We have recently developed an assay utilizing cell lines stably expressing a V2 receptor (V2R) mutant under the control of a tetracycline transactivator. This allows us to quantitate the level of functional and properly trafficked GPCRs present in each test well. Furthermore, the present inventor was able to easily turn V2R expression on and off, thus, being able to rapidly eliminate the majority of false positives from our screening results. This approach identified drugs for the treatment of nephrogenic diabetes insipidus, a disease caused by misfolding and misrouting of the vasopressin type 2 receptor, with a significant degree of novelty in therapeutic approach, relying on cellular mechanisms that are not currently represented in the molecular libraries assay pipeline; this offers an untapped opportunity for use of the HTS approach.

An assay for screening the Scripps Drug Discovery Library (SDDL) was used to miniaturize the primary hV2R[L83Q] pharmacoperone assay from its current 384-well format to a 1,536-well format and use this assay to screen a diversity-rich 10,000 compound subset of the SDDL.

Using the screen, it was possible to discover novel pharmacoperones from the entire >640,000 compound SDDL, which was screened in a tiered approach to identify and then confirm the potency of ~600 drug-like molecules. Hit-validation assays were to identify the molecules of the present invention.

Finally, the inventor was able to identify structure activity relations, prioritize hit series and confirm mechanism of action of the primary hits from both the existing compound libraries and other commercial sources. These, along with the primary hits, can be obtained and profiled for selectivity and non-specific toxicity. Orthogonal low throughput counter screens are used to confirm primary activity and identify less desirable compounds also acting as direct agonists or antagonists. While existing pharmacoperones were selected from antagonist screens; the present

inventor used the novel screen to identify pharmacoperones without the undesirable properties, which is a major advantage of the approach described herein.

The high throughput screening project is to identify pharmacoperone drugs of the Vasopressin 2 receptor (V2R). Figure 1 is an overview of the approach used to obtain the molecules for use
5 with the present invention.

The primary HTS. A total of 644,951 compounds were screened (517 plates) that identified 3,472 hits (0.54%). The S/B and Z' parameters were consistent with assay quality (S/B=4.83±0.84; Z' =0.73±0.09).

All 3,472 compounds were selected for confirmation and counterscreen (assays containing
10 +Doxycycline, which shuts the V2R gene off and should result in no activity of true pharmacoperones). This includes some cAMP mimetics that likely will be ruled out at counterscreen. These cAMP mimetics were included as these serve as a valuable control for the ability of the counterscreen to detect false positives.

From the primary V2R confirmation screen 1,694 compounds were selectively as active and a
15 Cluster ranking and Venn comparison was done. From this screen, 640 compounds were selected for dose response work based on Cluster Ranking and selectivity results.

Next, a V2R + DOX counterscreen (+DOX) was performed. The responses to forskolin (a false positive) and SR121463 (a positive control) were used and performed as expected. 3,734 compounds (15 plates) were screened in triplicate at 5.22 uM. The run statistics were
20 acceptable: S/B=7.08±0.32; Z' =0.84±0.03; Hit cutoff =16.35% (Average + 3SD DMSO-containing cells). There were 256 hits (6.86%).

Completion of the V2R CRC assays led to 147 compounds selectively as active. Dose Response plates can be used with LC-MS for confirmation of structure. A secondary assay can be used to further confirm activity and loss of activity in +Dox counterscreen in an orthologous assay and
25 evaluation of activity of the compounds identified as V2R antagonists.

Table 1 summarizes the results per compound in the various assays. The Compound Information, by sample ID, is the same in Table 1 as in FIG. 5, for example, the compound identified in the first row as SR-0100039454-1 is the first compound in FIG. 5, with the resulting graph also shown in FIG. 5.

30 Table 1. Summary of results per compound in the various assays.

Compound Information	Sample ID	SR-010003945 41-1	SR-010003969 78-1	SR-010005441 09-1	SR-010009137 32-1	SR-010004010 86-1	SR-010009064 63-1	SR-010009134 87-1	SR-010003969 77-1	SR-010009064 62-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	>	=	=	=	=	=	
	Final EC50 (M)	711.4E-9	1.1E-6	1.4E-6	1.5E-6	1.6E-6	1.7E-6	1.8E-6	1.9E-6	2.1E-6	
	Averaged Max % Response	62.98	91.44	61.05	51.41	87.04	86.25	86.18	90.81	66.25	
	StdDev Max % Response	3.16	1.05	8.42	4.45	0.40	1.93	2.01	0.87	3.73	
	Hill Slope	11.73	13.22	16.92		4.85	15.57	15.77	3.63	13.90	
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	16.2E-6	8.2E-6	9.3E-6	13.1E-6	9.3E-6	13.1E-6	13.1E-6	12.1E-6	13.1E-6	
	Averaged Max % Response	13.64	12.90	3.03	6.71	26.36	13.41	2.96	11.56	2.83	
	StdDev Max % Response	1.79	5.75	5.26	2.71	1.41	3.64	0.82	3.94	3.36	
	Hill Slope										
V2R No DOX Primay HTS	% Response	86.42	76.50	51.74	68.34	96.90	91.61	69.96	95.20	66.29	
V2R No Dox Confirmation	Avg % Response	96.12	100.55	81.35	82.46	91.71	97.52	88.05	95.69	95.87	
	StdDev % Response	1.77	0.27	1.83	2.30	0.82	0.86	1.21	0.70	0.62	
Promiscuity Analysis	Scripps FL Assays	2 of 46	1 of 46	1 of 46	2 of 18	2 of 44	3 of 18	1 of 18	1 of 46	2 of 18	

Compound Information	Sample ID	SR-010009119 23-1	SR-010009134 89-1	SR-010003970 12-1	SR-010009157 52-1	SR-010009134 93-1	SR-010009157 34-1	SR-010004265 69-1	SR-010004597 27-1	SR-010004010 63-1
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=
	Final EC50 (M)	2.2E-6	2.5E-6	3.E-6	3.E-6	3.1E-6	3.1E-6	3.4E-6	3.6E-6	3.6E-6
	Averaged Max % Response	84.55	81.23	71.05	84.92	70.94	82.49	73.49	60.75	89.76
	StdDev Max % Response	1.38	1.99	3.31	2.32	8.54	3.01	1.87	2.81	0.68
	Hill Slope	5.22	5.58	4.87	3.07	6.45	4.81	3.37	3.39	3.45
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>
	Final EC50 (M)	13.1E-6	13.1E-6	10.9E-6	13.1E-6	13.1E-6	13.1E-6	12.3E-6	10.9E-6	11.9E-6
	Averaged Max % Response	13.35	11.37	8.14	17.89	2.58	13.16	14.67	4.60	6.27
	StdDev Max % Response	4.55	6.15	1.15	5.68	5.57	4.32	4.16	5.61	4.76
	Hill Slope									
V2R No DOX Primay HTS	% Response	97.79	85.19	71.72	95.88	71.38	87.70	81.01	67.98	48.36
V2R No Dox Confirmation	Avg % Response	100.57	96.69	98.81	101.65	89.69	96.19	97.56	96.83	98.92
	StdDev % Response	0.64	1.24	0.38	0.83	2.38	1.25	0.84	0.29	0.49
Promiscuity Analysis	Scripps FL Assays	1 of 18	1 of 18	1 of 46	1 of 18	1 of 18	1 of 18	1 of 46	1 of 46	2 of 46

Compound Information	Sample ID	SR-010009134 92-1	SR-010009134 88-1	SR-010009134 98-1	SR-010009157 35-1	SR-010003970 00-1	SR-010009167 12-1	SR-010009134 86-1	SR-010009166 68-1	SR-010004772 49-1	V2R ACT LU MI_1536_3XE C50 DRUN1_05-12-2015
		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	3.8E-6	3.9E-6	4 E-6	4 E-6	4.1E-6	4.2E-6	4.4E-6	4.8E-6	999.4E-9	
	Averaged Max % Response	75.86	71.06	77.10	76.71	70.06	58.30	73.70	57.31	90.00	
	StdDev Max % Response	2.92	3.64	3.22	0.34	1.48	2.72	2.81	1.80	1.92	
	Hill Slope	4.82	4.72	3.21	3.61	12.06	11.28	14.70	10.96	3.43	
		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	13.1E-6	13.1E-6	13.1E-6	13.1E-6	11.8E-6	13.1E-6	13.1E-6	13.1E-6	9.2E-6	
	Averaged Max % Response	9.32	5.67	-1.1E+0	10.83	7.60	6.06	2.12	7.68	28.09	
	StdDev Max % Response	4.47	3.33	10.63	6.53	2.97	1.69	1.45	2.74	6.08	
	Hill Slope										
	% Response	92.95	77.50	80.60	37.99	37.39	72.10	77.44	65.23	100.61	
	V2R No DOX Primay HTS										
	Avg % Response	97.00	88.50	94.06	100.64	95.16	81.55	79.66	76.49	101.66	
	StdDev % Response	0.39	1.67	1.91	0.50	1.16	2.25	2.57	3.25	0.56	
	Scripps FL Assays	1 of 18	2 of 18	1 of 18	2 of 18	1 of 46	2 of 18	1 of 18	1 of 18	1 of 45	

Compound Information	Sample ID	SR-010003911 47-1	SR-010004771 09-1	SR-010003945 33-1	SR-010003933 45-1	SR-010003933 19-1	SR-010004772 57-1	SR-010009065 23-1	SR-010009108 68-1	SR-010003911 50-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	1.1E-6	1.4E-6	1.4E-6	1.4E-6	1.4E-6	1.6E-6	1.8E-6	1.8E-6	1.8E-6	
	Averaged Max % Response	69.00	85.83	69.64	75.99	75.87	84.61	84.24	64.57	83.19	
	StdDev Max % Response	7.21	3.28	0.88	3.60	5.56	2.53	2.79	8.68	1.24	
	Hill Slope	15.52	3.40	11.20	5.64	15.91	3.76	15.70	22.49	3.83	
V2R+DOX CounterScreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	8.4E-6	8.9E-6	9.2E-6	9.1E-6	10.4E-6	12.E-6	13.1E-6	13.1E-6	8.5E-6	
	Averaged Max % Response	1.13	17.44	1.85	15.48	2.99	19.29	5.93	9.29	19.77	
	StdDev Max % Response	3.40	4.75	6.48	7.71	3.97	1.99	2.30	2.33	5.89	
	Hill Slope										
V2R No DOX Primay HTS	% Response	53.67	88.48	39.37	86.50	37.62	65.69	77.32	27.44	73.37	
V2R No Dox Confirmation	Avg % Response	97.25	101.96	100.17	100.31	87.04	99.00	96.44	89.85	101.16	
	StdDev % Response	0.75	0.14	0.76	0.26	2.67	0.83	0.56	0.39	0.43	
Promiscuity Analysis	Scripps FL Assays	1 of 44	2 of 45	1 of 46	1 of 46	1 of 46	2 of 45	2 of 18	1 of 18	1 of 44	

Compound Information	Sample ID	SR-010009113 63-1	SR-010004200 20-1	SR-010005298 58-1	SR-010009065 24-1	SR-010003911 69-1	SR-010004495 45-1	SR-010009113 52-1	SR-010004773 13-1	SR-010003620 50-1	(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12- 2015
	Final EC50 (M)	1.8E-6	1.9E-6	1.9E-6	2.E-6	2.E-6	2.2E-6	2.2E-6	2.2E-6	2.3E-6	
	Averaged Max % Response	75.69	59.87	85.31	66.18	84.12	83.04	82.58	73.86	52.04	
	StdDev Max % Response	0.97	2.02	1.90	6.44	2.75	3.17	1.52	2.65	1.38	
	Hill Slope	15.72	15.52	3.29	14.74	3.97	4.68	5.33	4.00	14.08	
		>	>	>	>	>	>	>	>	>	
V2R+DOX Counterscreen Dose Response Assay	Final EC50 (M)	13.1E-6	11.9E-6	11.2E-6	13.1E-6	9.2E-6	11.1E-6	13.1E-6	12.6E-6	13.1E-6	
	Averaged Max % Response	4.67	13.98	28.51	11.93	13.61	17.69	16.01	14.50	14.82	
	StdDev Max % Response	6.64	7.90	1.79	4.03	4.57	0.81	2.67	2.63	4.28	
	Hill Slope										
V2R No DOX Primay HTS	% Response	89.84	87.02	81.44	50.40	53.33	84.06	72.18	82.05	60.97	
V2R No Dox Confirmation	Avg % Response	98.81	95.60	99.40	95.74	100.89	102.53	99.72	100.95	93.83	
	StdDev % Response	0.59	0.68	0.77	0.78	0.83	0.44	0.04	0.77	1.79	
Promiscuity Analysis	Scripps FL Assays	2 of 18	2 of 46	2 of 46	2 of 18	1 of 46	2 of 46	1 of 18	1 of 46	2 of 46	

Compound Information	Sample ID	SR-01000394536-1	SR-01000397010-1	SR-01000393346-1	SR-01000349662-1	SR-01000911785-1	SR-01000911361-1	SR-01000394915-1	SR-01000419948-1	SR-01000447644-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	2.4E-6	2.4E-6	2.4E-6	2.5E-6	2.5E-6	2.5E-6	2.5E-6	2.6E-6	2.6E-6	
	Averaged Max % Response	83.08	68.86	77.95	71.93	69.96	87.74	71.28	74.52	64.84	
	StdDev Max % Response	0.78	2.82	1.78	4.88	2.32	2.52	1.36	2.73	3.82	
	Hill Slope	3.67	6.51	4.05	4.85	5.86	4.94	3.39	3.71	5.02	
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	10.1E-6	10.E-6	10.5E-6	13.1E-6	13.1E-6	13.1E-6	10.1E-6	8.8E-6	12.5E-6	
	Averaged Max % Response	11.65	6.45	12.36	17.55	3.17	12.58	10.10	14.81	9.37	
	StdDev Max % Response	5.85	7.04	1.45	1.54	5.29	3.45	3.44	6.15	3.96	
	Hill Slope										
V2R No DOX Primay HTS	% Response	88.61	72.02	26.21	98.02	46.73	93.08	46.46	23.18	92.65	
V2R No Dox Confirmation	Avg % Response	102.72	98.18	99.58	100.47	93.03	99.29	100.31	101.20	96.60	
	StdDev % Response	0.41	1.81	1.04	0.78	0.70	0.97	0.56	0.55	1.38	
Promiscuity Analysis	Scripps FL Assays	2 of 46	1 of 46	1 of 46	2 of 46	2 of 18	1 of 18	1 of 46	1 of 46	1 of 46	

Compound Information	Sample ID	SR-010004246 25-1	SR-010004010 37-1	SR-010004211 38-1	SR-010009117 81-1	SR-010004199 45-1	SR-010004435 95-1	SR-010009174 75-1	SR-010002402 75-1	SR-010009113 50-1
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=
	Final EC50 (M)	2.7E-6	2.7E-6	2.8E-6	2.9E-6	2.9E-6	2.9E-6	3.E-6	3.E-6	3.E-6
	Averaged Max % Response	80.57	87.49	77.78	79.51	66.90	67.46	90.00	70.97	83.38
	StdDev Max % Response	3.52	1.15	3.95	1.46	0.79	2.61	1.49	5.10	0.99
	Hill Slope	4.74	4.79	3.33	3.61	5.02	12.71	4.80	4.36	4.81
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>
	Final EC50 (M)	12.6E-6	11.6E-6	11.5E-6	13.1E-6	8.6E-6	9.1E-6	13.1E-6	13.1E-6	13.1E-6
	Averaged Max % Response	6.02	16.89	15.69	16.20	16.51	7.98	5.76	17.86	16.59
	StdDev Max % Response	8.69	5.31	4.96	3.20	4.13	2.21	7.80	7.54	2.09
	Hill Slope									
V2R No DOX Primay HTS	% Response	65.05	99.37	60.74	79.61	89.58	48.37	74.42	93.82	92.30
V2R No Dox Confirmation	Avg % Response	100.13	100.60	102.28	95.13	88.68	94.31	93.98	100.02	98.53
	StdDev % Response	1.15	0.11	0.78	0.85	2.24	0.62	1.38	0.69	0.78
Promiscuity Analysis	Scripps FL Assays	2 of 46	2 of 44	2 of 46	1 of 18	1 of 46	1 of 46	2 of 18	2 of 46	2 of 18

Compound Information	Sample ID	SR-01000911779-1	SR-01000442265-1	SR-01000393320-1	SR-01000424623-1	SR-01000916723-1	SR-01000915656-1	SR-01000394964-1	SR-01000394917-1	SR-01000422037-1
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=
	Final EC50 (M)	3.1E-6	3.1E-6	3.2E-6	3.2E-6	3.2E-6	3.2E-6	3.2E-6	3.2E-6	3.3E-6
	Averaged Max % Response	85.99	78.96	61.28	77.09	88.80	67.94	60.52	61.84	79.81
	StdDev Max % Response	1.31	4.41	4.00	2.23	1.41	5.33	3.24	5.14	4.13
	Hill Slope	4.37	2.77	5.27	4.33	4.88	5.25	9.95	16.15	3.95
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>
	Final EC50 (M)	13.1E-6	9.9E-6	10.4E-6	13.1E-6	13.1E-6	13.1E-6	9.3E-6	9.2E-6	10.6E-6
	Averaged Max % Response	14.26	20.10	5.85	8.28	5.43	5.45	11.55	7.22	16.46
	StdDev Max % Response	4.95	4.56	4.76	3.38	5.74	6.30	5.51	4.20	1.99
	Hill Slope									
V2R No DOX Primay HTS	% Response	64.21	23.40	80.51	78.99	24.32	80.16	22.50	52.39	74.25
V2R No Dox Confirmation	Avg % Response	100.17	99.86	89.36	100.58	97.28	92.37	95.45	95.92	98.77
	StdDev % Response	0.56	0.60	1.35	0.48	0.43	0.26	0.61	1.74	0.23
Promiscuity Analysis	Scripps FL Assays	1 of 18	1 of 46	1 of 46	1 of 46	1 of 18	1 of 18	1 of 46	2 of 46	1 of 46

Compound Information	Sample ID	SR-01000401062-1	SR-01000916659-1	SR-01000392464-1	SR-01000200653-1	SR-01000911359-1	SR-01000917351-1	SR-01000447365-1	SR-01000420021-1	SR-01000911792-1
(155.4.1.1) V2R ACT LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=
	Final EC50 (M)	3.3E-6	3.4E-6	3.4E-6	3.4E-6	3.5E-6	3.5E-6	3.6E-6	3.6E-6	3.7E-6
	Averaged Max % Response	59.22	81.43	61.86	75.30	74.73	56.44	56.40	52.25	60.11
	StdDev Max % Response	2.28	2.55	4.35	1.67	0.94	3.10	3.33	4.45	3.47
	Hill Slope	13.14	5.97	3.67	4.40	15.34	7.25	17.63	5.18	4.44
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>
	Final EC50 (M)	8.9E-6	13.1E-6	9.6E-6	13.1E-6	13.1E-6	13.1E-6	11.1E-6	10.6E-6	13.1E-6
	Averaged Max % Response	10.55	11.11	11.11	13.23	11.29	3.23	9.80	7.02	5.58
	StdDev Max % Response	2.80	1.89	4.23	3.21	7.53	5.70	4.13	5.53	6.09
	Hill Slope									
V2R No DOX Primay HTS	% Response	93.65	97.16	64.14	86.28	85.22	77.14	22.70	31.58	89.55
V2R No Dox Confirmation	Avg % Response	80.80	89.54	88.02	98.50	96.97	83.47	94.84	99.82	97.18
	StdDev % Response	2.87	1.12	0.66	1.18	0.63	1.11	0.67	1.55	1.19
Promiscuity Analysis	Scripps FL Assays	1 of 44	1 of 18	2 of 46	2 of 47	1 of 18	1 of 18	1 of 46	1 of 46	2 of 18

Compound Information	Sample ID	SR-010003945 31-1	SR-010003924 61-1	SR-010004010 83-1	SR-010009085 72-1	SR-010009156 38-1	SR-010009166 57-1	SR-010009129 43-1	SR-010004495 46-1	SR-010009065 13-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	3.7E-6	3.7E-6	3.8E-6	3.9E-6	3.9E-6	3.9E-6	4.E-6	4.E-6	4.1E-6	
	Averaged Max % Response	76.44	59.73	71.34	71.34	77.84	71.08	75.11	71.68	79.12	
	StdDev Max % Response	3.63	4.87	3.74	3.65	1.51	2.40	4.00	3.93	2.66	
	Hill Slope	4.28	3.56	11.86	2.85	3.25	13.70	3.81	5.94	4.13	
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	10.E-6	10.4E-6	9.9E-6	13.1E-6	13.1E-6	13.1E-6	13.1E-6	11.8E-6	13.1E-6	
	Averaged Max % Response	8.58	3.76	7.82	5.70	5.44	6.47	10.64	9.47	6.48	
	StdDev Max % Response	4.92	4.78	2.63	5.39	6.47	5.63	2.16	2.56	7.32	
	Hill Slope										
V2R No DOX Primay HTS	% Response	54.99	41.27	32.19	75.81	81.40	82.50	89.29	76.70	26.21	
V2R No Dox Confirmation	Avg % Response	84.77	100.09	98.79	93.16	97.19	89.28	94.43	95.86	98.23	
	StdDev % Response	1.00	0.57	0.77	0.75	1.43	1.96	1.53	1.15	0.39	
Promiscuity Analysis	Scripps FL Assays	1 of 46	1 of 46	1 of 44	2 of 18	2 of 18	2 of 18	2 of 18	2 of 46	1 of 18	

Compound Information	Sample ID	SR-010004010 70-1	SR-010009113 48-1	SR-010003970 09-1	SR-010009174 74-1	SR-010004243 23-1	SR-010000052 18-1	SR-010003924 41-1	SR-010003912 00-1	SR-010004010 48-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	4.1E-6	4.2E-6	4.2E-6	4.3E-6	4.3E-6	4.3E-6	4.3E-6	4.4E-6	4.4E-6	
	Averaged Max % Response	74.96	77.61	63.59	65.12	53.75	55.21	67.57	52.54	54.20	
	StdDev Max % Response	4.07	3.12	1.79	3.06	6.67	5.05	4.73	3.00	5.92	
	Hill Slope	7.93	14.87	17.64	3.86	4.05	4.44	9.93	11.79	4.20	
V2R+DOX CounterScreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	12.7E-6	13.1E-6	11.7E-6	13.1E-6	9.5E-6	13.4E-6	12.5E-6	10.6E-6	10.4E-6	
	Averaged Max % Response	6.46	10.13	7.26	-392.4E-3	8.59	12.64	9.13	6.07	7.14	
	StdDev Max % Response	1.57	1.18	5.10	1.31	5.85	2.86	3.65	3.98	3.42	
	Hill Slope										
V2R No DOX Primay HTS	% Response	65.91	70.26	56.29	82.44	49.61	66.72	78.32	64.42	59.59	
V2R No Dox Confirmation	Avg % Response	92.22	102.35	89.39	93.29	87.78	96.81	90.28	93.55	85.70	
	StdDev % Response	0.46	0.76	0.64	1.49	1.38	1.10	1.09	2.73	4.47	
Promiscuity Analysis	Scripps FL Assays	2 of 46	1 of 18	2 of 46	1 of 18	1 of 46	2 of 45	1 of 46	1 of 46	1 of 44	

Compound Information	Sample ID	SR-01000401082-1	SR-01000911357-1	SR-01000394983-1	SR-01000911360-1	SR-01000911353-1	SR-01000917473-1	SR-01000005216-1	SR-01000396109-1	SR-01000477312-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	4.4E-6	4.5E-6	4.6E-6	4.7E-6	4.7E-6	4.8E-6	4.8E-6	4.8E-6	4.9E-6	
	Averaged Max % Response	53.94	71.36	61.58	78.08	75.99	69.30	65.23	63.11	58.05	
	StdDev Max % Response	3.02	0.70	4.93	1.58	1.33	2.03	0.84	3.37	3.13	
	Hill Slope	8.52	4.00	11.19	4.20	12.67	5.40	3.15	2.78	3.07	
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	9.1E-6	13.1E-6	12.E-6	13.1E-6	13.1E-6	13.1E-6	13.4E-6	9.6E-6	13.1E-6	
	Averaged Max % Response	7.01	10.96	10.51	6.32	3.94	6.24	18.80	0.64	17.77	
	StdDev Max % Response	3.48	4.11	4.41	5.94	8.21	4.43	2.87	8.32	4.39	
	Hill Slope										
V2R No DOX Primay HTS	% Response	32.18	66.56	40.00	50.78	46.78	65.55	79.60	40.26	83.42	
V2R No Dox Confirmation	Avg % Response	97.73	93.17	80.03	97.29	86.94	88.84	94.29	95.90	98.45	
	StdDev % Response	1.57	1.57	1.48	0.87	1.34	0.76	1.17	1.81	0.66	
Promiscuity Analysis	Scripps FL Assays	1 of 44	1 of 18	2 of 46	2 of 18	1 of 18	1 of 18	1 of 45	1 of 46	1 of 46	

Compound Information	Sample ID	SR-010009113 49-1	SR-010009137 36-1	SR-010009174 64-1	SR-010005855 03-1	SR-010005856 25-1	SR-010005895 32-1	SR-010004371 85-1	SR-010004372 64-1	SR-010005884 33-1
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=
	Final EC50 (M)	4.9E-6	4.9E-6	4.9E-6	1.4E-6	2.E-6	2.E-6	2.5E-6	3.2E-6	3.2E-6
	Averaged Max % Response	58.63	56.56	65.26	88.82	82.40	90.10	85.06	83.41	66.61
	StdDev Max % Response	2.80	2.37	1.10	1.46	1.10	1.21	2.05	4.94	3.68
	Hill Slope	15.95	10.12	12.49	10.25	3.27	2.90	3.58	5.18	3.45
V2R+DOX CounterScreen Dose Response Assay		>	>	>	>	>	>	>	>	>
	Final EC50 (M)	13.1E-6	13.1E-6	13.1E-6	11.3E-6	8.6E-6	11.1E-6	12.5E-6	10.7E-6	12.3E-6
	Averaged Max % Response	7.20	4.56	2.12	29.15	8.78	20.59	15.54	5.41	8.33
	StdDev Max % Response	2.11	6.56	4.42	2.20	4.64	3.64	2.09	2.48	0.98
	Hill Slope									
V2R No DOX Primay HTS	% Response	85.93	30.76	65.64	94.47	76.46	83.31	73.29	51.54	88.00
V2R No Dox Confirmation	Avg % Response	91.92	82.60	81.92	100.62	93.62	99.61	97.89	96.06	93.57
	StdDev % Response	1.06	2.73	0.36	0.40	1.83	0.31	0.52	0.68	1.20
Promiscuity Analysis	Scripps FL Assays	2 of 18	1 of 18	1 of 18	2 of 46	2 of 46	2 of 46	1 of 46	1 of 46	1 of 46

Compound Information	Sample ID	SR-010004686 29-1	SR-010004366 66-1	SR-010005884 37-1	SR-010003969 80-1	SR-010005896 23-1	SR-010000115 40-1	SR-010004100 23-1	SR-010009238 75-1	SR-010004926 19-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	3.4E-6	3.9E-6	4.1E-6	4.1E-6	4.2E-6	4.9E-6	1.9E-6	2.1E-6	2.4E-6	
	Averaged Max % Response	66.62	74.91	55.71	52.90	72.89	56.27	63.73	63.07	70.39	
	StdDev Max % Response	5.98	2.97	6.31	3.35	4.34	4.08	8.14	9.39	3.76	
	Hill Slope	1.85	3.39	4.14	4.76	3.22	14.97	5.53	18.04	4.64	
V2R+DOX CounterScreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	8.5E-6	11.1E-6	11.6E-6	9.2E-6	12.1E-6	13.4E-6	10.3E-6	13.1E-6	10.2E-6	
	Averaged Max % Response	11.23	10.40	13.63	6.59	4.12	9.59	11.44	28.41	12.18	
	StdDev Max % Response	3.08	1.62	8.39	4.59	3.23	4.29	4.67	3.19	3.36	
	Hill Slope										
V2R No DOX Primay HTS	% Response	55.43	67.61	44.43	78.49	79.68	84.15	49.12	51.50	91.86	
V2R No Dox Confirmation	Avg % Response	97.69	94.74	83.86	95.78	94.58	94.38	78.85	54.84	98.54	
	StdDev % Response	2.07	0.90	1.96	0.23	1.50	0.90	2.88	6.42	0.49	
Promiscuity Analysis	Scripps FL Assays	1 of 46	2 of 46	1 of 46	1 of 46	1 of 46	3 of 46	2 of 44	2 of 18	1 of 46	

Compound Information	Sample ID	SR-010009079 38-1	SR-010004316 13-1	SR-010002813 89-1	SR-010004920 22-1	SR-010005805 59-1	SR-010004223 52-1	SR-010009119 18-1	SR-010004315 75-1	SR-010005811 58-1	
(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015		=	=	=	=	=	=	=	=	=	
	Final EC50 (M)	2.6E-6	2.9E-6	3.1E-6	3.1E-6	3.3E-6	3.4E-6	3.5E-6	3.7E-6	4.E-6	
	Averaged Max % Response	76.33	85.14	84.00	72.92	76.55	66.11	70.65	66.25	69.26	
	StdDev Max % Response	0.71	3.71	1.99	1.37	4.18	2.02	1.16	3.52	6.52	
	Hill Slope	3.69	5.19	2.96	11.97	4.05	18.37	3.28	3.47	3.20	
V2R+DOX Counterscreen Dose Response Assay		>	>	>	>	>	>	>	>	>	
	Final EC50 (M)	13.1E-6	12.4E-6	13.1E-6	9.7E-6	8.1E-6	9.7E-6	13.1E-6	11.7E-6	10.8E-6	
	Averaged Max % Response	6.79	18.92	5.95	11.33	7.62	2.74	0.64	8.01	13.60	
	StdDev Max % Response	5.34	1.63	4.74	4.16	2.54	10.45	3.43	1.37	4.85	
	Hill Slope										
V2R No DOX Primay HTS	% Response	84.36	91.06	97.90	60.19	60.62	72.88	92.96	59.82	63.55	
V2R No Dox Confirmation	Avg % Response	95.60	102.23	99.24	94.36	85.79	92.86	91.90	100.41	92.19	
	StdDev % Response	1.08	0.77	0.20	0.80	2.25	0.33	2.31	0.88	0.82	
Promiscuity Analysis	Scripps FL Assays	1 of 18	2 of 46	1 of 46	2 of 46	2 of 46	2 of 46	2 of 18	1 of 46	1 of 44	

Compound Information	Sample ID	SR-01000280097-1	SR-01000577991-1	SR-01000368909-1	SR-01000313707-1	SR-01000577475-1	SR-01000582228-1	SR-01000330960-1	(155.4.1.1) V2R_ACT_LU MI_1536_3XE C50 DRUN1_05-12-2015
V2R+DOX Counterscreen Dose Response Assay	Final EC50 (M)	4.1E-6	4.2E-6	4.4E-6	4.5E-6	4.6E-6	4.6E-6	4.7E-6	V2R No DOX Primay HTS
	Averaged Max % Response	54.11	73.03	96.96	65.15	51.46	50.79	56.77	
	StdDev Max % Response	1.62	5.85	4.58	3.84	3.35	3.30	5.13	
	Hill Slope	1.76	2.79	51.54	12.93	11.61	10.77	5.40	
		>	>	>	>	>	>	>	
V2R No DOX Confirmation	Final EC50 (M)	13.1E-6	11E-6	13.1E-6	13.1E-6	10.3E-6	9.4E-6	13.1E-6	Promiscuity Analysis
	Averaged Max % Response	13.30	10.77	42.09	16.95	4.46	9.89	9.09	
	StdDev Max % Response	3.31	2.79	2.38	3.21	1.46	5.69	6.61	
	Hill Slope								
	% Response	69.93	74.81	93.07	71.79	65.34	24.02	92.31	
Scripps FL Assays	Avg % Response	90.82	88.59	86.10	92.15	85.93	49.55	89.76	Scripps FL Assays
	StdDev % Response	1.09	0.78	1.86	3.04	2.78	0.95	2.63	
Scripps FL Assays		2 of 46	2 of 44	2 of 46	2 of 46	2 of 44	1 of 46	1 of 46	

It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, kit, reagent, or composition of the invention, and vice versa. Furthermore, compositions of the invention can be used to achieve methods of the invention.

It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims.

All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.” The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.” Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form of containing, such as “contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited elements or method steps. In embodiments of any of the compositions and methods provided herein, “comprising” may be replaced with “consisting essentially of” or “consisting of”. As used herein, the phrase “consisting essentially of” requires the specified integer(s) or steps as well as those that do not materially affect the character or function of the claimed invention. As used herein, the term “consisting” is used to indicate the presence of the recited integer (e.g., a feature, an element, a characteristic, a property, a method/process step or a limitation) or group of integers (e.g., feature(s), element(s), characteristic(s), propertie(s), method/process steps or limitation(s)) only.

The term “or combinations thereof” as used herein refers to all permutations and combinations of the listed items preceding the term. For example, “A, B, C, or combinations thereof” is

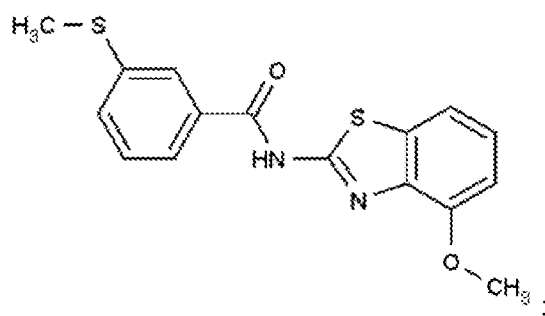
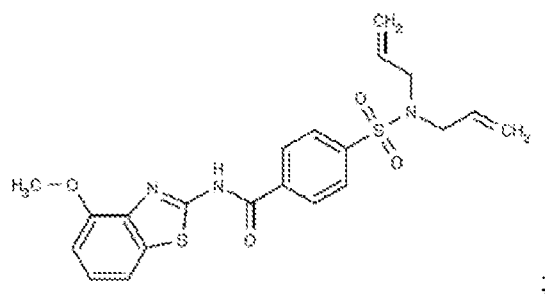
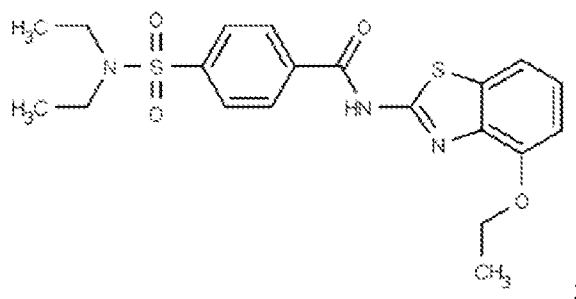
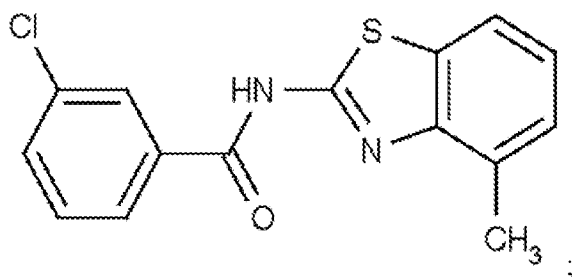
intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, AB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled
5 artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

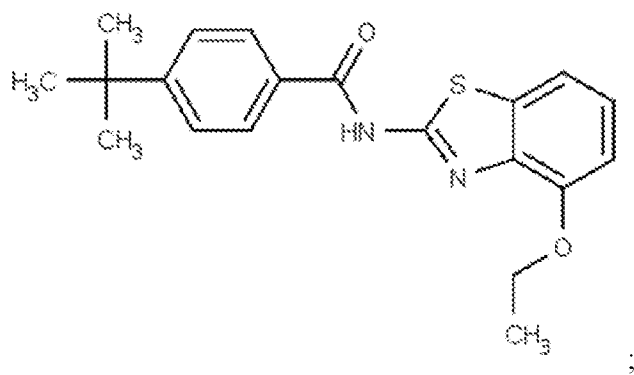
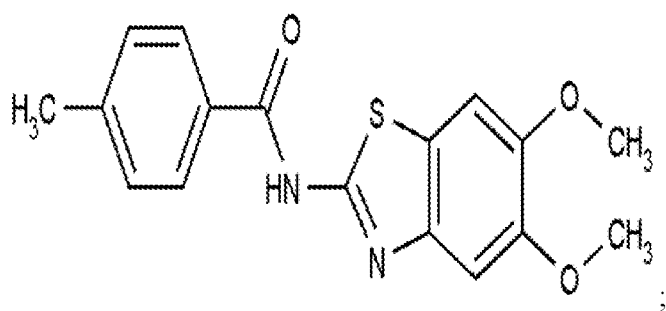
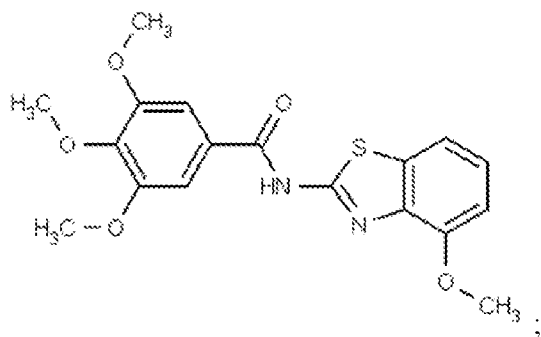
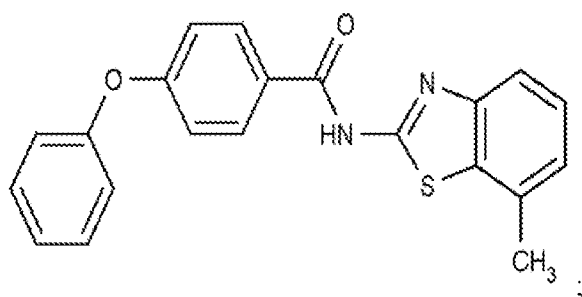
As used herein, words of approximation such as, without limitation, "about", "substantial" or "substantially" refers to a condition that when so modified is understood to not necessarily be absolute or perfect but would be considered close enough to those of ordinary skill in the art to
10 warrant designating the condition as being present. The extent to which the description may vary will depend on how great a change can be instituted and still have one of ordinary skilled in the art recognize the modified feature as still having the required characteristics and capabilities of the unmodified feature. In general, but subject to the preceding discussion, a numerical value herein that is modified by a word of approximation such as "about" may vary from the stated
15 value by at least $\pm 1, 2, 3, 4, 5, 6, 7, 10, 12$ or 15%.

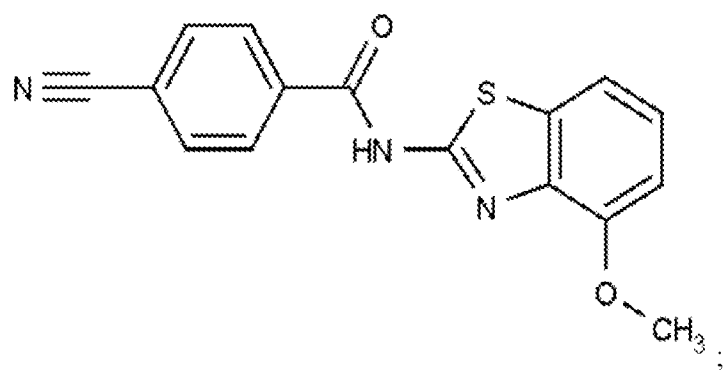
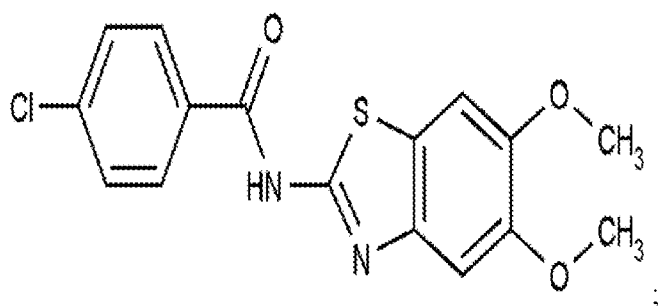
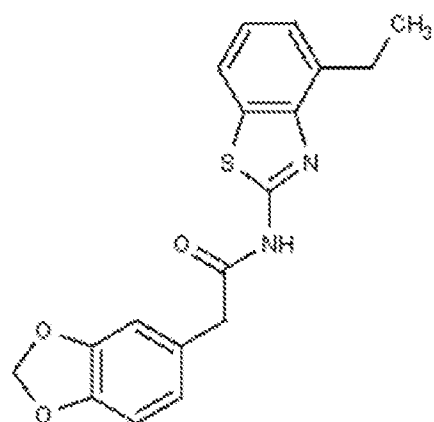
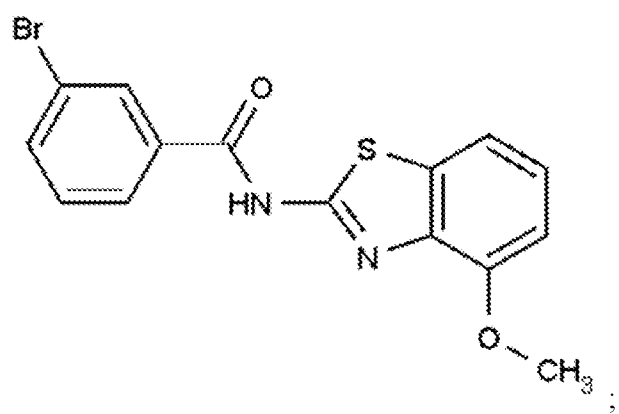
All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or
20 methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

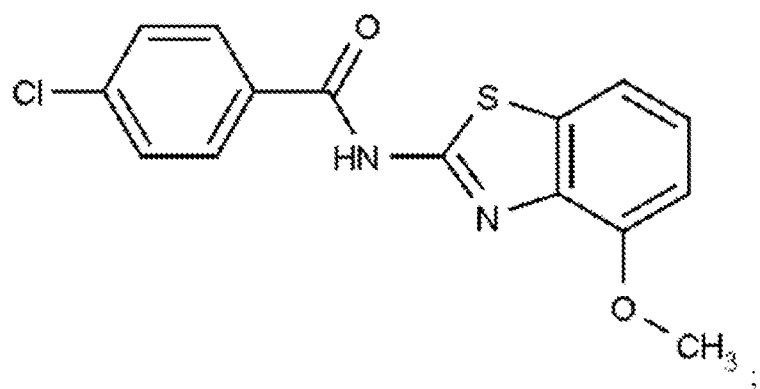
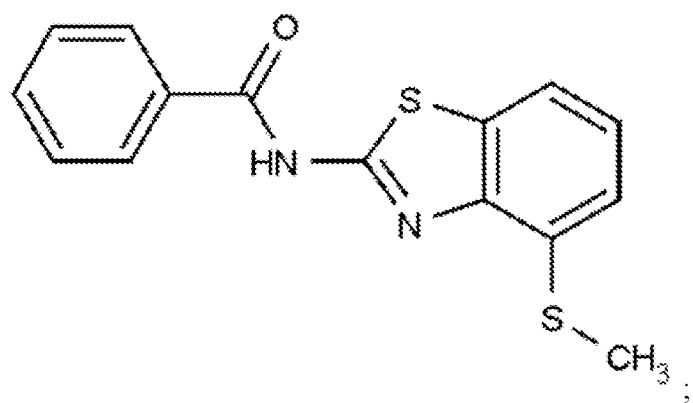
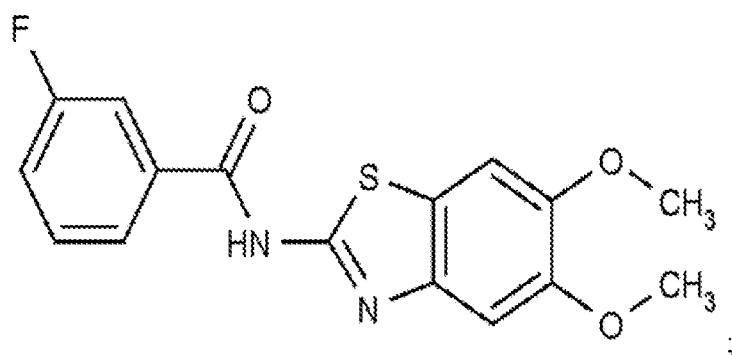
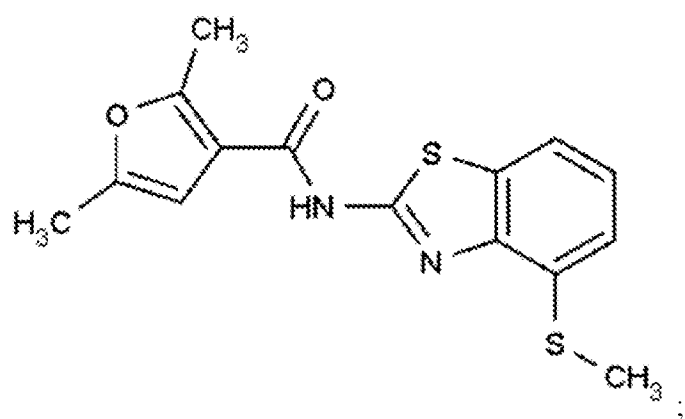
Claims

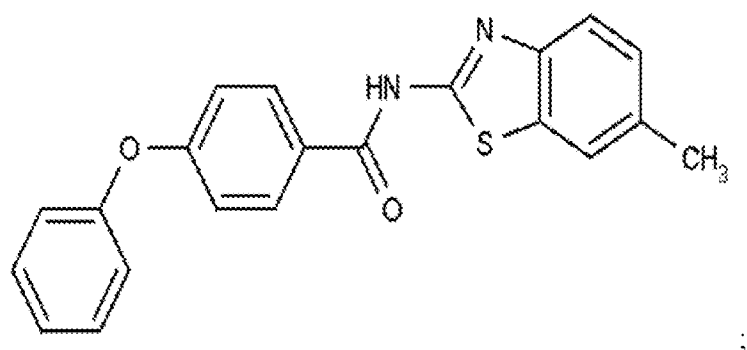
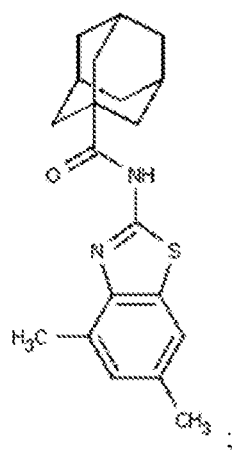
1. A composition for correcting the misfolding on a vasopressin type 2 receptor (V2R) mutant protein in a cell comprising an effective amount of one or more of the following compounds:

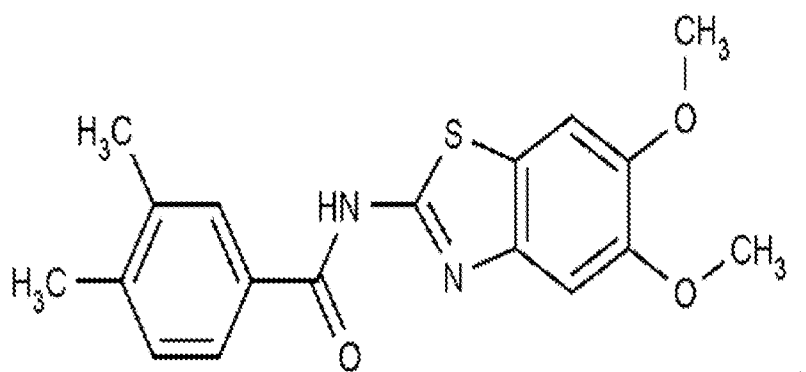




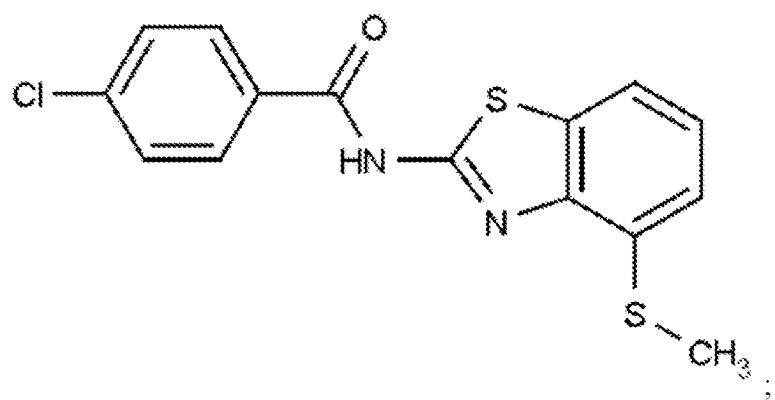




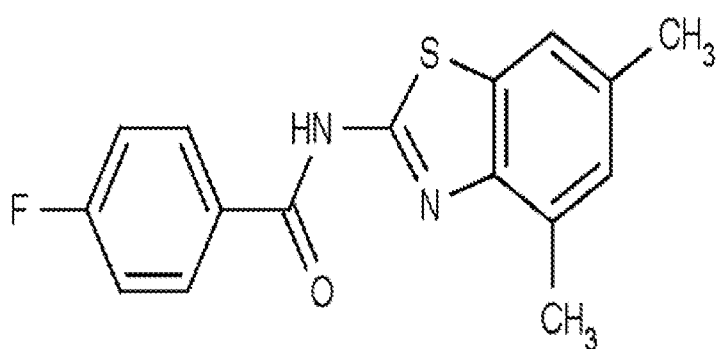




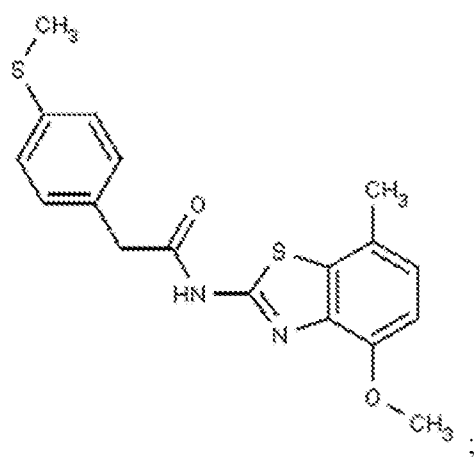
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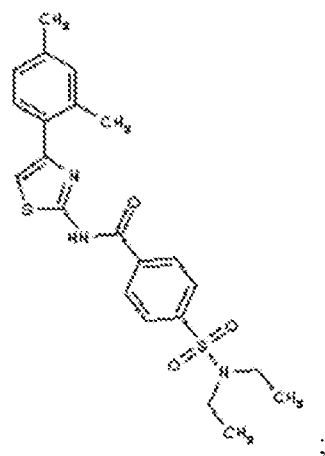
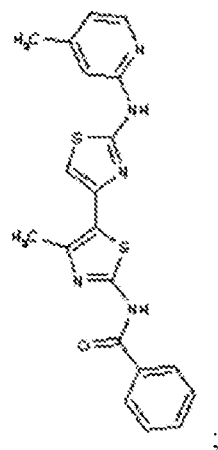
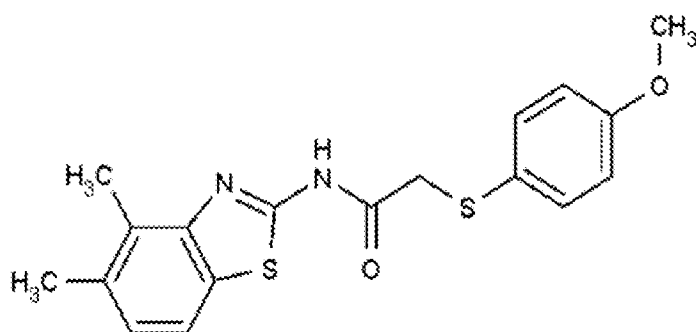
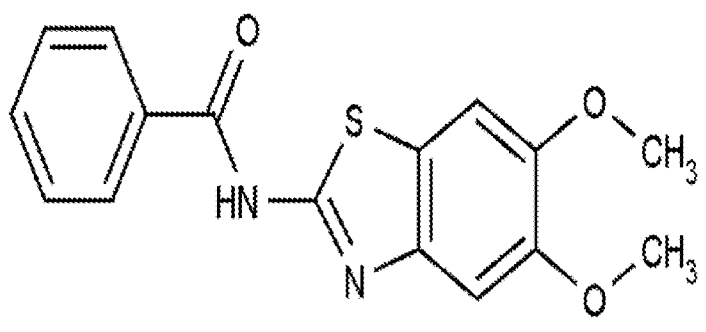


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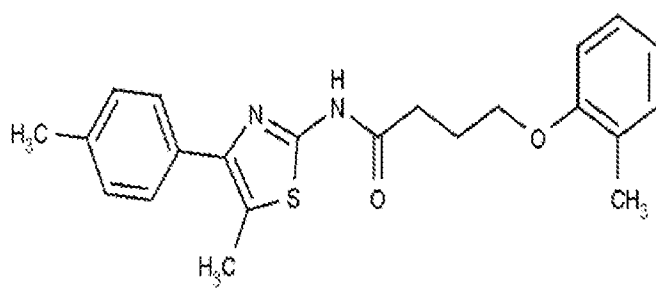


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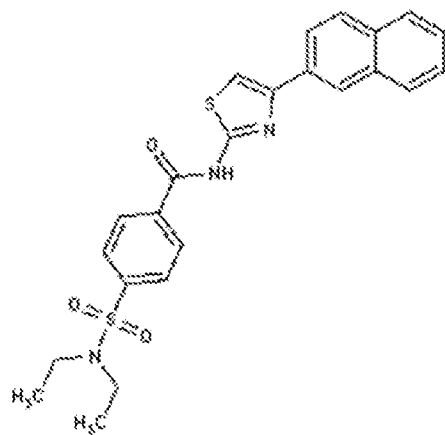




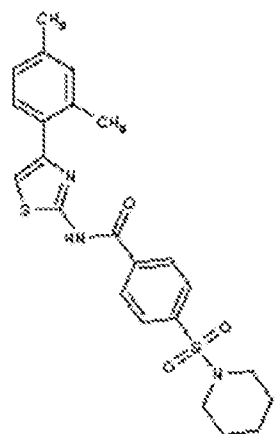
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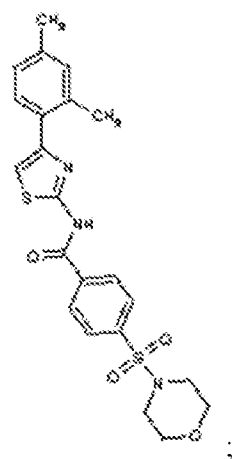
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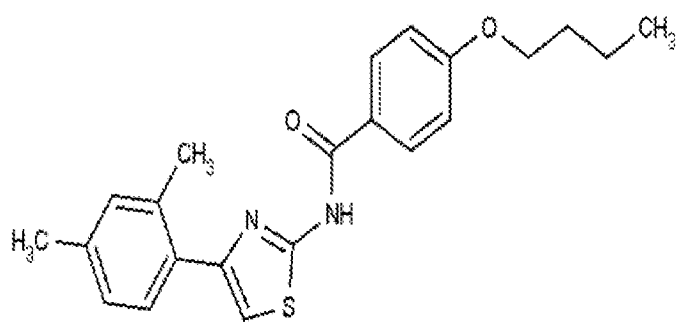
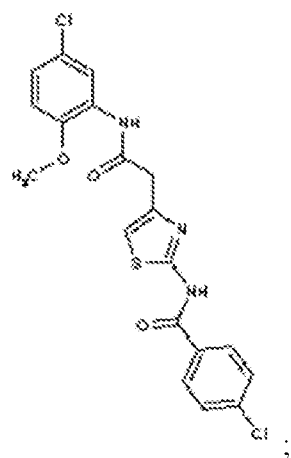
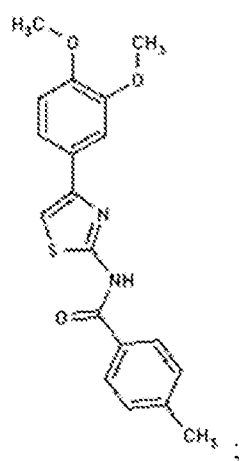
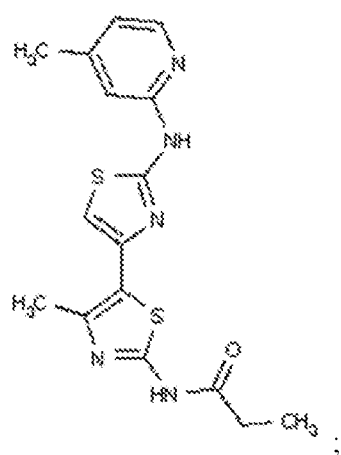
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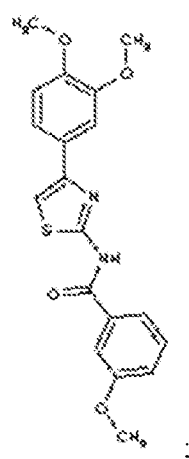
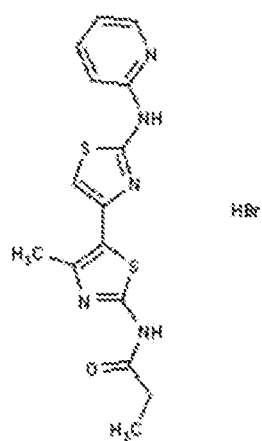
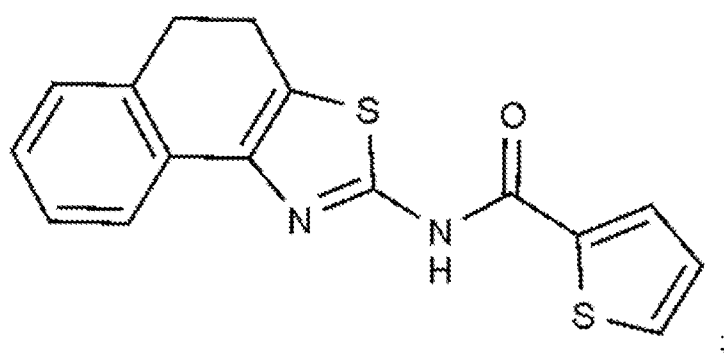
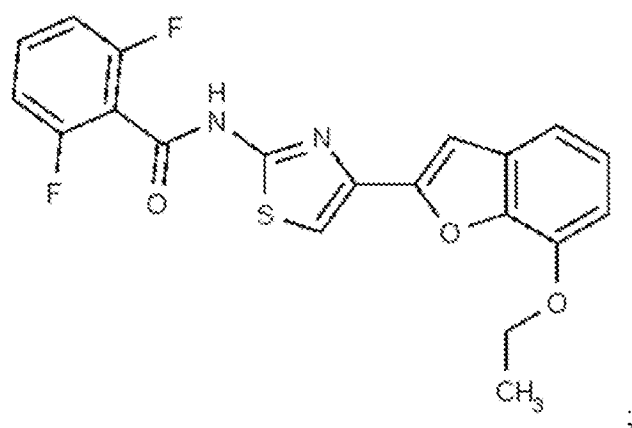


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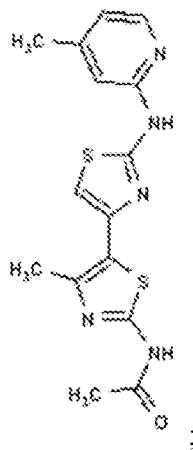
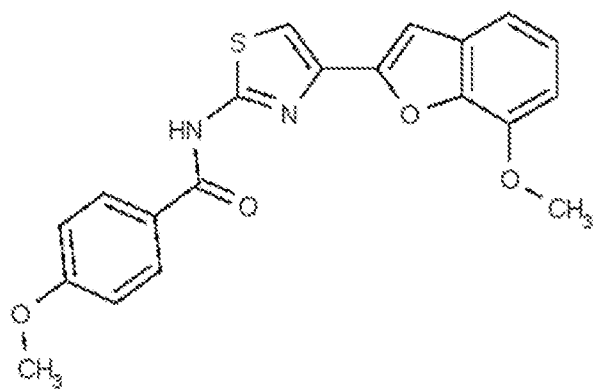
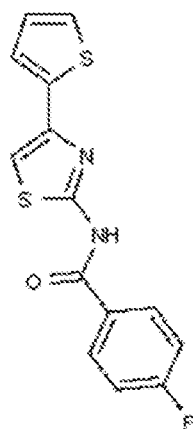
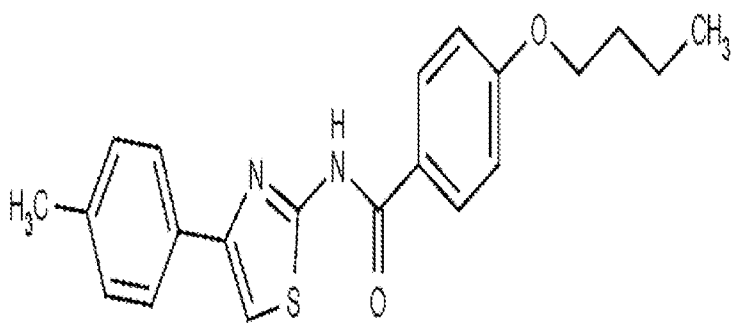


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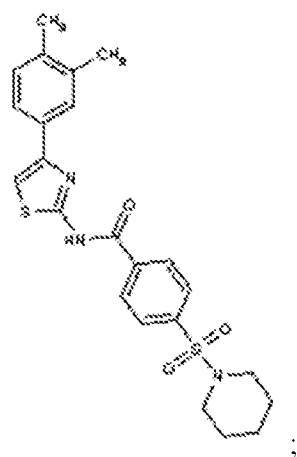
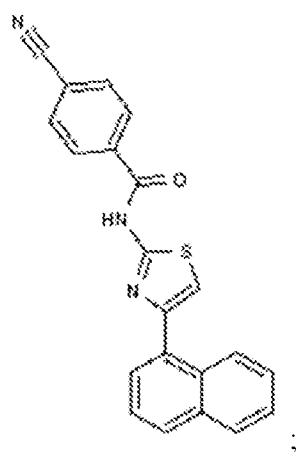
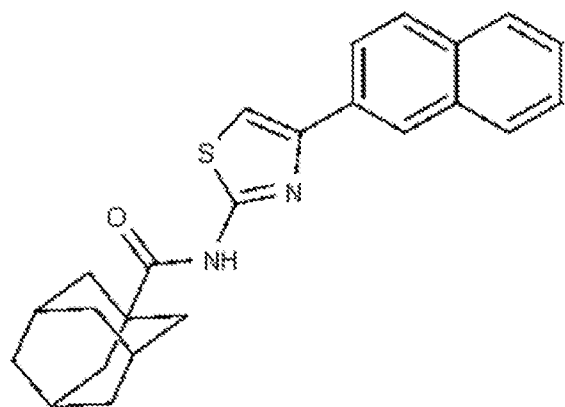
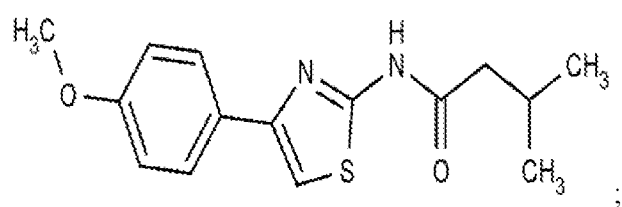
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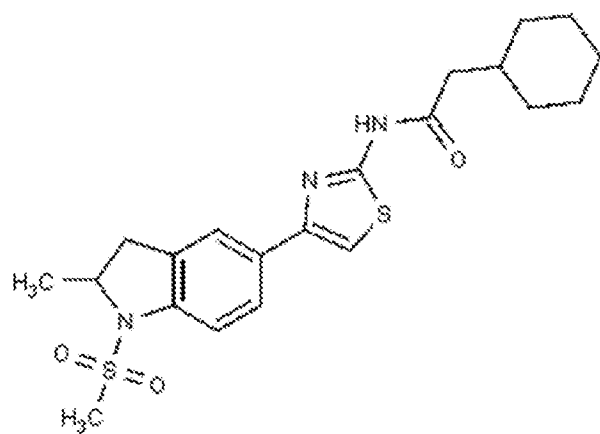
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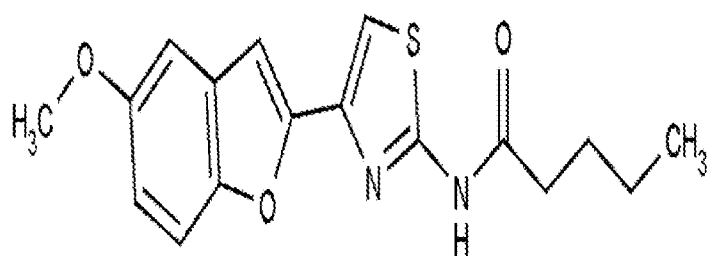
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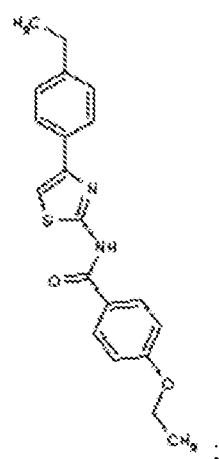
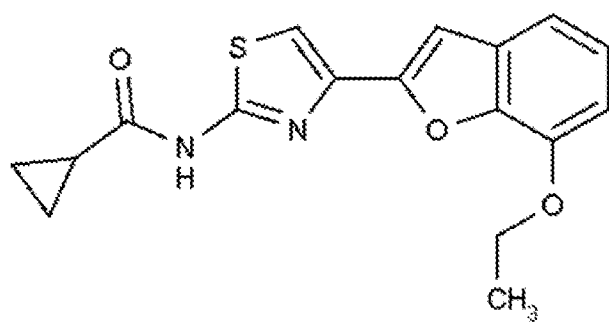
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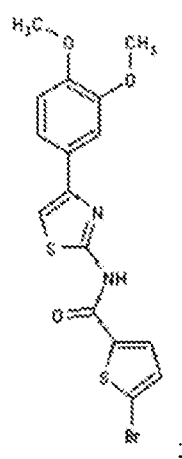
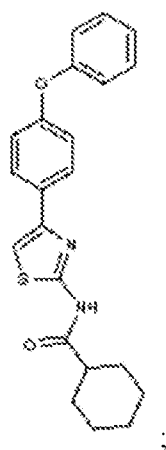


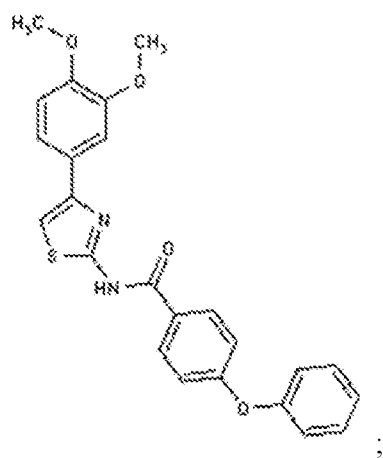
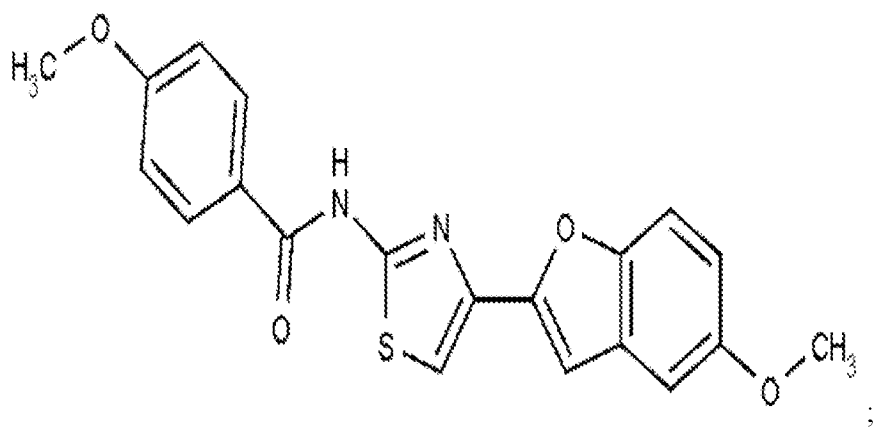
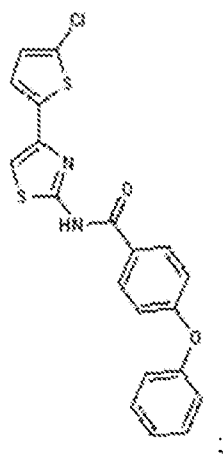
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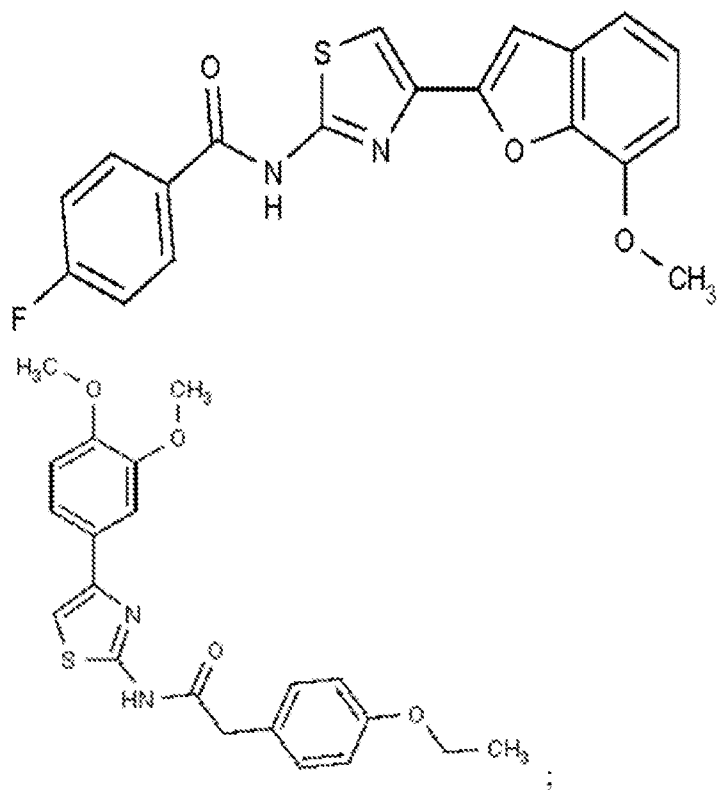
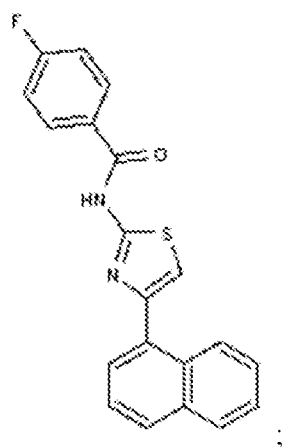
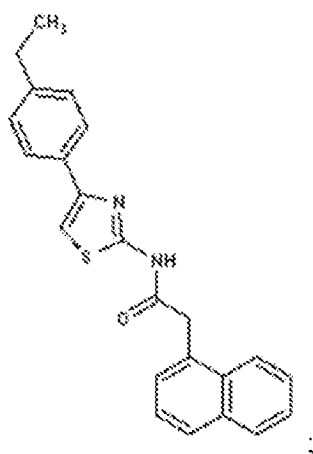


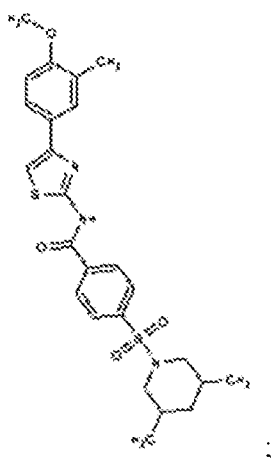
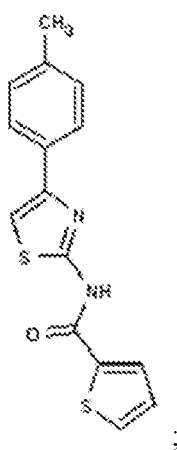
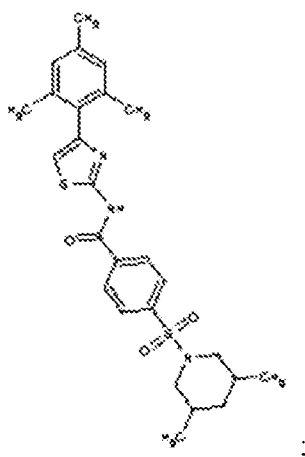
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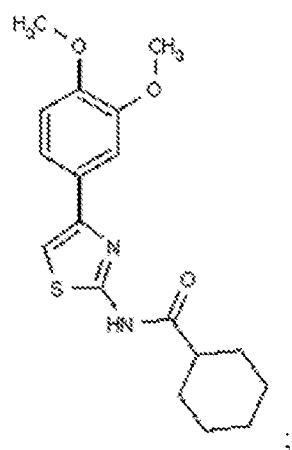
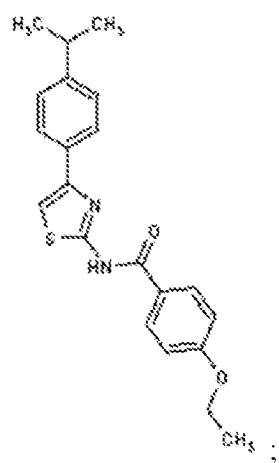
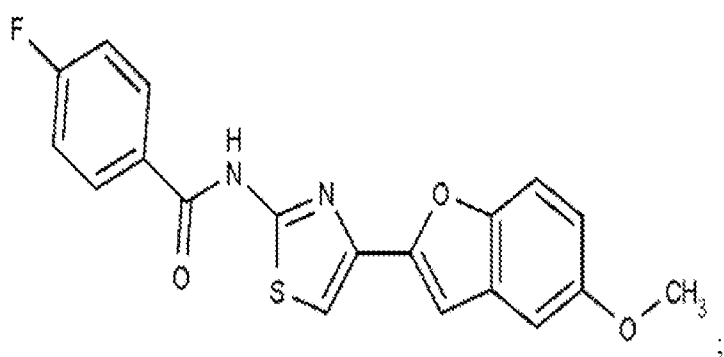
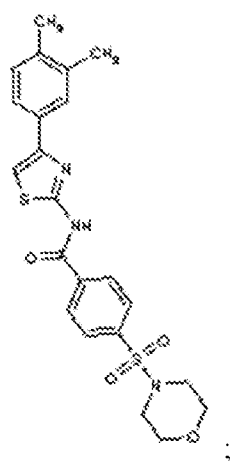


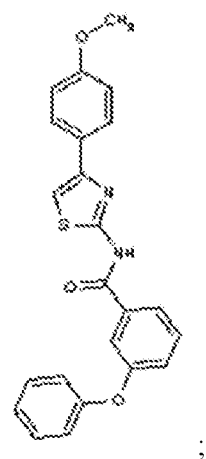
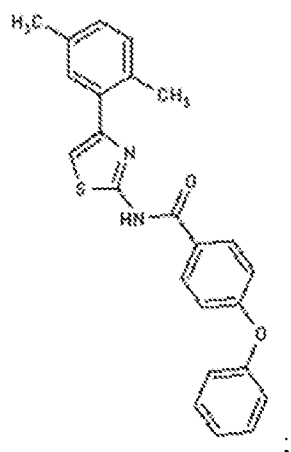


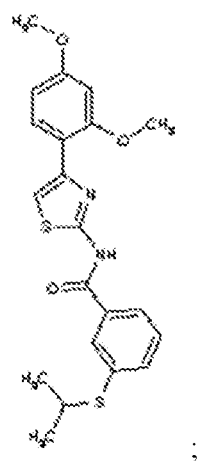




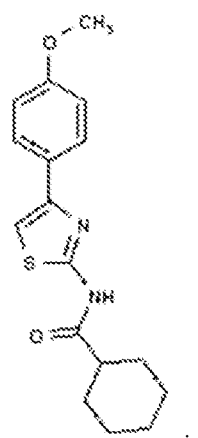




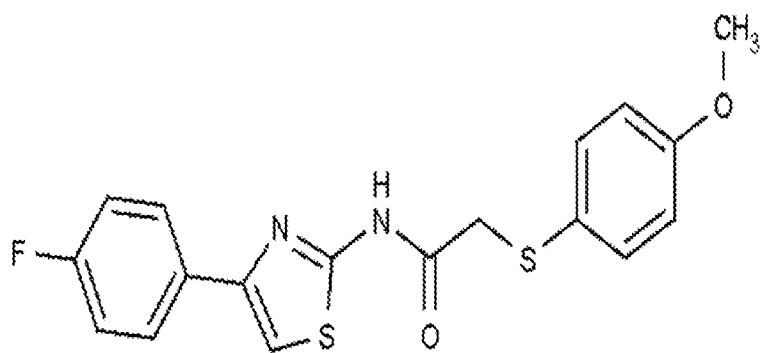




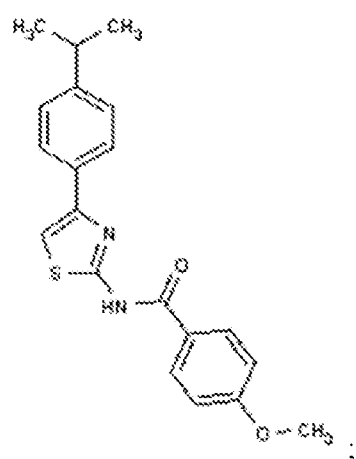
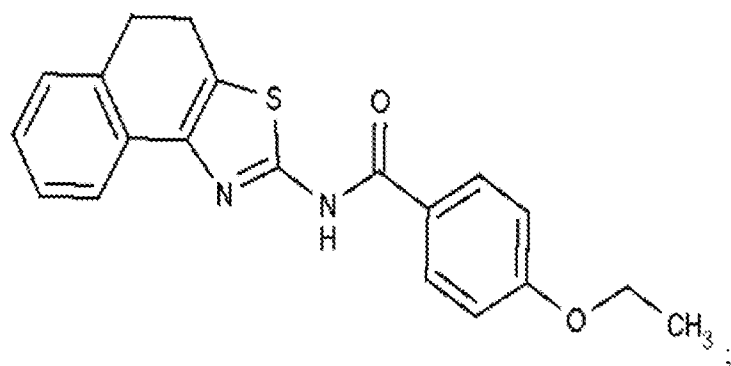
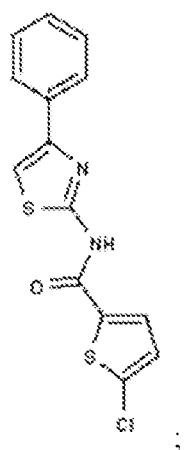
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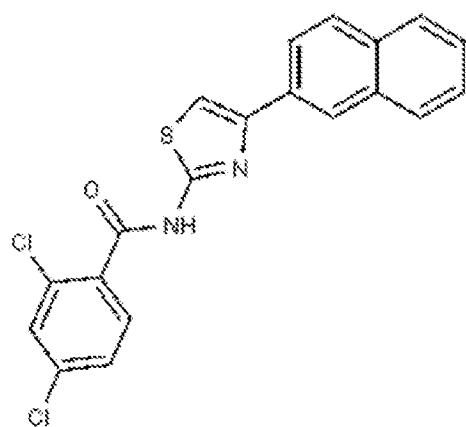


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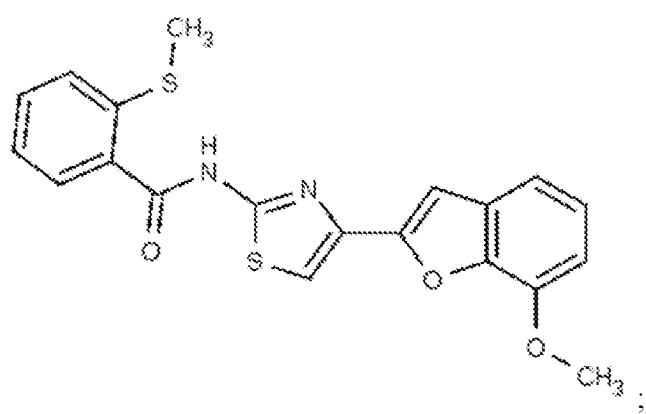


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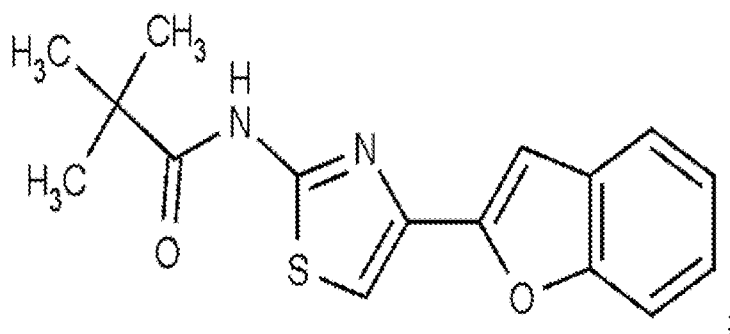




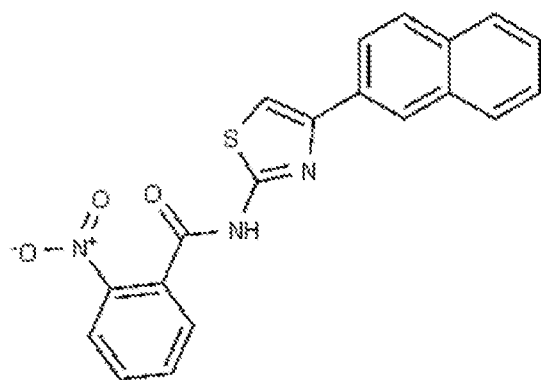
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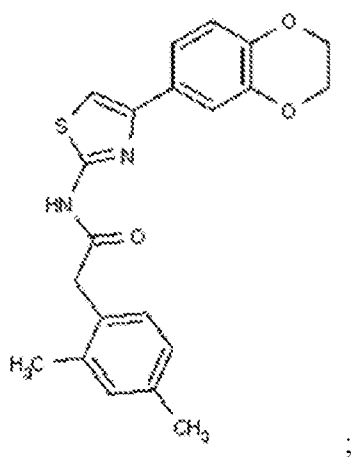
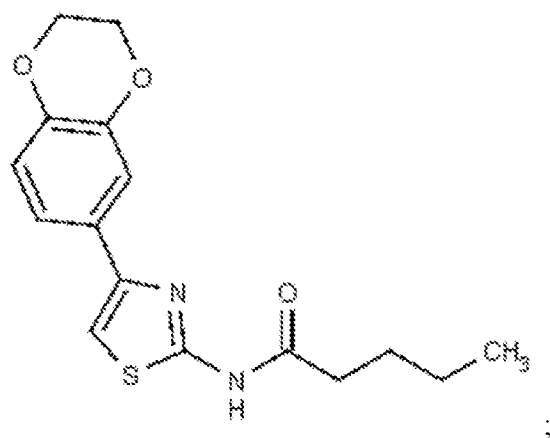
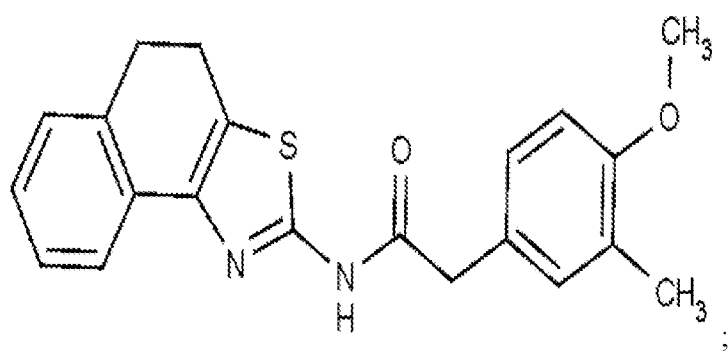
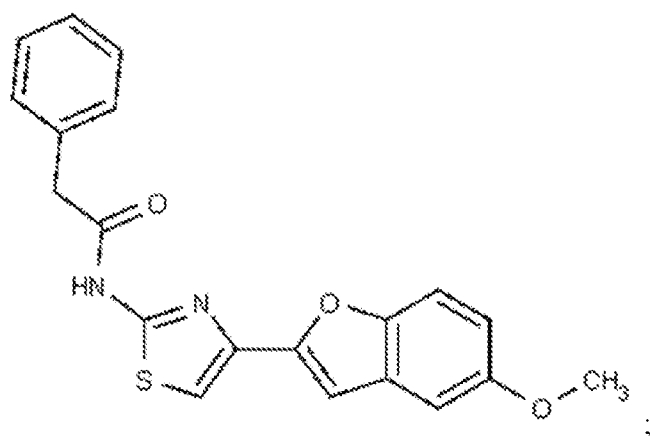
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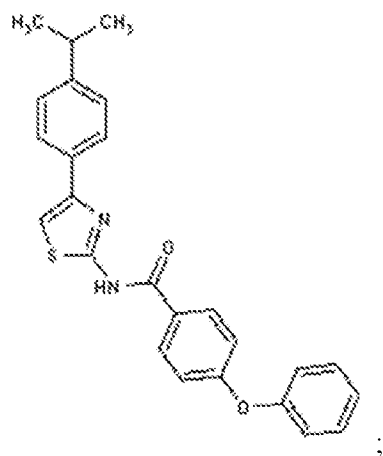
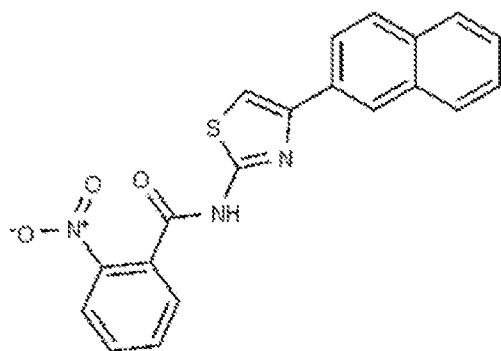
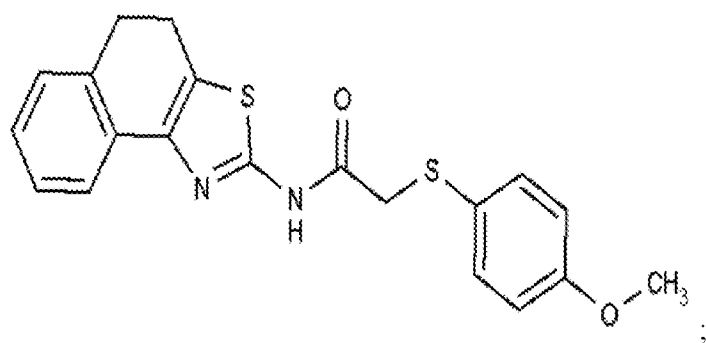
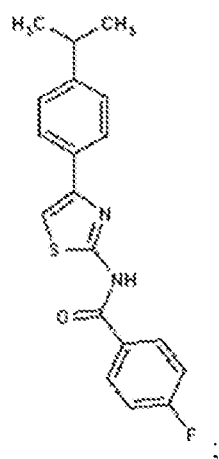


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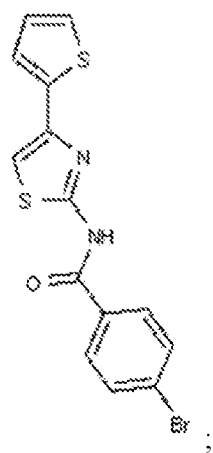
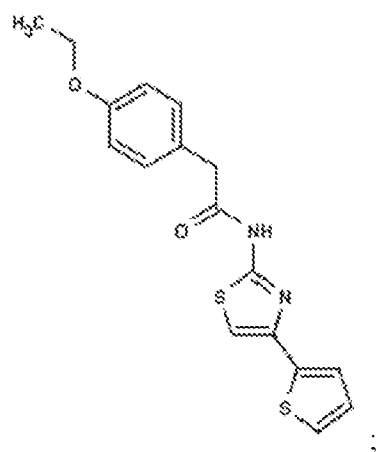
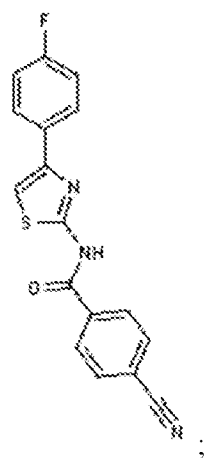
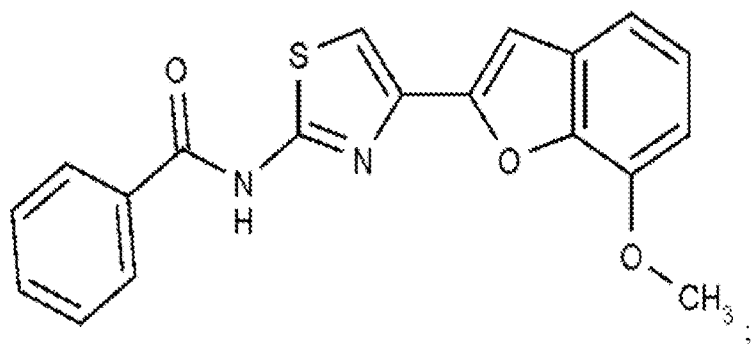


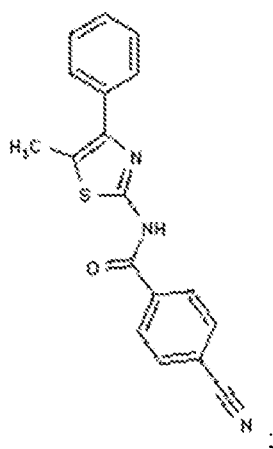
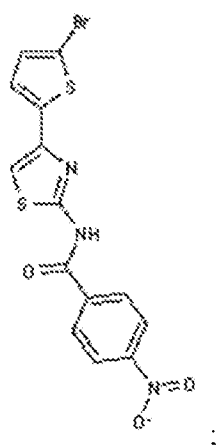
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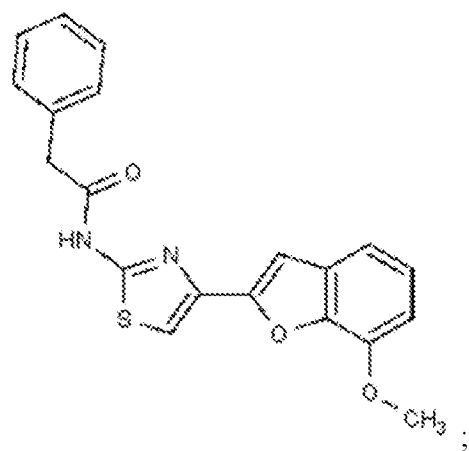
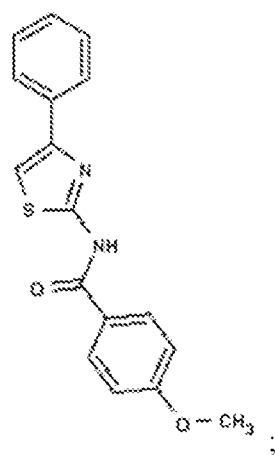
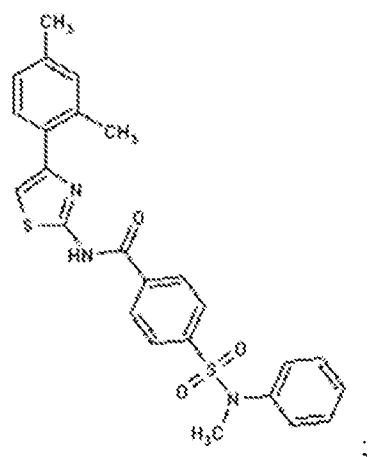


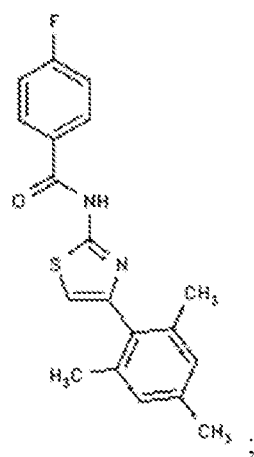
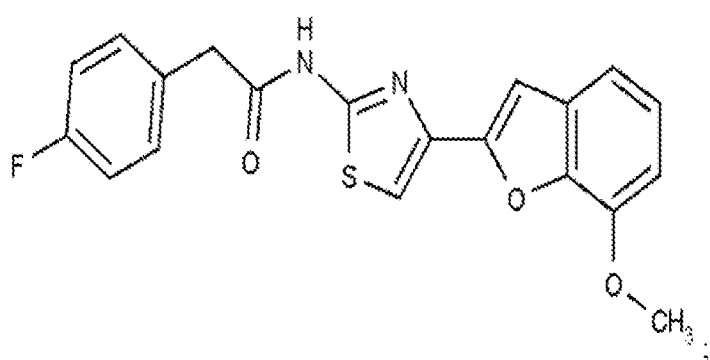
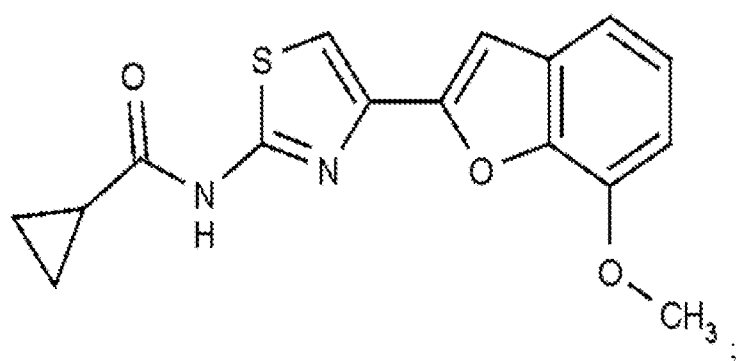
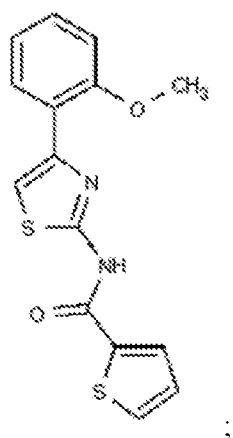


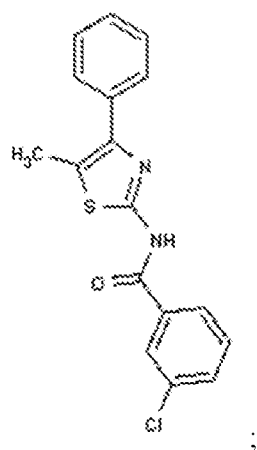
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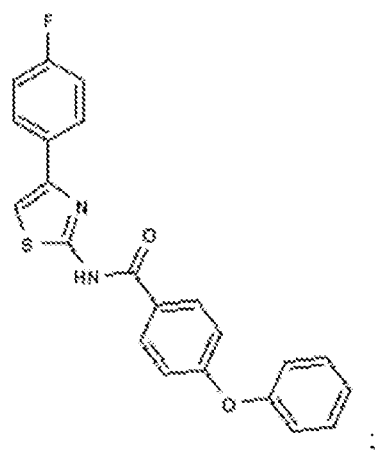




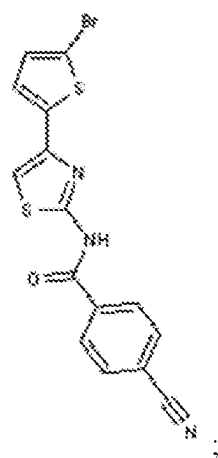




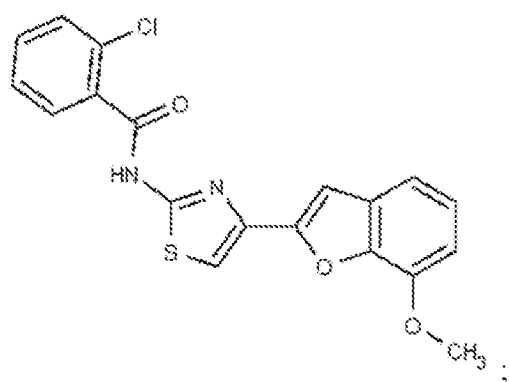
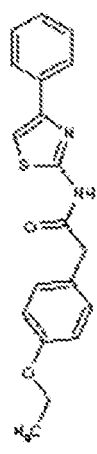
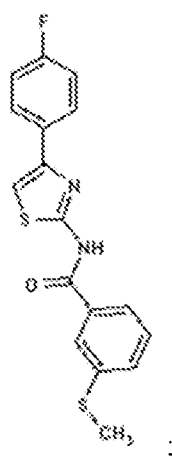
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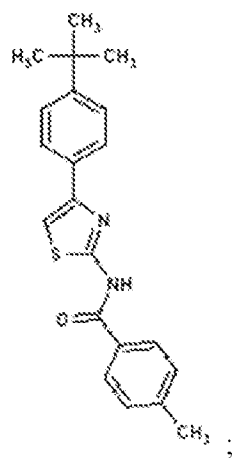
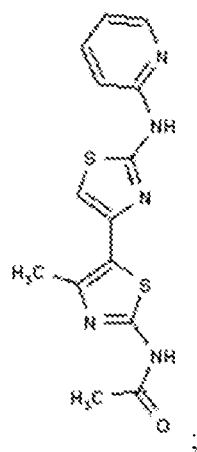


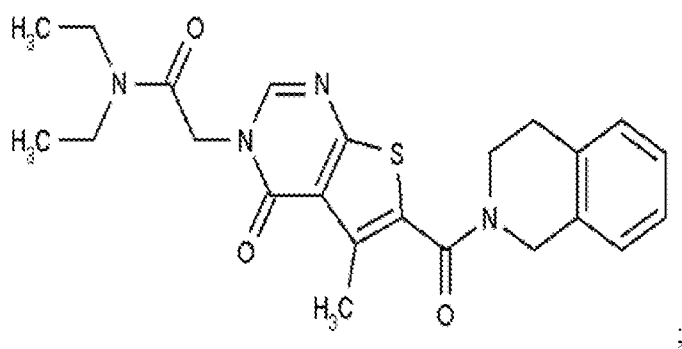
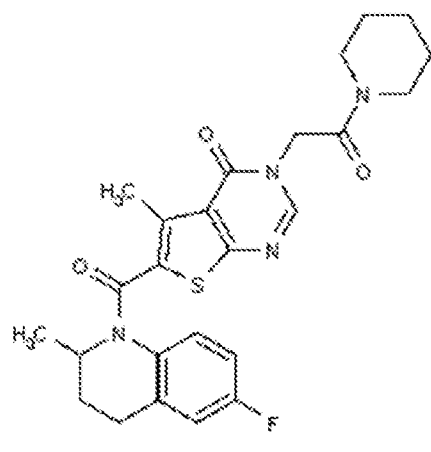
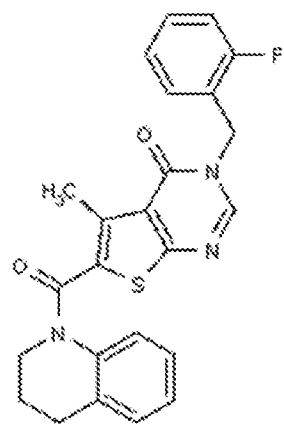
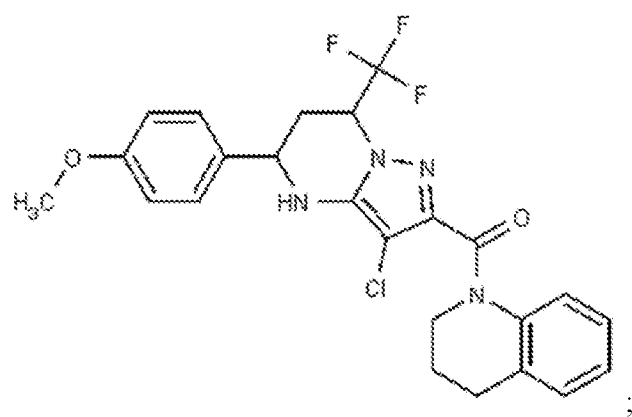
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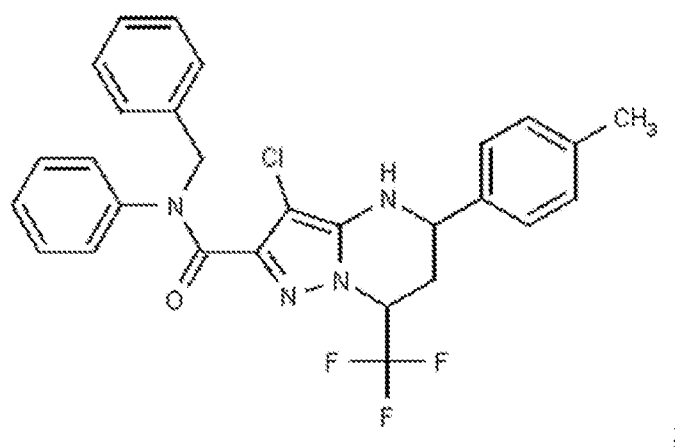
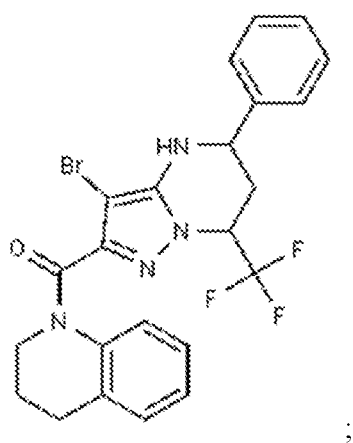
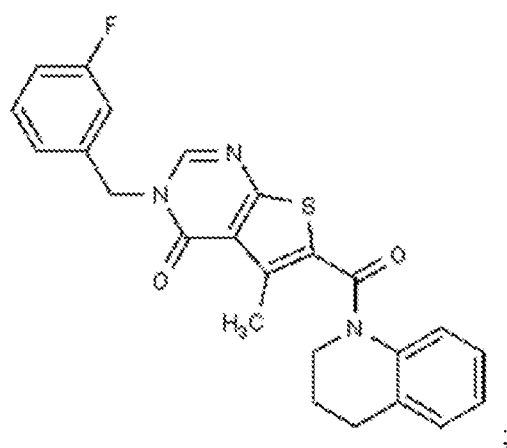


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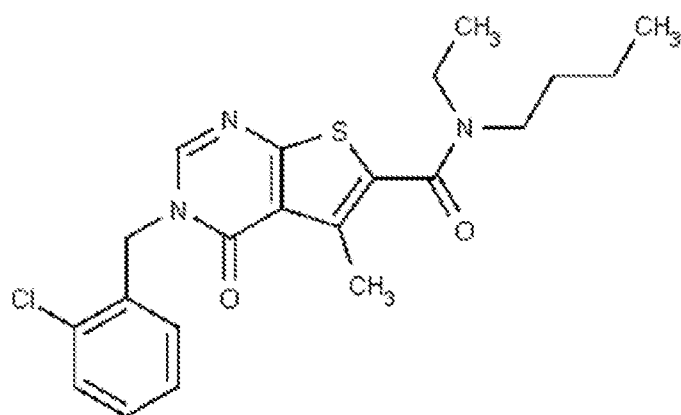




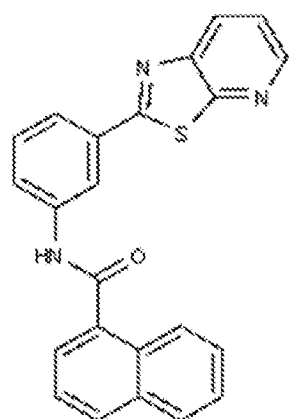




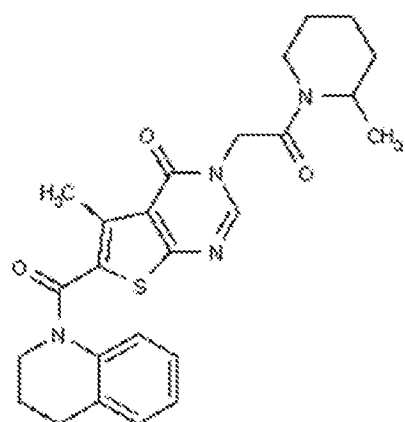
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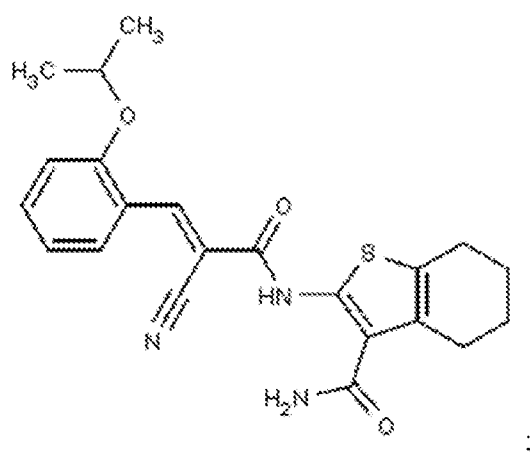
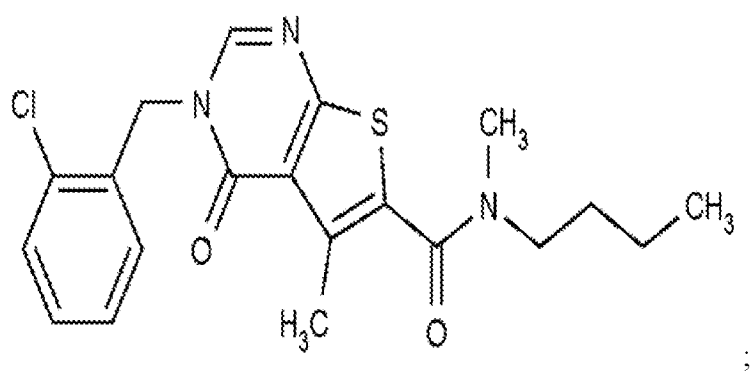
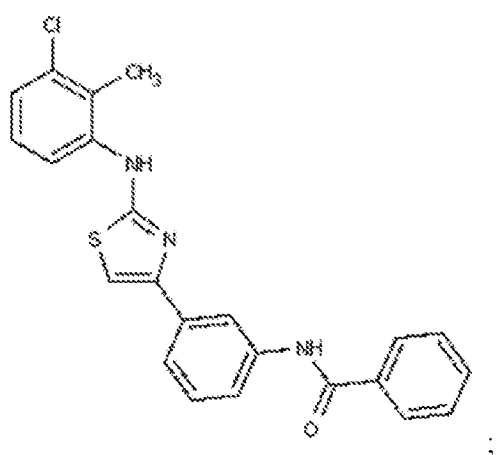
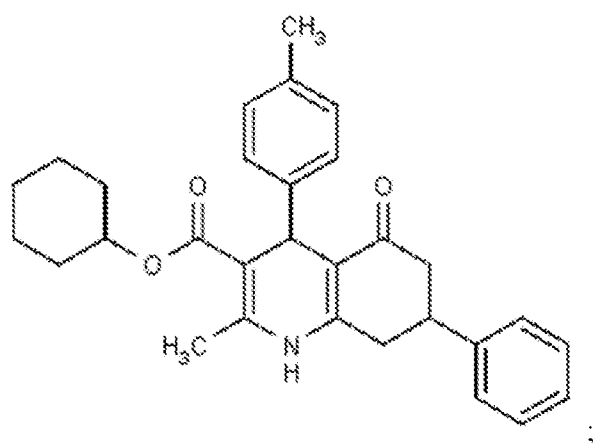
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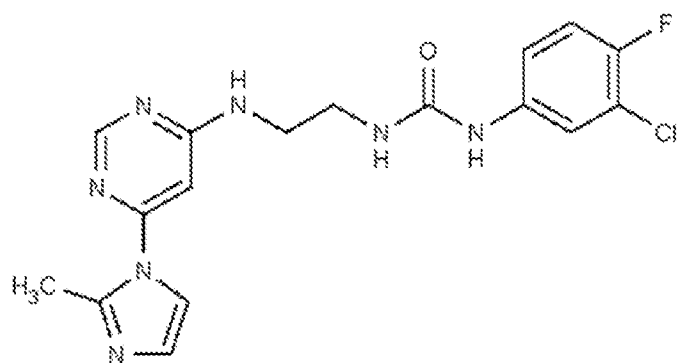


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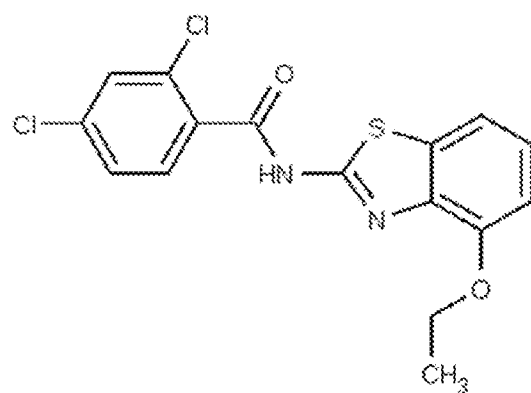


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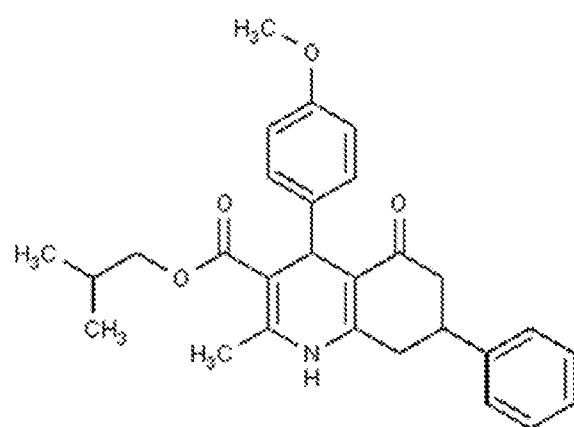




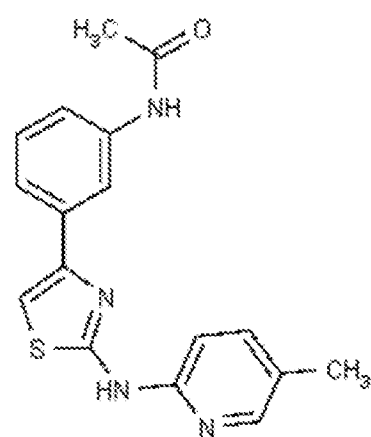
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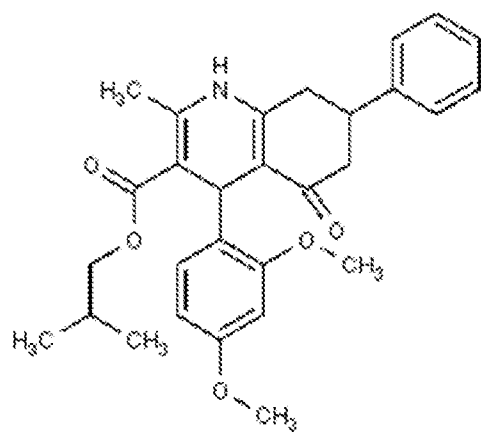


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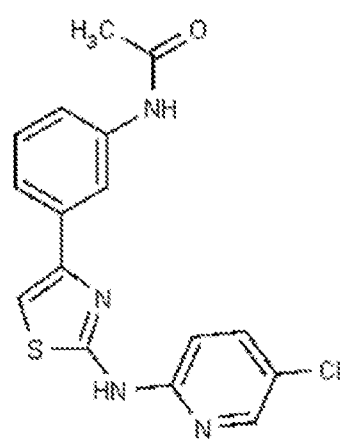


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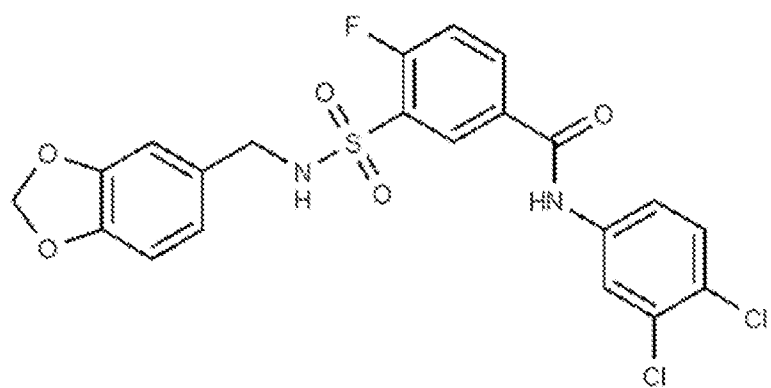
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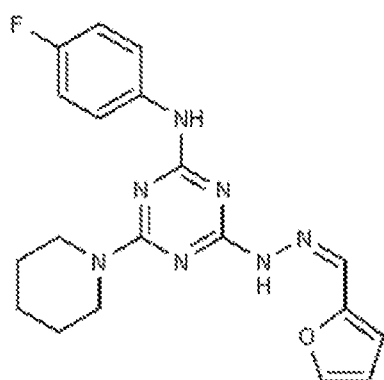
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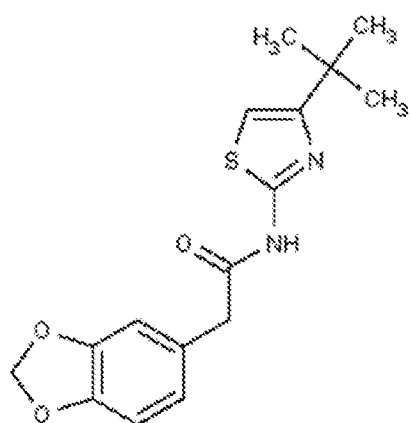


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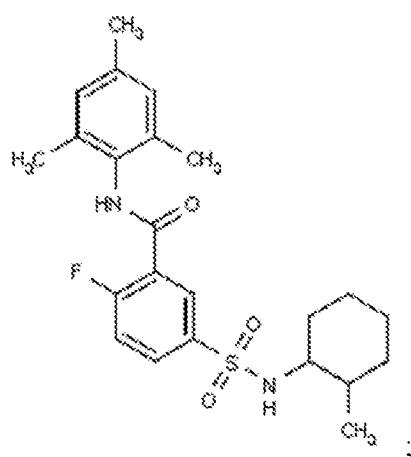


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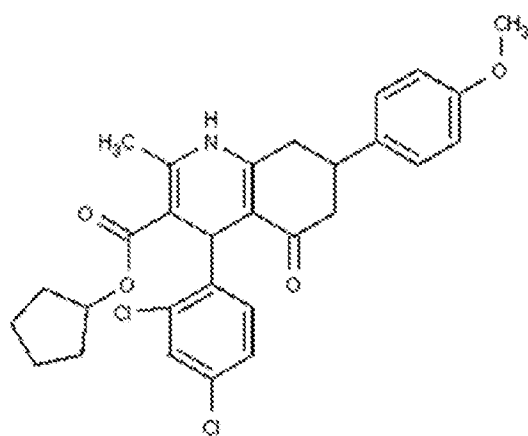
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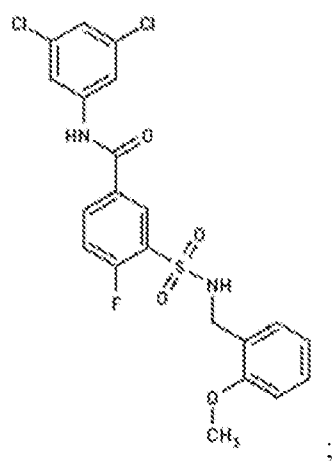
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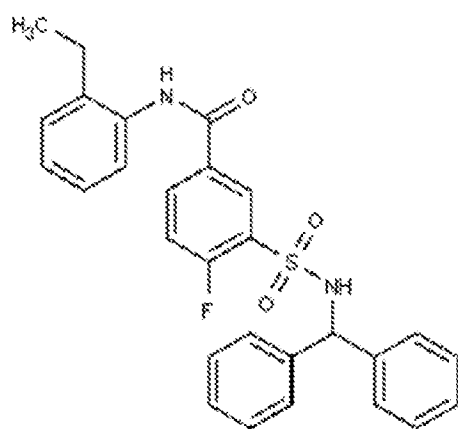
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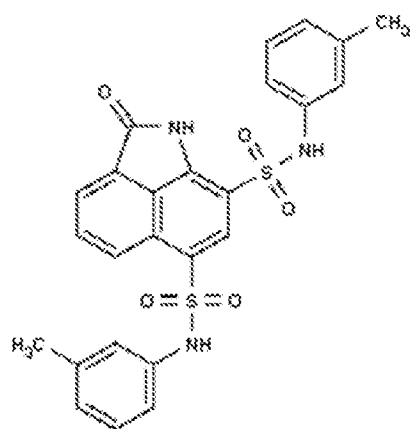
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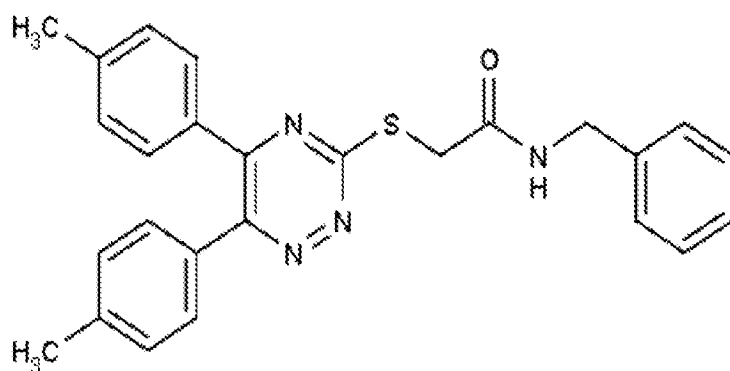
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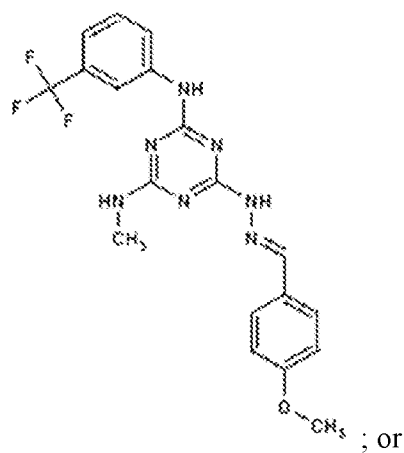
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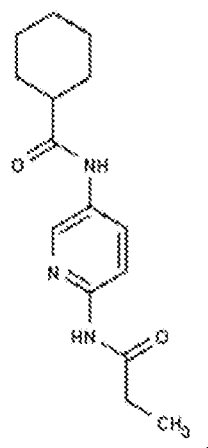
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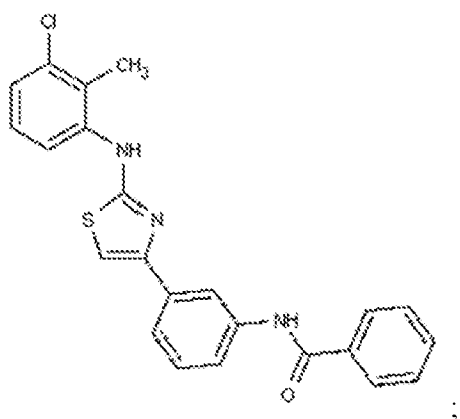
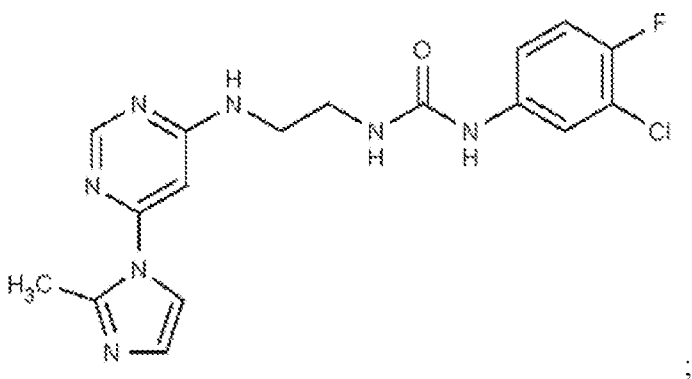
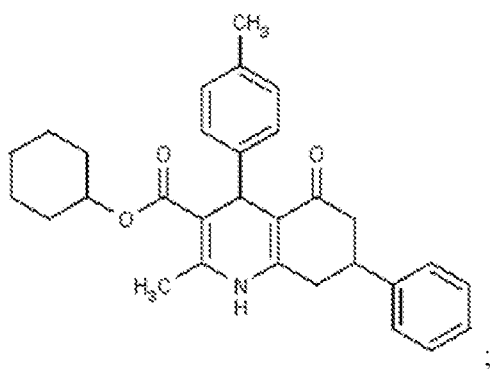
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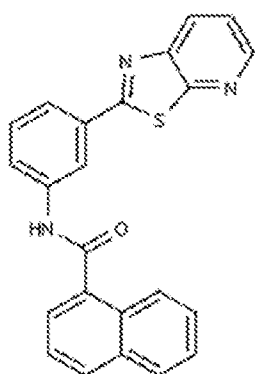


- 5 2. The composition of claim 1, wherein the composition is adapted for oral, parenteral, enteral, rectal, intravenous, transdermal, intramuscular, pulmonary, or intranasal administration.
3. The composition of claim 1, wherein the composition is adapted into a solution, suspension, cream, ointment, lotion, enema, elixir, syrup, emulsion, gum, insert, jelly, foam, paste, pastille, spray, magma or poultice.
- 10 4. The composition of claim 1, wherein the compound is effective as a pharmacoperone.

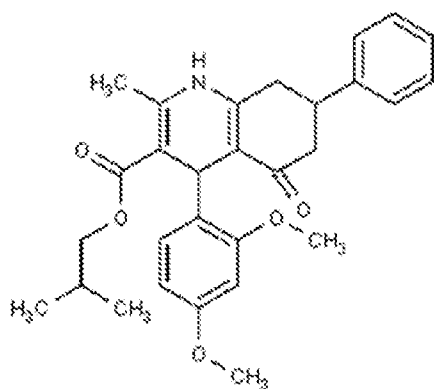
5. The composition of claim 1, wherein the compound is an hV2R[L⁸³Q] pharmacoperone.
6. The composition of claim 1, wherein the compound is formulated as a salt selected from sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, or pamoate.
7. The composition of claim 1, wherein the molecule is formulated with an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base.
8. The composition of claim 1, wherein the molecule is formulated with bases, 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; tributylamine; 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; an amino acid, arginine, or lysine.
9. The composition of claim 1, wherein the composition is formulated for at least one of an immediate-release, mixed-release, pulsatile-release, or sustained-release.
10. A method of treating a subject with a G protein coupled receptors (GPCRs) misfolded, misrouted, or both misfolded and misrouted protein comprising:
obtaining a sample from the subject suspected of having a G protein coupled receptor (GPCR) that is misfolded, misrouted, or both misfolded and misrouted; and
providing the subject with an effective amount of a pharmacoperone that prevents misfolding, misrouting, or both misfolding and misrouting of the GPCR protein.
11. The method of claim 10, wherein the misfolded, misrouted, or both misfolded and misrouted protein causes nephrogenic diabetes insipidus.
12. The method of claim 10, wherein the misfolded, misrouted, or both misfolded and misrouted protein is a vasopressin 2 receptor.

13. The method of claim 10, wherein the disease is caused by a misfolding and misrouting of the vasopressin type 2 receptor.
14. The method of claim 10, wherein the pharmacoperone is selected from at least one of a aminobenzothiazole amide, aminobenzothiazole benzamide, aminothiazole benzamide, aryl aminothiazole amide, aryl aminothiazole benzamide, or a heteroaryl amide.
15. The method of claim 10, wherein the pharmacoperone is selected from at least one of:

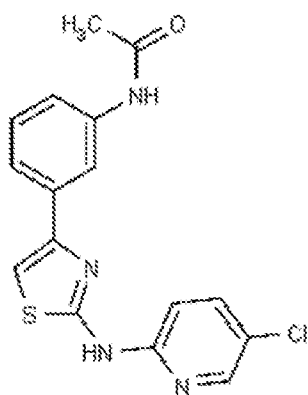




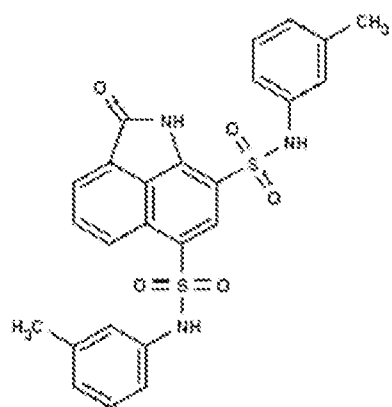
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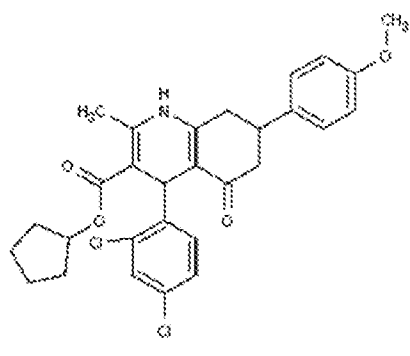
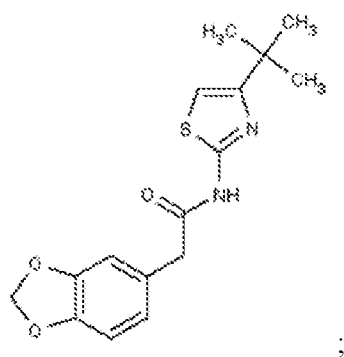
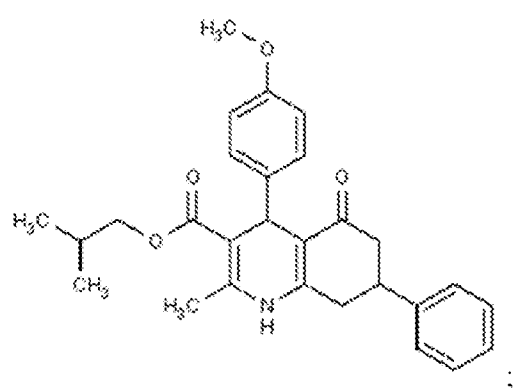
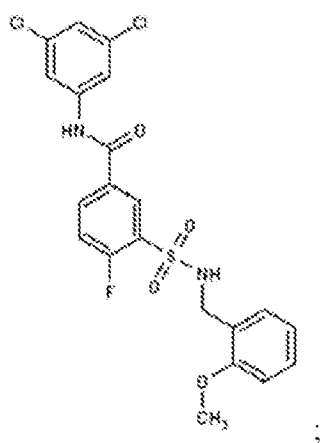
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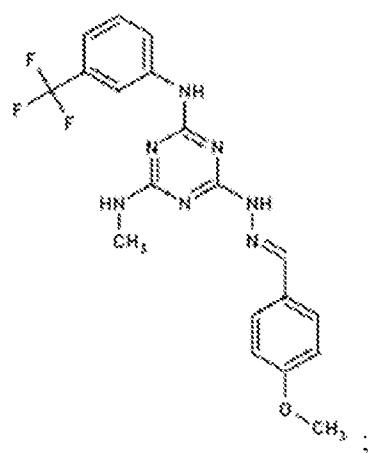
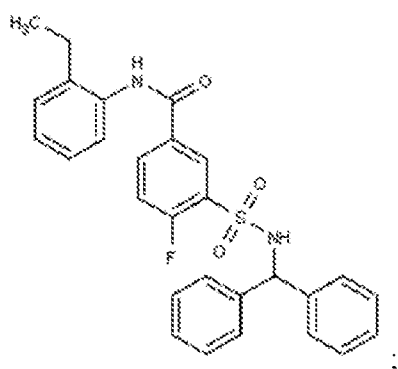
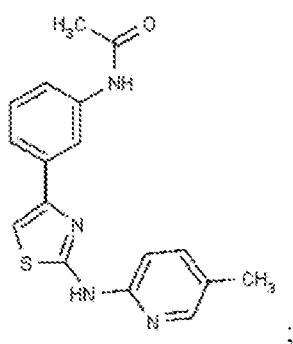
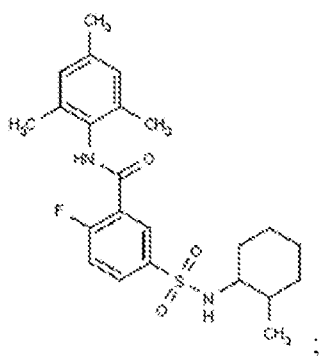


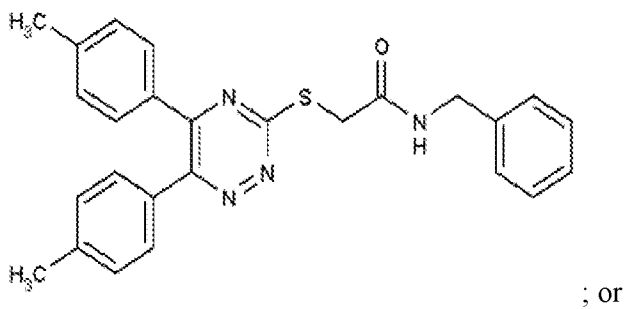
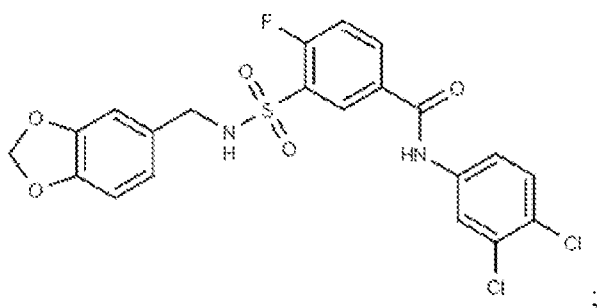
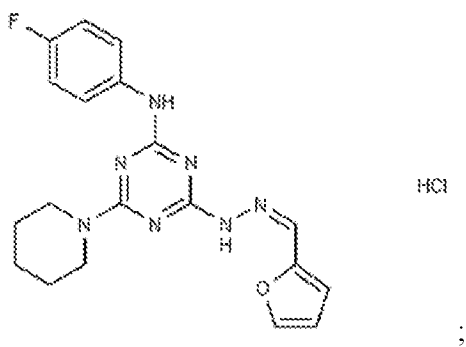
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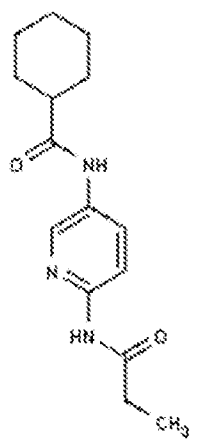
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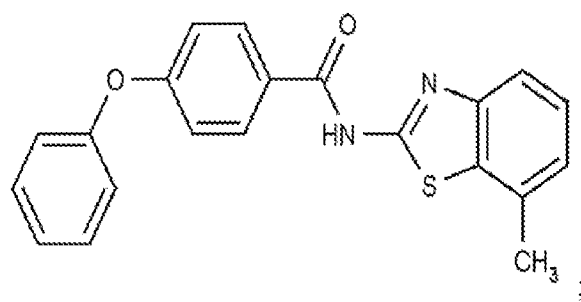
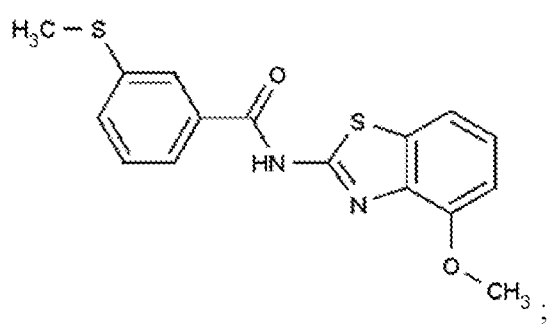
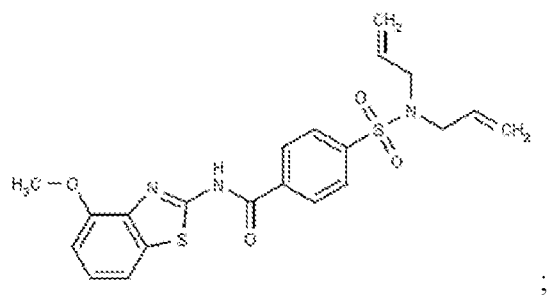
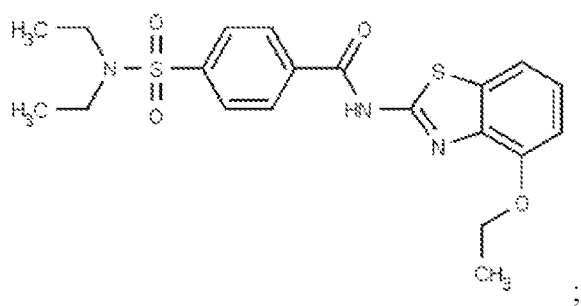
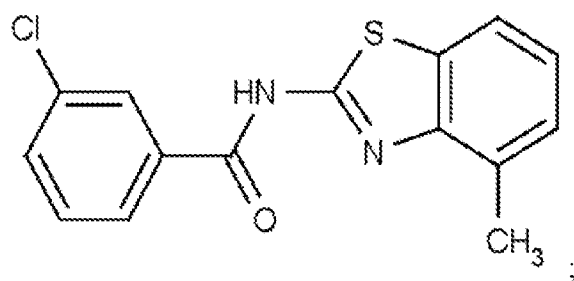


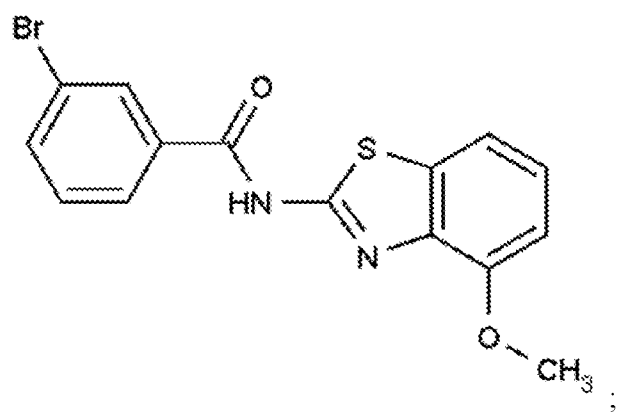
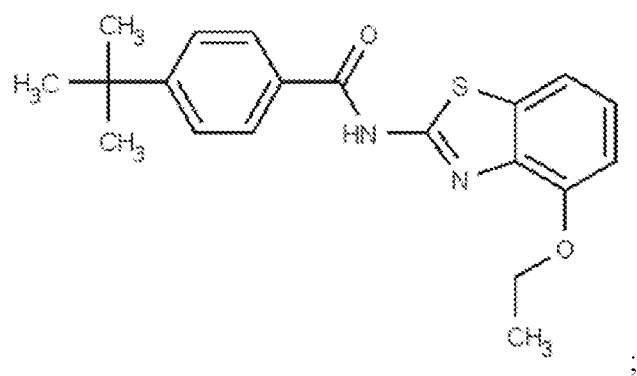
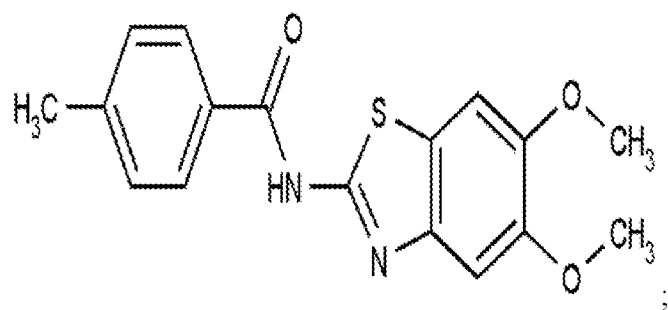
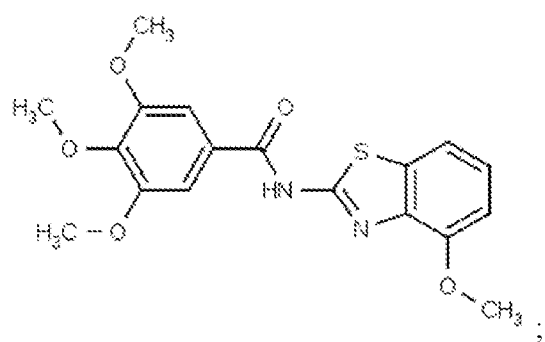
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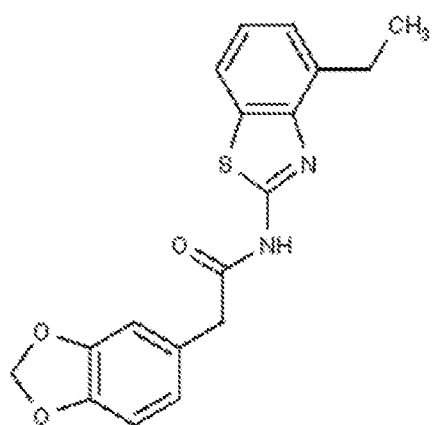


- 5 16. A method of treating a subject with a misfolded vasopressin 2 receptor (V2R) with comprising:
- identifying a subject with a misfolded V2R;
 - providing the subject with an effective amount of a V2R pharmacoperone selected from:

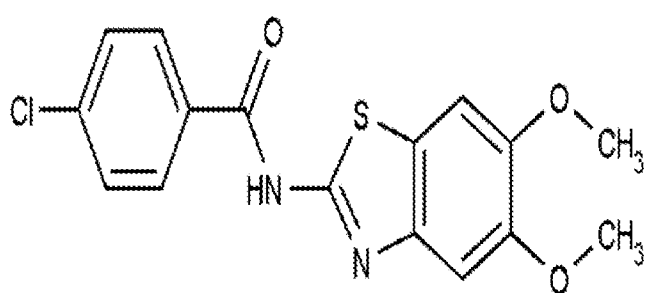
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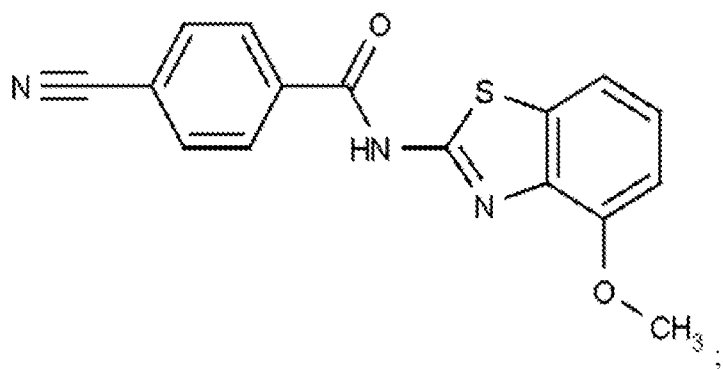




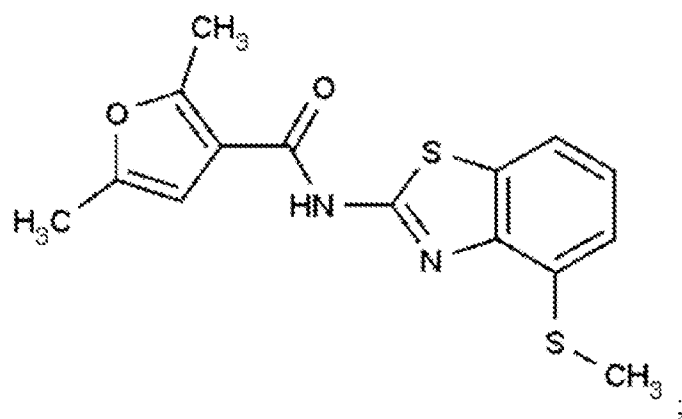
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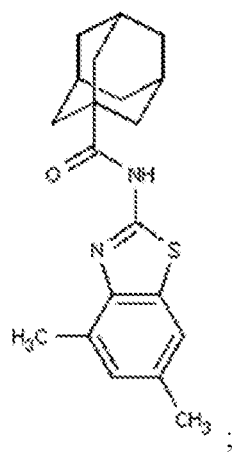
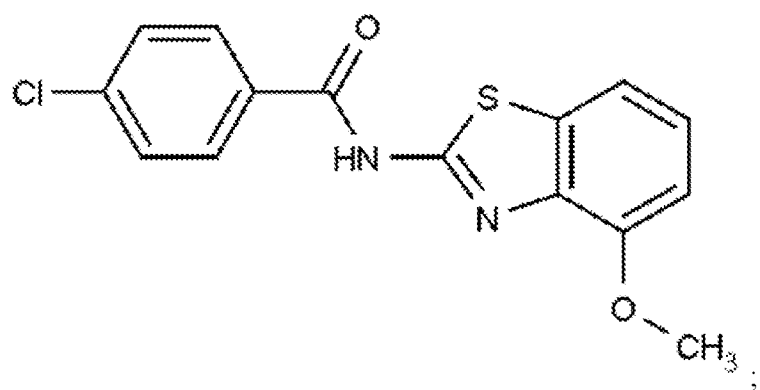
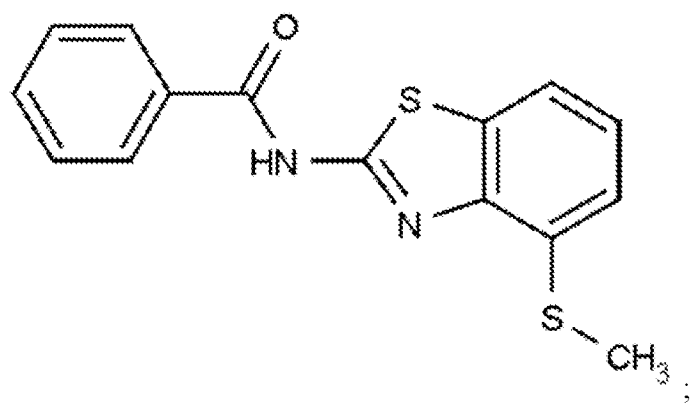
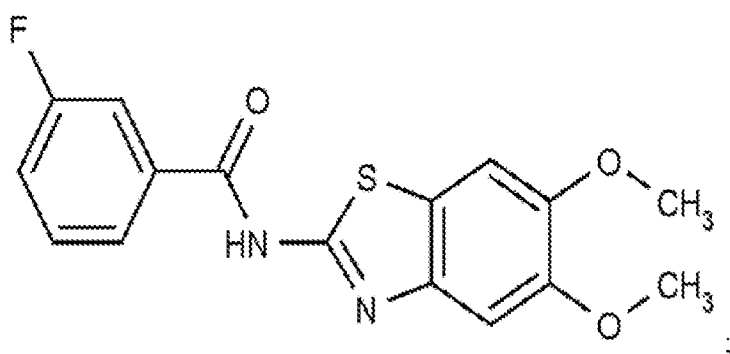
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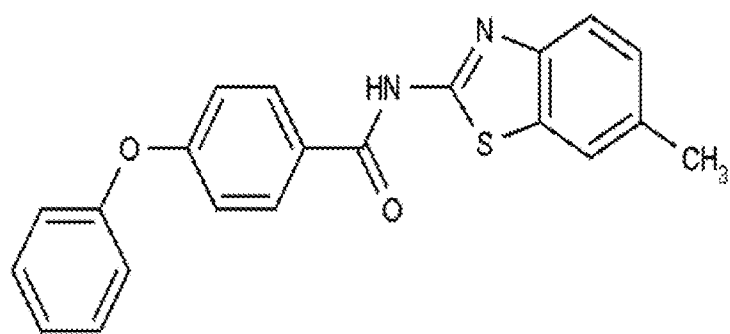
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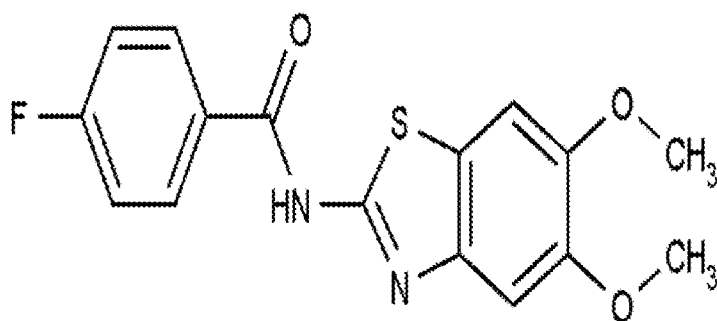
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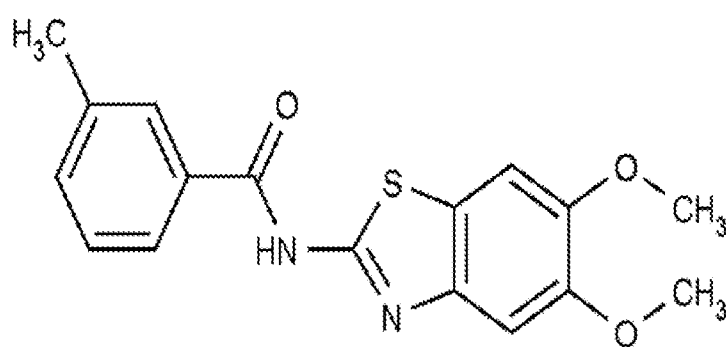
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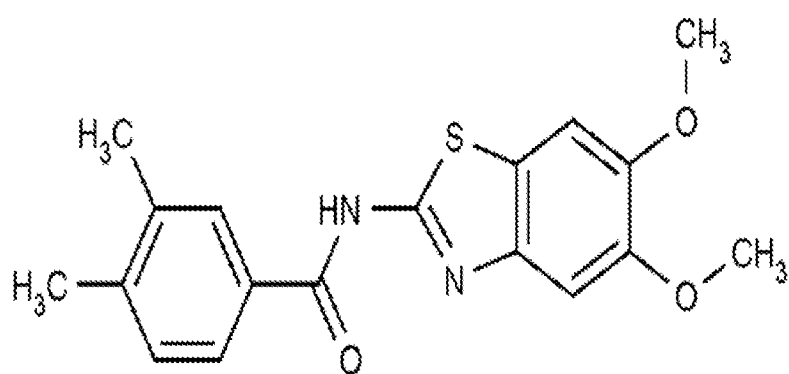
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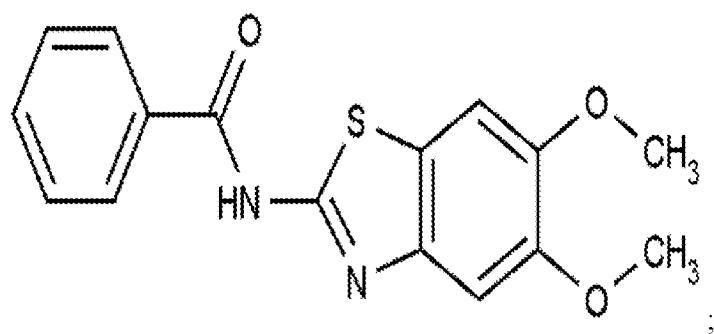
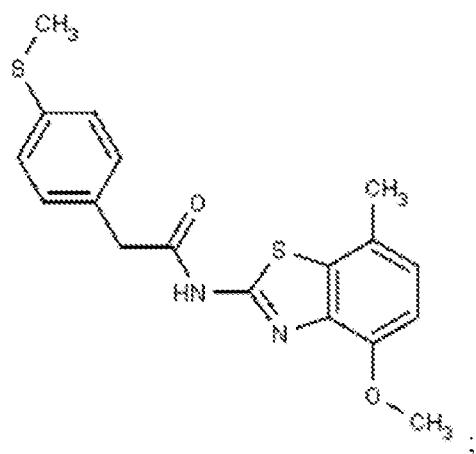
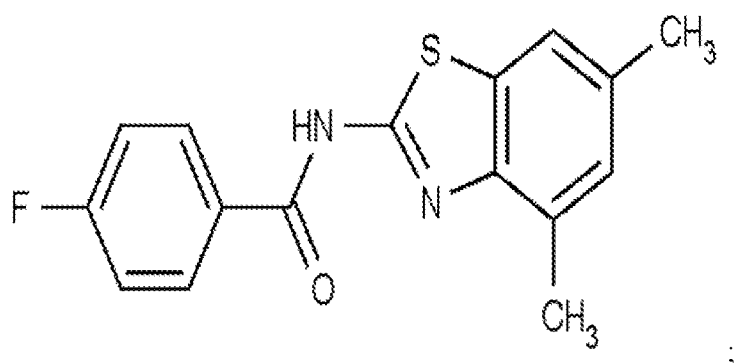
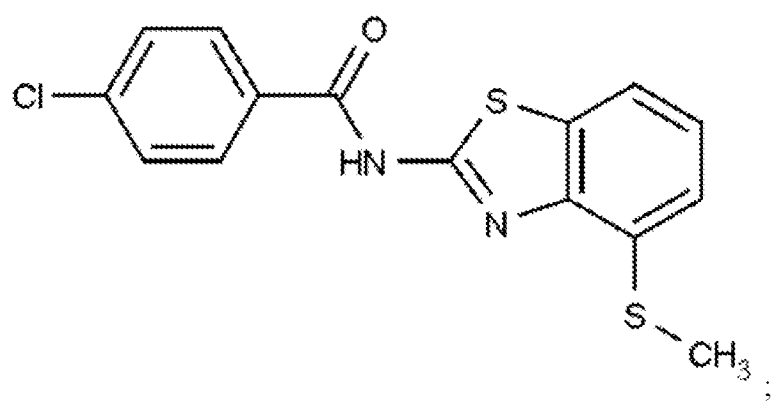


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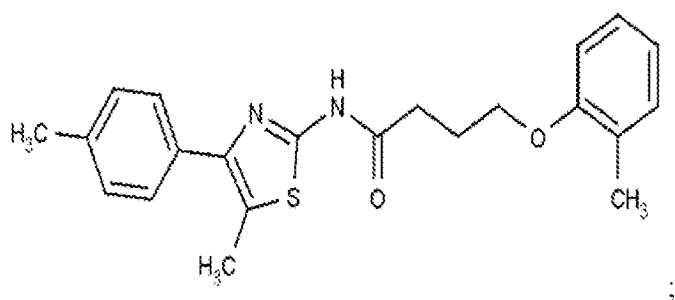
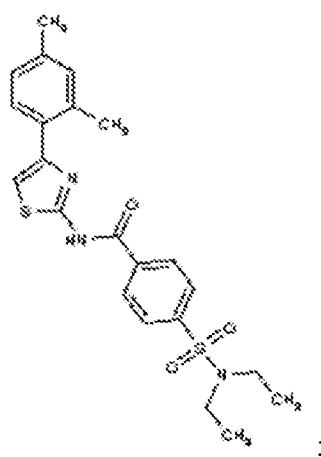
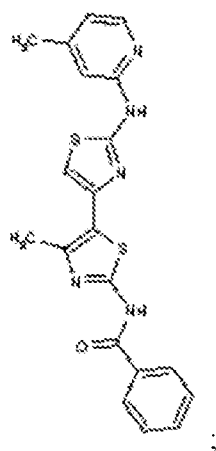
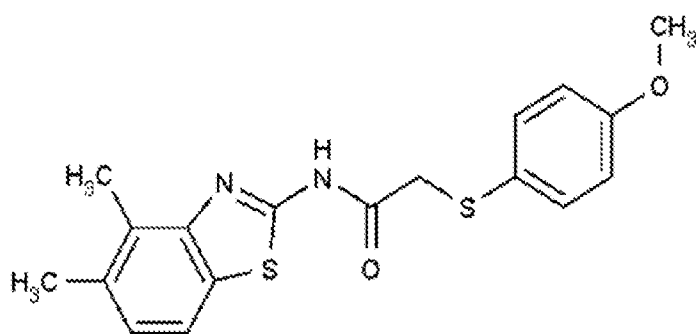


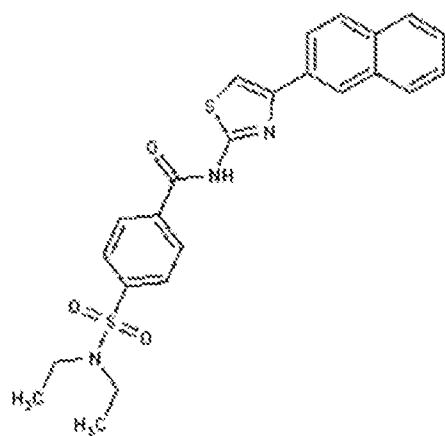
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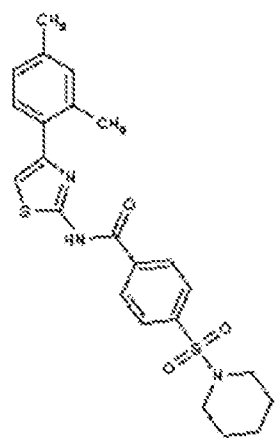


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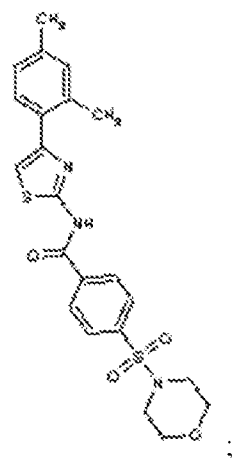




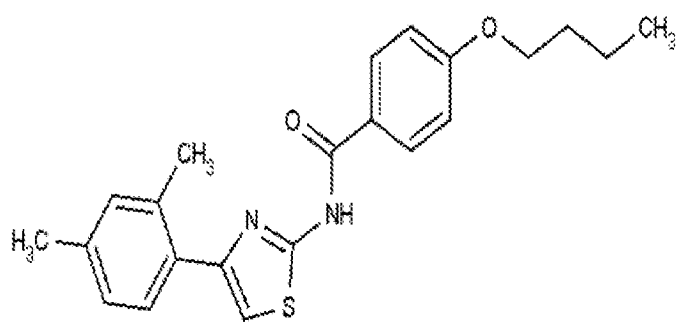
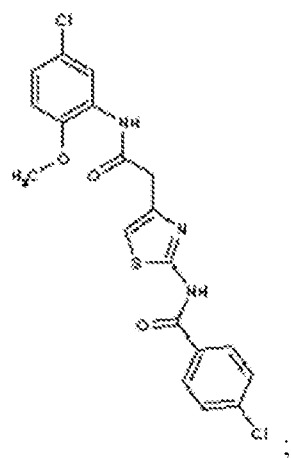
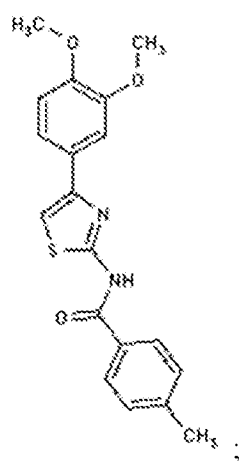
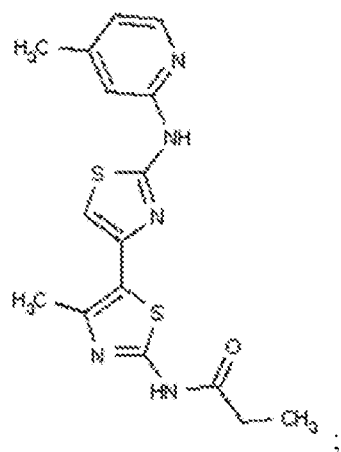
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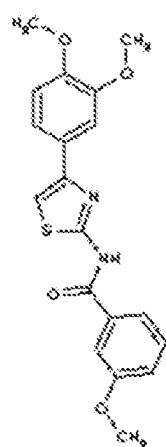
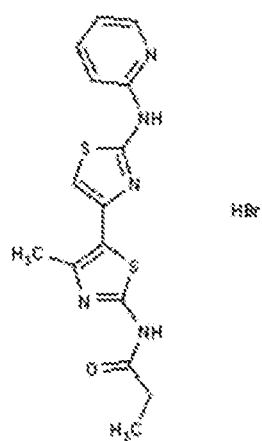
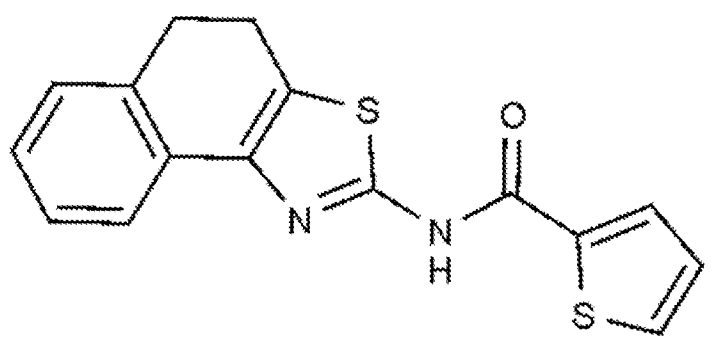
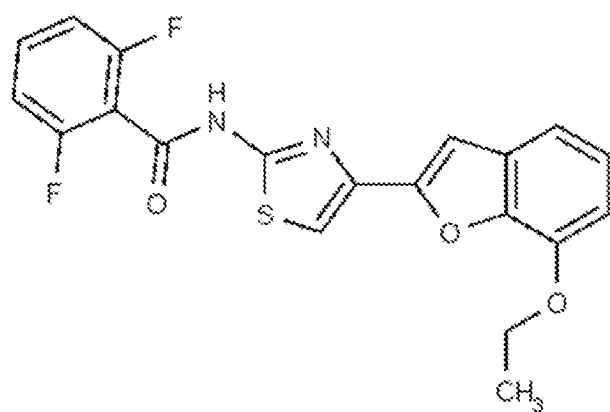


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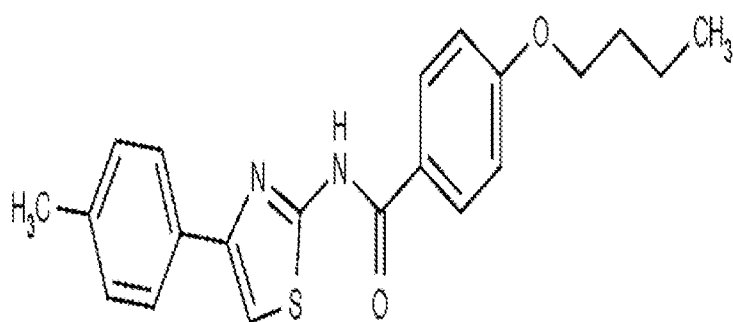


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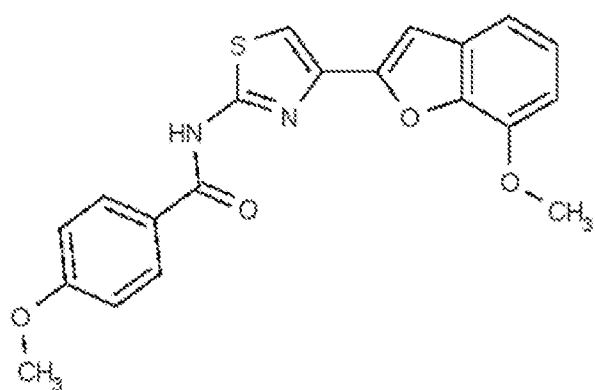
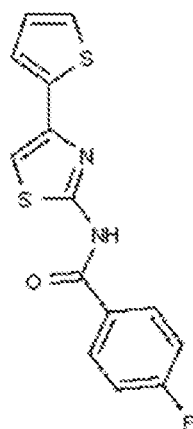




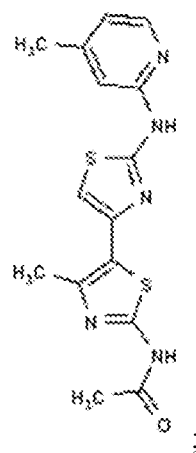
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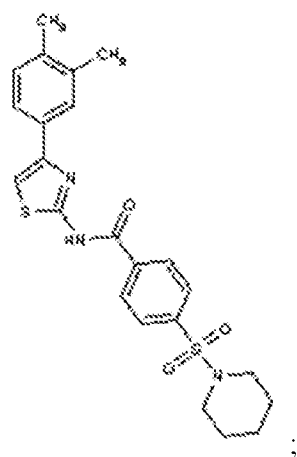
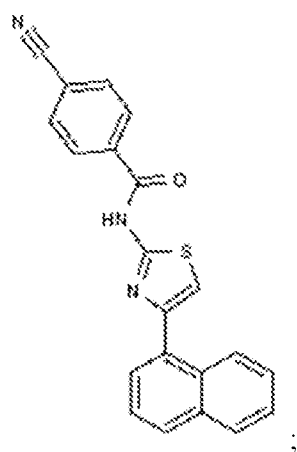
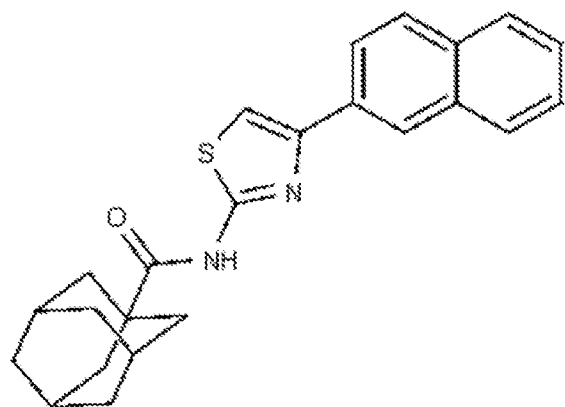
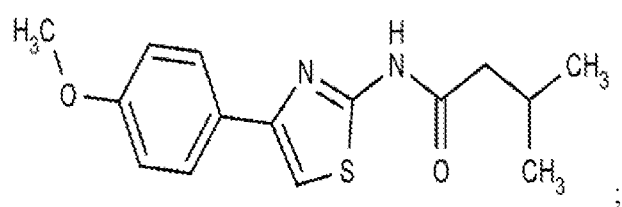


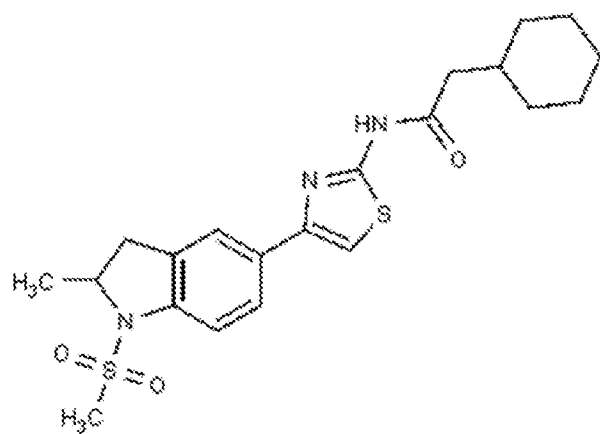
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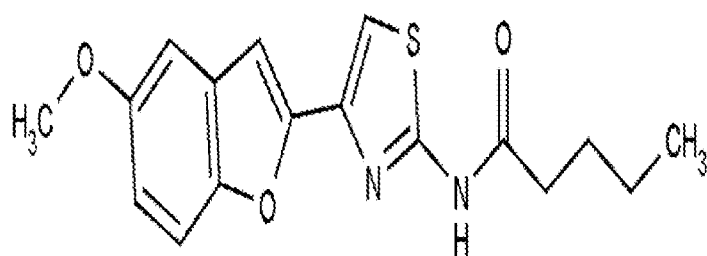
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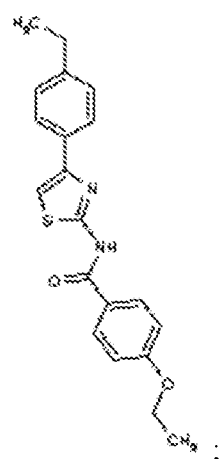
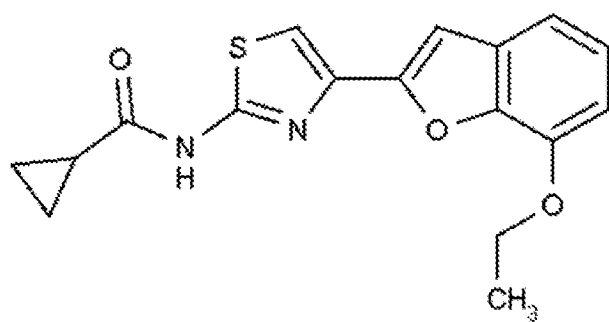


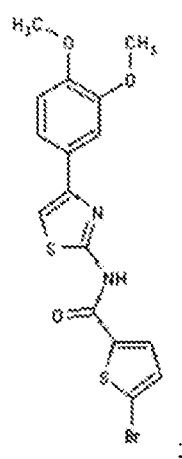
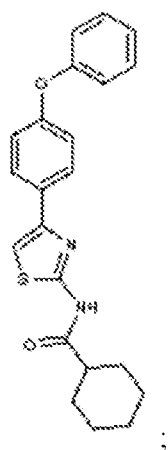


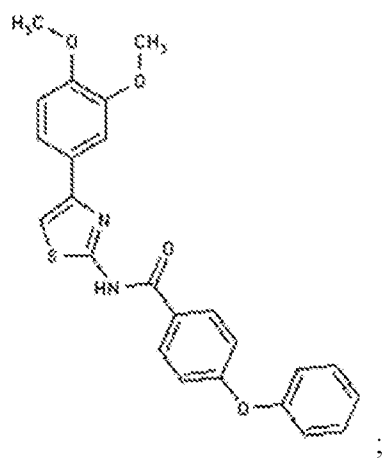
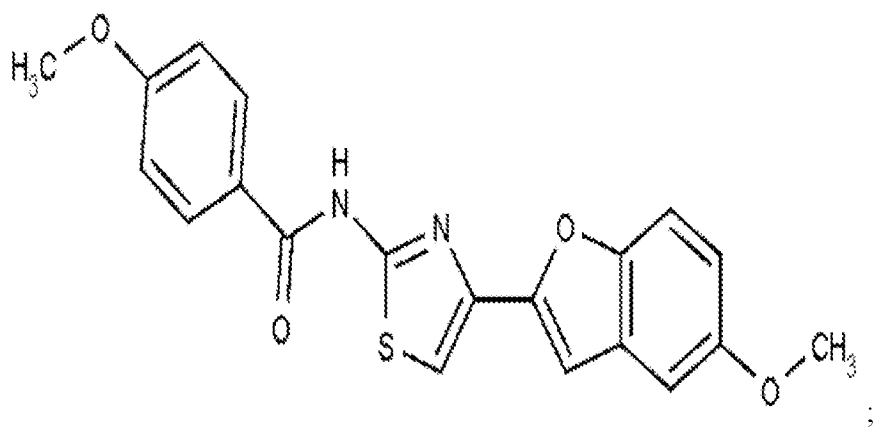
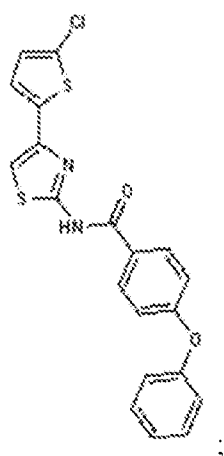
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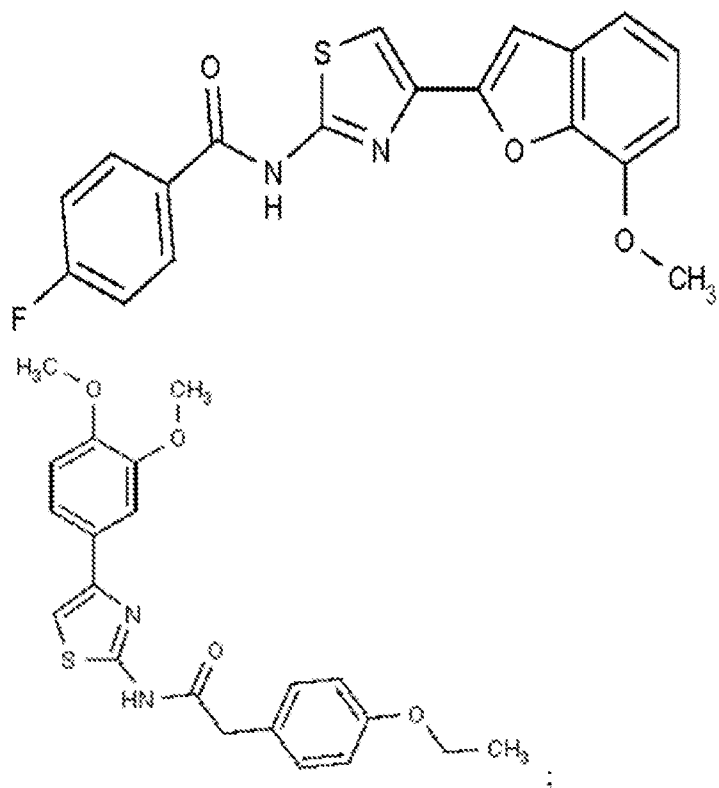
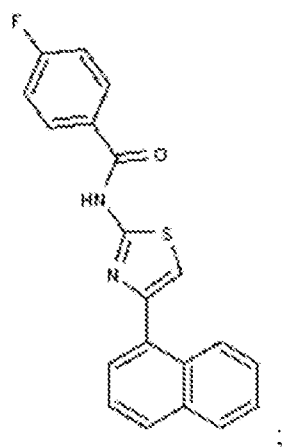
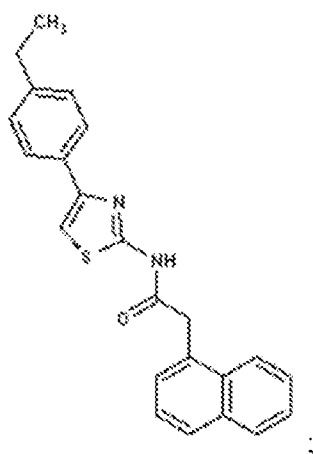


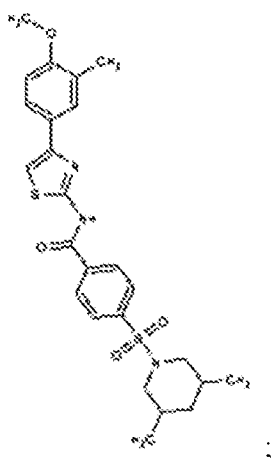
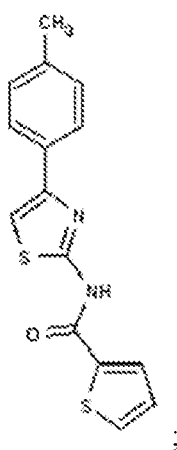
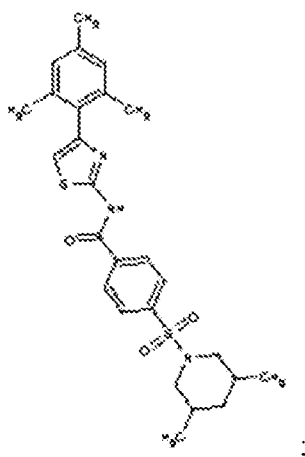
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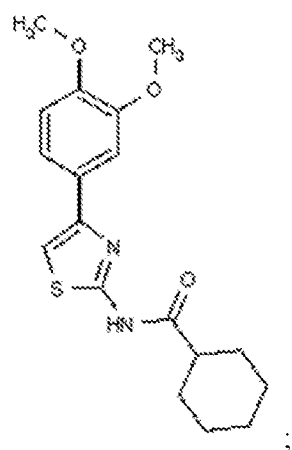
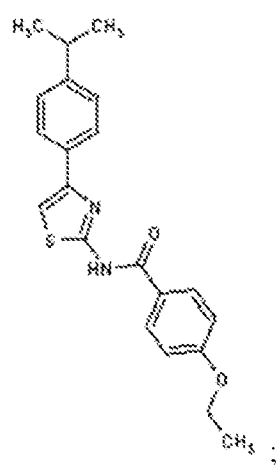
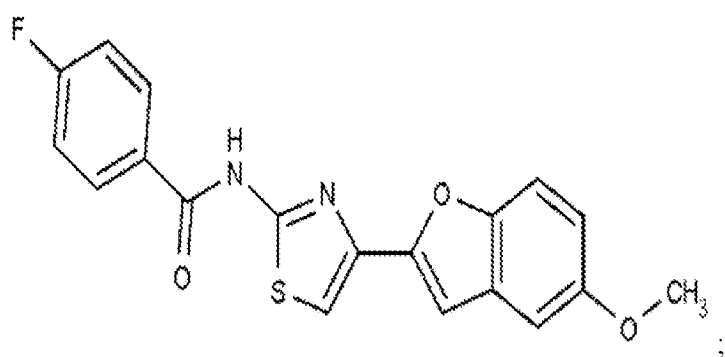
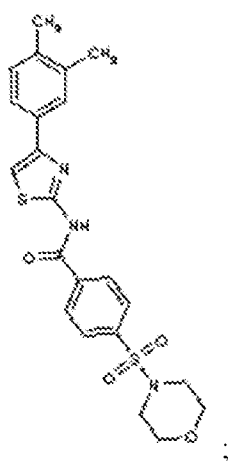


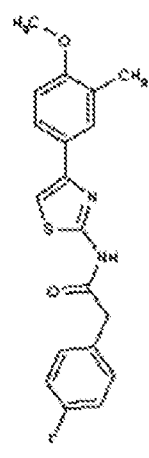
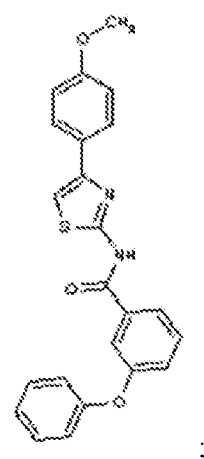
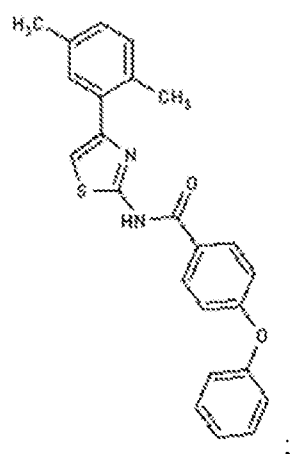


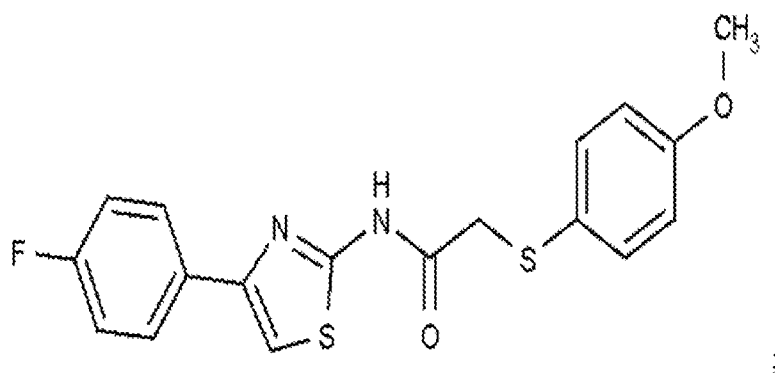
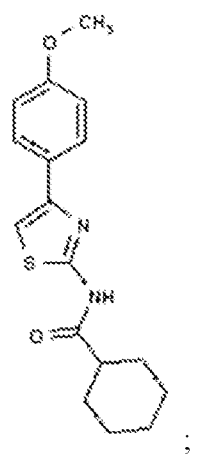
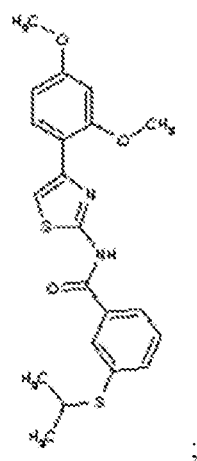


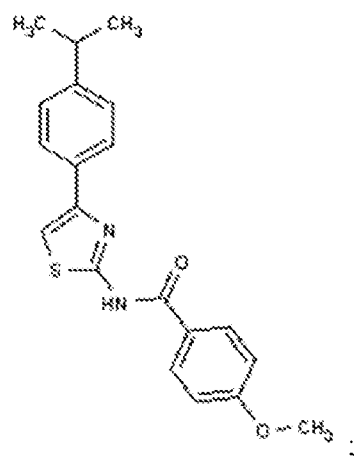
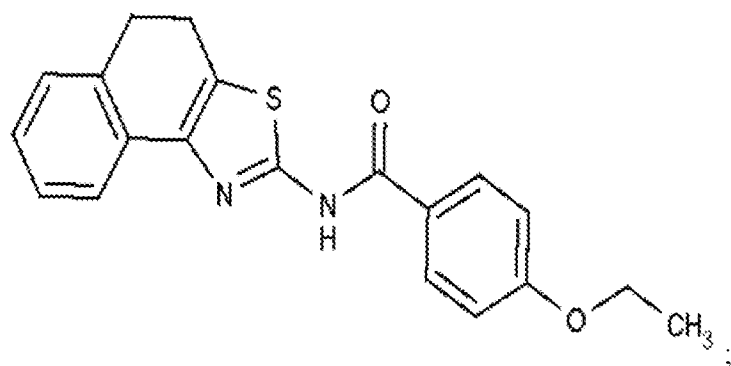
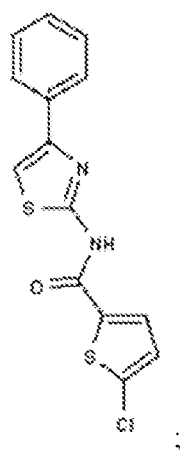


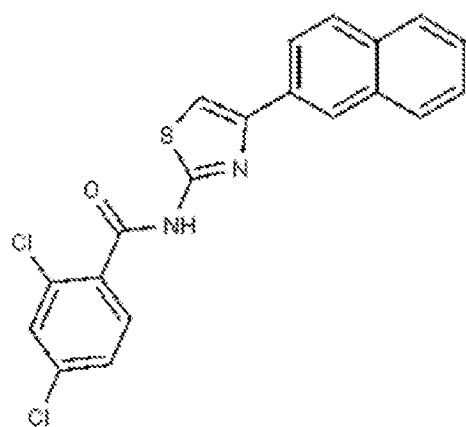




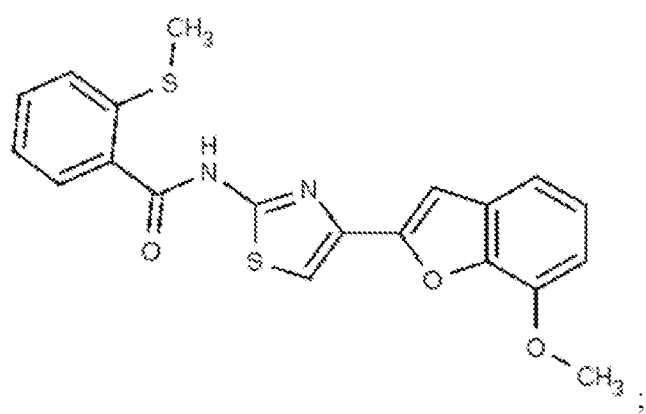




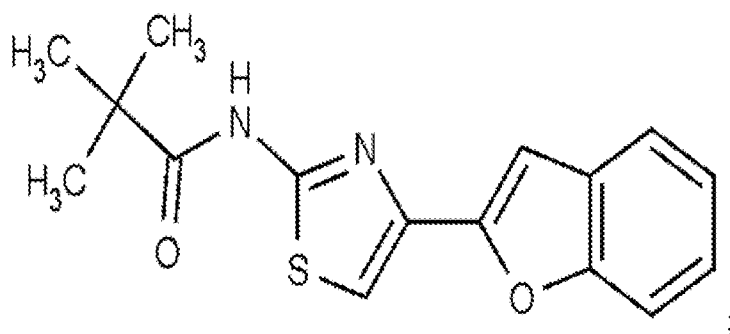




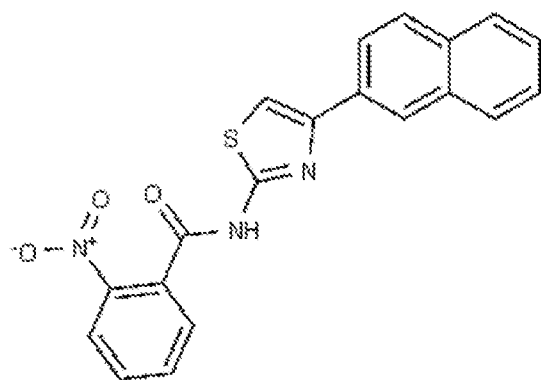
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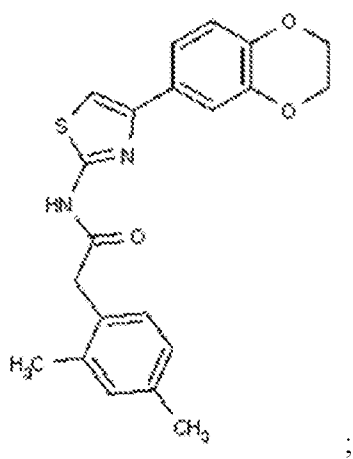
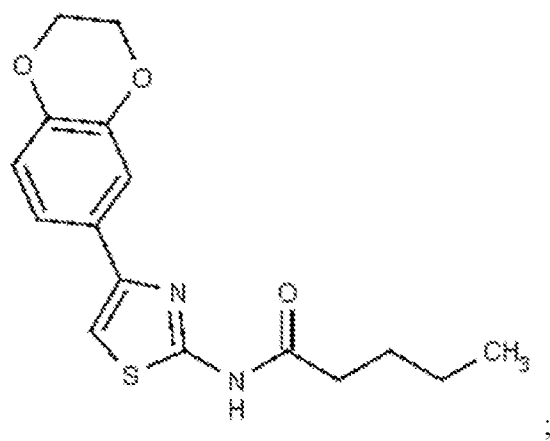
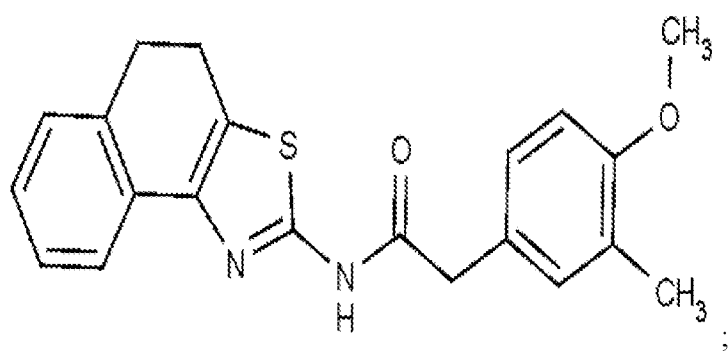
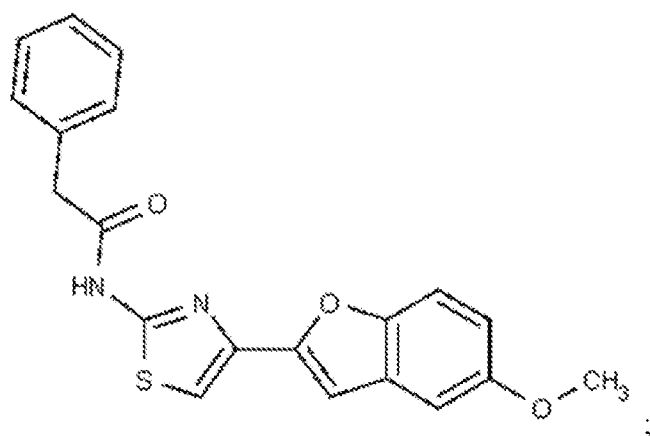
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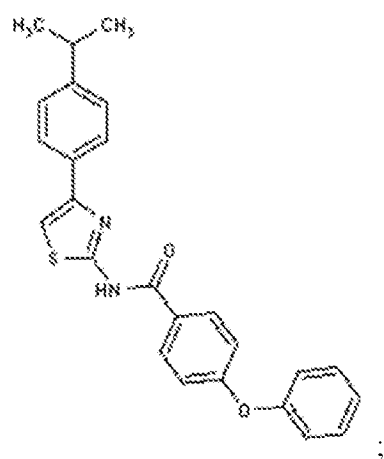
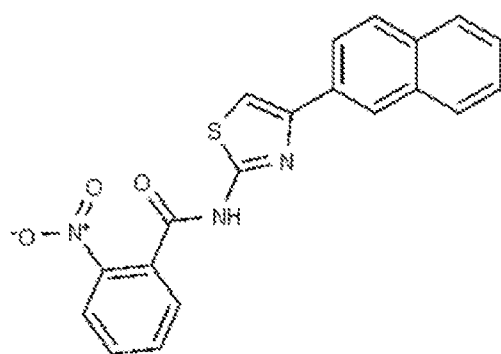
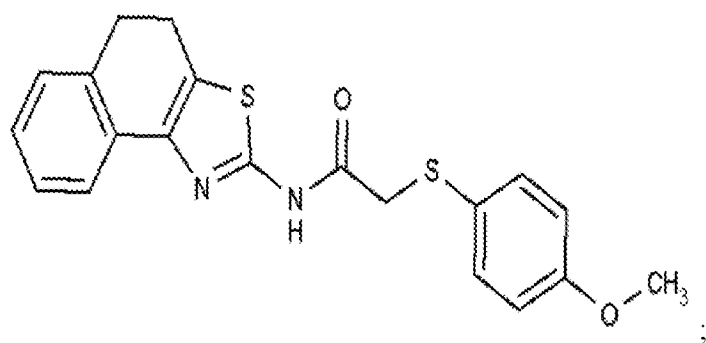
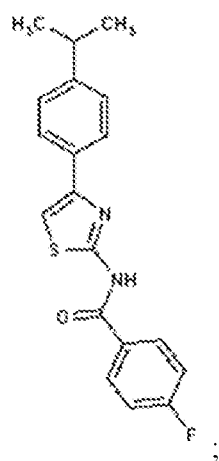


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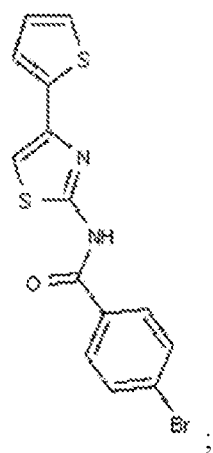
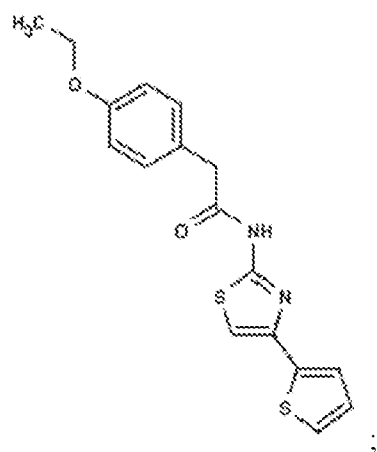
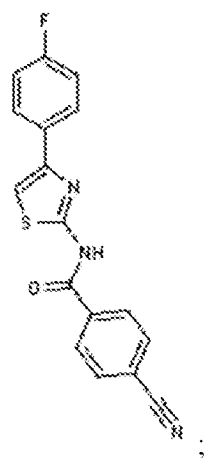
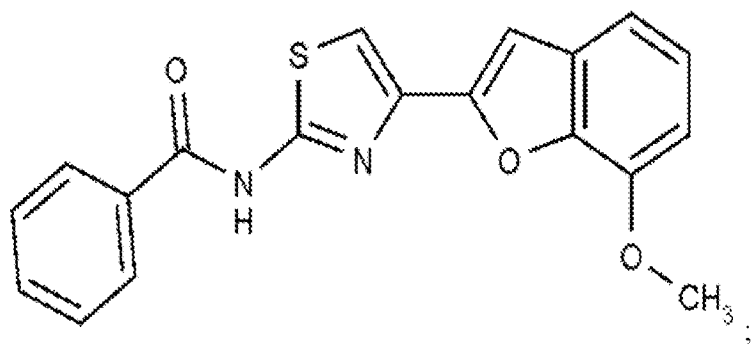


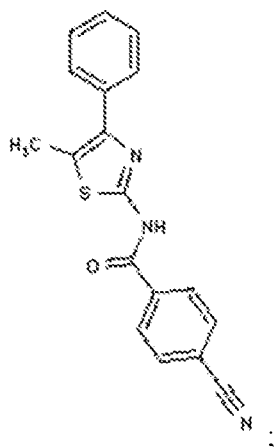
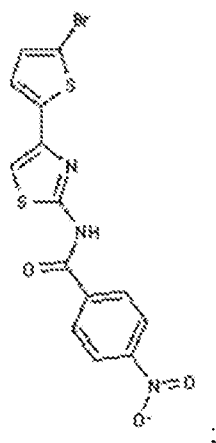
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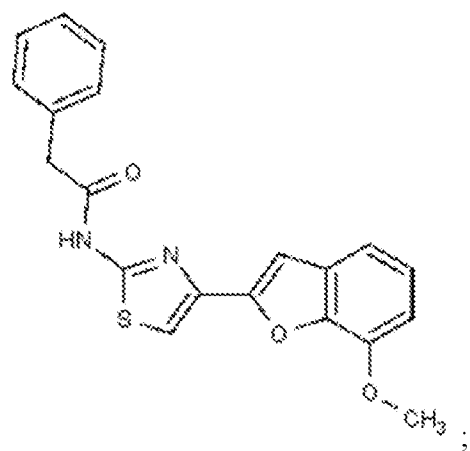
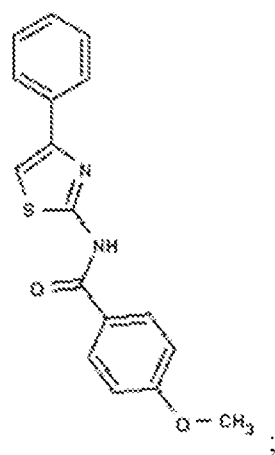
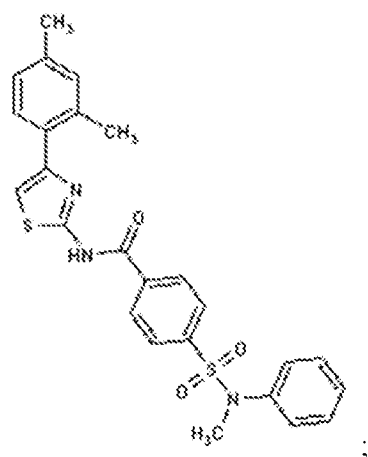


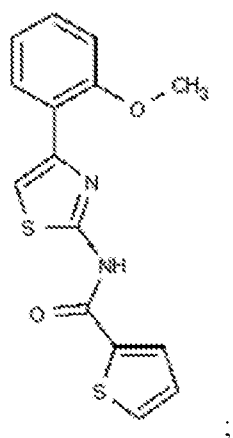


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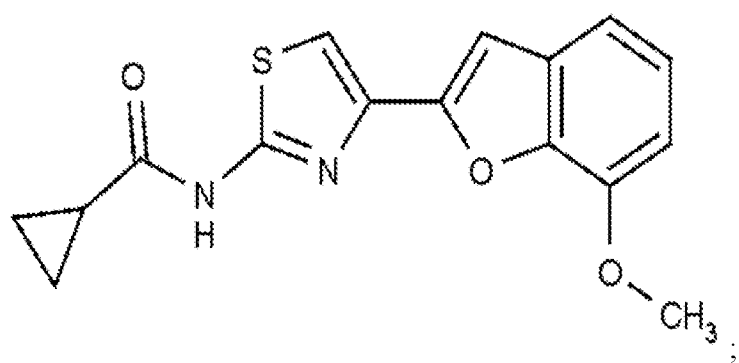




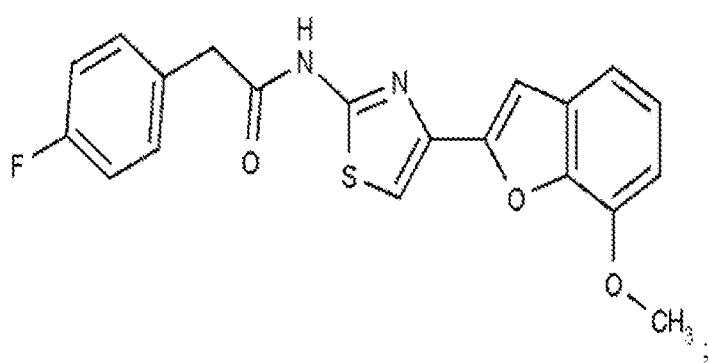




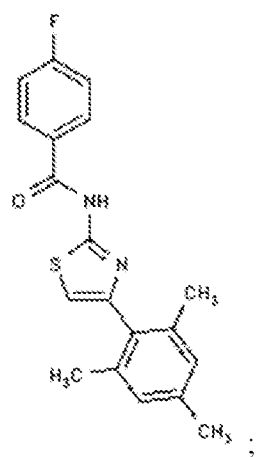
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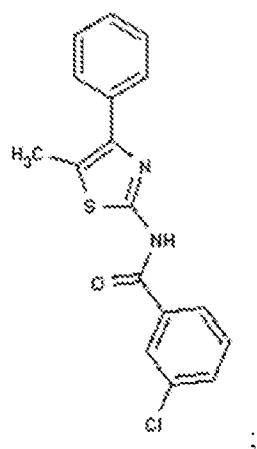
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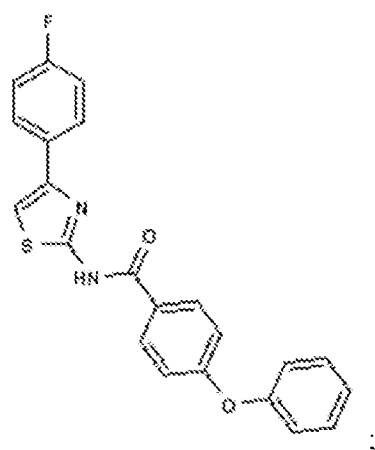
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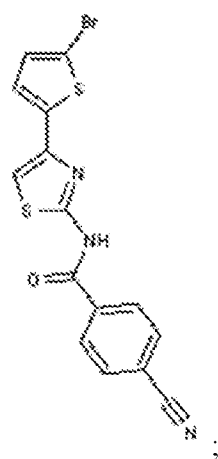
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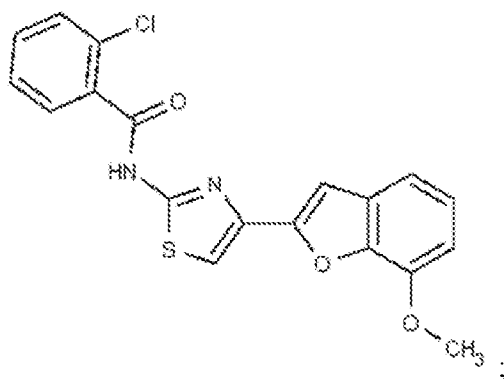
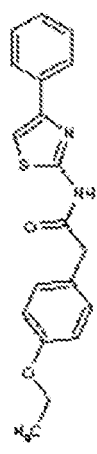
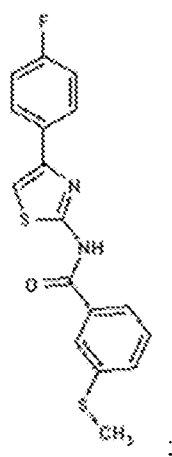
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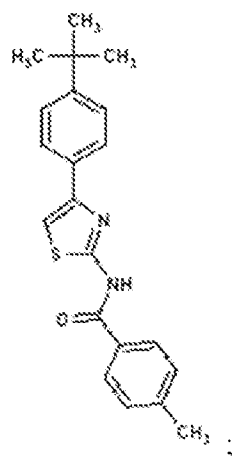
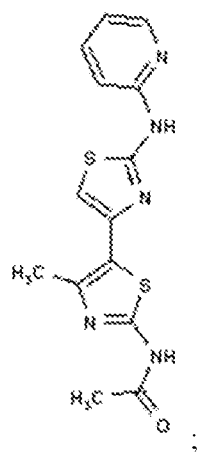


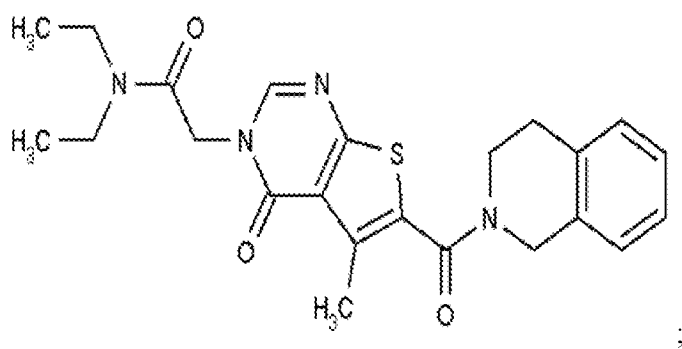
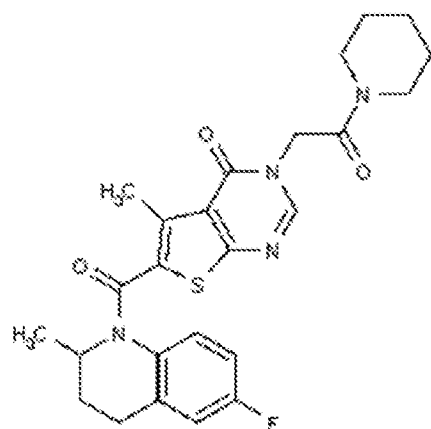
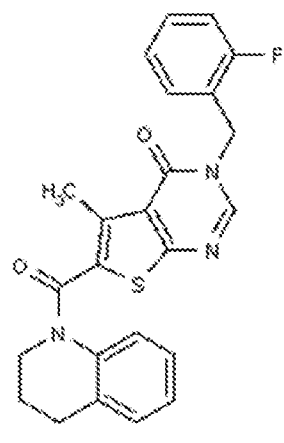
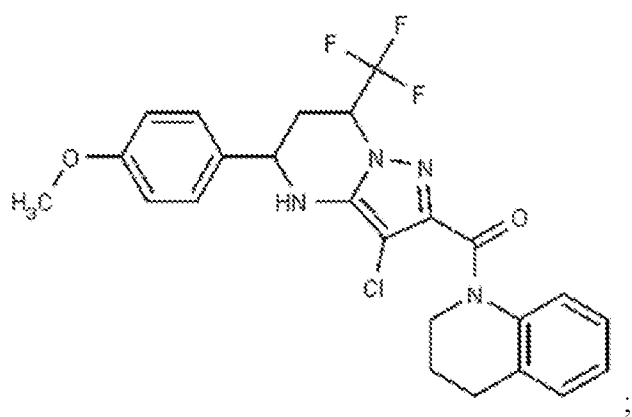
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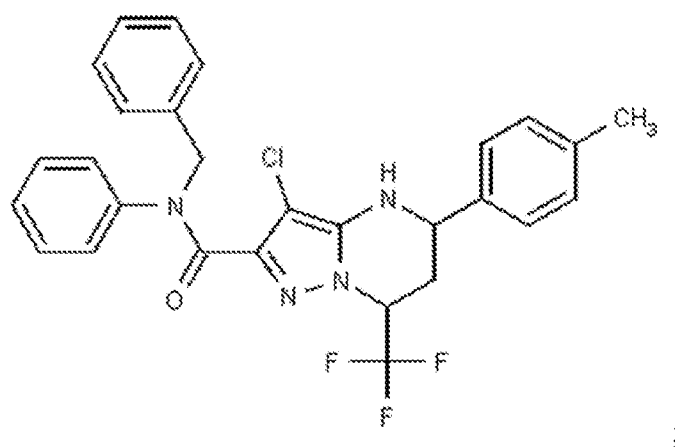
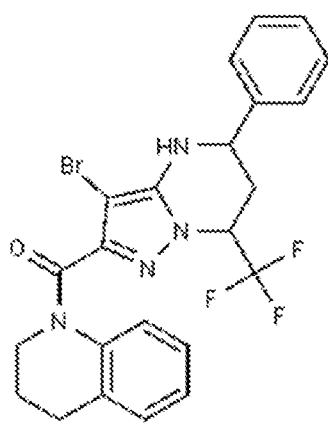
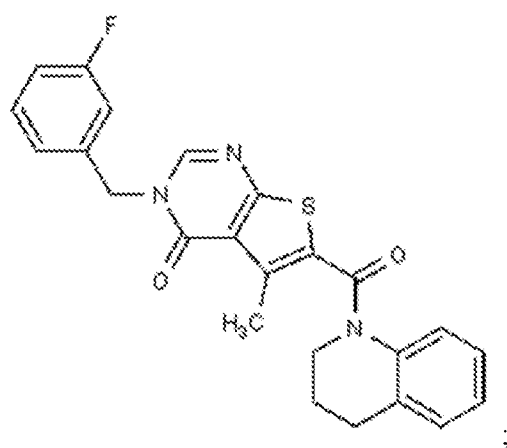


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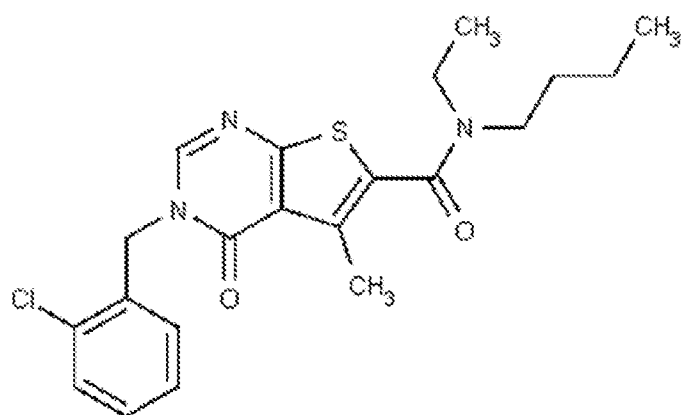




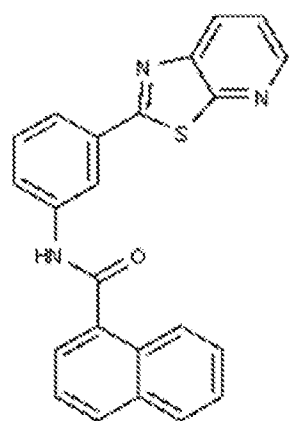




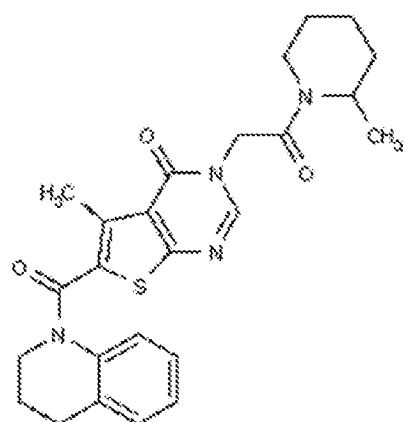
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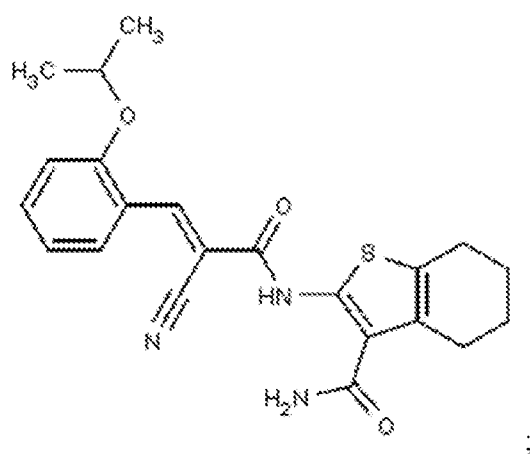
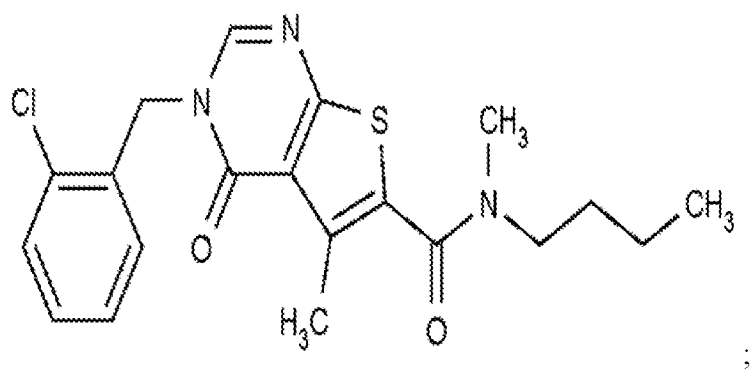
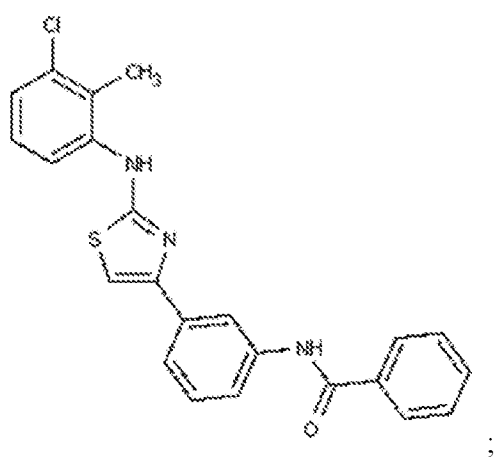
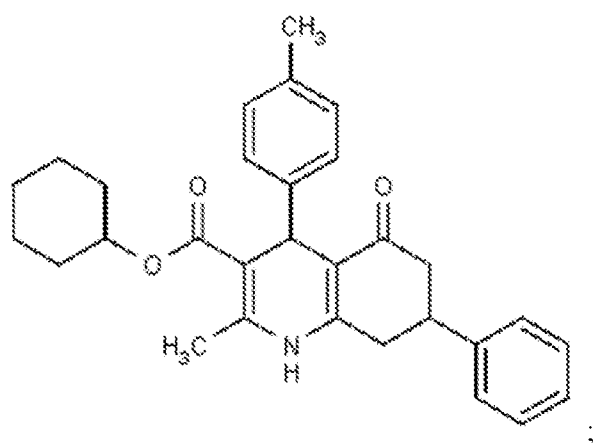
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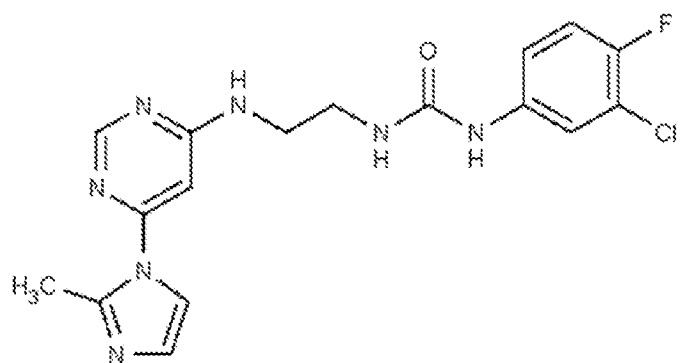


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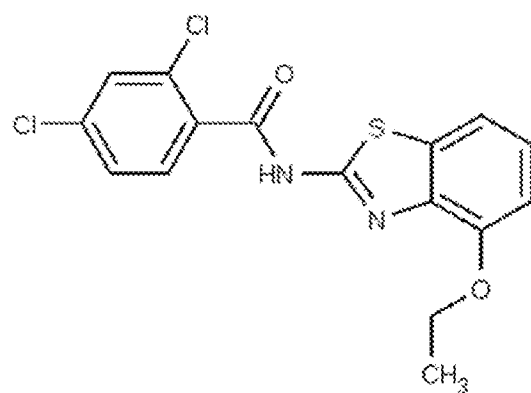


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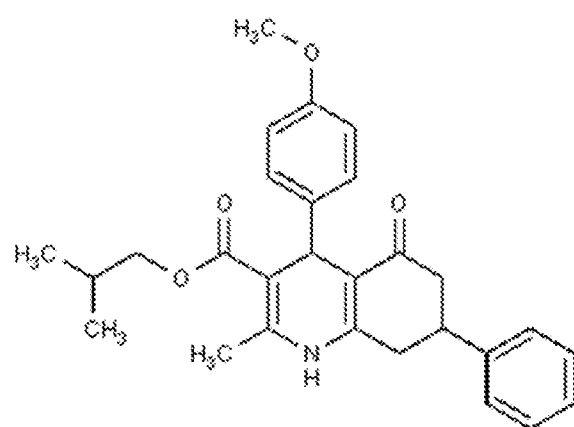




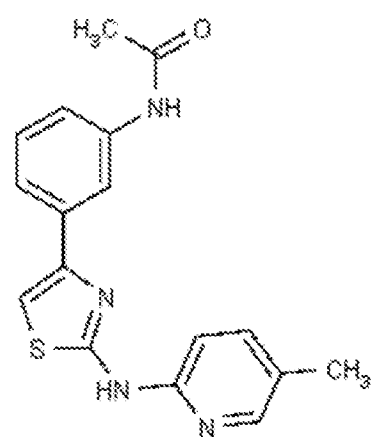
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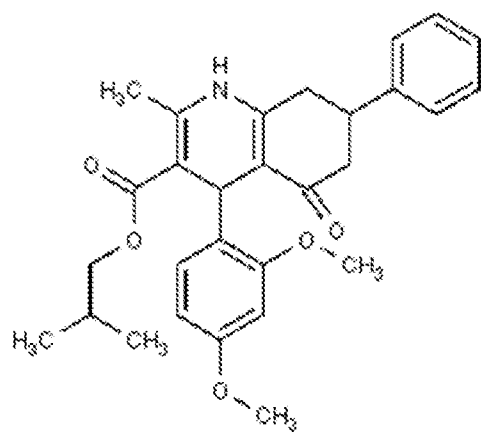


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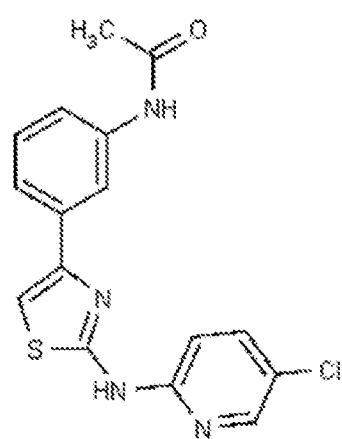


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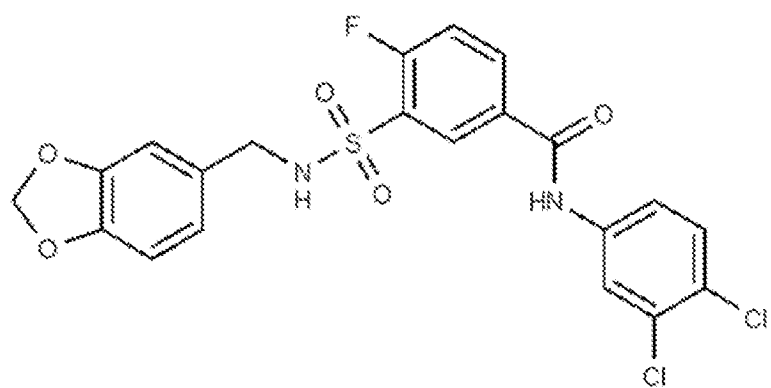
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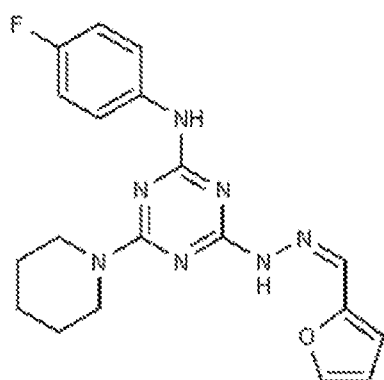
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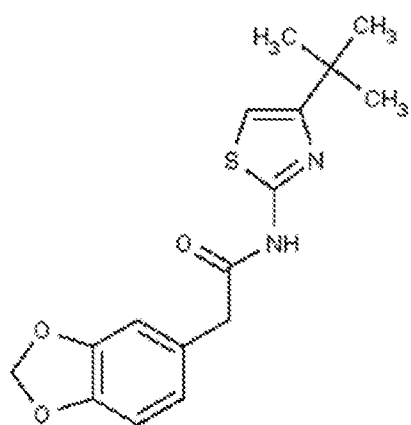


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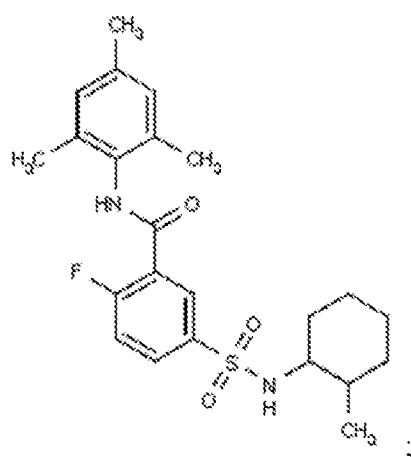


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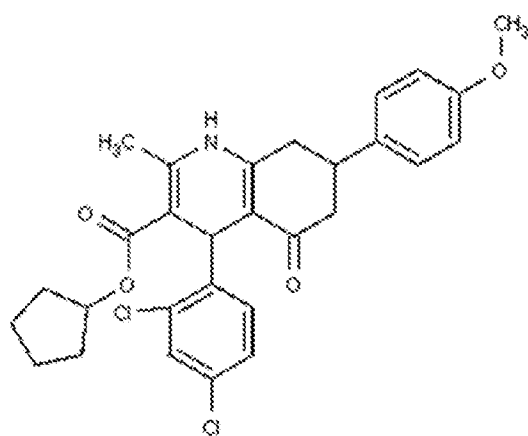
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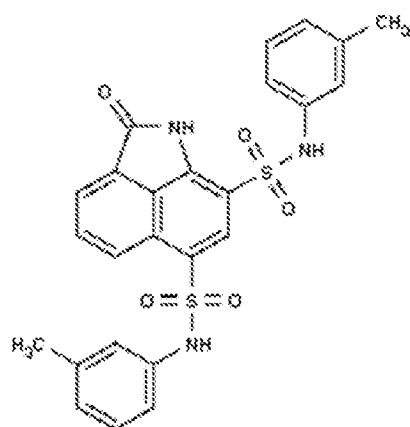
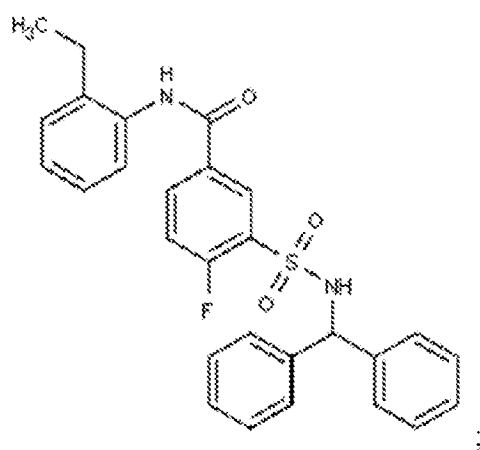
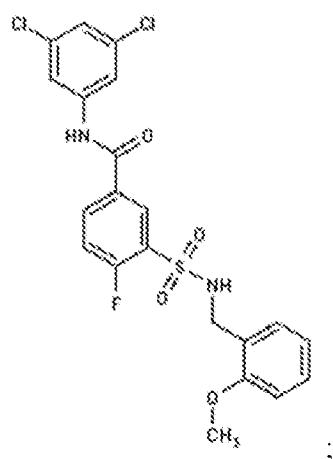
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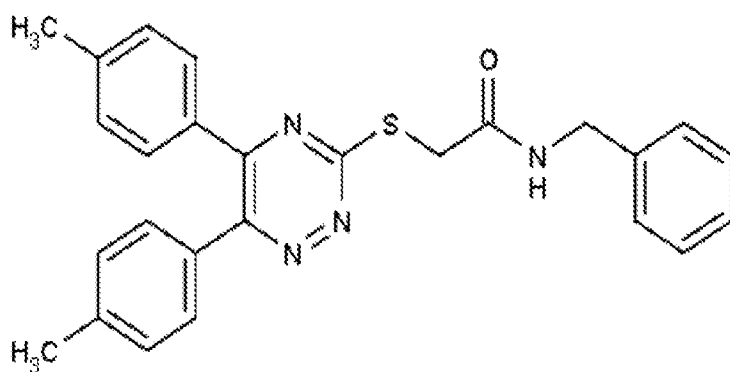
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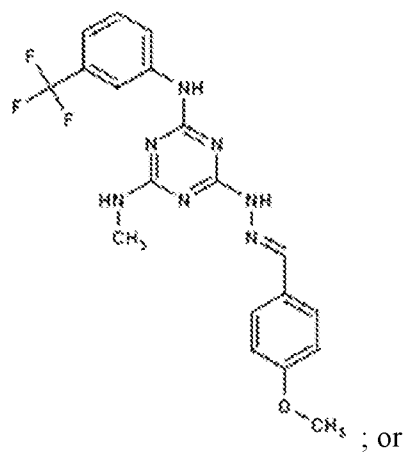
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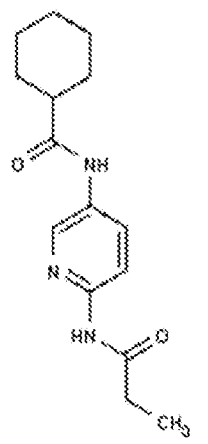
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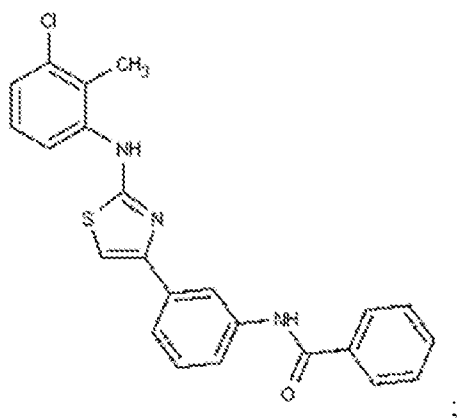
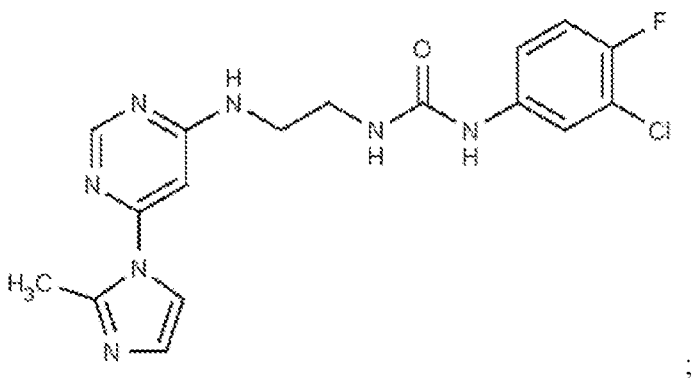
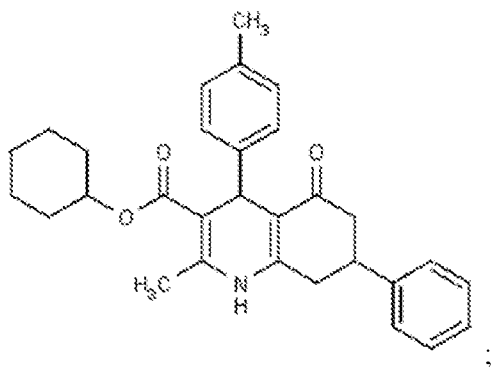


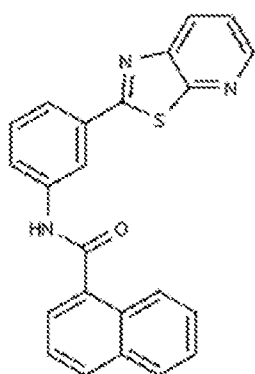
- 5 17. The method of claim 16, wherein the composition is adapted for oral, parenteral, enteral, rectal, intravenous, transdermal, intramuscular, pulmonary, or intranasal administration.
18. The method of claim 16, wherein the composition is adapted into a solution, suspension, cream, ointment, lotion, enema, elixir, syrup, emulsion, gum, insert, jelly, foam, paste, pastille, spray, magma or poultice.
- 10 19. The method of claim 16, wherein the compound is effective as a pharmacoperone.

20. The method of claim 16, wherein the compound is an hV2R[L⁸³Q] pharmacoperone.
21. The method of claim 16, wherein the compound is formulated as a salt selected from 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, or pamoate.
22. The method of claim 16, wherein the molecule is formulated with an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base.
23. The method of claim 16, wherein the molecule is formulated with bases, 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; tributylamine; 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; an amino acid, arginine, or lysine.
24. The method of claim 16, wherein the composition is formulated for at least one of an immediate-release, mixed-release, pulsatile-release, or sustained-release.
25. A method of evaluating a candidate drug believed to be useful in treating a disease caused by a misfolded and misdirected protein, the method comprising:
- a) obtaining a cell or tissue suspected of having a disease or condition caused by the misfolded and misdirected protein from a set of patients suspected of having a disease or condition;
- b) administering the candidate drug a cell or tissue of the patients, and a placebo to a second subset of cells or tissues that do not have the disease or disease condition; and
- c) determining if the candidate drug causes the protein to fold correctly and be directed to the correct cellular location that is statistically significant as compared to any change occurring in the second subset of cells or tissues, wherein a statistically significant reduction in misfolding and misdirecting of the protein indicates that the candidate drug is useful in treating said disease or condition.

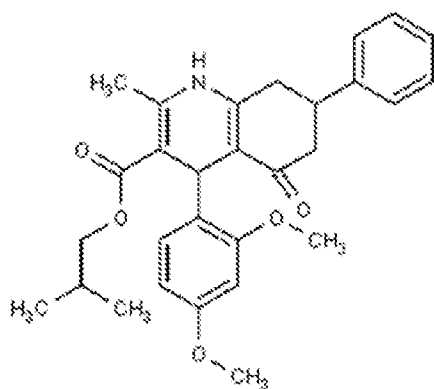
26. The method of claim 25, wherein the candidate drug is selected from at least one of a aminobenzothiazole amide, aminobenzothiazole benzamide, aminothiazole benzamide, aryl aminothiazole amide, aryl aminothiazole benzamide, or a heteroaryl amide.

27. The method of claim 25, wherein the candidate drug is selected from at least one of:

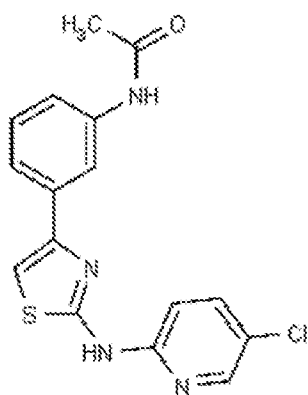




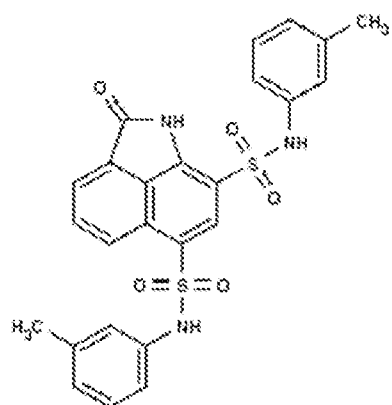
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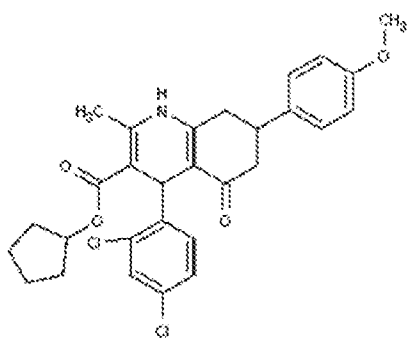
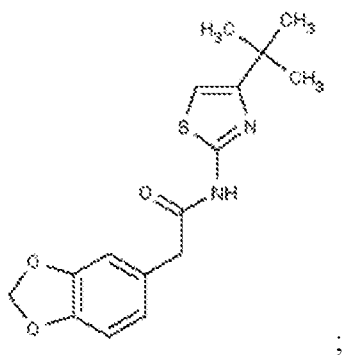
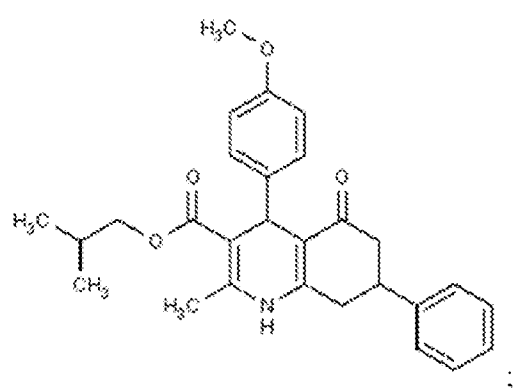
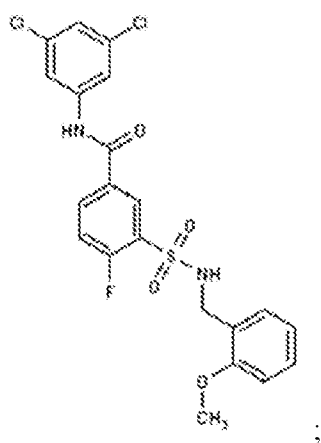
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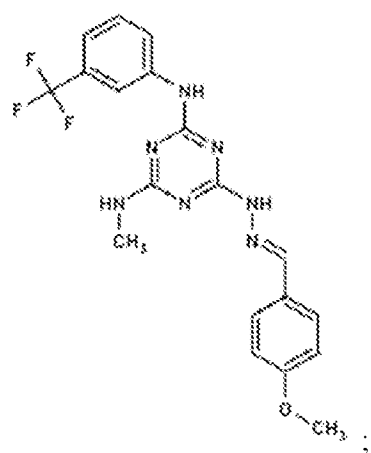
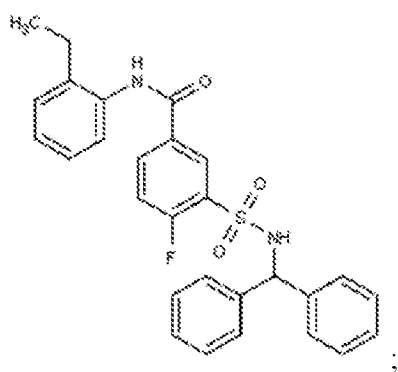
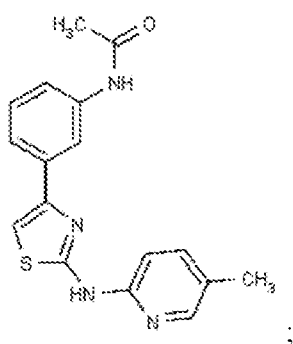
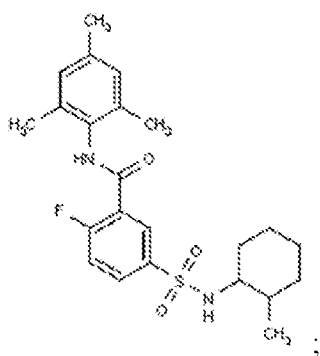


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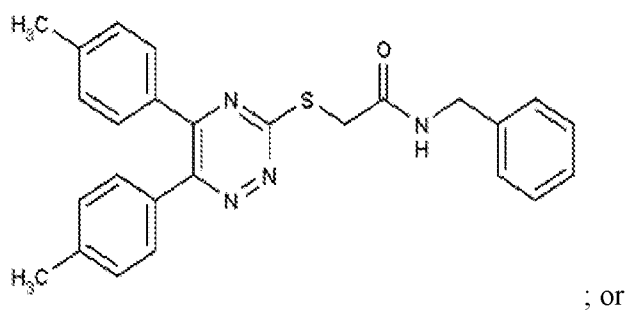
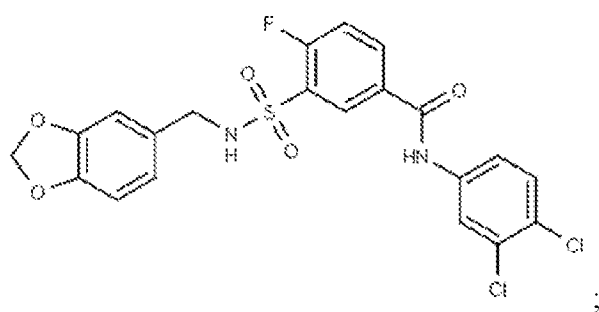
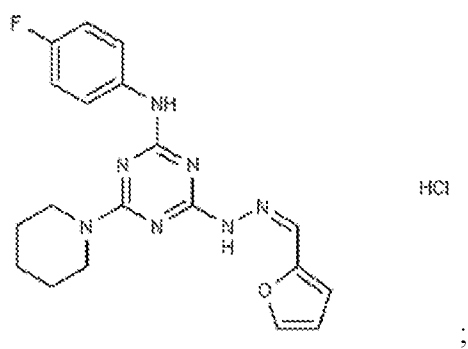


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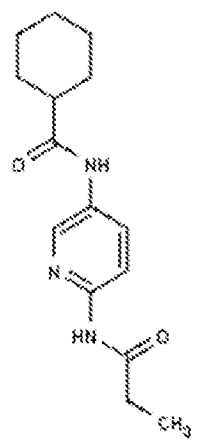




123



; or



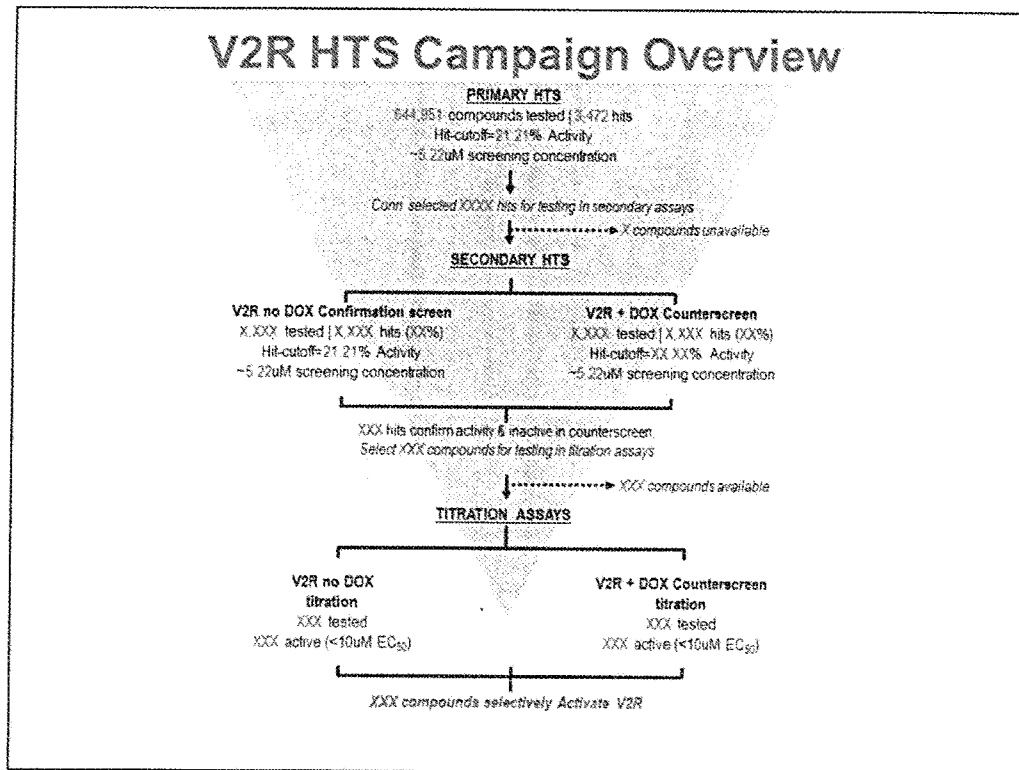


FIG. 1

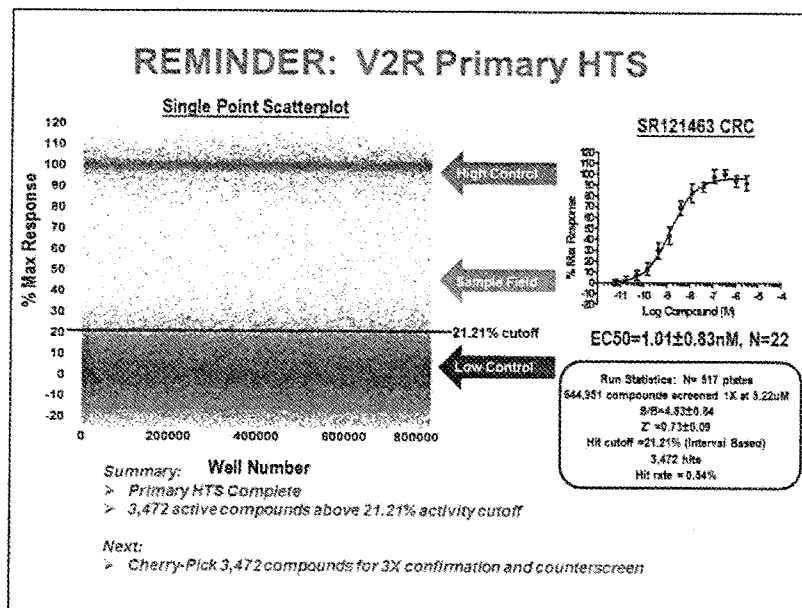


FIG. 2

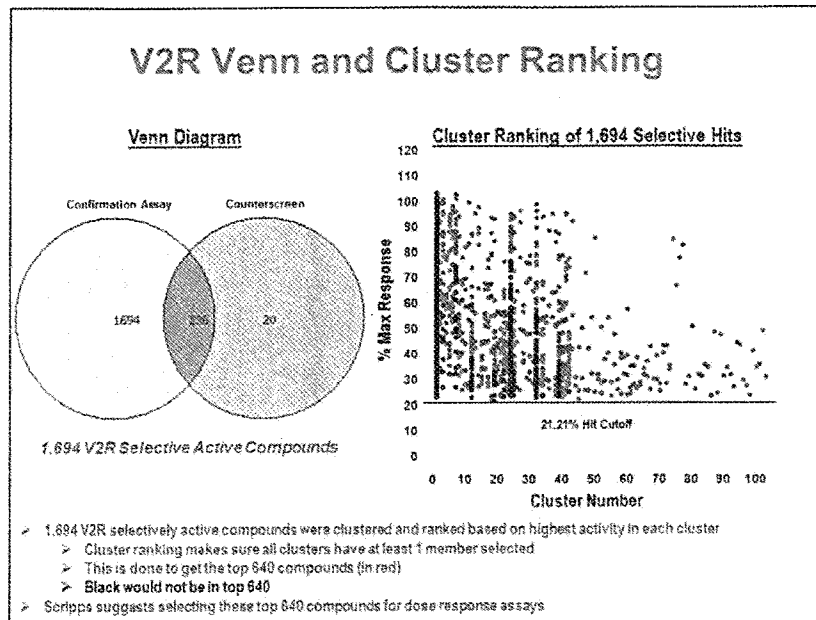


FIG. 3

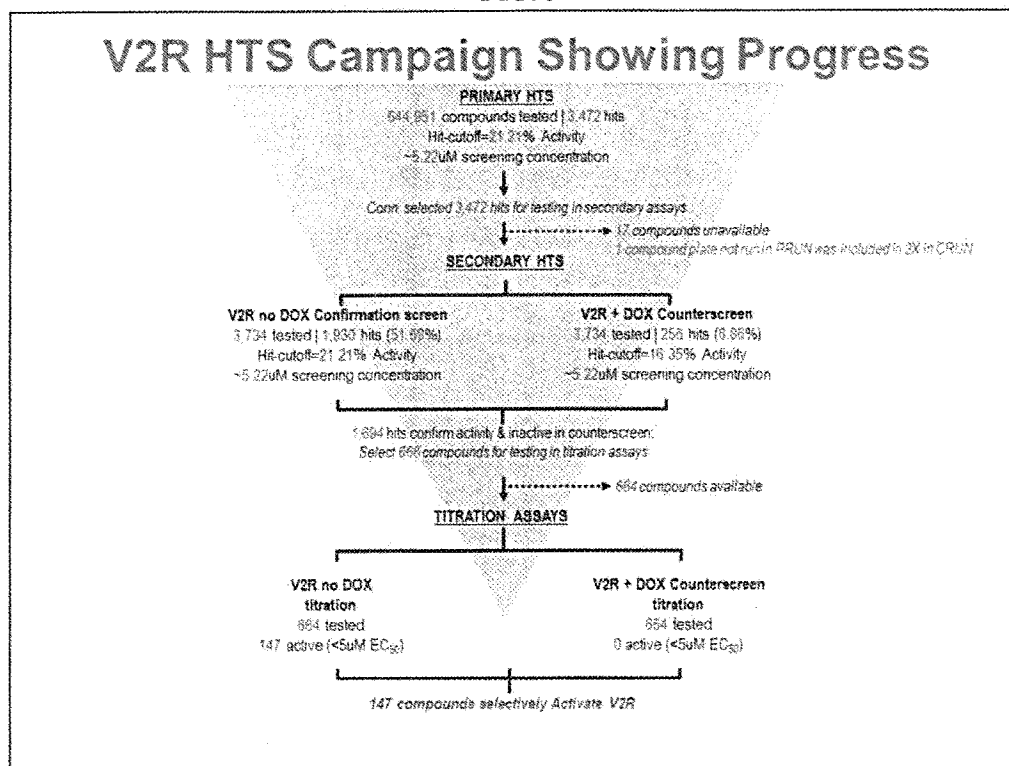


FIG. 4

Compound Information

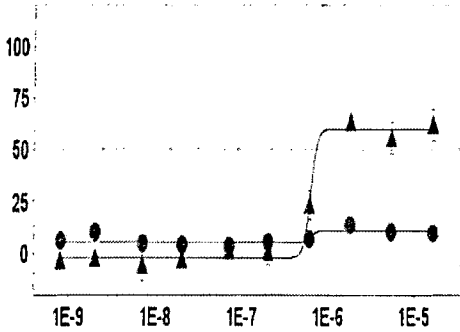
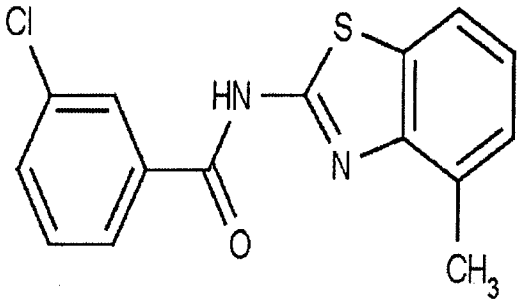
FIG. 5

Sample ID

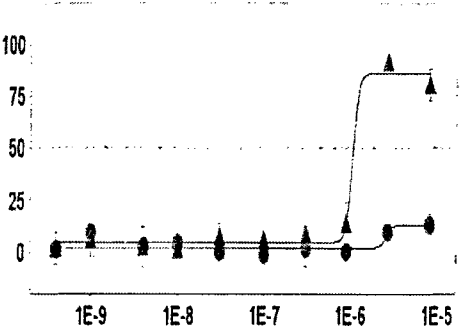
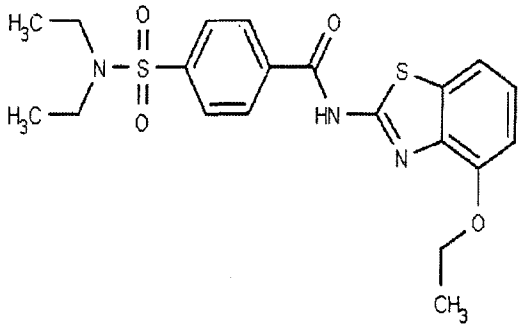
Structure

Dose Response Curve

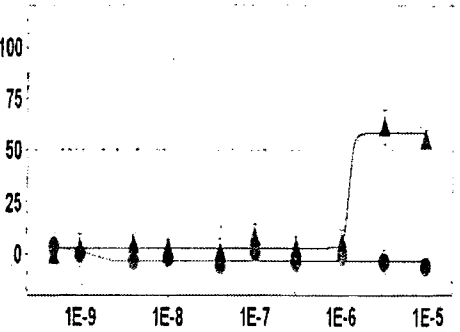
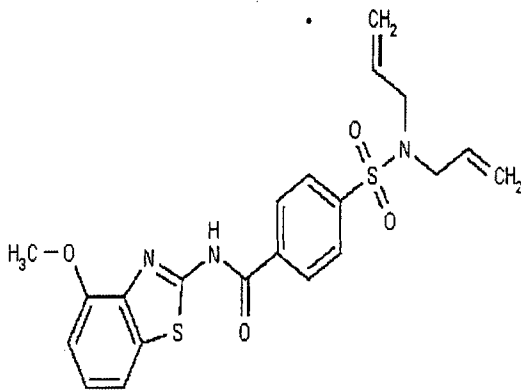
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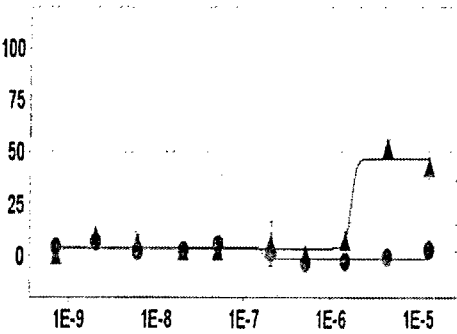
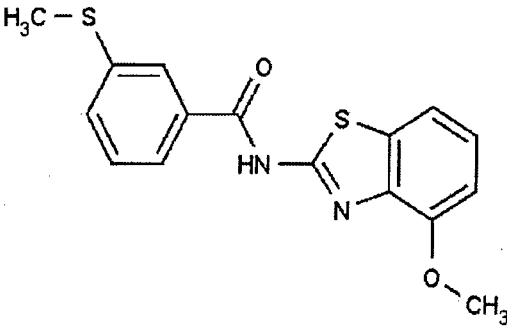
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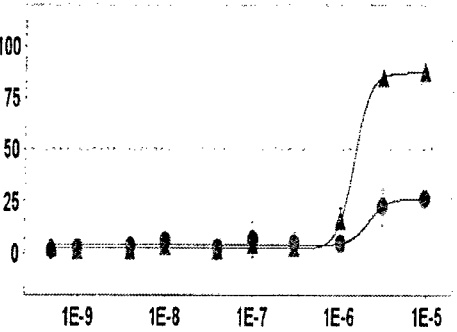
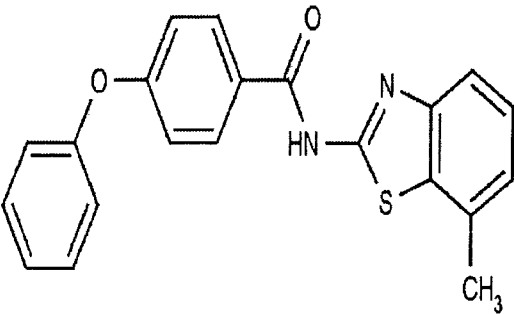
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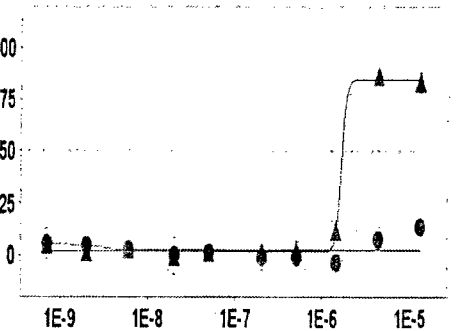
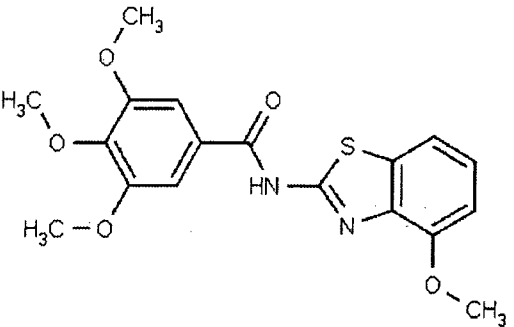
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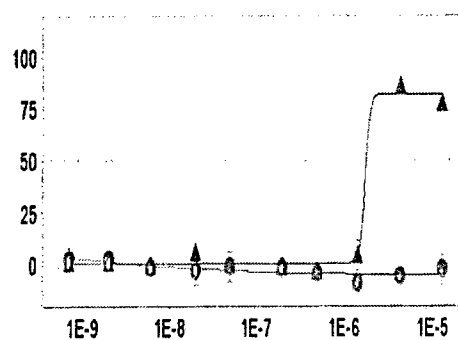
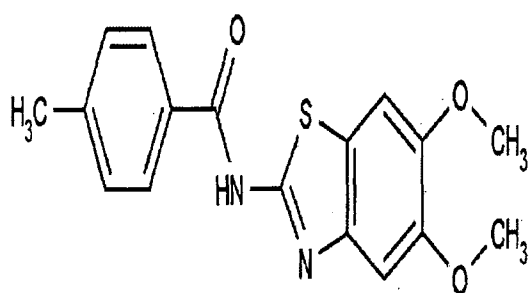
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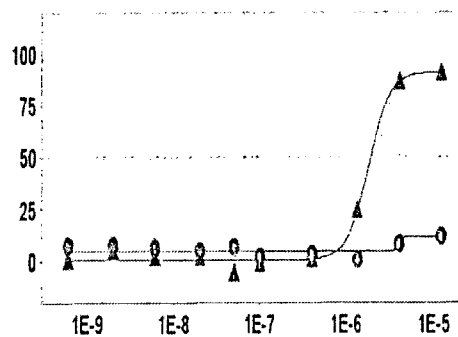
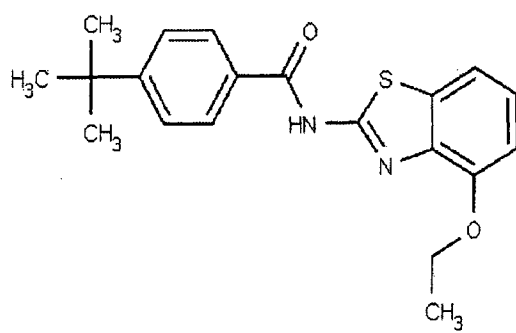
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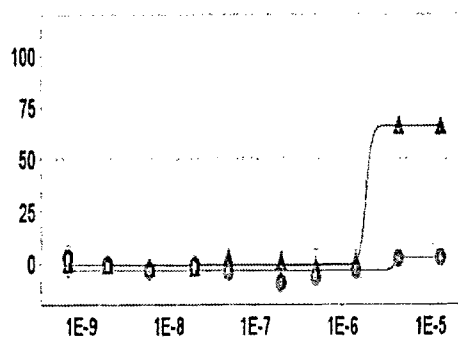
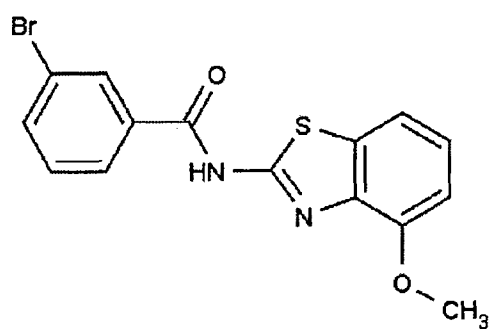
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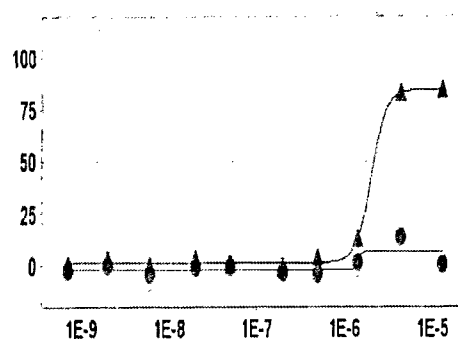
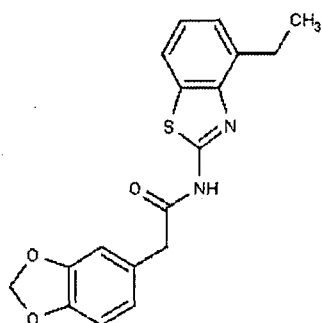
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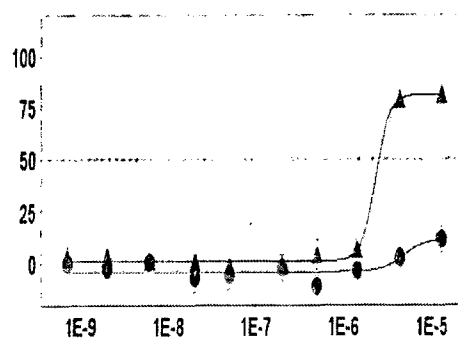
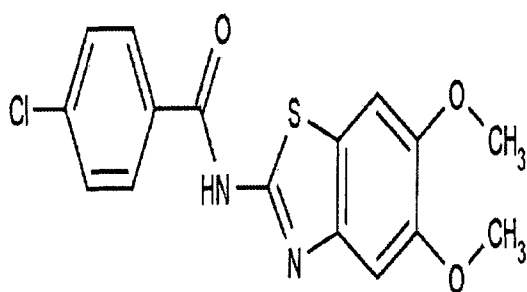
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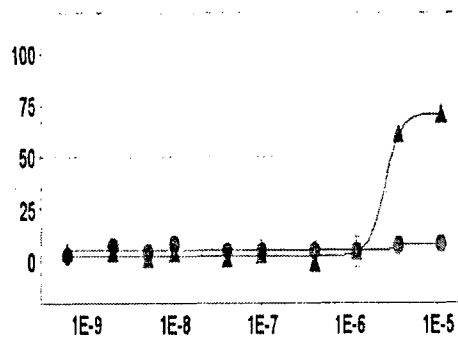
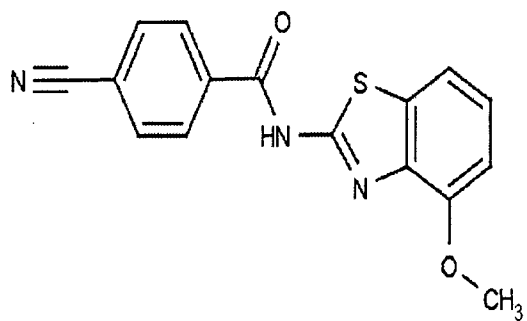
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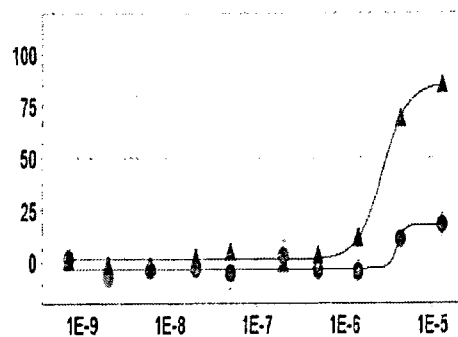
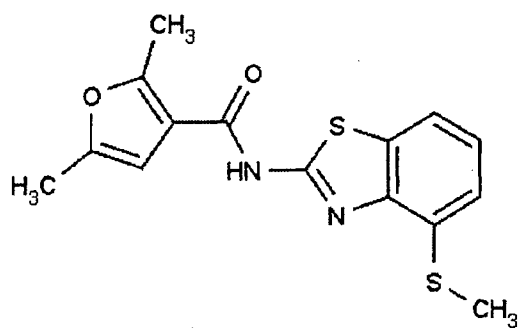
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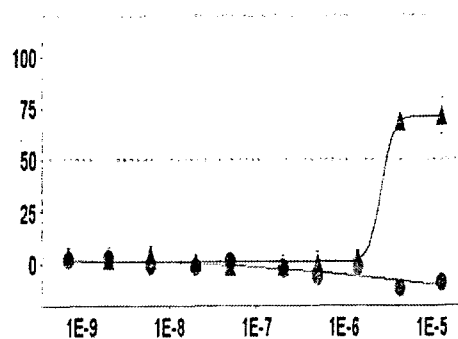
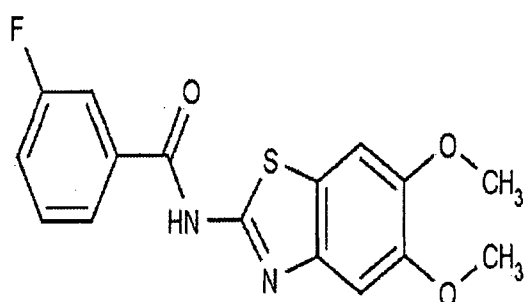
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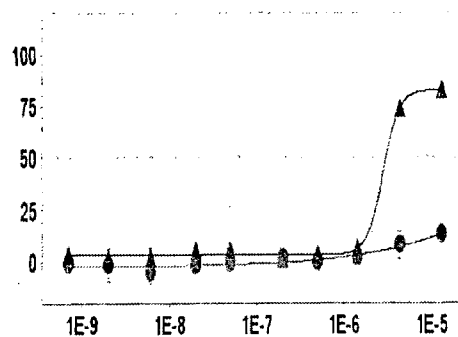
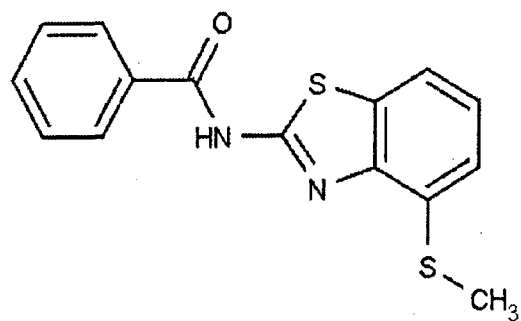
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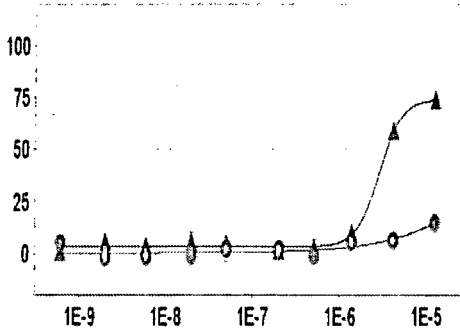
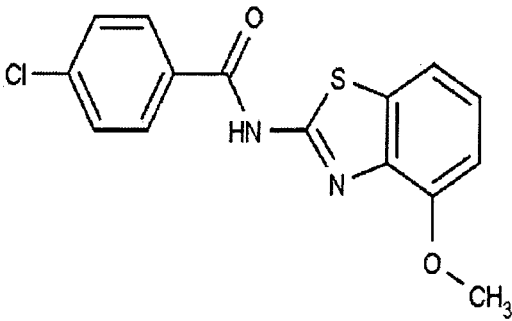
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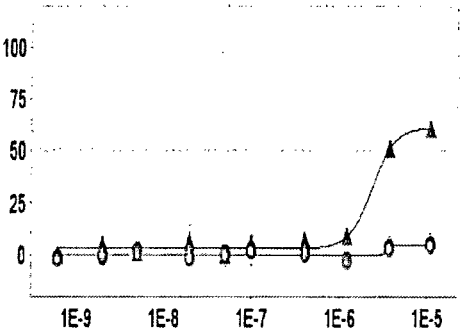
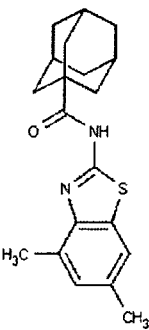
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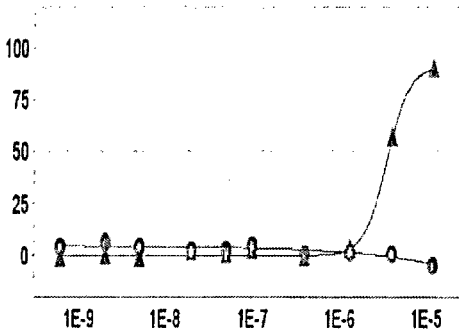
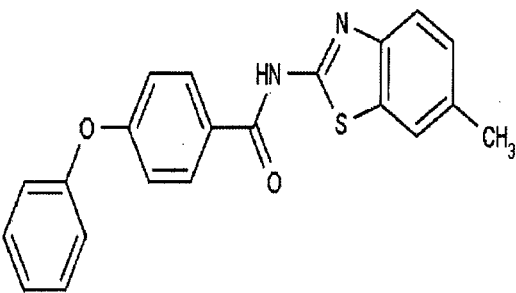
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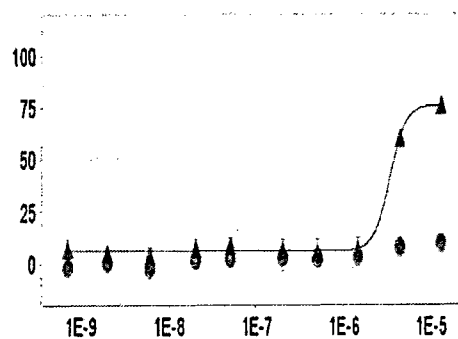
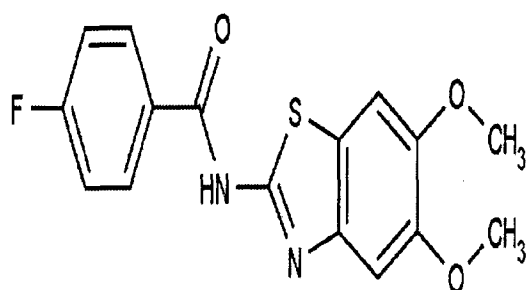
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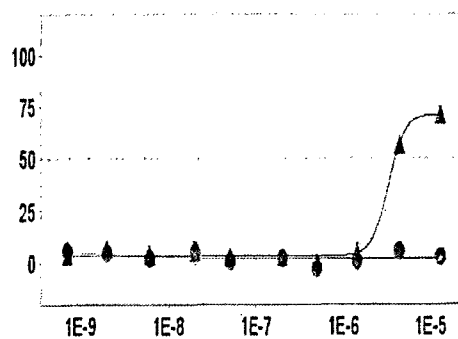
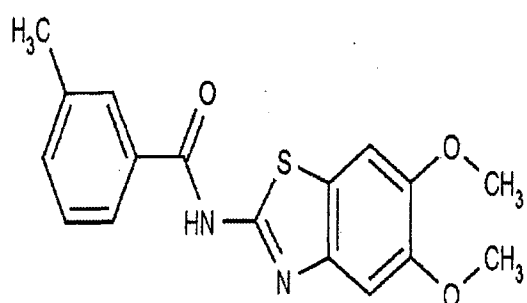
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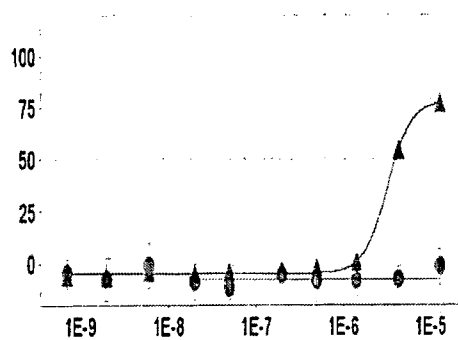
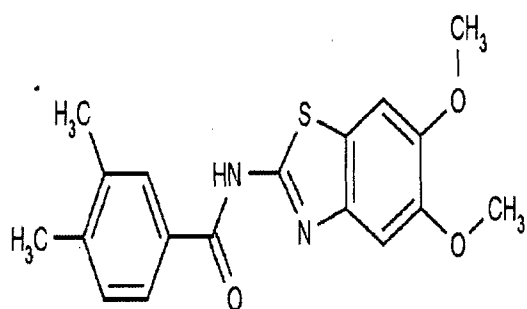
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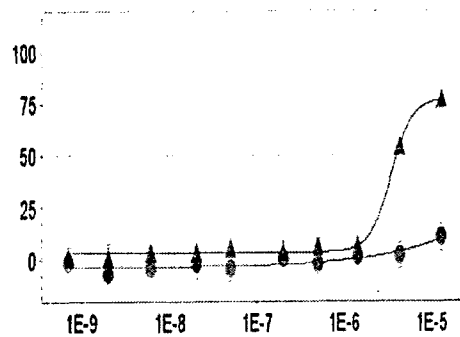
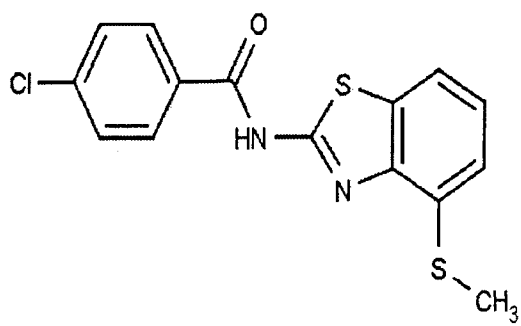
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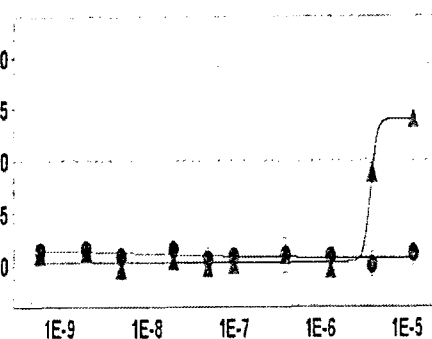
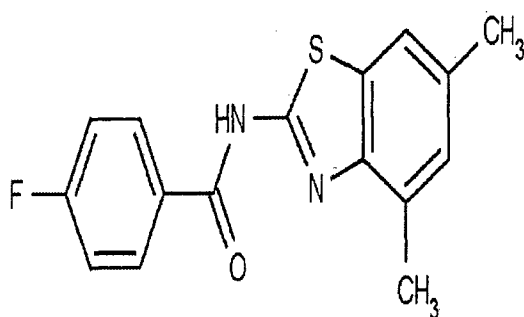
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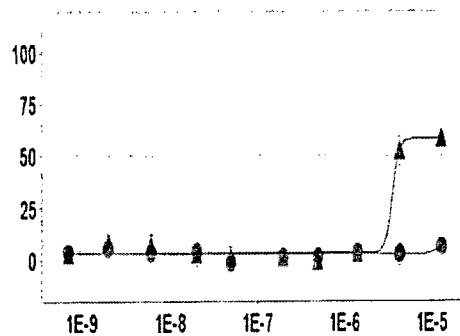
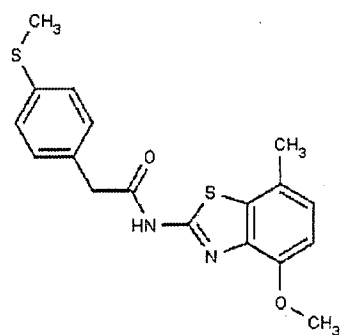
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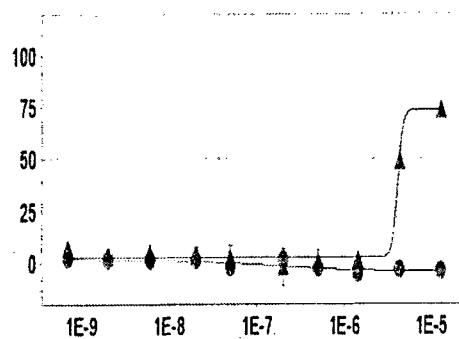
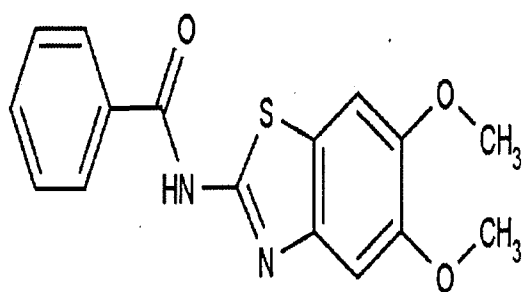
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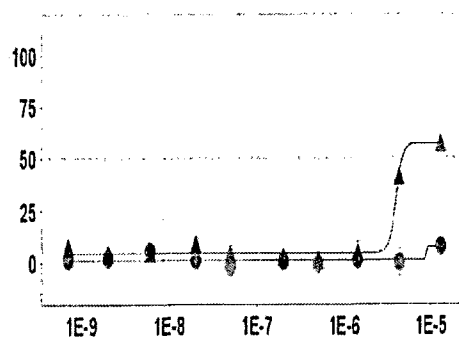
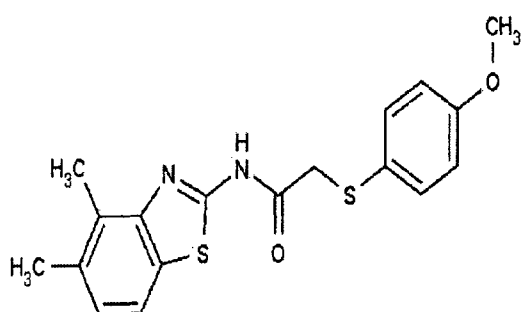
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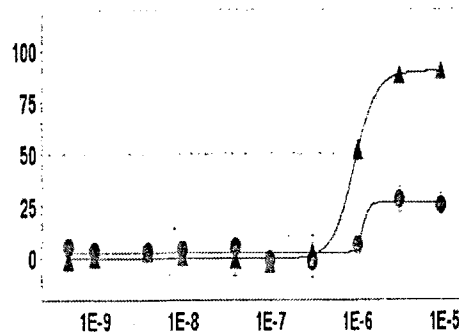
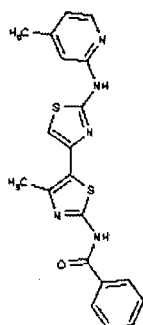
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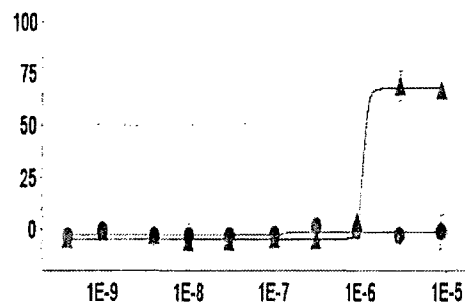
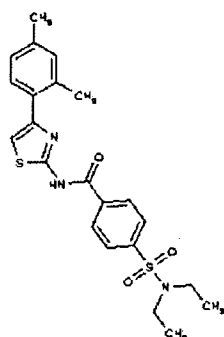
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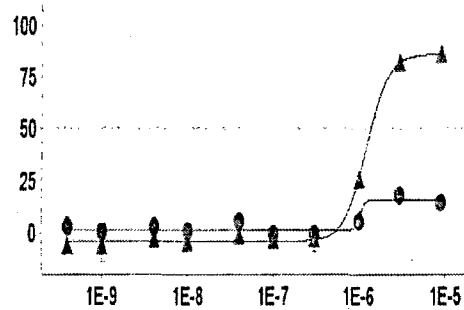
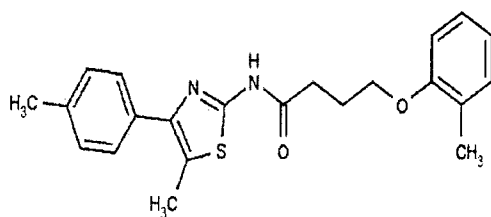
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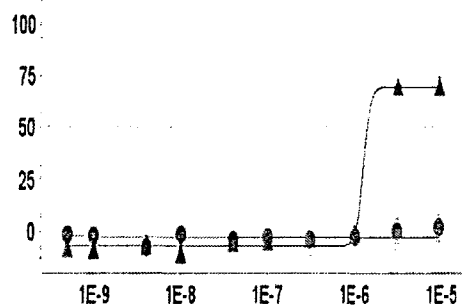
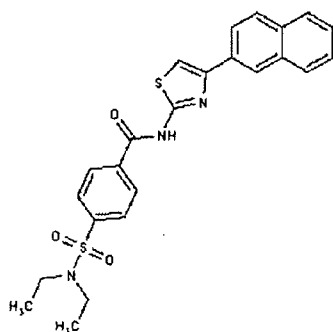
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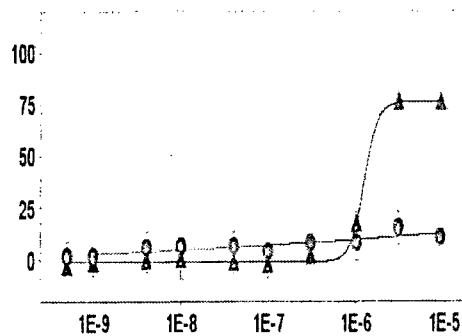
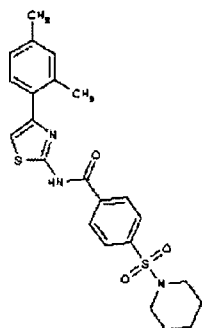
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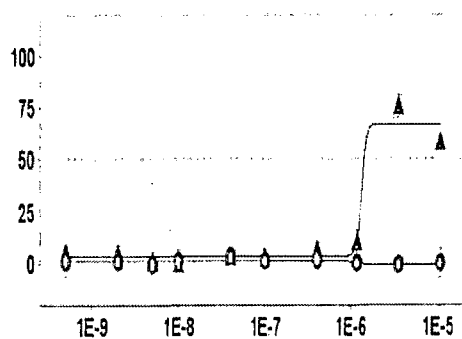
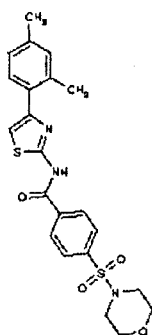
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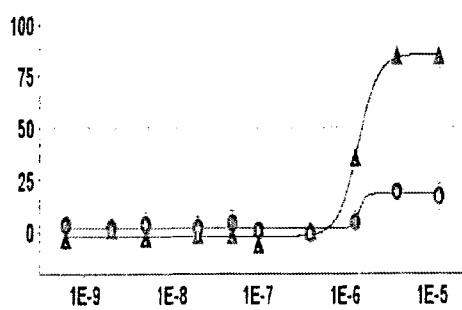
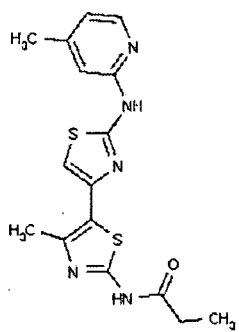
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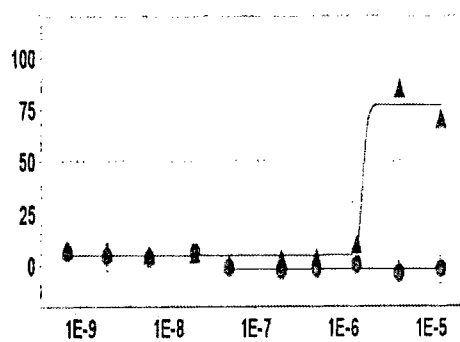
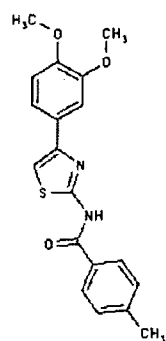
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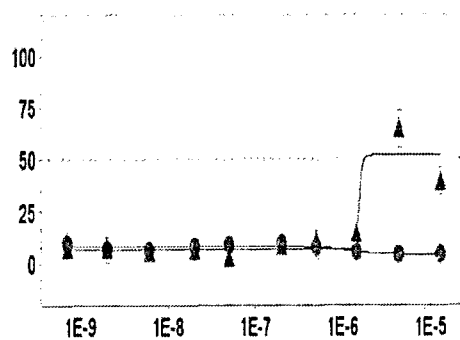
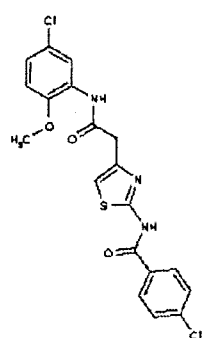
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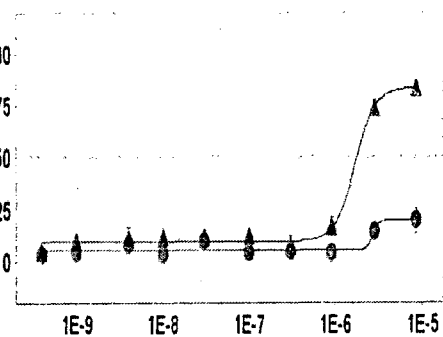
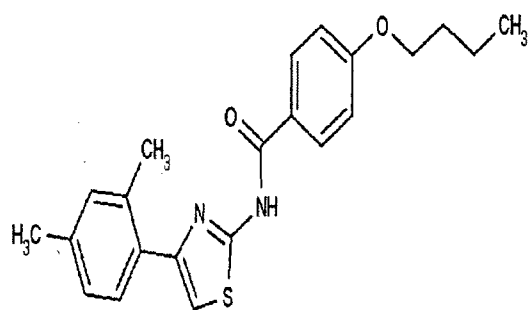
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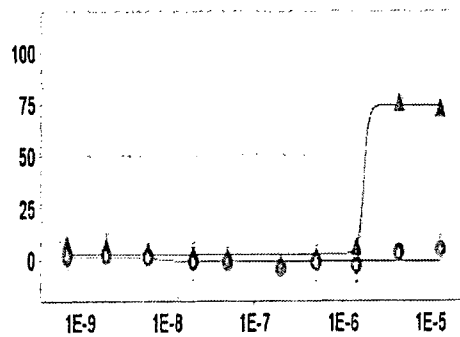
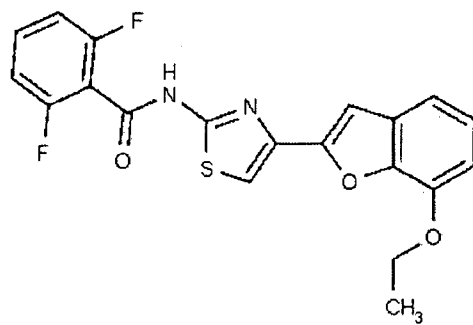
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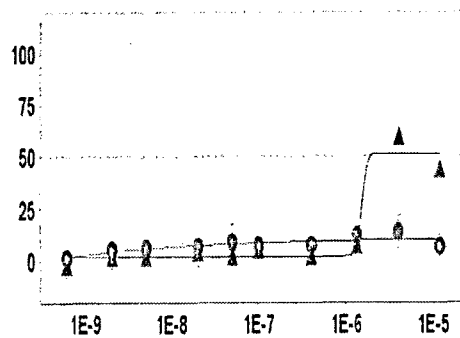
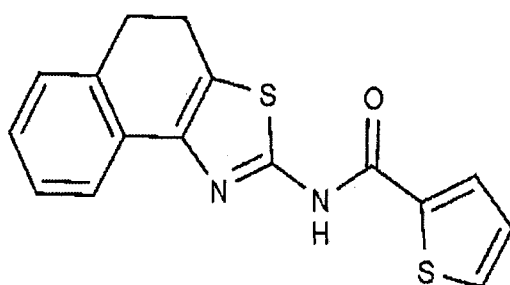
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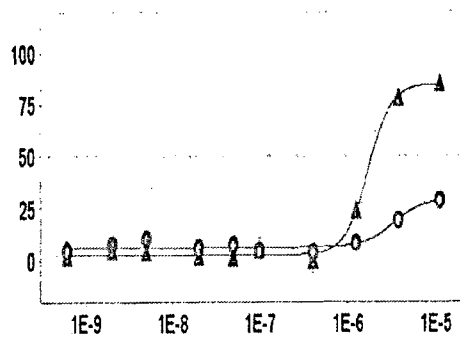
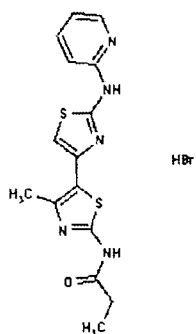
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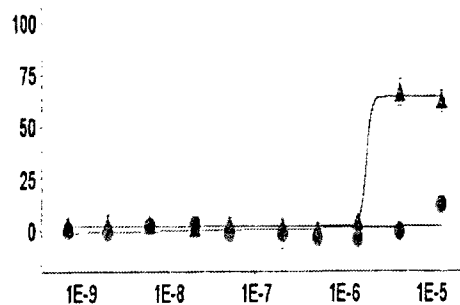
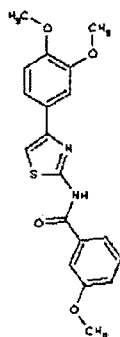
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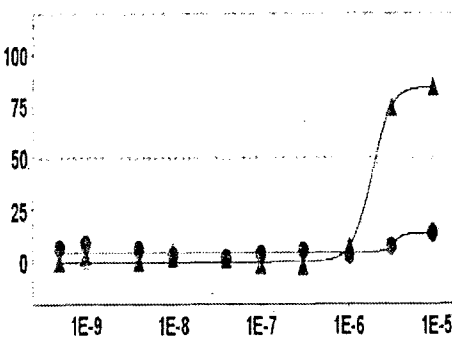
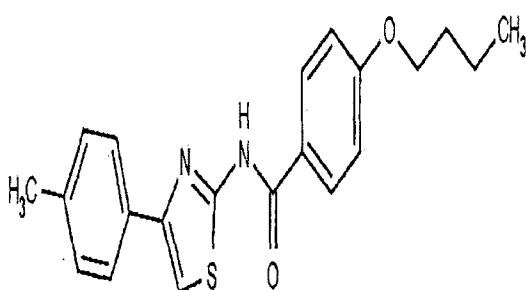
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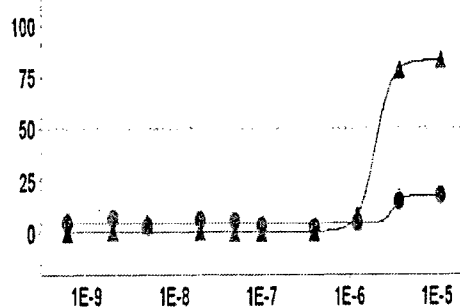
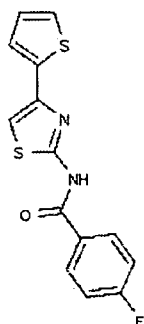
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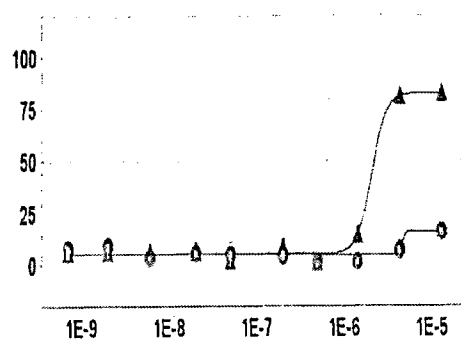
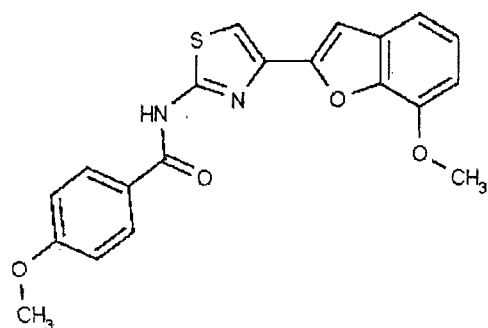
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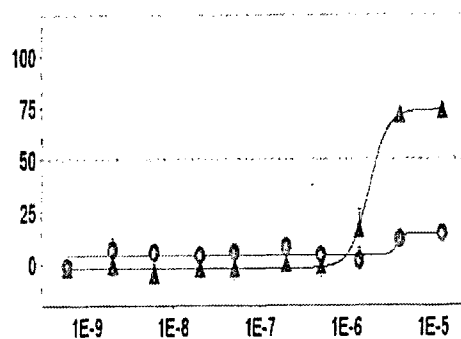
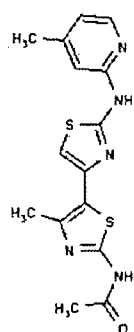
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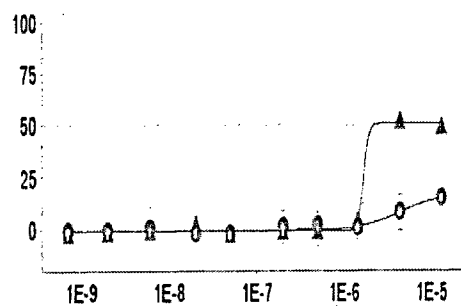
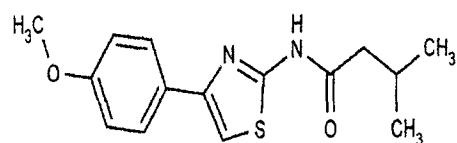
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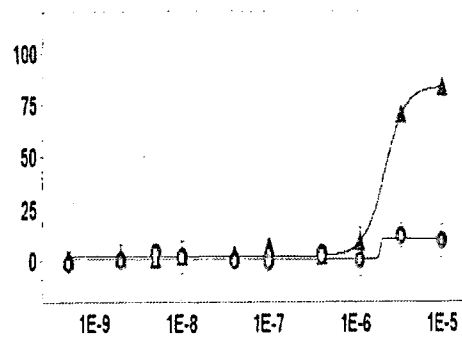
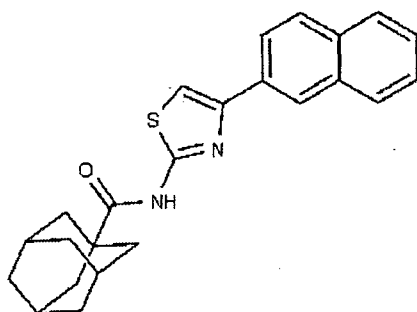
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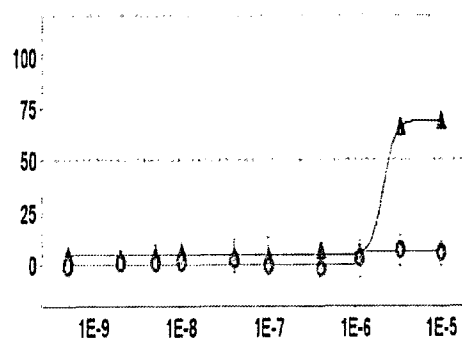
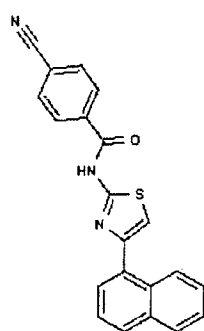
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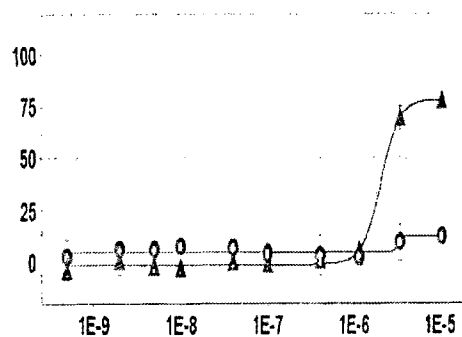
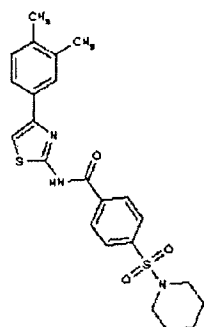
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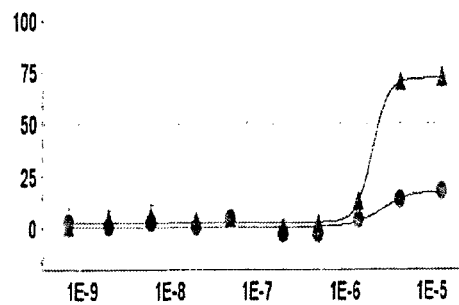
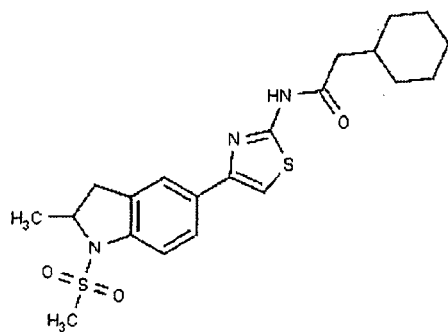
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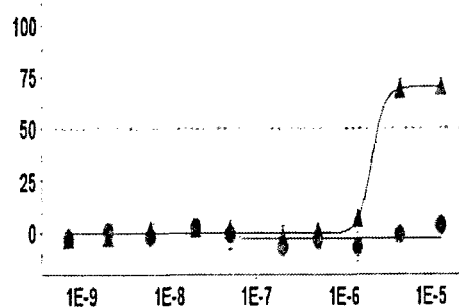
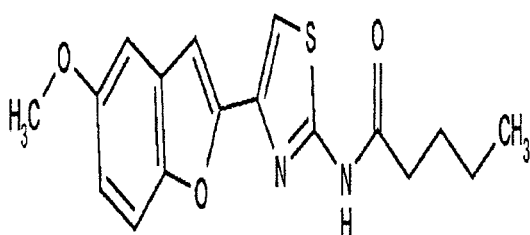
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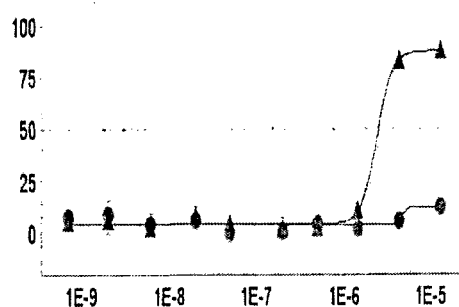
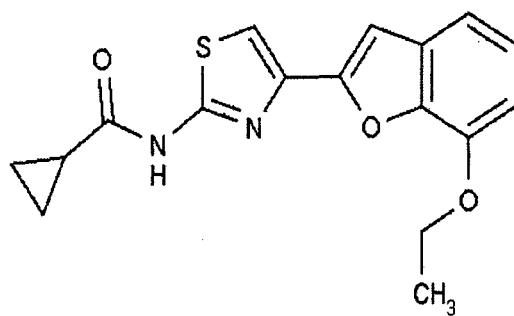
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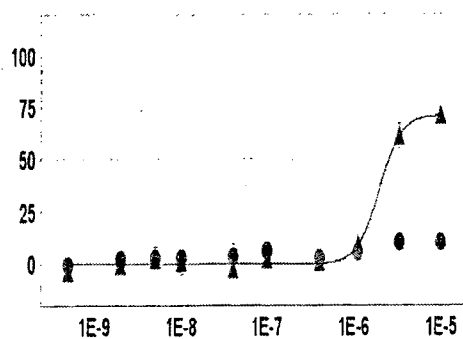
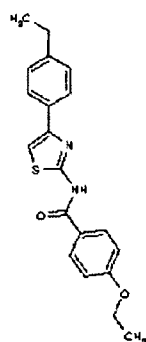
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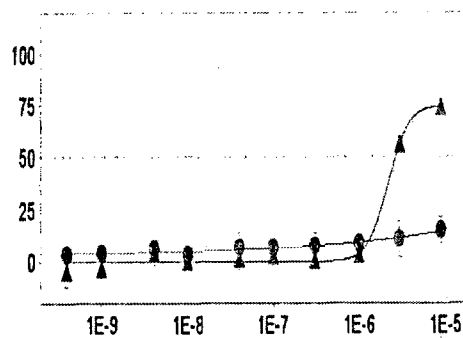
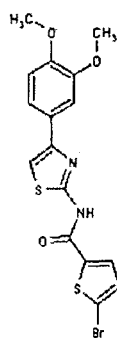
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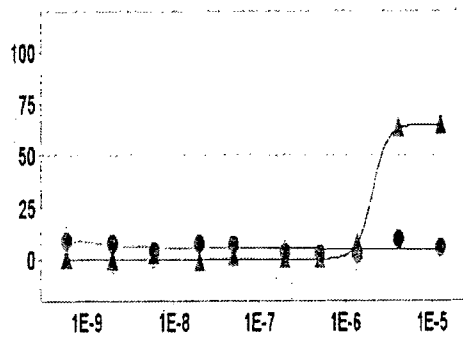
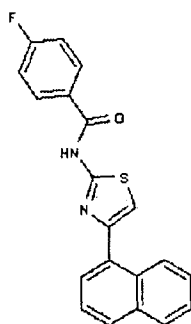
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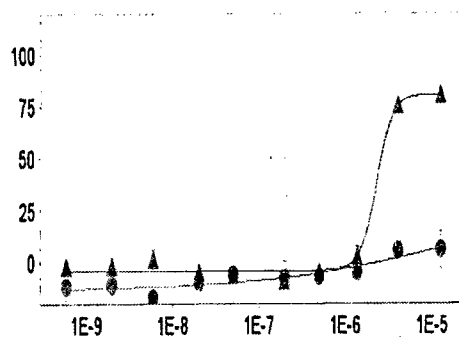
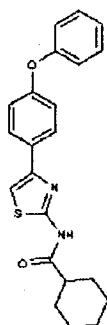
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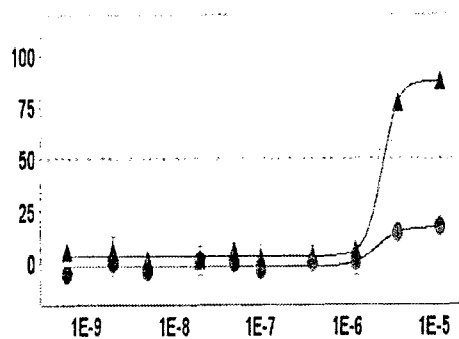
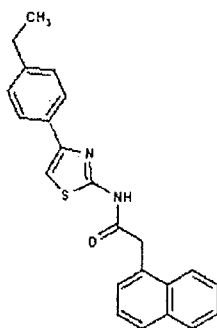
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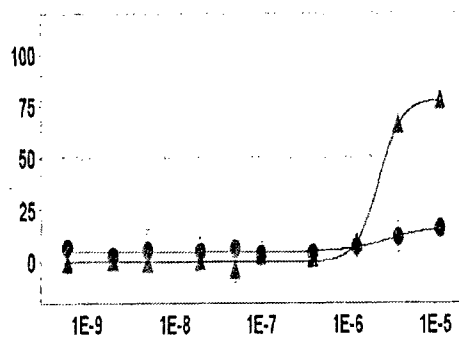
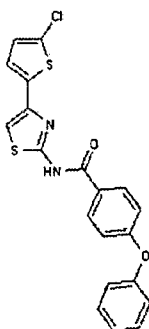
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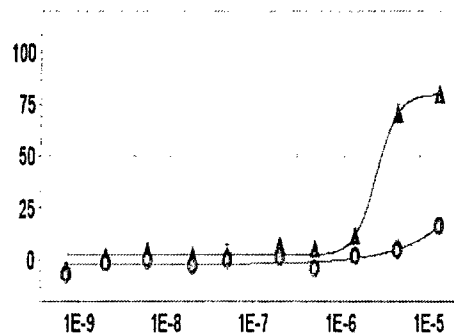
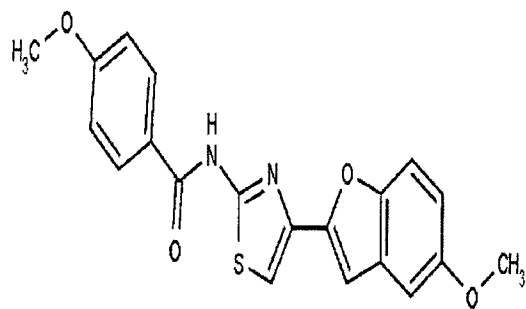
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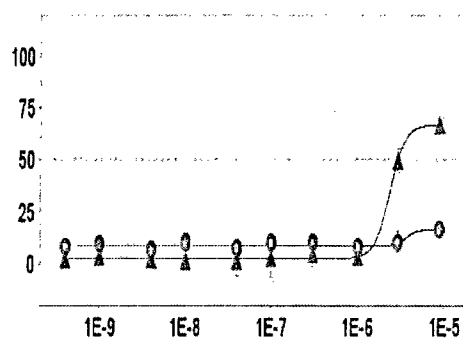
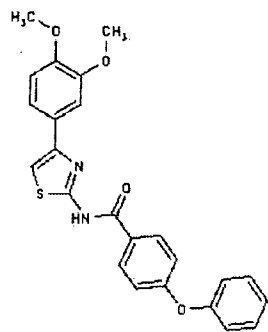
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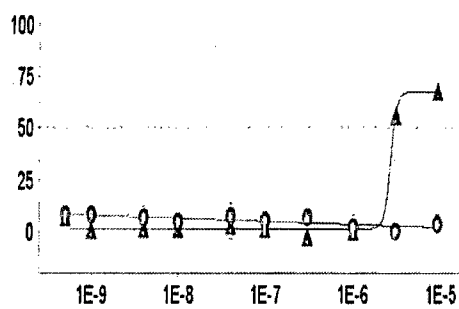
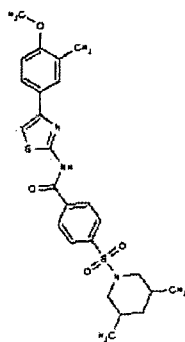
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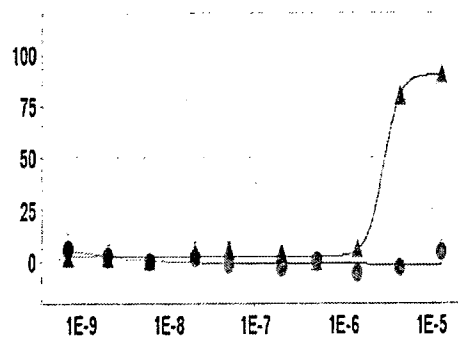
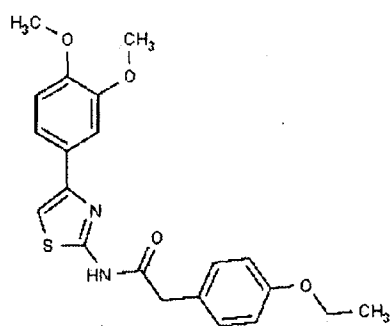
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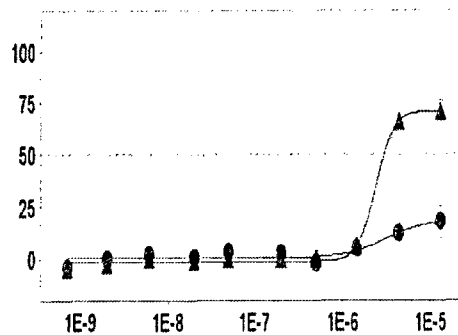
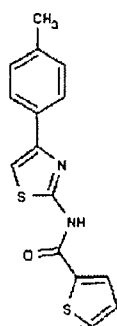
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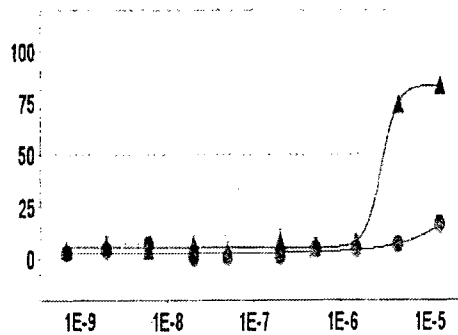
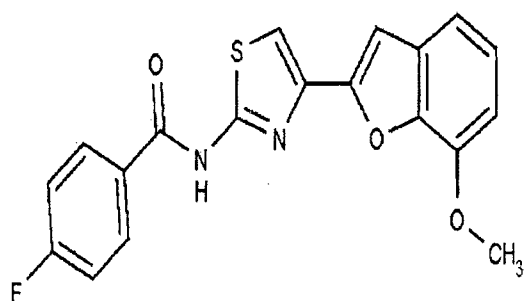
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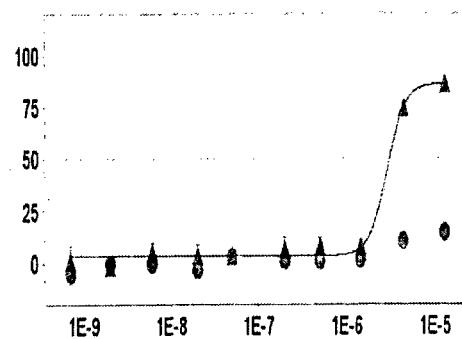
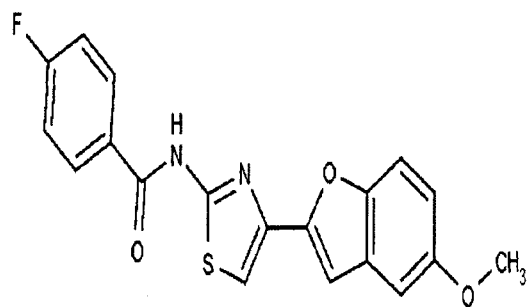
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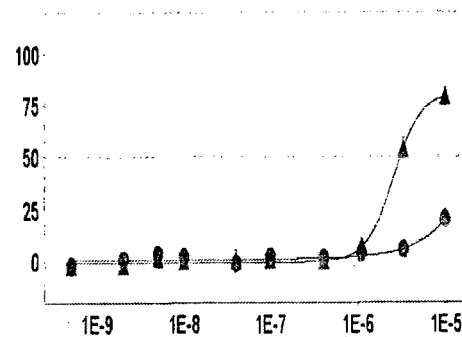
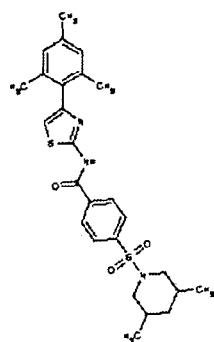
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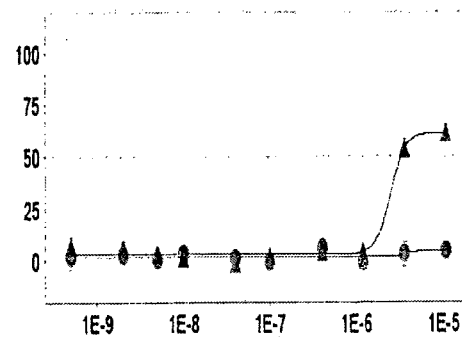
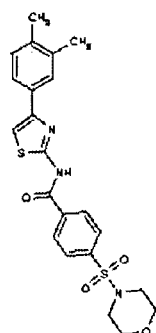
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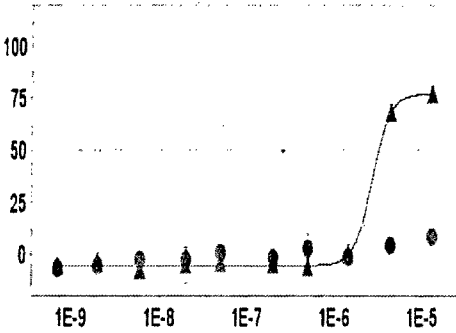
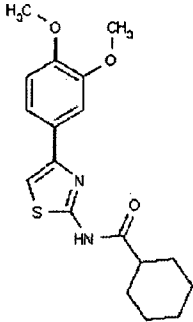
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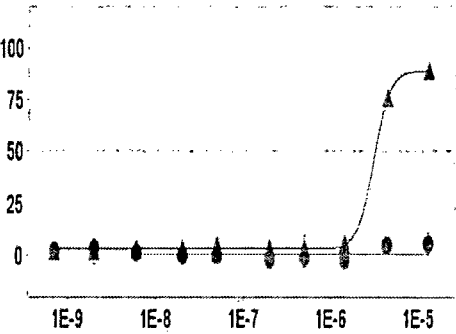
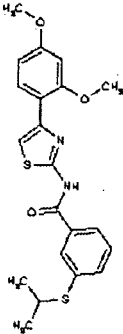
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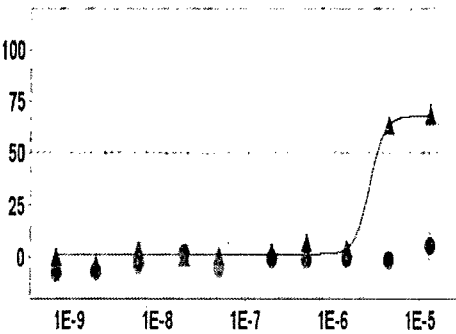
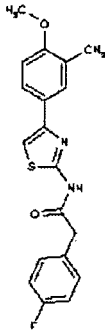
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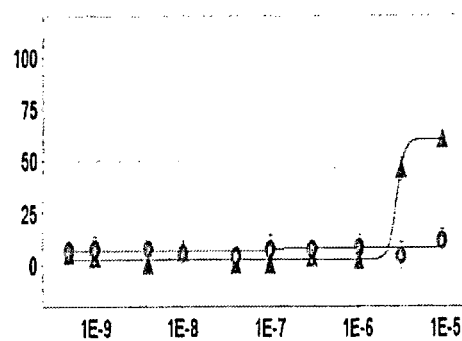
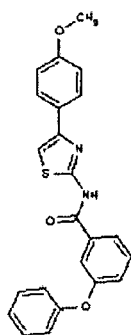
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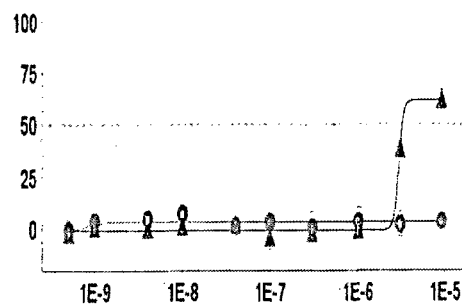
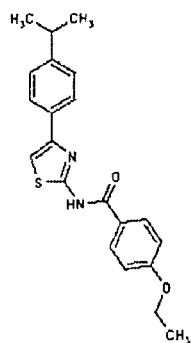
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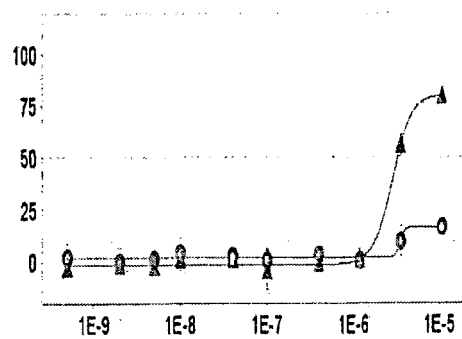
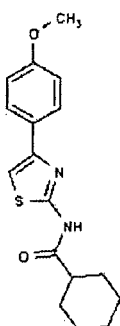
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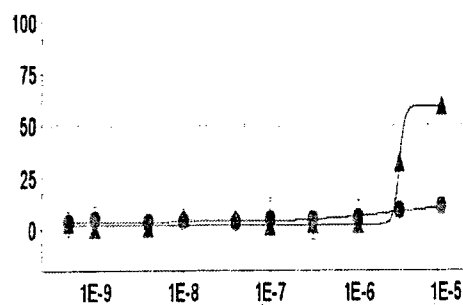
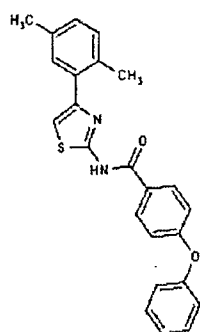
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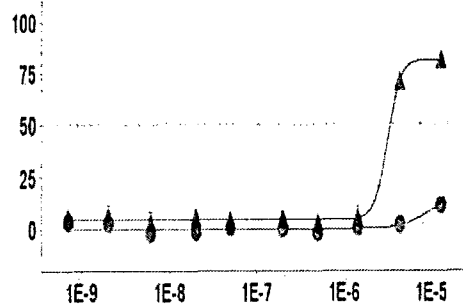
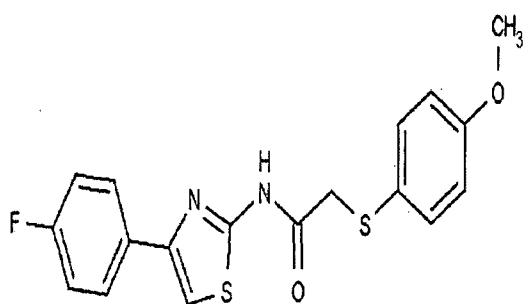
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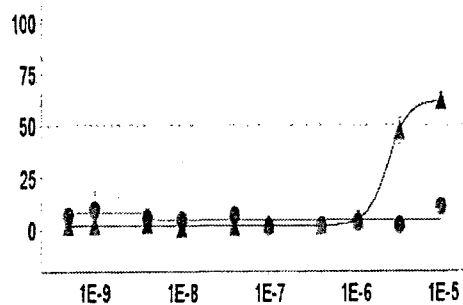
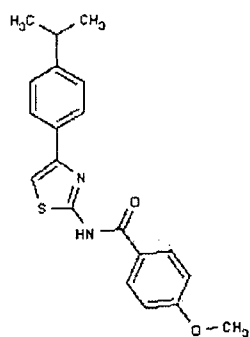
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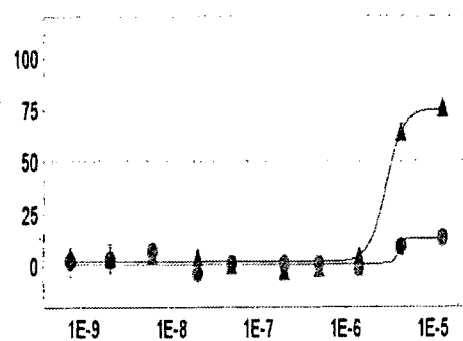
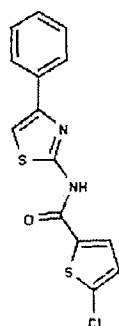
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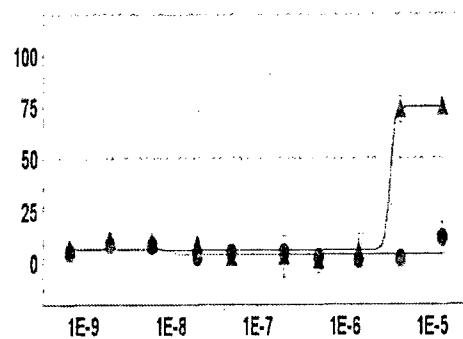
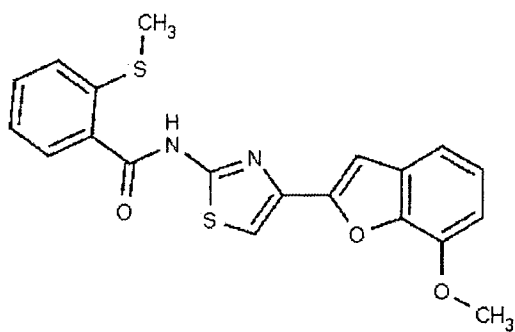
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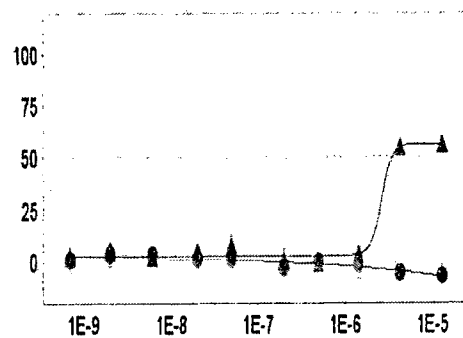
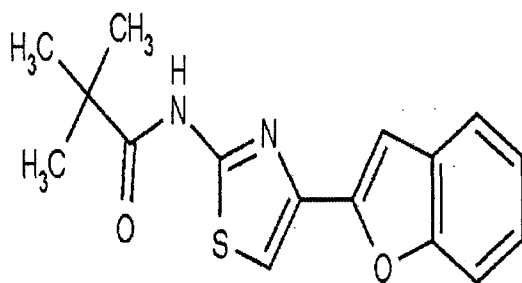
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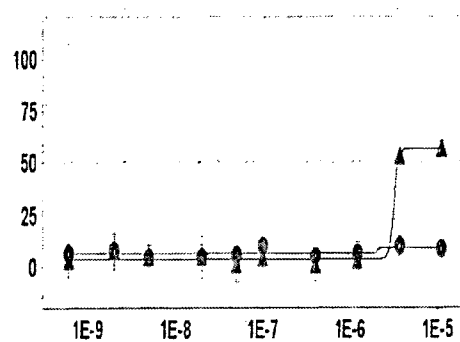
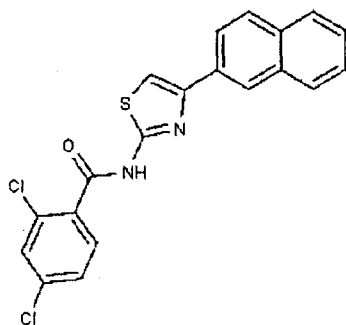
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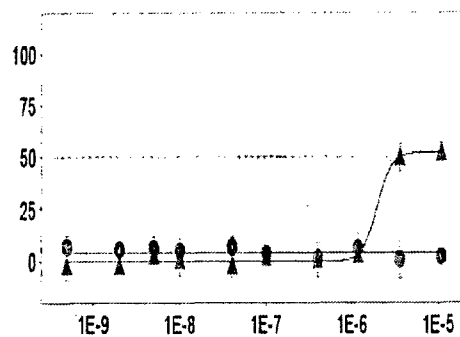
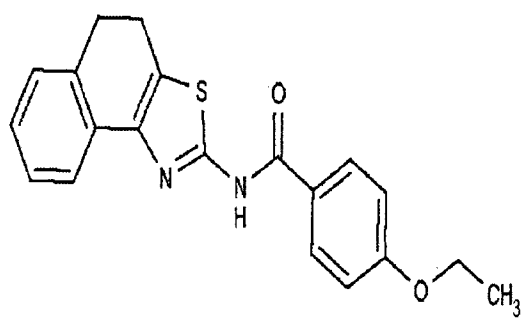
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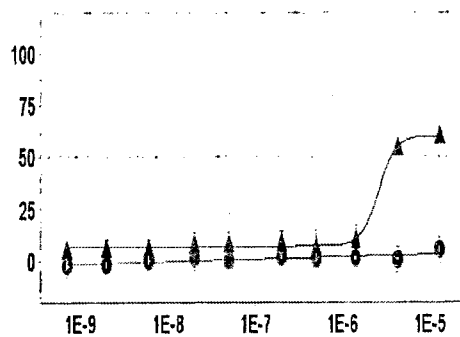
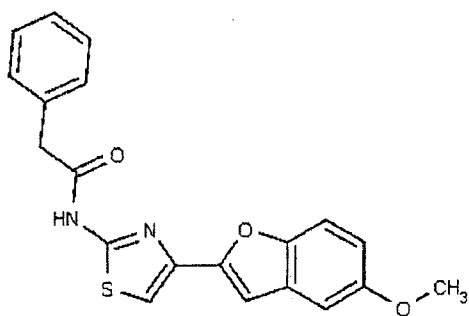
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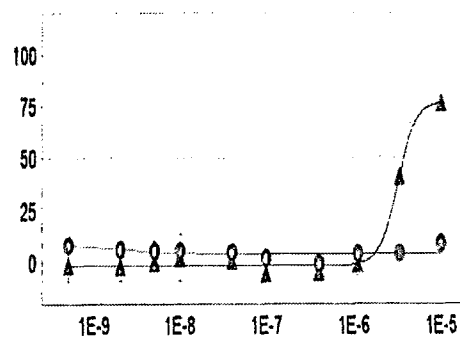
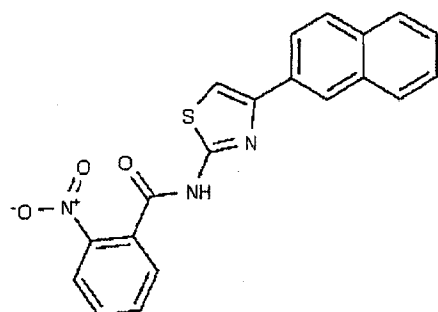
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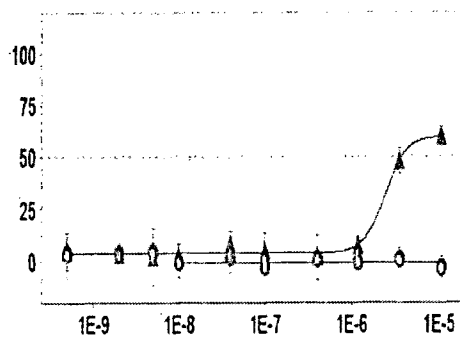
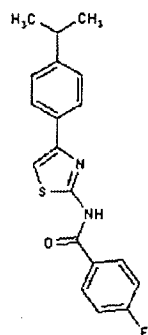
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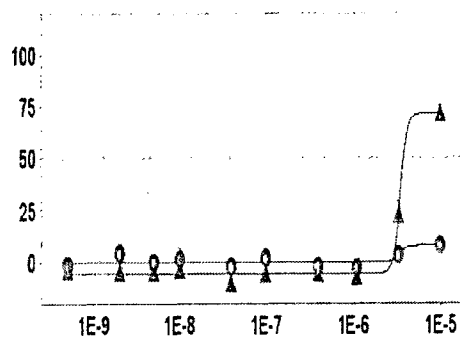
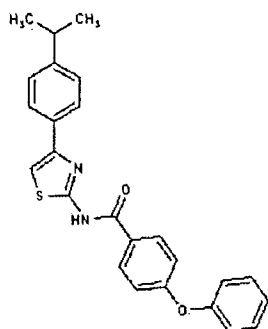
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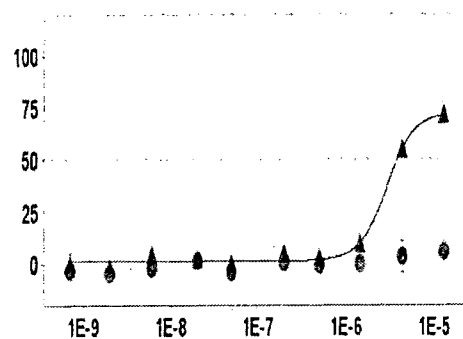
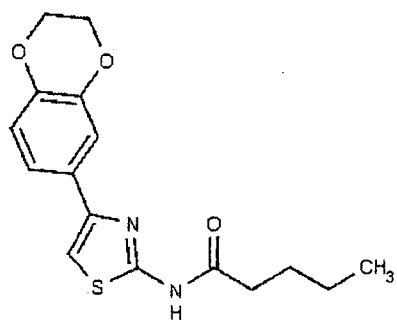
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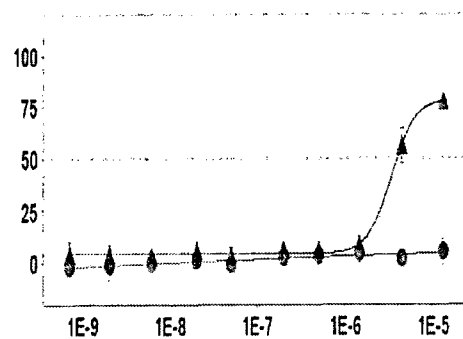
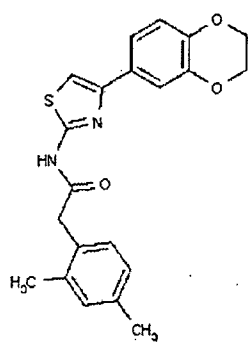
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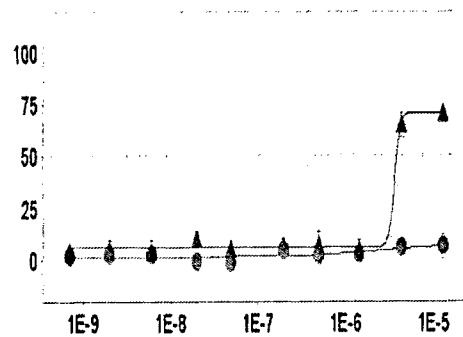
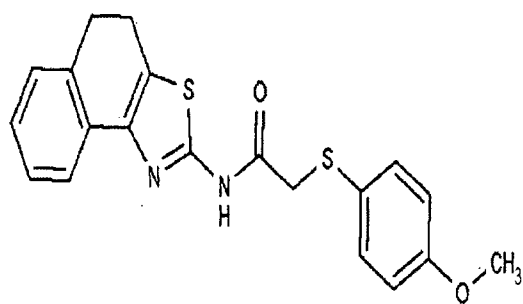
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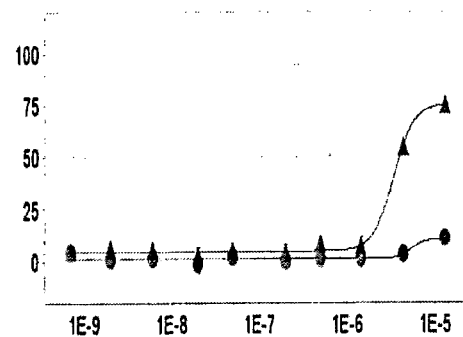
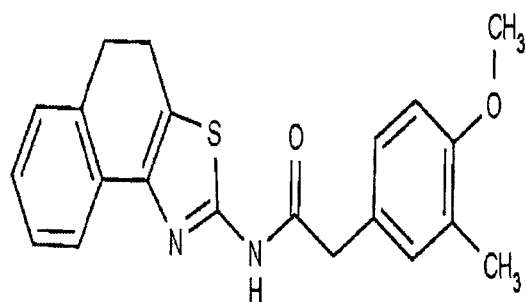
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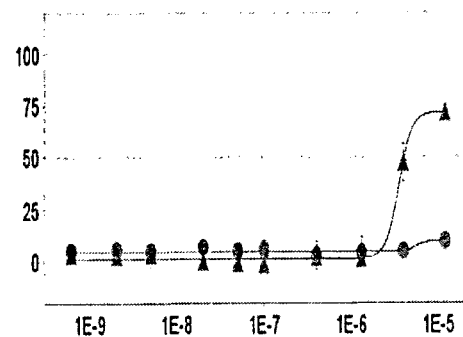
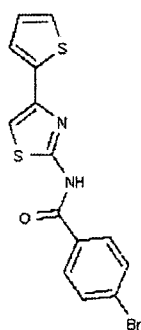
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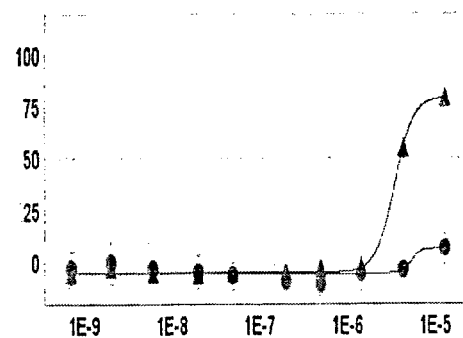
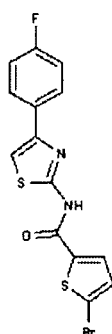
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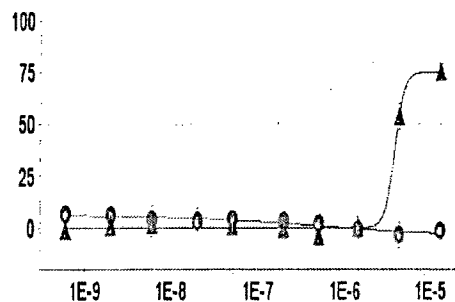
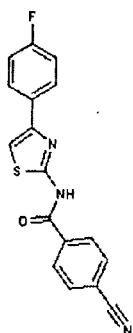
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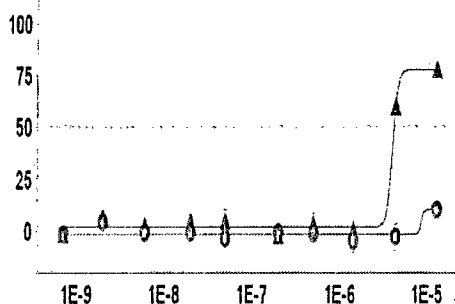
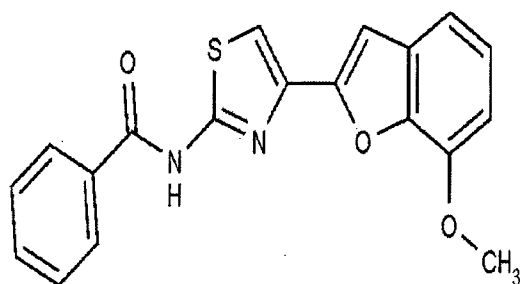
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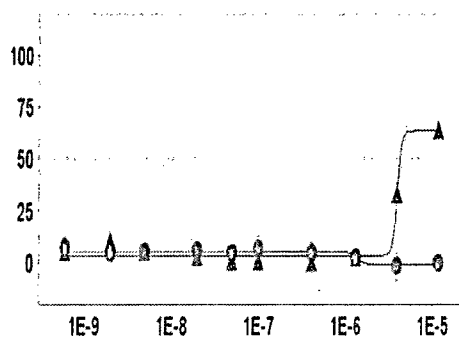
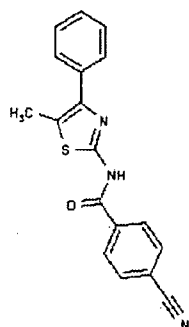
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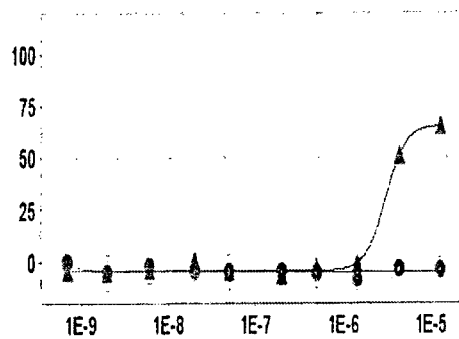
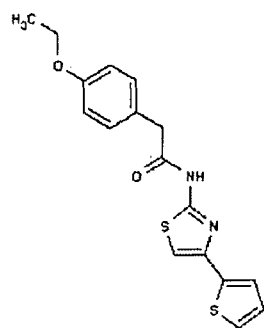
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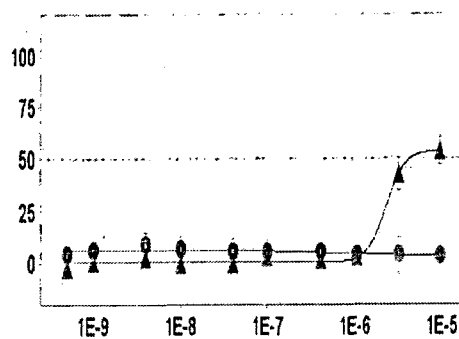
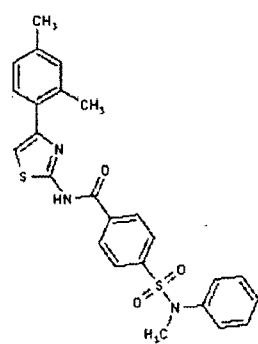
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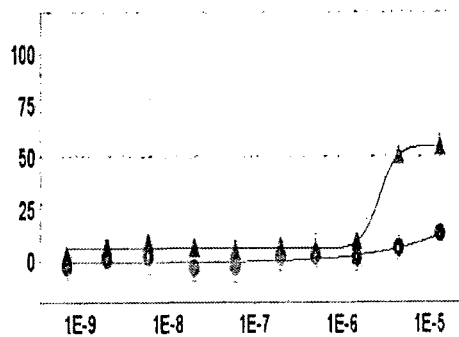
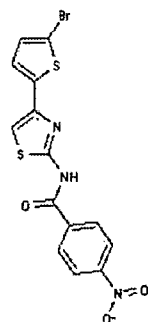
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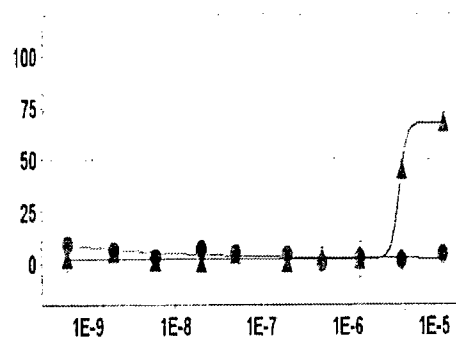
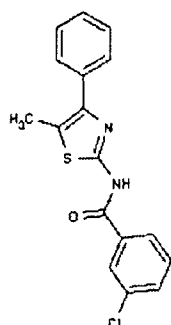
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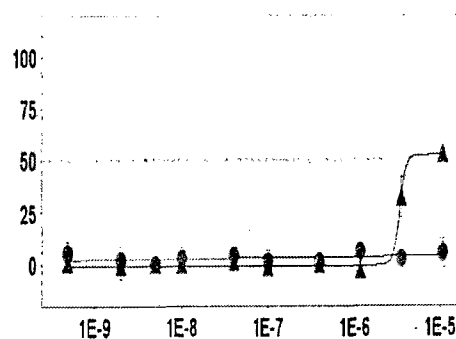
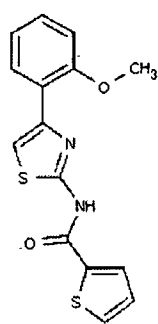
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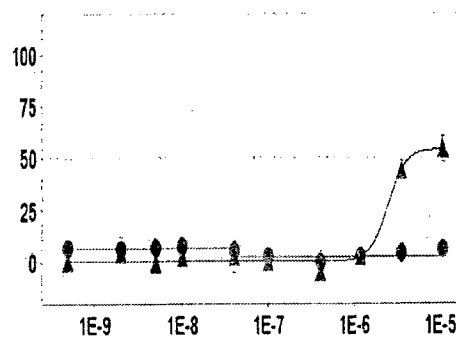
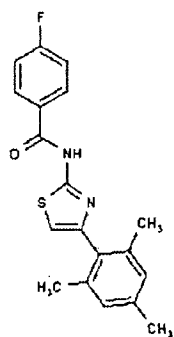
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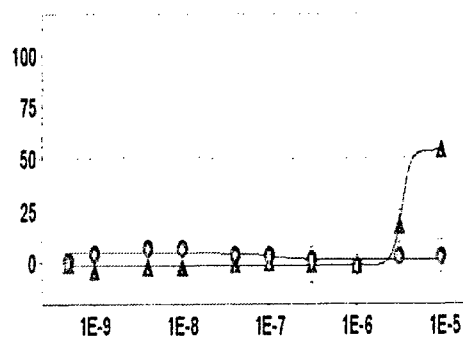
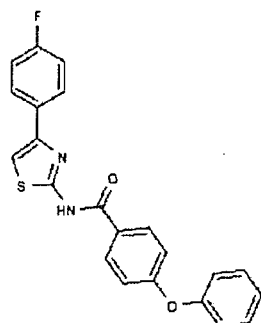
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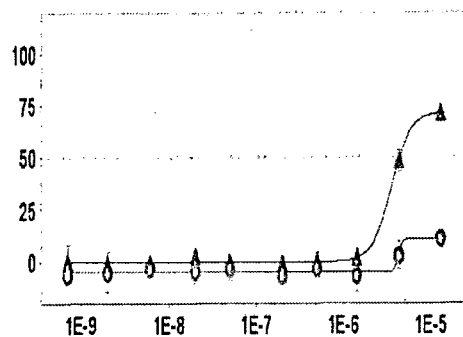
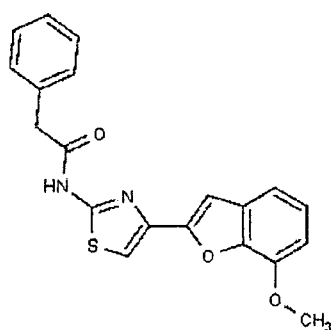
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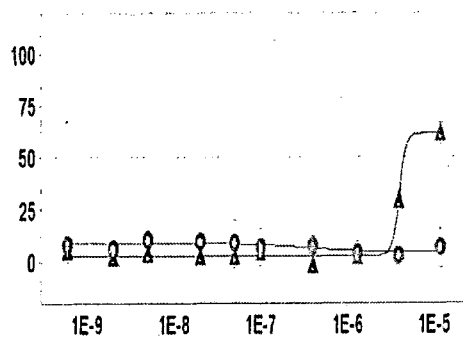
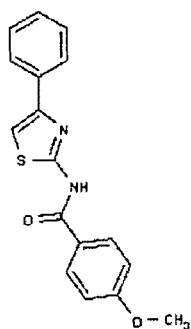
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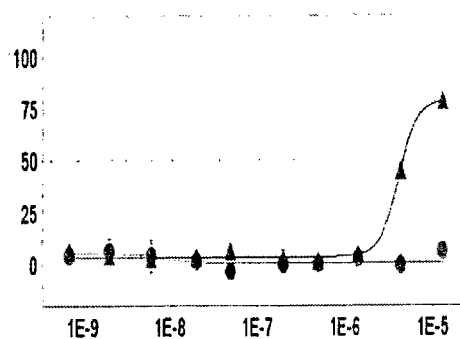
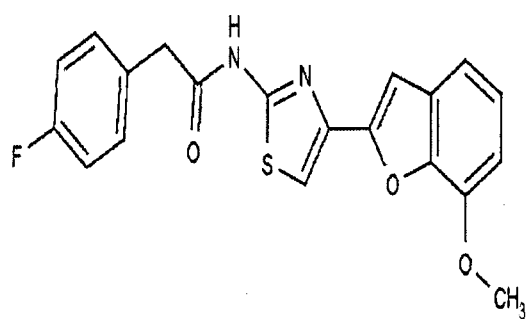
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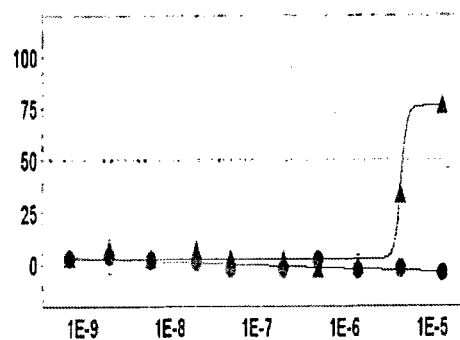
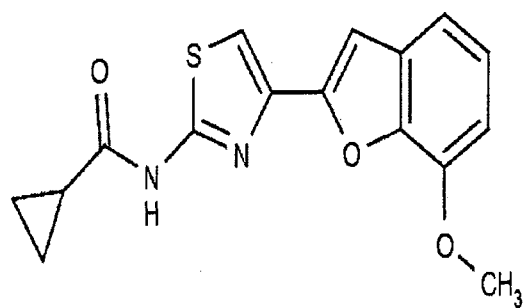
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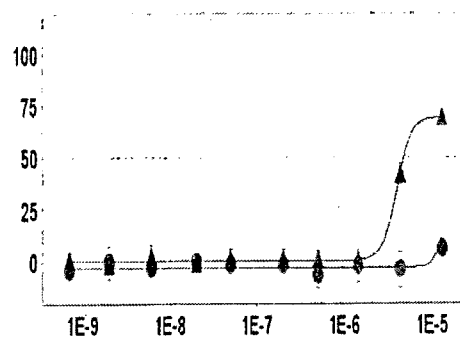
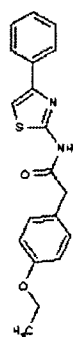
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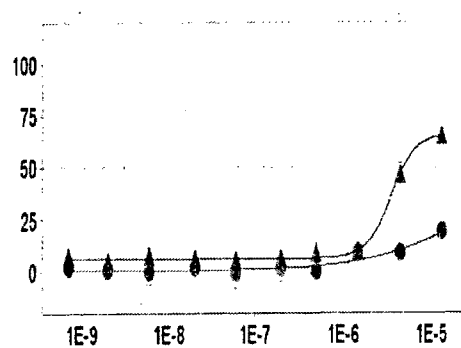
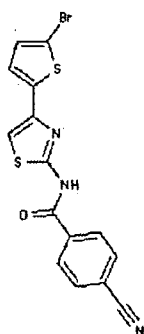
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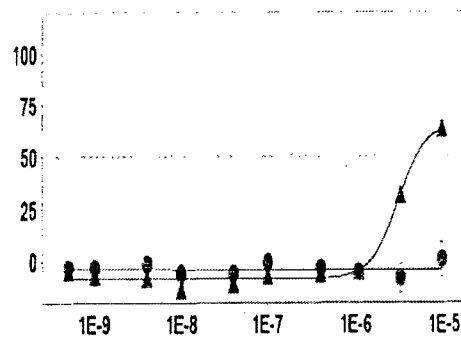
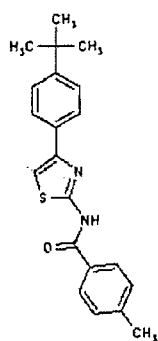
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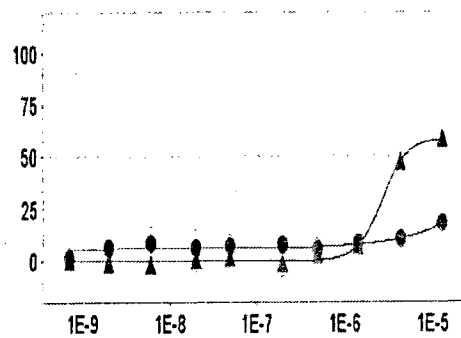
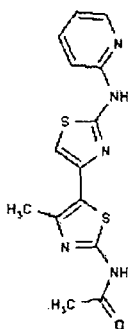
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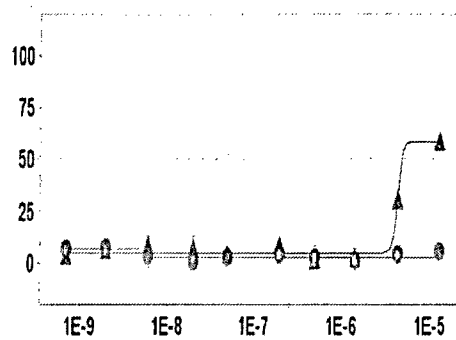
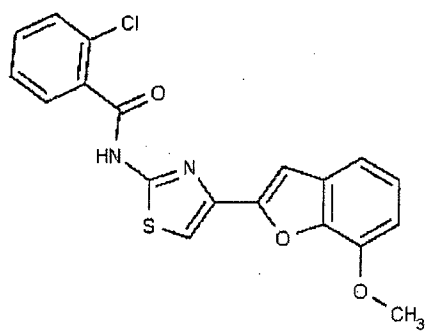
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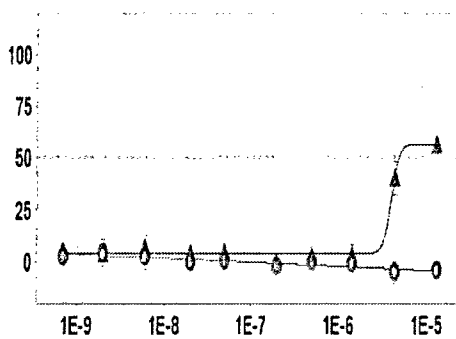
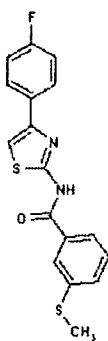
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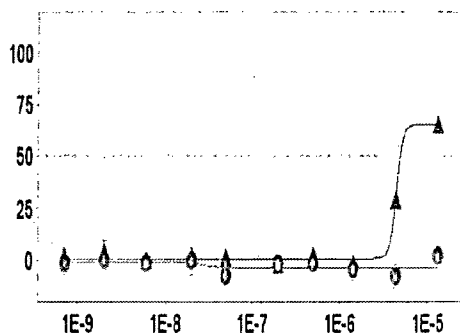
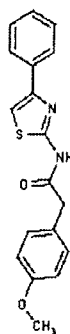
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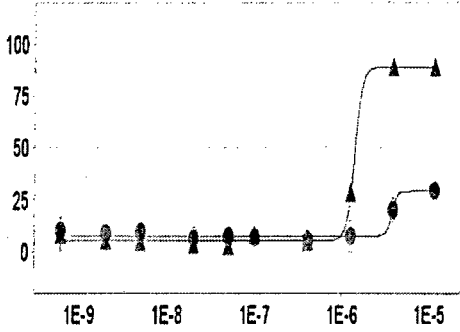
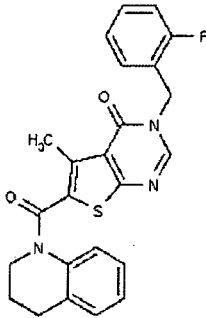
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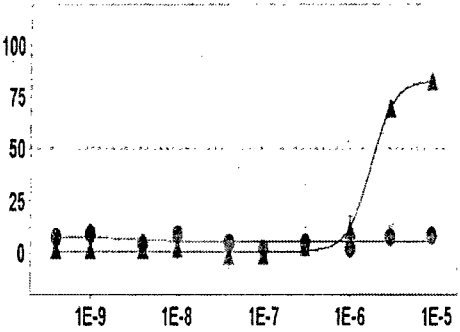
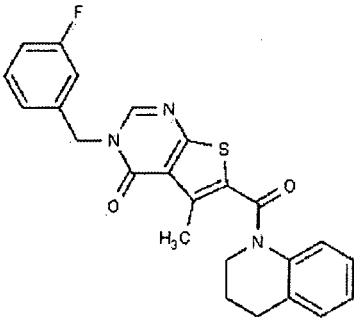
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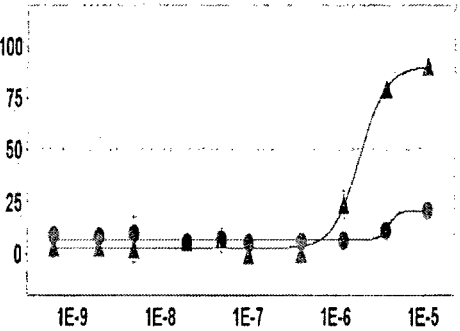
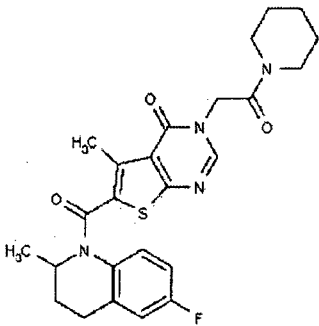
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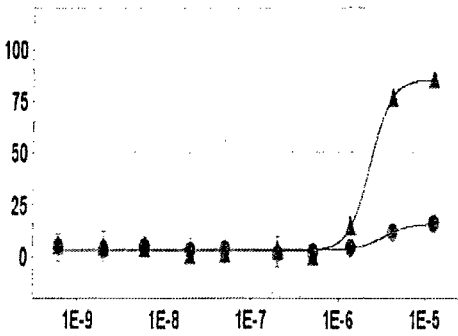
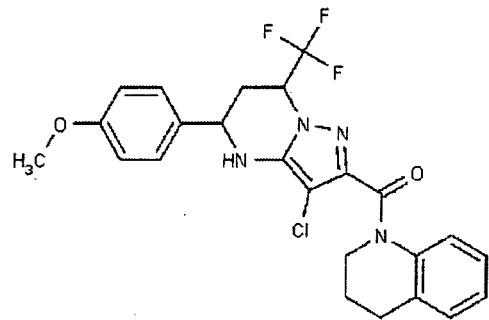
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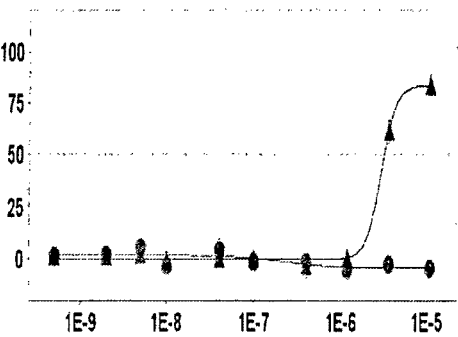
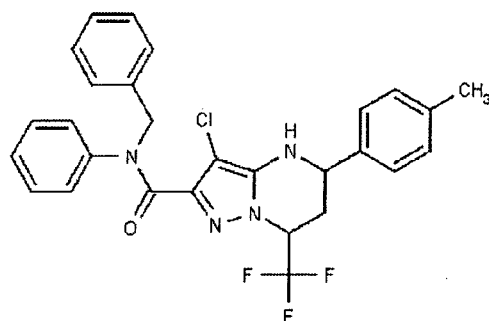
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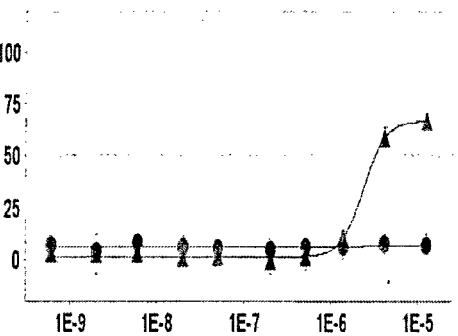
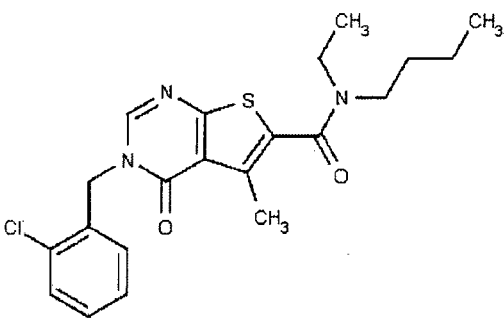
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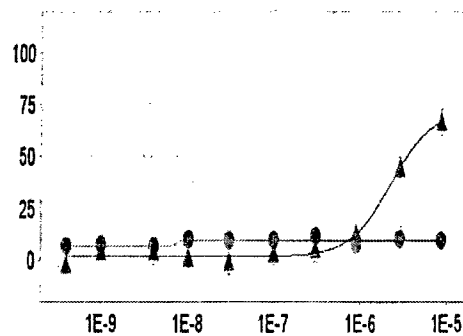
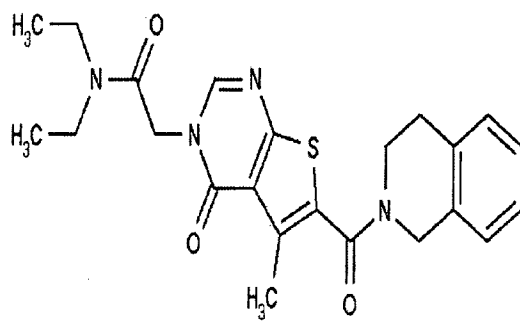
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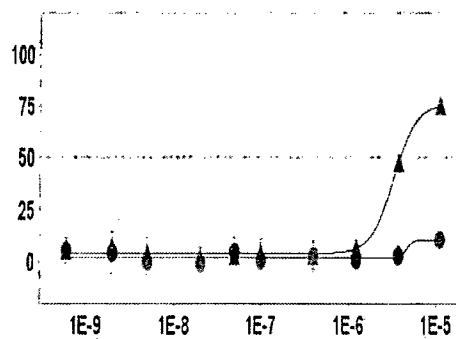
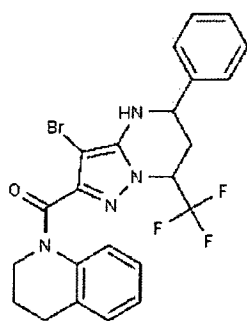
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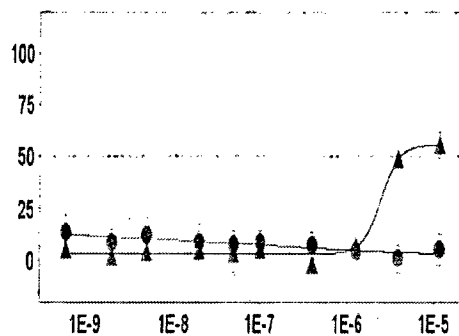
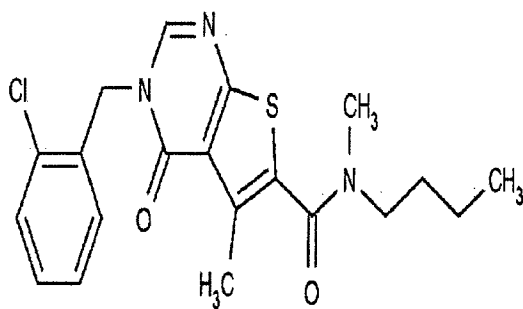
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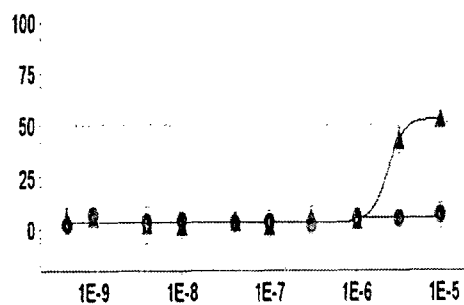
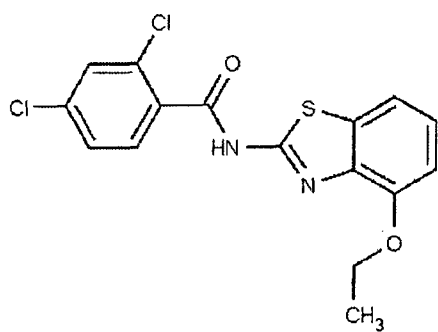
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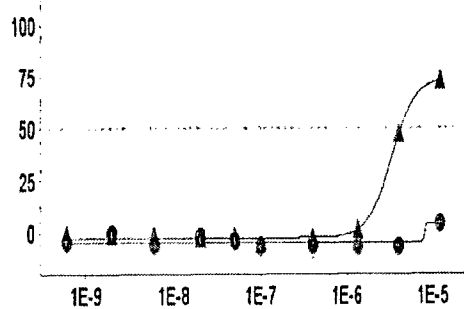
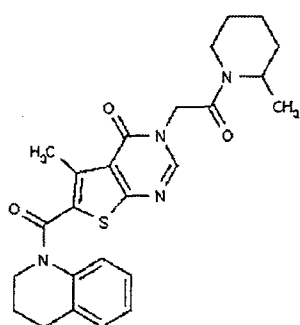
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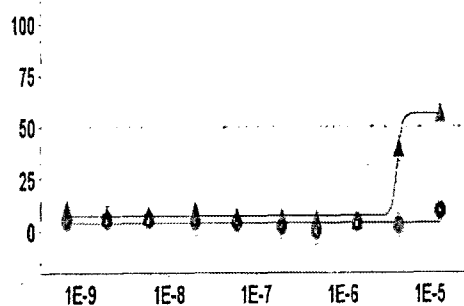
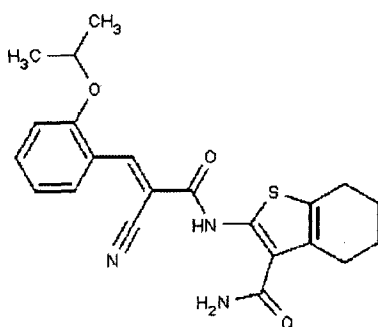
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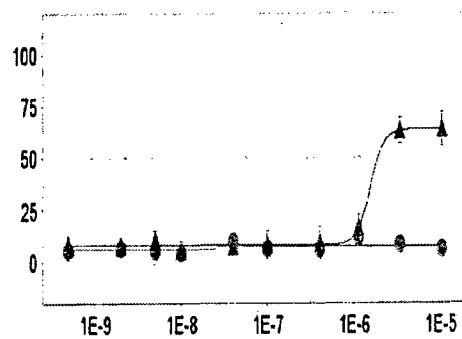
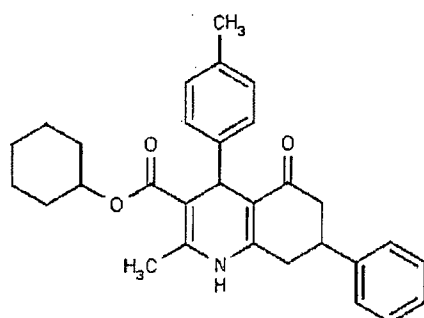
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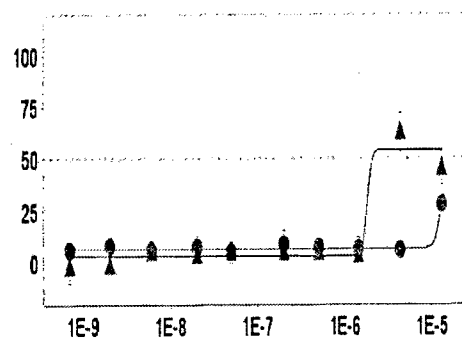
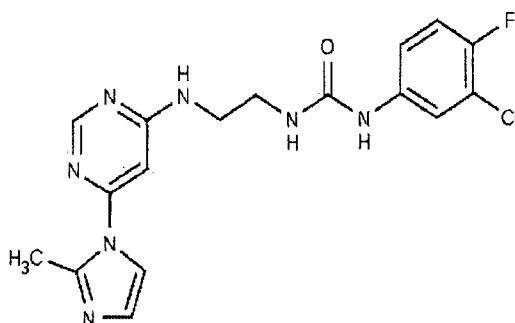
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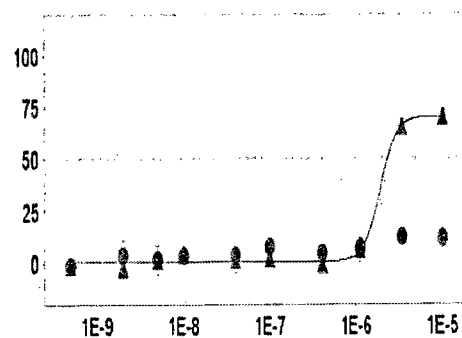
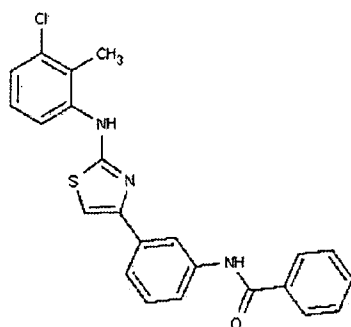
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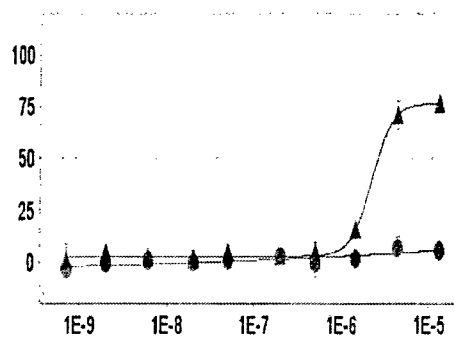
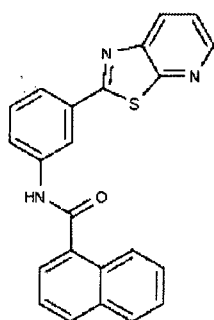
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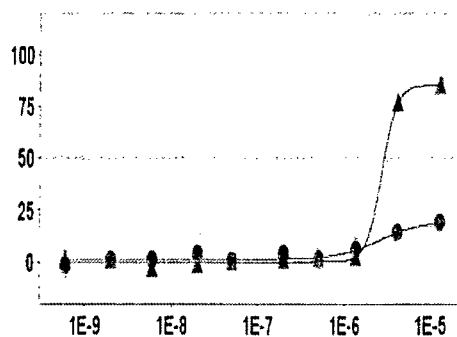
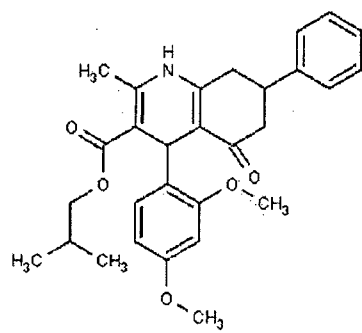
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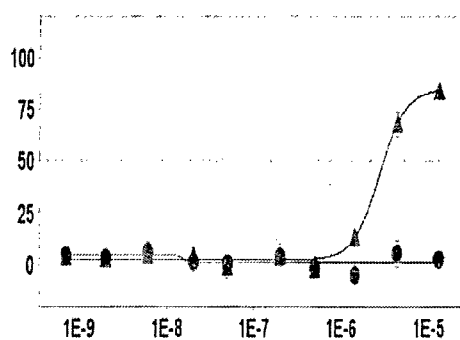
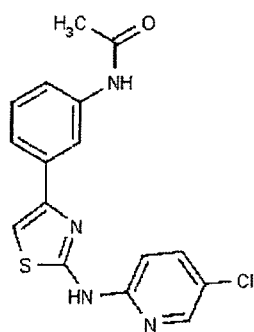
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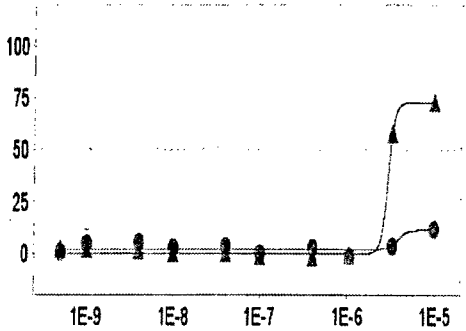
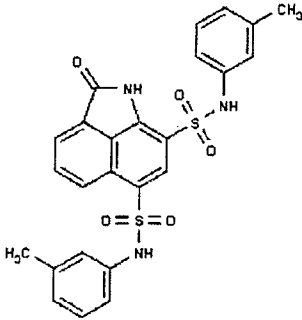
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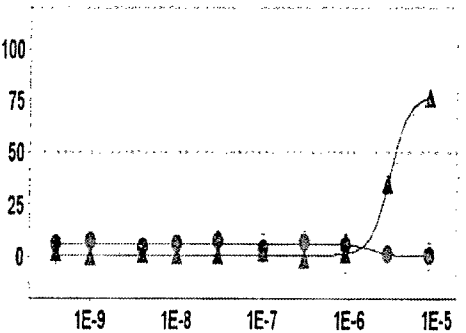
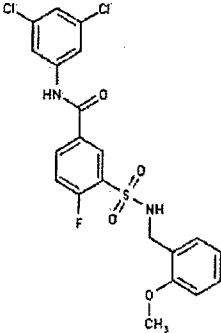
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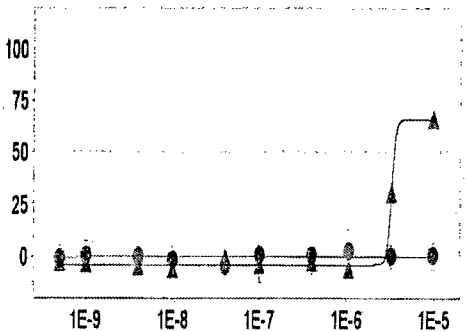
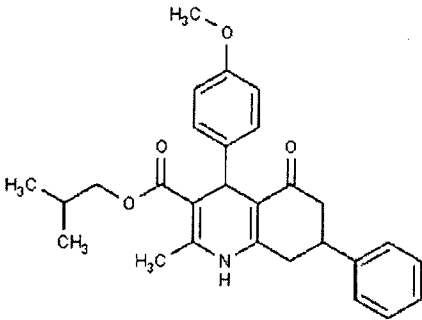
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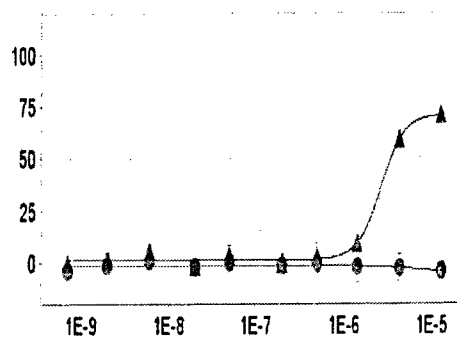
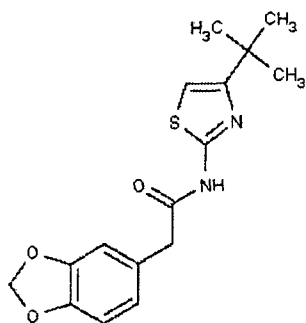
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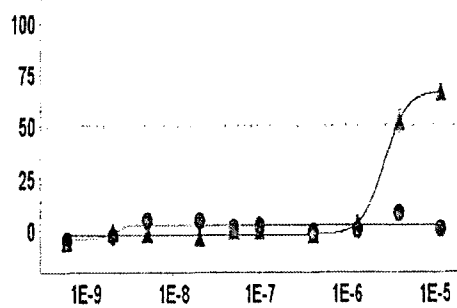
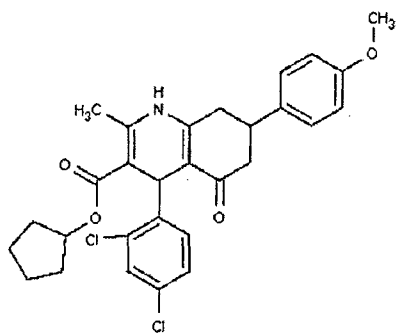
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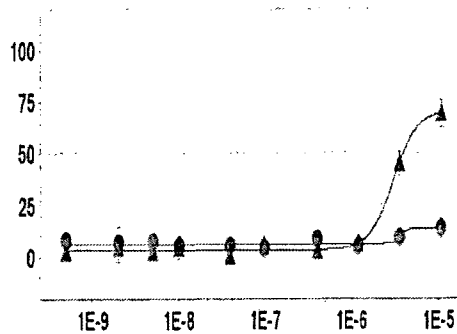
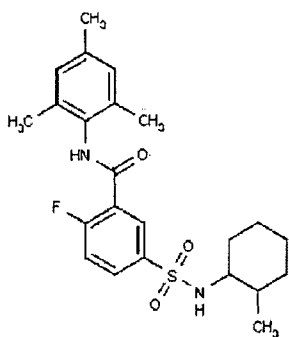
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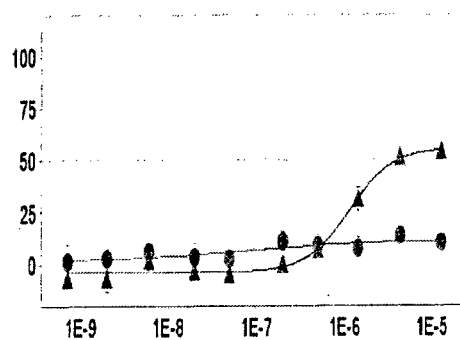
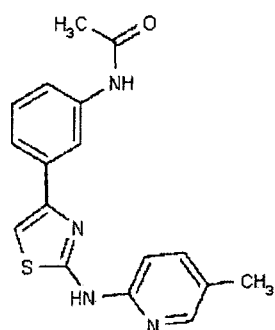
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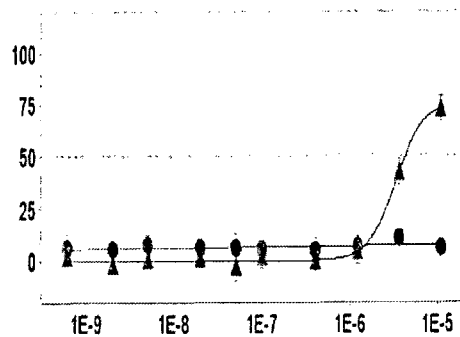
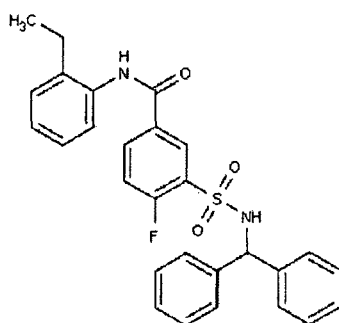
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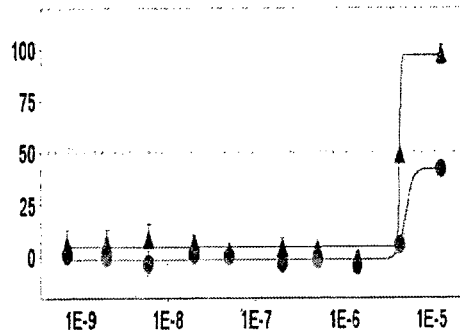
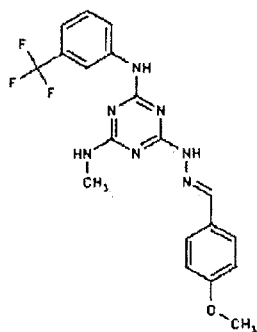
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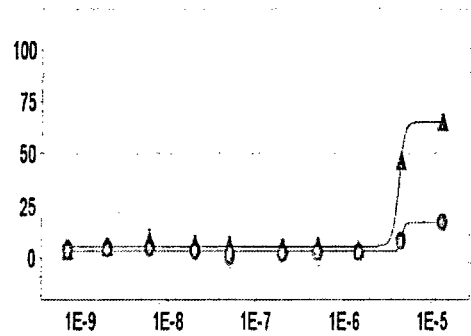
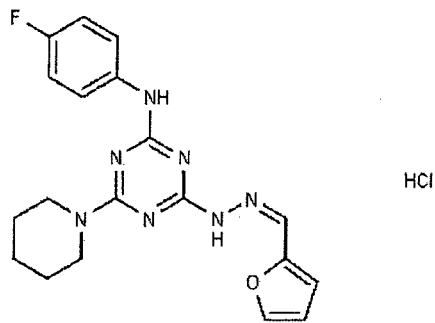
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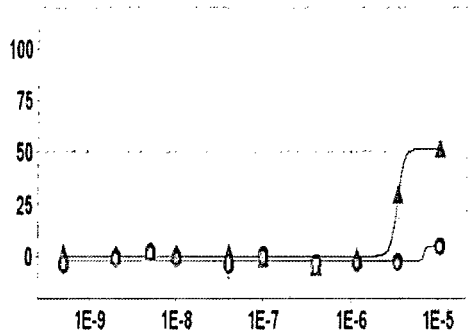
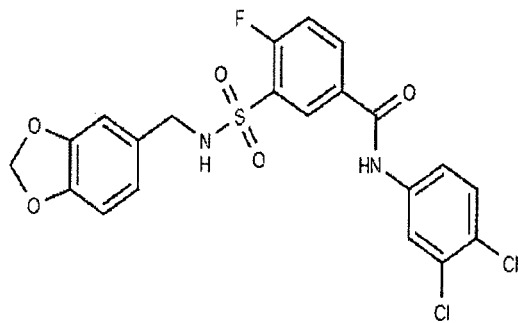
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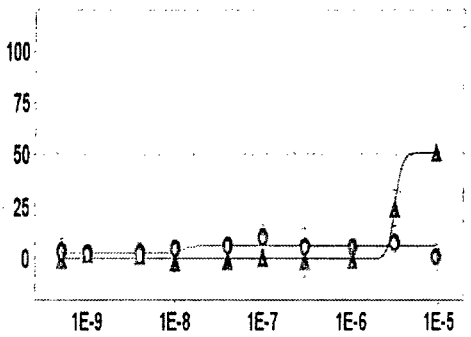
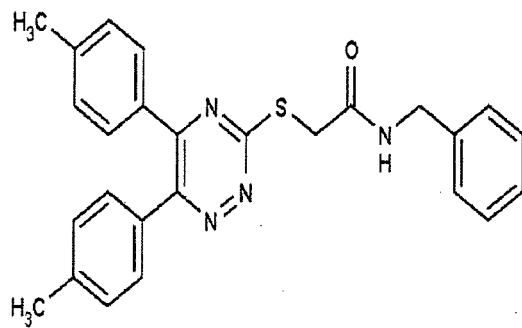
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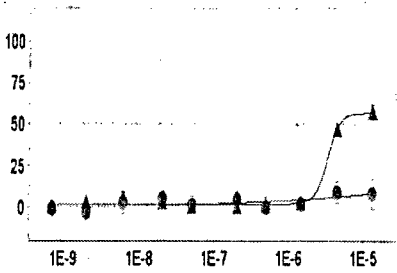
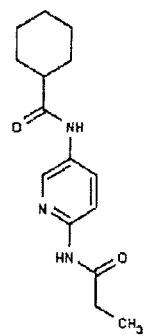
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SR-01000582228-1



SR-01000330960-1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/056502

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/428 (2006.01) A61K 31/166 (2006.01) A61K 31/15 (2006.01) G01N 33/53 (2006.01) G01N 33/567 (2006.01) A61P 43/00 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

STN (registry, HCAPlus): structure searches based on the compounds of invention 1; search based on the registry numbers of invention 1; **STN (HCAPlus, Medline, Embase, Biosis) keywords:** G protein coupled receptor, GPCR, Seven transmembrane domain receptor, 7TM receptor, heptahelical receptor, serpentine receptor, G protein linked receptor, Vasopressin, antidiuretic hormone, arginine vasopressin, argipressin, ADH, AVP, Misfold, misroute, protein & like terms, synonyms and plurals in various combinations; **EPOQUE (Epodoc, WPIAP) keywords:** G protein coupled receptor, GPCR, Seven transmembrane domain receptor, 7TM receptor, heptahelical receptor, serpentine receptor, G protein linked receptor, Vasopressin, antidiuretic hormone, arginine vasopressin, argipressin, ADH, AVP, Misfold, misroute, protein & like terms, synonyms and plurals in various combinations; **Patentscope/AusPat/Intess/PAMS Nose/Espacenet/PubMed:** Applicant/Inventor search & keywords/IPC (ie. TEXAS TECH UNIVERSITY SYSTEM, CONN, Michael, A61K, vasopressin, pharmacoperone, pharmacological chaperone, chaperonin, nephrogenic diabetes insipidus); **Google/Google Patents/Google Scholar keywords:** G- protein coupled receptor, GPCR, misfolded, misrouted, protein, pharmacoperone, pharmacological chaperone, chaperonin, vasopressin, assay, patient, subject, tissue, cells, screen, drug & like terms/related terms/synonyms/plurals in various combinations

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 27 January 2017	Date of mailing of the international search report 27 January 2017
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au	Authorised officer Corrina Parker AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262223661

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-14 and 16-26 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2016/056502
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/078115 A2 (VIOPHARMA, INCORPORATED) 16 September 2004 abstract; pages 7, 9; table 1 – compound 33; claim 11	1-3,6-9
X	US 2005/0203019 A1 (CONN, P.M.) 15 September 2005 abstract; paragraphs [0116], [0017], [0225], [0226], [0026], [0229]; claims 16, 25, 26, 31, 32, 35, 36	10-14,25,26
X	SONG, E.Y., <i>et al.</i> , “Synthesis of amide and urea derivatives of benzothiazole as Raf-1 inhibitor”. <i>European Journal of Medicinal Chemistry</i> , 2008, vol. 43, pages 1519-1524 page 1521 – compound 3	1
X	BICHET, D.G., <i>et al.</i> , “Decrease in urine volume and increase in urine osmolality after SR49059 administration in five adult male patients with X-linked nephrogenic diabetes insipidus”. NDI Foundation, 2002 Global Researcher Conference Proceeding, April 26-28 2002, Amsterdam, The Netherlands at the Château Marquette Conference Centre [online], [retrieved from internet on 23 November 2016], <URL: http://www.ndif.org/proceedings/97-Decrease_in_urine_volume_and_increase_in_urine_osmolality_after_SR49059_adminis-tration_in_five_adult_male_patients_with_Xlinked_nephrogenic_diabetes_insidipus abstract	10-13
X	BERNIER, V., <i>et al.</i> , “Pharmacologic Chaperones as a Potential Treatment for X-Linked Nephrogenic Diabetes Insipidus”. <i>Journal of the American Society of Nephrology</i> , 2006, vol. 17, pages 232-243 abstract	10-13
A	WO 2005/037845 A1 (RIGEL PHARMACEUTICALS, INC) 28 April 2005	
A	WO 2001/097786 A2 (F. HOFFMANN-LA ROCHE AG) 27 December 2001	
A	US 2008/0039629 A1 (RAMESH, U.V. et al) 14 February 2008	
A	US 2008/0125419 A1 (ALANINE, A., et al) 29 May 2008	

Supplemental Box

Continuation of: Box III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

For Markush claims, the requirement of a technical interrelationship and the same corresponding special technical features defined by PCT Rule 13.2 is considered to be met when all alternatives are of a similar nature. When the Markush grouping is for alternatives of chemical compounds, they are regarded as being of a similar nature where the following criteria are fulfilled:

- a) All alternatives have a common property or activity; **and**
- b) A common structure is present, that is, a significant structural element is shared by all of the alternatives.

As noted in the PCT Guidelines, the words '*significant structural element is shared by all of the alternatives*' refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, *and* the common structure is essential to the common property or activity.

The International Searching Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

Invention 1: Claims 1-14 and 16-26 (in part): Compositions comprising compounds having the substructure N-(benzo[d]thiazol-2-yl)acetamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 2: Claims 1-14 and 16-26 (in part): Compositions comprising compounds having the substructure N-(thiazol-2-yl)formamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 3: Claims 1-14 and 16-26 (in part): Compositions comprising compounds having the substructure 7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-2-carbaldehyde and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 4: Claims 1-14 and 16-26 (in part): Compositions comprising compounds having the substructure 3-(λ 3-methyl)-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbaldehyde and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 5: Claims 1-27 (in part): Compositions comprising the compound N-(3-(thiazolo[5,4-b]pyridin-2-yl)phenyl)-1-naphthamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 6: Claims 1-27 (in part): Compositions comprising compounds having the substructure 3-((λ 1-oxidaneyl)carbonyl)-2-methyl-7-phenyl-4,6,7,8-tetrahydroquinolin-5(1H)-one and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 7: Claims 1-27 (in part): Compositions comprising compounds having the substructure N-(3-(2-aminothiazol-4-yl)phenyl)formamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 8: Claims 1-14 and 16-26 (in part): Compositions comprising the compound (E)-2-(2-cyano-3-(2-isopropoxyphenyl)acrylamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 9: Claims 1-27 (in part): Compositions comprising the compound 1-(3-chloro-4-fluorophenyl)-3-(2-(((6-(2-methyl-1H-imidazol-1-yl)pyrimidin-4-yl)amino)ethyl)urea and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 10: Claims 1-27 (in part): Compositions comprising compounds having the substructure 5-(λ 3-methyl)benzo[d][1,3]dioxole and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Supplemental Box

Invention 11: Claims 1-27 (in part): Compositions comprising compounds having the substructure 4-(2-methylenehydrazineyl)-N-phenyl-1,3,5-triazin-2-amine and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 12: Claims 1-27 (in part): Compositions comprising compounds having the substructure 3-((λ2-azaneyl)sulfonyl)-N-phenylbenzamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 13: Claims 1-27 (in part): Compositions comprising the compound 2-oxo-N6,N8-di-m-tolyl-1,2-dihydrobenzo[cd]indole-6,8-disulfonamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 14: Claims 1-27 (in part): Compositions comprising the compound N-benzyl-2-((5,6-di-p-tolyl-1,2,4-triazin-3-yl)thio)acetamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

Invention 15: Claims 1-27 (in part): Compositions comprising the compound N-(6-propionamidopyridin-3-yl)cyclohexanecarboxamide and methods of using them in correcting the misfolding on a vasopressin type 2 mutant protein in a cell.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship.

The only feature common to all the claimed inventions and which provides a technical relationship among them is their use in correcting the misfolding on a vasopressin type 2 mutant protein in a cell. This feature satisfies criterion (a) above. However, there is no significant structural element shared by all the inventions. Consequently, criterion (b) is not satisfied.

Consequently, there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

As the search and examination for the additional inventions will each require more than negligible additional search and examination effort over that for the first invention additional search fees are warranted. As no additional search fees were paid the search and examination is restricted to invention 1.

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2016/056502	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2004/078115 A2	16 September 2004	WO 2004078115 A2	16 Sep 2004
US 2005/0203019 A1	15 September 2005	US 2005203019 A1	15 Sep 2005
		US 7842470 B2	30 Nov 2010
		AU 2002351468 A1	12 May 2003
		AU 2004208990 A1	19 Aug 2004
		AU 2004208990 B2	11 Nov 2010
		CA 2514449 A1	19 Aug 2004
		EP 1599494 A2	30 Nov 2005
		US 2004191251 A1	30 Sep 2004
		US 7695917 B2	13 Apr 2010
		US 2010144605 A1	10 Jun 2010
		US 2011065661 A1	17 Mar 2011
		WO 03038036 A2	08 May 2003
		WO 2004069859 A2	19 Aug 2004
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		EP 1680431 A1	19 Jul 2006
		US 2005130974 A1	16 Jun 2005
		US 2008039629 A1	14 Feb 2008
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		AR 031244 A1	17 Sep 2003
		AU 8181701 A	02 Jan 2002
		AU 2001281817 B2	24 Nov 2005
		BR 0112395 A	08 Jul 2003
		CA 2413086 A1	27 Dec 2001
		CN 1437471 A	20 Aug 2003
		EC SP024399 A	06 Feb 2003
		EP 1303272 A2	23 Apr 2003
		EP 1303272 B1	13 Feb 2008
		EP 1797878 A2	20 Jun 2007

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2016/056502	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		HK 1058148 A1	24 Mar 2006
		HR P20020962 A2	28 Feb 2005
		HU 0301315 A2	28 Aug 2003
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