TREATMENT METHOD

FIELD OF THE INVENTION

The present invention relates to methods of treating ocular neovascular disorders in a mammal. The methods comprise administering pyrimidine derivatives, benzodiazepinyl derivatives, and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

Neovascularization, also called angiogenesis, is the process of forming new blood vessels. Neovascularization occurs during normal development, and also plays an important role in wound healing following injury to a tissue. However, neovascularization has also been implicated as an important cause of a number of pathological states including, for example, cancer, rheumatoid arthritis, atherosclerosis, psoriasis, and diseases of the eye.

Eye diseases associated with vascular leaking and/or neovascularization are responsible for the vast majority of visual morbidity and blindness in developed countries (Campochiaro (2004) *Expert Opin. Biol. Ther.* 4:1395-402). One example of such a disorder is diabetic retinopathy, a common complication in individuals with diabetes mellitus and the fifth leading cause of new blindness. The most important contributors to the development of diabetic retinopathy are hyperglycemia and hypoxemia that lead to increased vasopermeability, endothelial cell proliferation, and pathological neovascularization (Chorostowska-Wynimko *et al. J. Physiol. Pharmacol.* (2005) 56 Suppl 4:65-70). These vascular abnormalities result in fluid leakage in the macula, which can result in progressive vision loss.

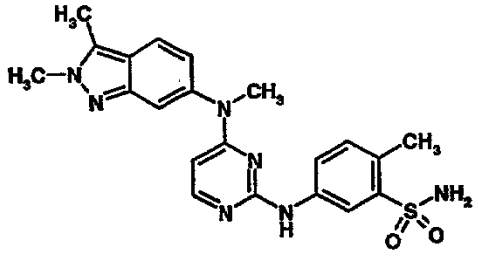
Another eye disorder in which neovascularization plays a role is age-related macular degeneration (AMD), which is the major cause of severe visual loss in the elderly. The vision loss in AMD results from choroidal neovascularization (CNV). The neovascularization originates from choroidal blood vessels and grows through Bruch's membrane, usually at multiple sites, into the sub-retinal pigmented epithelial space and/or the retina (see, for example, Campochiaro *et al.* (1999) *Mol. Vis.* 5:34). Leakage and bleeding from these new blood vessels results in vision loss.

Eye disorders associated with ocular neovascularization are a major cause of vision loss and blindness. Accordingly, there remains a need for new methods of treating ocular neovascular disorders.

SUMMARY OF THE INVENTION

The present invention is directed to new methods for treating ocular neovascular disorders. The methods comprise the step of administering pyrimidine derivatives, benzodiazepinyl derivatives, and pharmaceutical compositions containing the same.

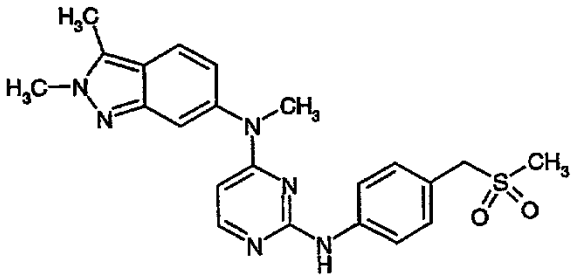
In one aspect, the invention provides a method of treating an ocular neovascular disorder in a mammal comprising administering to the mammal a compound of formula (I):



(I)

or salt or solvate thereof.

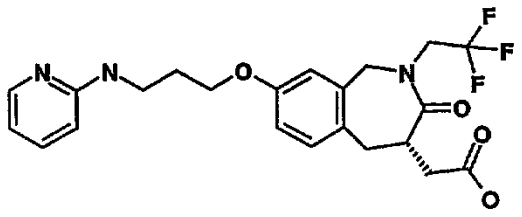
In another aspect, the invention provides a method of treating an ocular neovascular disorder in a mammal, comprising administering to the mammal a compound of formula (II):



(II)

or salt or solvate thereof.

In another aspect, the invention encompasses a method of treating an ocular neovascular disorder in a mammal comprising administering to the mammal a compound of formula (III):



(III)

or salt or solvate thereof.

The invention also encompasses the use of a compound of formula (I), formula (II), formula (III), or salt or solvate thereof for the preparation of a medicament useful in the treatment of ocular neovascular disorders.

Also provided is the use of a compound of formula (I), formula (II), formula (III), or salt or solvate thereof in the treatment of ocular neovascular disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

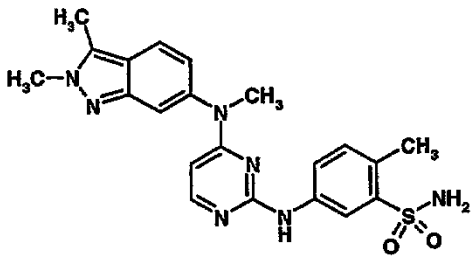
Figure 1 shows the effect of the VEGF receptor inhibitor described in Example 1 in a regression model for choroidal neovascularization (CNV) in mice. In this regression model, CNV was induced in mice by laser burns on the posterior pole of the retina. Seven days after the laser-induced injury, the mice began a regime in which they were given either vehicle alone or 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide at the indicated doses. Seven days after this regime was initiated, the size of the CNV lesions was quantitated. The results are graphically summarized in Figure 1. See the Examples section for additional information.

Figure 2 shows the effect of pre-treatment with the VEGF receptor inhibitor described in Example 1, the vitronectin receptor antagonist described in Example 3, or a combination thereof on injury-induced CNV in mice in a prevention model for CNV. The results are graphically summarized in Figure 1. See the Examples section for additional information.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides new methods of treating ocular neovascular disorders in mammals. The methods comprise the step of administering pyrimidine derivatives, benzodiazepinyl derivatives, and pharmaceutical compositions containing the same to a mammal. According to one aspect, the compound to be administered is pazopanib ((5-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide) or a salt or solvate thereof. According to another aspect, the compound to be administered is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a salt or solvate thereof. The present inventors have demonstrated that mice that are treated with pazopanib following a laser-induced injury to the retina show a decrease in the size of the resulting choroidal neovascular lesions when compared with untreated mice. In addition, the inventors have shown that mice treated with pazopanib, (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a combination of these compounds prior to laser-induced injury to the retina show a decrease in size of the resulting choroidal neovascular lesions. Accordingly, the inventors have demonstrated that pazopanib, (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, and their derivatives, salts, and solvates are useful as therapeutic agents for treating disorders associated with neovascularization in the eye.

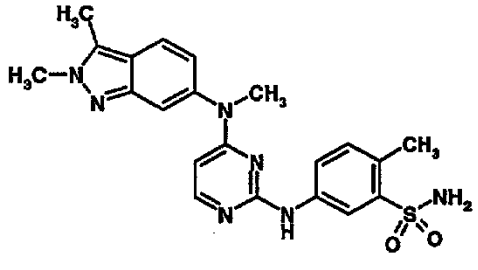
In one aspect, the invention provides a method of treating an ocular neovascular disorder in a mammal comprising administering to the mammal a compound of formula (I):



(I)

or salt or solvate thereof.

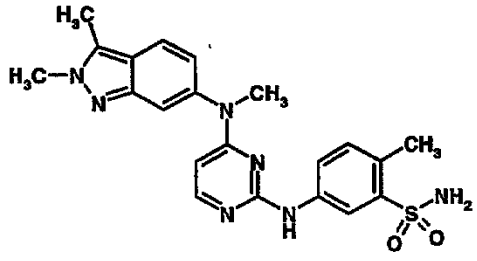
In a particular embodiment, the invention provides a method of treating an ocular neovascular disorder in a mammal, comprising administering to the mammal a compound of formula (I'):



HCl

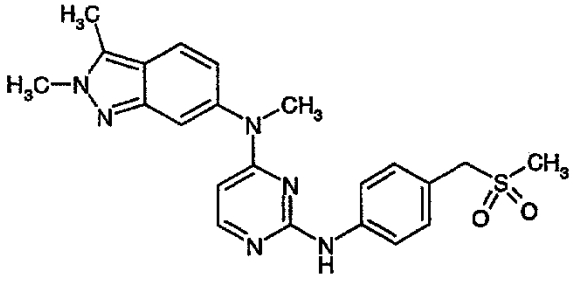
(I').

In another embodiment, the invention encompasses a method of treating an ocular neovascular disorder in a mammal, comprising administering to the mammal a compound of formula (I''):



HCl • H_2O (I'').

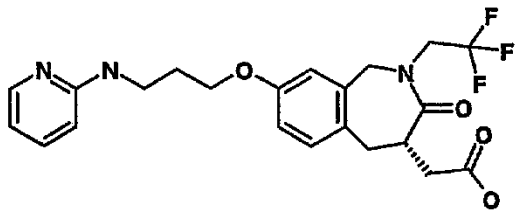
In another aspect, the invention provides a method of treating an ocular neovascular disorder in a mammal, comprising administering to the mammal a compound of formula (II):



(II)

or salt or solvate thereof.

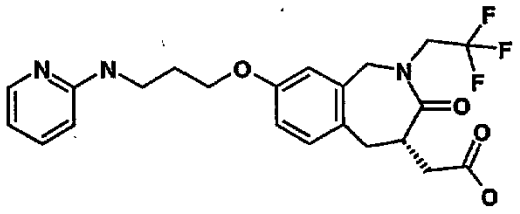
The invention also encompasses combination therapies. Accordingly, in some embodiments, the methods of treatment comprise the step of administering a compound of formula (III):



(III)

or salt or solvate thereof to the mammal in conjunction with the administration of a compound of formula (I), formula (II), or salt or solvate thereof.

In another aspect, the invention encompasses a method of treating an ocular neovascular disorder in a mammal comprising administering to the mammal a compound of formula (III)



(III)

or salt or solvate thereof.

In another aspect, the invention encompasses the use of a compound of (I), formula (II), formula (III), or salt or solvate thereof for the preparation of a medicament useful in the treatment of ocular neovascular disorders.

Also provided is the use of a compound of formula (I), formula (II), formula (III), or a salt or solvate thereof in the treatment of ocular neovascular disorders.

In some embodiments of the invention, the ocular neovascular disorder is a choroidal neovascular disorder or a retinal neovascular disorder. In particular embodiments, the ocular neovascular disorder is selected from exudative age-related macular degeneration, angiod streaks, uveitis, and macular edema.

The term "ocular neovascular disorder" as used herein means a disorder in which new blood vessels are generated in the eye in a pathogenic manner. Ocular neovascular disorders that may be treated according to the methods of the invention include those characterized by vascular leakage. Ocular neovascular disorders may result in partial or full loss of vision. The neovascular disorders to be treated in the methods of the invention may occur in any part of the eye including, for example, the cornea, iris, retina, vitreous, and choroid.

The term "choroidal neovascular disorder" as used herein means a disorder characterized by an invasion of new blood vessels through Bruch's membrane, the innermost layer of the choroid.

The term "retinal neovascular disorder" as used herein refers to a disorder associated with the growth of new blood vessels originating from the retinal veins and extending along the vitreal surface of the retina.

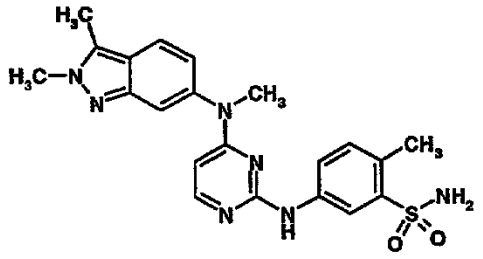
Non-limiting examples of ocular vascular disorders that may be treated according to the methods of the invention include exudative age-related macular degeneration (AMD), angiod streaks, pathological myopia, ocular histoplasmosis syndrome, breaks in Bruch's membrane, macular edema (including diabetic macular edema), sarcoidosis and uveitis. Additional examples of disorders that may be treated by the disclosed methods include atrophic AMD, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, proliferative vitreoretinopathy, retinopathy of prematurity, retinal degeneration, chronic glaucoma, retinal detachment, and sickle cell retinopathy.

The invention provides methods for the treatment of ocular neovascular disorders. As used herein, "treatment" means any manner in which one or more symptoms associated with the disorder are beneficially altered. Accordingly, the term includes healing, prevention, or amelioration of a symptom or side effect of the disorder or a decrease in the rate of advancement of the disorder.

According to the methods of the invention, treatment of an ocular vascular disorder may be obtained by the administration of an effective amount of one or more therapeutic agents to the subject to be treated. As used herein, the term "effective amount" means the amount of a therapeutic agent that is sufficient to treat, prevent and/or ameliorate one or more symptoms of the disorder.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, compounds of formula (I), (II), (III), or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. In particular embodiments, the solvent used is water.

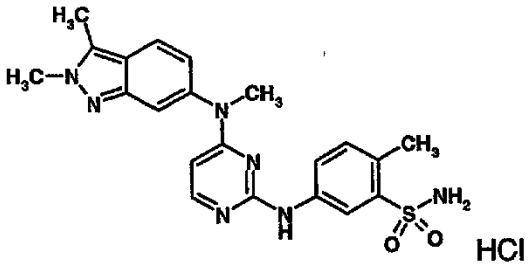
In one embodiment, the methods of preventing or treating ocular neovascular disorders disclosed herein include administering a compound of formula (I):



(I)

or a salt or solvate thereof.

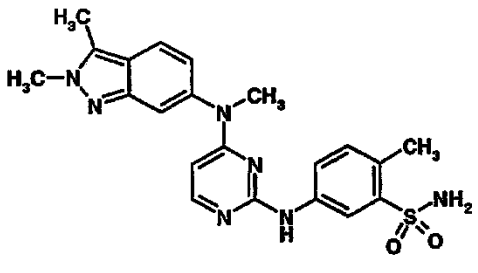
In certain embodiment, the salt of the compound of formula (I) is a hydrochloride salt. In a particular embodiment, the salt of the compound of formula (I) is a monohydrochloride salt as illustrated by formula (I'). The monohydrochloride salt of the compound of formula (I) has the chemical name 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride.



(I')

In another embodiment, the salt of the compound of formula (I) is a monohydrochloride monohydrate solvate of the compound of formula (I). The monohydrochloride monohydrate solvate of the compound of formula (I) has the

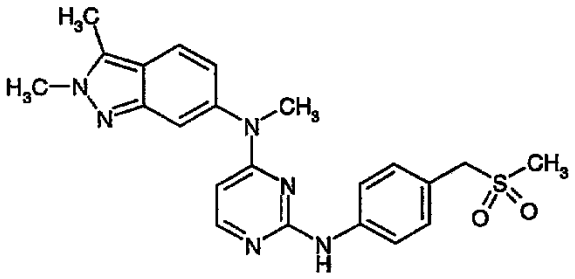
chemical name 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride monohydrate, as illustrated in formula (I").



HCl• H_2O

(I")

The invention also encompasses methods of preventing or treating ocular neovascular disorders disclosed herein include administering a compound of formula (II):



(II)

or salt or solvate thereof. This compound has the chemical name N^4-(2,3-dimethyl-2*H*-indazol-6-yl)-N^4-methyl-N^2-[4-[(methylsulfonyl)methyl]phenyl}-2,4-pyrimidinediamine.

The free base, salts and solvates of the compound of formula (I) or (II) may be prepared, for example, according to the procedures of International Patent Application No. PCT/US01/49367 filed December 19, 2001, and published as WO 02/059110 on August 1, 2002, and International Patent Application No. PCT/US03/19211 filed June 17, 2003, and published as WO 03/106416 on December 24, 2003, or according the methods provided herein. Compounds of formula (III) and derivatives thereof may be prepared according the methods of U.S. Patent No. 6,825,188 or the methods described herein.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in a compound of the present invention. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds used in the methods of the invention may be administered alone, or they may be administered in a pharmaceutical composition. Accordingly, the invention further provides for the use of pharmaceutical compositions in the treatment methods of the present invention. The pharmaceutical compositions include a compound of formula (I), (II), (III) and salts or solvates thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 1μg to 1g, such as 5μg to 500μg, 10μg-250μg, 0.5mg to 700mg, 2mg to 350mg, or 5mg to100 mg of a compound of formula (I), (II), (III), or salts or solvates thereof depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient

per unit dose. In certain embodiments, the unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

The compound of formula (I), (II), (III), or salt or solvate thereof may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal, sublingual, and ocular), vaginal, and parenteral (including subcutaneous, intramuscular, intraveneous, intradermal, extraocular, intraocular (including, for example, intravitreal, subretinal, subscleral, intrachoroidal, and subconjuctival), intrathecal, and epidural)). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient.

The methods of the present invention may also be employed in combination with other methods for the treatment of ocular neovascular disorders. In some embodiments, the methods of the invention encompass a combination therapy in which a compound of formula (I), (II), (III), or a salt or solvate thereof is administered in conjunction with one or more additional therapeutic agents for the treatment of neovascular disorders. Non-limiting examples of additional therapeutic agents that may be used in a combination therapy include pegaptanib, ranibizumab, PKC412, nepafenac, and integrin receptor antagonists (including vitronectin receptor agonists). See, for example, Takahashi *et al.* (2003) *Invest. Ophthalmol. Vis. Sci.* 44: 409-15, Campochiaro *et al.* (2004) *Invest. Ophthalmol. Vis. Sci.* 45:922-31, van Wijngaarden *et al.* (2005) *JAMA* 293:1509-13, U.S. Patent No. 6,825,188 to Callahan *et al.*, and U.S. Patent No. 6,881,736 to Manley *et al.*; each of which is herein incorporated by reference for their teachings regarding these compounds. In particular embodiments, the compounds of formula (I) or formula (II) or salt or solvate thereof is administered in conjunction with a compound of formula (III) or salt or solvate thereof.

Where a combination therapy is employed, the therapeutic agents may be administered together or separately. The same means for administration may be used for more than one therapeutic agent of the combination therapy; alternatively, different therapeutic agents of the combination therapy may be administered by different means. When the therapeutic agents are administered separately, they may be administered simultaneously or sequentially in any order, both close and remote in time. The amounts of the compound of formula (I), (II), (III), and/or and the other

pharmaceutically active agent or agents and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders can be prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets can be formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as

bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs can be prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The agents for use according to the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Agents for use according to the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer,

polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent. Formulations to be administered to the eye will have ophthalmically compatible pH and osmolality. One or more ophthalmically acceptable pH adjusting agents and/or buffering agents can be included in a composition of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, and sodium lactate; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers can be included in an amount required to maintain pH of the composition in an ophthalmically acceptable range. One or more ophthalmically acceptable salts can be included in the composition in an amount sufficient to bring osmolality of the composition into an ophthalmically acceptable range. Such salts

include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists that may be generated by means of various types of metered dose pressurized aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

In some embodiments of the present invention, the pharmaceutical formulations are adapted for intraocular administration by means of intraocular injection or other device for ocular delivery. Examples of ocular devices that may be used in the methods of the invention include periocular or intravitreal devices, contact lenses and liposomes. See, for example, U.S. Pat. Nos. 3,416,530; 3,828,777; 4,014,335; 4,300,557; 4,327,725; 4,853,224; 4,946,450; 4,997,652; 5,147,647; 5,164,188; 5,178,635; 5,300,114; 5,322,691; 5,403,901; 5,443,505; 5,466,466; 5,476,511; 5,516,522; 5,632,984; 5,679,666; 5,710,165; 5,725,493; 5,743,274; 5,766,242; 5,766,619; 5,770,592; 5,773,019; 5,824,072; 5,824,073; 5,830,173; 5,836,935;

5,869,079, 5,902,598; 5,904,144; 5,916,584; 6,001,386; 6,074,661; 6,110,485; 6,126,687; 6,146,366; 6,251,090; 6,299,895; 6,331,313; 6,416,777; 6,649,184; 6,719,750; 6,660,960; and U.S. Patent Publication Nos. 2003/0064088, 2004/0247645, and, 2005/0113806; each of which is herein incorporated by reference for purposes of their teachings of optical devices.

The ocular delivery device may be designed for the controlled release of one or more therapeutic agents with multiple defined release rates and sustained dose kinetics and permeability. Controlled release may be obtained through the design of polymeric matrices incorporating different choices and properties of biodegradable/bioerodable polymers (e.g. poly(ethylene vinyl) acetate (EVA), superhydrolyzed PVA), hydroxyalkyl cellulose (HPC), methylcellulose (MC), hydroxypropyl methyl cellulose (HPMC), polycaprolactone, poly(glycolic) acid, poly(lactic) acid, polyanhydride, of polymer molecular weights, polymer crystallinity, copolymer ratios, processing conditions, surface finish, geometry, excipient addition and polymeric coatings that will enhance drug diffusion, erosion, dissolution and osmosis.

Formulations for drug delivery using ocular devices may combine one or more active agents and adjuvants appropriate for the indicated route of administration. For example, the active agents may be admixed with any pharmaceutically acceptable excipient, lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, and/or polyvinyl alcohol, tableted or encapsulated for conventional administration. Alternatively, the compounds may be dissolved in polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. The compounds may also be mixed with compositions of both biodegradable and non-biodegradable polymers, and a carrier or diluent that has a time delay property. Representative examples of biodegradable compositions can include albumin, gelatin, starch, cellulose, dextrans, polysaccharides, poly (D,L-lactide), poly (D,L-lactide-co-glycolide), poly (glycolide), poly (hydroxybutyrate), poly (alkylcarbonate) and poly (orthoesters) and mixtures thereof. Representative examples of non-biodegradable polymers can include EVA copolymers, silicone rubber and poly (methylacrylate), and mixtures thereof.

Pharmaceutical compositions for ocular delivery also include in situ gellable aqueous composition. Such a composition comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid. Suitable gelling agents include but are not limited to thermosetting polymers. The term "in situ gellable" as used herein is includes not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid, but also includes more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye. See, for example, Ludwig (2005) Adv. Drug Deliv. Rev. 3;57:1595-639, herein incorporated by reference for purposes of its teachings of examples of polymers for use in ocular drug delivery.

It is understood by those skilled in the art that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question. For example, those suitable for oral administration may include flavoring agents.

According to the methods of the invention, a specific compound of formula (I), (II), or (III) is administered to a mammal. Typically, the amount of one of the administered agents of the present invention will depend upon a number of factors including, for example, the age and weight of the mammal, the precise condition requiring treatment, the severity of the condition, the nature of the formulation, and the route of administration. Ultimately, the amount will be at the discretion of the attendant physician or veterinarian.

Typically, the compound of formula (I) , (II), (III), or salt or solvate thereof will be given in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day. In particular embodiments the compound is administered locally (for example, to the eye) and the total amount of a compound administered may be 1µg to 10 mg, such as 5µg to 500µg, or 10µg-250µg.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

EXAMPLES

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological*

Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
µL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
N (Normal)	Kg (kilogram)
i. v. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	RT (room temperature);
min (minutes);	h (hours);
mp (melting point);	TLC (thin layer chromatography);
T_r (retention time);	RP (reverse phase);
DCM (dichloromethane);	DCE (dichloroethane);
DMF (*N*,*N*-dimethylformamide);	HOAc (acetic acid);
TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
TIPS (triisopropylsilyl);	TBS (*t*-butyldimethylsilyl);
HPLC (high pressure liquid chromatography);	
THF (tetrahydrofuran);	DMSO (dimethylsulfoxide);
EtOAc (ethyl acetate);	DME (1,2-dimethoxyethane);
EDTA	ethylenediaminetetraacetic acid
FBS	fetal bovine serum
IMDM	Iscove's Modified Dulbecco's medium
PBS	phosphate buffered saline
RPMI	Roswell Park Memorial Institute
RIPA buffer	*
RT	room temperature

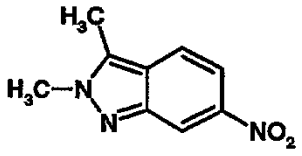
*150 mM NaCl, 50 mM Tris-HCl, pH 7.5, 0.25% (w/v) -deoxycholate, 1% NP-40, 5 mM sodium orthovanadate, 2 mM sodium fluoride, and a protease inhibitor cocktail.

Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at room temperature unless otherwise noted.

The following examples describe the syntheses of intermediates particularly useful in the synthesis of compounds of formula (I) and (II):

Intermediate Example 1

Preparation of 2,3-dimethyl-6-nitro-2H-indazole



Procedure 1:

To a stirred solution of 18.5 g (0.11 mol) of 3-methyl-6-nitro-*1H*-indazole in 350 ml acetone, at room temperature, was added 20 g (0.14 mol) of trimethyloxonium tetraflouroborate. After the solution was allowed to stir under argon for 3 hours, the solvent was removed under reduced pressure. To the resulting solid was added saturated aqueous $NaHCO_3$ (600 mL) and a 4:1 mixture of chloroform-isopropanol (200 ml), the mixture was agitated and the layers were separated. The aqueous phase was washed with additional chloroform: isopropanol (4 x 200 mL) and the combined organic phase was dried (Na_2SO_4). Filtration and removal of solvent gave a tan solid. The solid was washed with ether (200 mL) to afford 2,3-dimethyl-6-nitro-*2H*-indazole as a yellow solid (15.85 g, 73 %). ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 4.14 (s, 3H), 2.67 (s, 3H). MS (ES+, m/z) 192 (M+H).

Procedure 2:

Trimethyl orthoformate (11 mmol, 1.17 g) was added over a 2 min period to a solution of boron trifluoride etherate (12.5 mmol, 1.77 g in methylene chloride (2.0 mL) which had been cooled to -30 °C. The mixture was warmed to 0 °C for 15 min and was then cooled to -70 °C. The nitro indazole (10 mmol, 1.77 g) was slurried in methylene chloride (30 mL) and was added all at once to the cooled mixture. The mixture was stirred at -70 °C for 15 min and at ambient temperature for 17 h. After 17 h the mixture

was red and heterogeneous. The reaction mixture was quenched with saturated sodium bicarbonate solution (20 mL) and the organic layer separated. The aqueous layer was extracted with methylene chloride (30 mL). The methylene chloride layers were combined and extracted with water (30 mL). The methylene chloride layer was distilled under reduced pressure until ~ 10 mL remained. Propanol (10 mL) was added and the remainder of the methylene chloride removed under reduced pressure, resulting in a yellow slurry. The product was isolated by filtration to give 2,3-dimethyl-6-nitro-*2H*-indazole (65 %, 7mmol, 1.25 g) as a light yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 4.14 (s, 3H), 2.67 (s, 3H). MS (ES+, m/z) 192 (M+H).

Procedure 3:

In a 25 ml round bottom flask 3-methyl-6-nitroindazole (7.27 mmol, 1.28 g) was dissolved with stirring in DMSO (4.0 mL) and was treated with concentrated sulfuric acid (7.27 mmol, 0.73 g) to yield a thick slurry. The slurry was treated with dimethyl sulfate (21.1 mmol, 2.66 g). The mixture was heated under nitrogen at 50 °C for 72 h. After 72 h a thick yellow slurry was obtained. The slurry was cooled and was slowly treated with saturated sodium bicarbonate solution (10 mL). The mixture was extracted with methylene chloride (2 x 20 mL). The methylene chloride layers were combined and back extracted with water (20 mL). The methylene chloride layer was treated with propanol (10 mL) and the methylene chloride was removed by distillation under reduced pressure. The solid was isolated by filtration and the yellow solid washed with heptane (5 mL) and air-dried. The 2,3-dimethyl-6-nitro-*2H*-indazole product (70%, 0.97 g) was obtained as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 4.14 (s, 3H), 2.67 (s, 3H). MS (ES+, m/z) 192 (M+H).

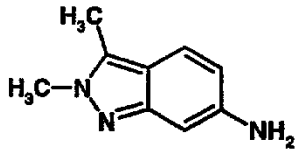
Procedure 4:

Into a 250 mL 3-necked round bottom flask was placed 3-methyl-6-nitro-1H-indazole sulfuric acid salt (5.0 g, 18.2 mmol) and methylene chloride (25 mL). The mixture was stirred at 25 °C and was treated with DMSO (5 mL). Dimethyl sulfate (6.7 g, 5.0 mL, 53.0 mmol) was added via syringe and the reaction was heated at reflux in a 70 °C bath. After 7 h HPLC analysis showed 9% starting material. At this point heating was stopped and the workup begun. Saturated sodium bicarbonate solution (35 mL)

was added to the reaction mixture at RT. The layers were allowed to separate and the aqueous layer was extracted with methylene chloride (25 mL). The methylene chloride layers were combined and washed with water (2 x 25 mL). The methylene chloride layer was distilled under reduced pressure until half the volume was removed. Propanol (25 mL) was added and distillation under reduced pressure was continued until all the methylene chloride had been removed. This yielded a yellow slurry, which was allowed to stir at 25 °C for 1 h. The product was isolated via filtration and the resulting yellow solid was washed with heptane (10 mL). This yielded 2,3-dimethyl-6-nitro-2H-indazole (70%, 2.43 g) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 4.14 (s, 3H), 2.67 (s, 3H). MS (ES+, m/z) 192 (M+H).

Intermediate Example 2

Preparation of 2,3-dimethyl-6-amino-2H-indazole:



Procedure 1:

To a stirred solution of 2,3-dimethyl-6-nitro-*2H*-indazole (1.13 g) in 2-methoxyethyl ether (12 ml), at 0 ºC, was added a solution of 4.48 g of tin(II) chloride in 8.9 ml of concentrated HCl dropwise over 5 min. After the addition was complete, the ice bath was removed and the solution was allowed to stir for an additional 30 min. Approximately 40 ml of diethyl ether was added to reaction, resulting in precipitate formation. The resulting precipitate was isolated by filtration and washed with diethyl ether, and afforded a yellow solid (1.1 g, 95 %), the HCl salt 2,3-dimethyl-2*H*-indazol-6-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.77 (d, J = 8.9 Hz, 1H), 7.18 (s, 1H), 7.88 (m, 1H), 4.04 (s, 3H), 2.61 (s, 3H). MS (ES+, m/z) 162 (M+H).

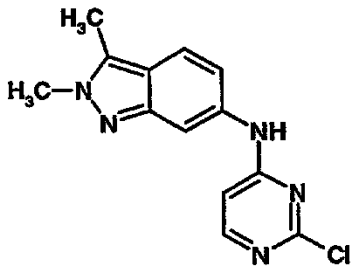
Procedure 2:

A 2-L 3-necked round bottom flask was fitted with nitrogen inlet and outlet and with mechanical stirring. A moderate nitrogen flow was initiated and the reactor was charged with 10 % Pd/C (50% water wet, 6.0 g). Stirring was initiated and the reactor was charged with methanol (750 mL) and the product of Intermediate Example 1 (50 g). Ammonium formate (82.54 g) was dissolved in water (120 mL). The water solution

of ammonium formate was added to the reaction solution at an addition rate, which kept the reaction temperature at or between 25 and 30°C. The reaction was allowed to proceed at 25°C. After 6 h the reaction was judged to be finished based on HPLC analysis. The mixture was filtered and the catalyst washed with methanol (50 mL). The methanol layers were combined and the solvent removed under reduced pressure. The residue was dissolved in water (200 mL) and was extracted with methylene chloride (3 x 250 mL). The methylene chloride layers were combined and solvent removed under vacuum to remove approximately half the solvent. Heptane (400 mL) was added and the vacuum distillation continued until approximately 300 mL reaction product slurry remained. The product was isolated by filtration and dried under vacuum at 50°C for 4 h. to yield 2,3-dimethyl-6-amino-2H-indazole as the free base. (40.76 g, 96.7 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.31 (d, J = 8.9 Hz, 1H), 6.45 (d, J = 8.9 Hz, 1H), 6.38 (s, 1H), 4.95 (s, br, 2H), 3.85 (s, 3H), 2.44 (s, 3H) MS (ES+, m/z) 162 (M+H).

Intermediate Example 3

Preparation of N-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2H-indazol-6-amine



Procedure 1

To a stirred solution of the product of Intermediate Example 2 (2.97 g, .015 mol) and $NaHCO_3$ (5.05 g, .06 mol) in THF (15 mL) and ethanol (60 mL) was added 2,4-dichloropyrimidine (6.70 g, .045 mol) at rt. After the reaction was stirred for four hours at 85 °C, the suspension was cooled to rt., filtered and washed thoroughly with ethyl acetate. The filtrate was concentrated under reduced pressure, and the resulting solid was triturated with ethyl acetate to yield *N*-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2*H*-indazol-6-amine (89 %, 3.84 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, J = 9.0 Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 6.37 (s, 1H), 5.18 (br s, 1H), 3.84 (s, 3H), 2.43 (s, 3H). MS (ES+, m/z) 274 (M+H).

Procedure 2

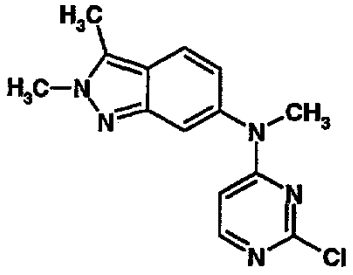
To a 1-L 3-necked flask equipped with air-driven mechanical stirrer, thermometer, and nitrogen inlet/outlet was charged a solution of the product of Intermediate Example 2 (32.89 g, 0.204 mol, 1.0 equiv) in 425 mL (13 volumes) of EtOH/THF (4/1), sodium bicarbonate (51.42 g, 0.612 mol, 3.0 equiv) and then 2,4-dichloropyrimidine (45.59 g, 0.306 mol, 1.5 equiv). The flask contents were heated to 75°C and held at 74 – 76 °C for 6 – 7 hrs. The progress of the reaction was checked by HPLC (the product of Intermediate Example 2 < 2%). The reaction contents were cooled to 20 – 25 °C over 30 min, and kept at 20 – 25 °C for 30 min. Then the reaction contents were further cooled to 10 - 12°C over 30 min, and kept at that temperature for an additional 10 min. The contents were filtered and filter cake washed with EtOAc (2 x 100 mL, 3.0 volumes), and deionized water (514 mL, 15.6 volumes). The filter cake was then dried in a vacuum oven at 35°C overnight to afford the desired product 44.75 g as a white solid (80.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, J = 9.0 Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 6.37 (s, 1H), 5.18 (br s, 1H), 3.84 (s, 3H), 2.43 (s, 3H). MS (ES+, m/z) 274 (M+H).

Procedure 3

To a 2 L jacketed reactor was charged with IMS (1000 mL), the product of Intermediate Example 2 (100 g, 0.620 mol, 1 equiv), Sodium Hydrogen Carbonate (107g, 1.27 mol, 2.05 equiv), and 2,4-dichloropyrimidine (101 g, 0.682 mol, 1.1 equiv). The solution was stirred and heated to reflux with a jacket temperature of 85 °C for 8 hours. The resulting slurry was then cooled to 50 °C, and water (500 mL) was added to maintain the temperature between 40 and 50°C. The reaction was then stirred at an internal temperature of 50°C for one hour, and then cooled to 20°C. The solid product was collected by filtration, washed with water (750 mL X 2), and followed by with EtOAc (450 mL X 1). After drying at overnight, under vacuum at 60 °C afforded 135 g (80%) of *N*-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2*H*-indazol-6-amine.

Intermediate Example 4

Preparation of N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine



Procedure 1

To a stirred solution of the product of Intermediate Example 3 (7.37 g) in DMF (50 ml) was added Cs_2CO_3 (7.44 g, 2 eqv.) and iodomethane (1.84 ml, 1.1 eqv.) at room temperature. The mixture was stirred at rt overnight. The reaction mixture was then poured into an ice-water bath, and the precipitate was collected via filtration and washed with water. The precipitate was air-dried to afford *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine as an off-white solid (6.43 g, 83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 1.0 Hz, 1H), 6.88 (m, 1H), 6.24 (d, J = 6.2 Hz, 1H), 4.06 (s, 3H), 3.42 (s, 3H), 2.62 (s, 3H). MS (ES+, m/z) 288 (M+H).

Procedure 2

A 3L 3-necked flask equipped with air-driven mechanical stirrer, thermometer, addition funnel and nitrogen inlet/outlet was charged with DMF (272 mL, 5 volumes) and the product of Intermediate Example 3 (54.4 g, 0.20 mol, 1.0 equiv) with stirring. The reaction mixture was further charged with cesium carbonate (194.5 g, 0.60 mol, 3.0 equiv) while maintaining the reaction temperature between 20 ~ 25°C. The reaction mixture was stirred at 20 ~ 25°C for 10 minutes. Iodomethane (45.1 g, 0.32 mol, 1.6 equiv) was charged over ~ 10 minutes while maintaining the temperature 20 ~ 30°C. The reaction mixture was stirred at 20 ~ 30°C (Typically, the reaction is complete in 1 ~ 2 hours). Deionized H_2O (925 mL, 17 volumes) was added over ~ 30 minutes while maintaining the temperature at 25 ~ 40°C. The reaction mixture was stirred at 20 ~ 25°C for 40 minutes. The product was isolated by filtration and then the filter cake washed with H_2O / DMF (6 : 1, 252 mL, 4.6 volumes). The wet cake was dried under vacuum at 40 ~ 45°C and *N*-(2-chloropyrimidin-4-yl)-*N*,2,3-trimethyl-2*H*-indazol-6-amine

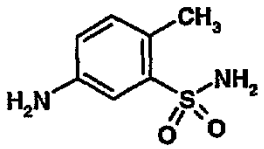
(51.7 g, 90.4%) was isolated as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 7.0 Hz, 1H), 7.50 (d, J = 1.0 Hz, 1H), 6.88 (m, 1H), 6.24 (d, J = 6.2 Hz, 1H), 4.06 (s, 3H), 3.42 (s, 3H), 2.62 (s, 3H). MS (ES+, m/z) 288 (M+H).

Procedure 3

To a 2 L jacketed reactor was charged with DMF (383 mL), dimethyl carbonate (192 mL), the product of Intermediate Example 3 (115 g, 0.420 mol, 1 equiv) and Potassium Carbonate (174 g, 1.26 mol, 3 equiv). The suspension was stirred and heated to reflux with a jacket temperature of 135°C for 6 hours. The resulting slurry was then cooled to 60°C, and water (1150 mL) was added slowly maintaining the reaction temperature between 50 and 65 °C. The reaction was then cooled down to 20°C and stirred at an internal temperature of 20°C for two hours, and then cooled to 10°C and held overnight after which it was filtered. The solid was washed with water (230 mL X 2) at room temperature, and rinsed with the mixture IMS:Water (1:1) (230 mL X 1). After drying at overnight, under vacuum at 60°C afforded 101 g (83%) of N-(2-chloropyrimidin-4-yl)-N,2,3-trimethyl-2H-indazol-6-amine.

Intermediate Example 5

Preparation of 5-amino-2-methylbenzenesulfonamide



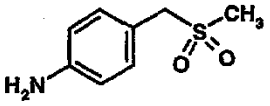
Procedure 1

To a stirred solution of 2-methyl-5-nitrobenzenesulfonamide (4.6 g, 0.021 mol) in 2-methoxyethyl ether (43 mL), at 0ºC, was added a solution of 16.1 g of tin(II) chloride in 32 mL of concentrated HCl dropwise over 15 min. After the addition was complete, the ice bath was removed and the solution was allowed to stir for an additional 30 min. Approximately 130 mL of diethyl ether was added to reaction. The mixture was stirred vigorously for 1 h. The mixture was basified with a solution of NaOH and $NaHCO_3$, and extracted with ethyl acetate (x 3). The combined ethyl acetate layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give crude product. Trituation of the crude product with methanol provided 2.4 g of pure 5-amino-2-methylbenzenesulfonamide as light brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.11-

7.10 (m, 3H), 6.95 (d, J = 8.1 Hz, 1H), 6.60 (dd, J = 8.1 & 2.4 Hz, 1H), 5.24 (s, 2H), 2.36 (s, 3H). MS (ES+, m/z) 187 (M+H).

Intermediate Example 6

Preparation of 4-[(methylsulfonyl)methyl]aniline



Procedure 1

Combine 4-nitrobenzyl bromide (40 g, 0.185 mol) and sodium methanesulphinic acid (19.5 g, 1 eqv.) in ethanol (460 mL, ~0.4M). The mixture was stirred and heated to 80 °C under reflux. After 3 hr the reaction mixture was cooled to rt and filtered to collected off-white solid. The solid was washed with EtOH twice and air-dried to provide 37 g of methyl 4-nitrobenzyl sulfone. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.27 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 4.71 (s, 2H), 2.96 (s, 3H). MS (ES+, m/z) 216 (M+H).

Combined methyl 4-nitrobenzyl sulfone (9.5 g, 0.044 mol) and 10% Pd/C (0.95 g, 0.1 w/w) in ethyl acetate (220 mL, ~0.2M). The mixture was placed under Parr shaker with 40 psi of hydrogen. After ~3 hr, the reaction mixture was poured into 50% of MeOH/EtOAc (400 mL) and stirred vigorously for 30 min. The mixture was filtered through a pad of celite and silica gel. The black material on top of the pad was removed and placed into 80% MeOH/EtOAc (200 mL) and stirred vigorously for 30 min. The mixture was again filtered through a pad of celite and silica gel. The process is repeated a couple times. Combined all filtrates. Evaporated and dried. Trituation with EtOAc provided pure 4-[(methylsulfonyl)methyl]aniline. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.03 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 8.6 Hz, 2H), 5.20 (s, 2H), 4.20 (s, 2H), 2.79 (s, 3H). MS (ES+, m/z) 186 (M+H).

Procedure 2

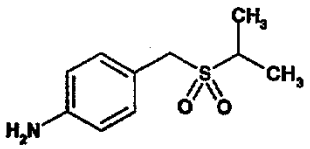
Charge a round bottom flask (1.0 L), equipped with magnetic stir bar and reflux condenser, with 4-nitrobenzyl bromide (40 g, 0.185 mol, 1.0 eq.), sodium methanesulphinic acid (21.7 g, 0.213 mol, 1.15 eq.) and ethanol (400 mL, 200 proof, 10 vol.). Stir and heat the mixture to 80 °C under reflux for 2 hours. Check the progress of the reaction by fast-HPLC (reaction is deemed complete when HPLC indicates 4-

nitrobenzyl bromide < 0.5%). Cool the mixture to room temperature. Filter and wash the cake with ethanol (40 mL). The wet cake (15 g, 46.2 mmol) was used for next step hydrogenation with out further dry.

Charge a 500 mL of hydrogenation flask with above wet cake methyl 4-nitrobenzyl sulfone (15 g, 46.2 mmol, used "as is"), 10% Pd/C (0.1 g, 1% w/w) and ethanol (120 mL, 200 proof) and water (40 mL). Swap the atmosphere of reactor with hydrogen (3 times). Shake the reactor under H_2 (65 psi) at room temperature for 30 minutes and at 50 °C for two hour. Check the progress of the reaction by HPLC (reaction is deemed complete when HPLC indicates methyl 4-nitrobenzyl sulfone < 0.2 %). Heat the mixture to 80 °C. Filter the hot solution through a pad of celite (2.0 g) and rinse the pad with EtOH (10 mL). Transfer the filtrate into the crystallizing a round bottom flask (500 mL). Distil the slurry under house vacuum at 60 °C until a volume of 60 mL is left. Cool the slurry to 0 °C over for one hour. Isolate the crystals by vacuum filtration and wash the vessel and crystals with ethanol (10 mL). Dry the product under house vacuum at 50 °C to constant weight. Obtained off-white solid (7.3 g). The yield is 85% for combined two steps with 99% purity of product by HPLC.

Intermediate Example 7

Preparation of 4-[(isopropylsulfonyl)methyl]phenylamine

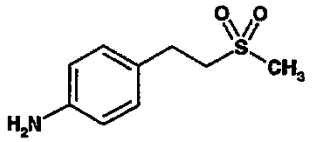


To a solution of 1-(bromomethyl)-4-nitrobenzene (3.0 g, 17.4 mmol) in ethanol (50 mL) was added sodium-2-thiopropoylate (2.7 g, 17.4 mmol). After 12h the solvent was removed under reduced pressure, the remaining residue was diluted with EtOAc and filtered to remove the residual salts. The solvent was dried over $MgSO_4$ and removed under reduced pressure and the product was carried forward without further purification. Next the sulfide was diluted with CH_2Cl_2 (50 mL) and m-chloroperoxybenzoic acid (~70%) (6.6 g, 38.4 mmol) was added in portions. The reaction was judged to be complete by tlc and the solvent was removed under reduced pressure. The remaining residue was diluted with EtOAc and washed with 1M NaOH (2 x 100 mL). The solvent was dried over $MgSO_4$ and removed under reduced

pressure and the product was carried forward without further purification. Next the residue was diluted with glyme (8.0 mL) and a solution of $SnCl_2$ (13.8 g, 69 mmol) in HCl (8.0 mL) was added dropwise. The solution was allowed to stir for 2h, and the reduction was judged to be complete by tlc. The reaction mixture was diluted with Et_2O, which resulted in the precipitation of the product as the HCl salt. The solids were collected and washed with Et_2O (2 x 100 mL), to afford pure aniline (~2.4 g, 65%). ^1H NMR (300 MHz, d_6DMSO+$NaHCO_3$) δ 7.37 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.41 (s, 2H), 3.18-3.09 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H).

Intermediate Example 8

Preparation of 4-[2-(methylsulfonyl)ethyl]aniline

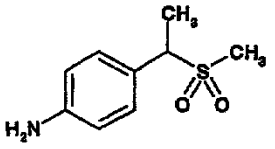


To a solution of 1-(bromoethyl)-4-nitrobenzene (3.0 g, 13.0 mmol) in ethanol (70 mL) was added Sodium thiomethoxide (1.0 g, 14.0 mmol). After 12h the solvent was removed under reduced pressure, the remaining residue was diluted with EtOAc and filtered to remove the residual salts. The solvent was dried over MgSO4 and removed under reduced pressure and the product was carried forward without further purification. Next the sulfide was diluted with CH_2Cl_2 (100 mL) and m-chloroperoxybenzoic acid (~70%) (8.2 g, 48.8 mmol) was added in portions. The reaction was judged to be complete by tlc and the solvent was removed under reduced pressure. The remaining residue was diluted with EtOAc and washed with 1M NaOH (2 x 100 mL). The solvent was dried over $MgSO_4$ and removed under reduced pressure and the product was carried forward without further purification. Next the residue was added to a slurry of Palladium on Carbon (10 mol %) in EtOAc (50 mL) in a Parr shaker vessel. The reaction was then place under 40 atm of Hydrogen gas. The solution was allowed to shake for 2h, and the reduction was judged to be complete by tlc. The reaction mixture was filtered over a pad of celite and washed with EtOAc and the solvent was removed under reduced pressure to afford a crude solid. The mixture was recrystallized in hot EtOAc to afford the pure aniline (~1.8 g, 69%). ^1H

NMR (300 MHz, d_6DMSO+$NaHCO_3$) δ 6.93 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.09 (bs, 2H), 3.31-3.26 (m, 2H), 2.92 (s, 3H), 2.84-2.79 (m, 2H).

Intermediate Example 9

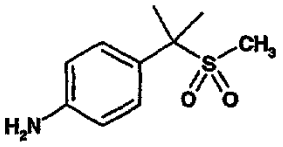
Preparation of 4-[1-(methylsulfonyl)ethyl]aniline



To a solution of 4-nitrophenylcarbonol (3.0 g, 17.9 mmol) and triethylamine (3.5 mL, 21.0 mmol) in CH_2Cl_2 (100mL) was added methanesulfonylchloride (1.7 mL, 21.0 mmol) dropwise. The reaction was judged to be complete by tlc after 1h and was quenched with saturated aqueous NaHCO3. The reaction mixture was diluted with EtOAc and the organic layer separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting residue was dissolved in ethanol (100 mL) and Sodium thiomethoxide (1.5 g, 21.0 mmol) was added in portions. After 12h the solvent was removed under reduced pressure, the remaining residue was diluted with EtOAc and filtered to remove the residual salts. The solvent was dried over $MgSO_4$ and removed under reduced pressure and the product was carried forward without further purification. Next the sulfide was diluted with CH_2Cl_2 (100 mL) and m-chloroperoxybenzoic acid (~70%) (10.8 g, 62 mmol) was added in portions. The reaction was judged to be complete by tlc and the solvent was removed under reduced pressure. The remaining residue was diluted with EtOAc and washed with 1M NaOH (2 x 100 mL). The solvent was dried over $MgSO_4$ and removed under reduced pressure and the product was carried forward without further purification. Next the residue was added to a slurry of Palladium on Carbon (10 mol %) in EtOAc (50 mL) in a Parr shaker vessel. The reaction was then place under 40 atm of Hydrogen gas. The solution was allowed to shake for 2h, and the reduction was judged to be complete by tlc. The reaction mixture was filtered over a pad of celite and washed with EtOAc and the solvent was removed under reduced pressure to afford a crude solid. The mixture was recrystallized in hot EtOAc to afford the pure aniline (~2.0 g, 57%). ^{1}H NMR (300 MHz, d_6DMSO+$NaHCO_3$) δ 7.06 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 5.21 (s, 2H), 4.23 (q, J = 7.1 Hz, 1H), 2.70 (s, 3H), 1.21 (d, J = 7.1 Hz, 3H).

Intermediate Example 10

Preparation of 4-[1-methyl-1-(methylsulfonyl)ethyl]aniline



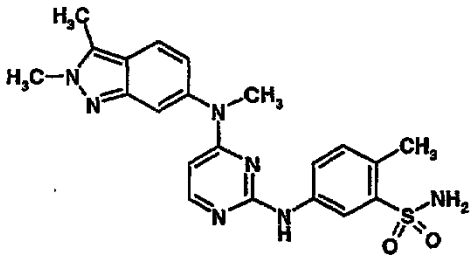
To a stirred solution of t-butoxide (5.76g, 0.051 mol) in THF was added methyl 4-nitrobenzyl sulfone (5 g, 0.023 mol) followed by iodomethane (2.89 ml, 0.046 mol). The mixture was stirred at rt for 1 hr. Additional t-butoxide (2.9 g) and iodomethane (0.5 ml) were added. The mixture was stirred at rt for additional 1 hr. The mixture was diluted with EtOAc and acidified with 6N HCl. The mixture was extracted with ethyl acetate (x 3). The combined ethyl acetate layers were dried over anhydrous MgSO4, filtered and evaporated. The solid was trituated with ethanol to give pure 1-[1-methyl-1-(methylsulfonyl)ethyl]-4-nitrobenzene.

To a stirred solution of 1-[1-methyl-1-(methylsulfonyl)ethyl]-4-nitrobenzene (3.32 g, 0.014 mol) in 2-methoxyethyl ether (70 mL), at 0 ºC, was added a solution of 10.35 g of tin(II) chloride in 20.5 mL of concentrated HCl dropwise over 15 min. After the addition was complete, the ice bath was removed and the solution was allowed to stir for an additional 30 min. Approximately 70 mL of diethyl ether was added to reaction. The mixture was stirred vigorously for 1 h. Precipitate was formed and was collected via filtration. The solid was dissolved in CH_2Cl_2 and washed with 1N NaOH. The mixture was extracted with CH_2Cl_2 (x 3). The combined CH_2Cl_2 layers were dried over anhydrous $MgSO_4$, filtered and evaporated to give 4-[1-methyl-1-(methylsulfonyl)ethyl]aniline as an off white solid. ^1H NMR (300 MHz, DMSO-d_6) δ 7.21 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.6 Hz, 2H), 5.23 (s, 2H), 2.58 (s, 3H), 1.64 (s, 6H).

Example 1: ***Preparation of pazopanib (5-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide) and salts and solvates thereof***

Example 1a

Preparation of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide



Procedure 1

To a solution of Intermediate Example 4 (200 mg, 0.695 mmol) and 5-amino-2-methylbenzenesulfonamide (129.4 mg, 0.695 mmol) in isopropanol (6 ml) was added 4 drops of conc. HCl. The mixture was heated to reflux overnight. The mixture was cooled to rt and diluted with ether (6 ml). Precipitate was collected via filtration and washed with ether. The hydrochloride salt of 5-({4-[(2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino]-pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide was isolated as an off-white solid. ^{1}H NMR (400 MHz, d_6DMSO+$NaHCO_3$) δ 9.50 (br s, 1H), 8.55 (br s, 1H), 7.81 (d, *J* = 6.2 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.69 (m, 1H), 7.43 (s, 1H), 7.23 (s, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.86 (m, 1H), 5.74 (d, *J* = 6.1 Hz, 1H), 4.04 (s, 3H), 3.48 (s, 3H), 2.61 (s, 3H), 2.48 (s, 3H). MS (ES+, m/z) 438 (M+H).

Procedure 2

A 250-mL 3-necked flask equipped with a magnetic stir bar, thermometer, reflux condenser, and nitrogen inlet/outlet was charged with ethanol (60 mL, 10 volumes), the product of Intermediate Example 4 (6.00 g, 20.85 mmol, 1.0 equiv) and 5-amino-2-methylbenzenesulfonamide (4.00 g, 21.48 mmol, 1.03 equiv) with stirring. The reaction mixture was heated to 70 °C. After stirring the reaction mixture at 68 – 72 °C for 3 hrs, 4M HCl in dioxane (0.11 mL, 0.44 mmol, 0.02 equiv) was charged over ca. 2 min. The reaction mixture was stirred at 68 - 72 °C until < 1.5% by area of the starting product of Intermediate Example 4 was remaining by HPLC analysis (Typically, this reaction is complete in > 8 hrs). The reaction mixture was cooled to 20 °C over ca. 30 min and stirred at 20 - 22 °C for 40 min. The product was then isolated by filtration and the filter

cake washed with ethanol (20 mL, 3.3 volumes). The wet cake was dried under vacuum at 45 - 50 °C. The monohydrochloride salt of 5-({4-[(2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino]-pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide (9.52 g, 96.4%) was isolated as a white solid. ^{1}H NMR (400 MHz, d_6DMSO+$NaHCO_3$) δ 9.50 (br s, 1H), 8.55 (br s, 1H), 7.81 (d, J = 6.2 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.69 (m, 1H), 7.43 (s, 1H), 7.23 (s, 2H), 7.15 (d, J = 8.4 Hz, 1H), 6.86 (m, 1H), 5.74 (d, J = 6.1 Hz, 1H), 4.04 (s, 3H), 3.48 (s, 3H), 2.61 (s, 3H), 2.48 (s, 3H). MS (ES+, m/z) 438 (M+H).

Procedure 3:

To a stirred suspension of the product of Intermediate Example 4 (1.1 g, 3.8 mmol) in 14 mL of MeOH, was added 5-amino-2-methylbenzenesulfonamide (0.78 g, 4.2 mmol, 1.1 equiv) at room temperature. The reaction mixture was heated at reflux for 3 h, then 4 M HCl in 1,4-dioxane (19 µL, 0.076 mmol) was added in one portion. After 4 h, the suspension was cooled to room temperature, and filtered. The resulting solid was washed with 10 mL of MeOH and dried in vacuo to yield 1.3 g (72%) of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methyl benzenesulfonamide monohydrochloride as a white solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ 10.95 (s, 1H), 8.36 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.64-7.59 (m, 2H), 7.40 (m, 3H), 6.93 (dd, J = 8.8, 2.0 Hz, 1H), 5.92 (s, 1H), 4.08 (s, 3H), 3.57 (s, 3H), 2.65 (s, 3H), 2.56 (s, 3H).

Procedure 4

To a stirred suspension of the product of Intermediate Example 4 (1.1 g, 3.7 mmol) in 10 mL of THF, was added 5-amino-2-methylbenzenesulfonamide (0.70 g, 3.8 mmol, 1.0 equiv) at room temperature. The reaction mixture was heated at reflux for 3 h, then 4 M HCl in 1,4-dioxane (18 µL, 0.072 mmol) was added in one portion. After 5 h, the suspension was cooled to room temperature, and filtered. The resulting solid was washed with 16 mL of THF and dried in the air to yield 1.6 g (92%) of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzene sulfonamide monohydrochloride as a light yellow solid.

Procedure 5

To a stirred suspension of the product of Intermediate Example 4 (1.0 g, 3.6 mmol) in 10 mL of CH_3CN, was added 5-amino-2-methylbenzenesulfonamide (0.70 g, 3.8 mmol, 1.0equiv) at room temperature. The reaction mixture was heated at reflux for

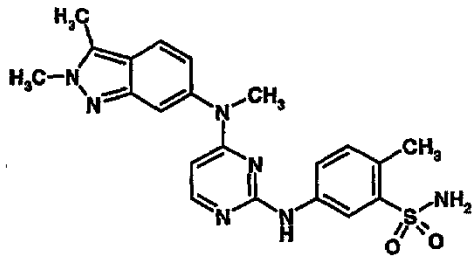
3 h, then 4 M HCl in 1,4-dioxane (18 μL, 0.076 mmol) was added in one portion. After 20 h, the suspension was cooled to room temperature, and filtered. The resulting solid was washed with 10 mL of CH_3CN and dried in the air to yield 1.3 g (73%) of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methyl benzenesulfonamide monohydrochloride as an off-white solid.

Procedure 6

To a 2 L jacketed reactor was charged with MeOH (1005 mL), the product of Intermediate Example 4 (84 g, 0.292 mol, 1 equiv) and 5-amino-2-methylbenzenesulfonamide (60 g, 0.320 mol, 1.1 equiv). The solution was stirred and heated to 50 °C and 4M HCl in Dioxane (1.46 mL, 2 mol%) was added. The solution was then stirred and heated to reflux with a jacket temperature of 85 °C for 10 hours. The resulting slurry was then cooled to 20-25 °C and filtered. The filtered solid was washed with acetonitrile (293 mL X 2) at room temperature. After drying at overnight, under vacuum at 60 °C afforded 116 g (81%) of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methyl benzenesulfonamide monohydrochloride.

Example 1b

Preparation of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride monohydrate.

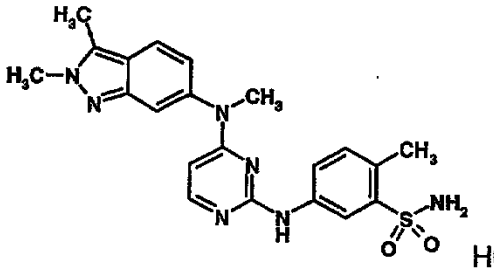


$HCl \cdot H_2O$ (I")

To a round bottom flask, was added 2.6 g of the monohydrochloride salt of Example 1a, procedure 1, any form. Then added was 39 mL of isopropanol (15 volumes). The mixture was heated to 75 deg C in an oil bath, then 14 mL of 0.05N aqueous HCl (5.4 volumes) was added. The clear solution was cooled to 65 deg C, then seeded with the monohydrate of the monohydrochloride salt of Example 1, procedure 1 (0.05-0.1 wt %). The cloudy solution was stirred at 65 deg C for 60 minutes, then cooled to 0 deg C at ~0.25-0.5 deg C/min. The resulting white solid was filtered and dried to constant weight under vacuum at RT to give 88% yield of 5 -({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzene sulfonamide monohydrochloride monohydrate.

Example 1c

Preparation of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride anhydrate.



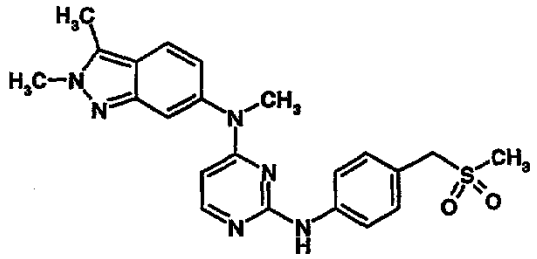
HCl

To a 1 L jacketed reactor was charged with acetonitrile (563 mL), water (188 mL) the monohydrochloride salt of Example 1, procedure 6 (50 g, 0.105 mol). The solution was stirred and heated to the jacket temperature at 85°C and a clear solution was obtained. The solution was then cooled down to 45°C and held for 90 minutes to cause crystallization of the hydrate After the 90 min hold, the solution was cooled down to 0°C, held for an hour and then filtered through a filter-dryer. The filtered solids were then washed with acetonitrile (200 mL X 1) at 0°C. The solids were blown in the filter-dryer with nitrogen at 25°C until the LOD was less than 25%. Acetonitrile (300 mL) was charged to the solids in filter-dryer, and stirred at 60°C for at least 8 hours or until the form conversion was complete (no monohydrate remaining) as observed by DATR to form 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride anhydrate. The contents of the filter-dryer were cooled to ~30°C, and the filtrate was pushed off using nitrogen pressure.

The filtercake was blown with nitrogen at ~60 °C under vacuum until the LOD was less than 0.5%. The contents were cooled to 20 °C yielding 37.5 g (75%) of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride anhydrate.

Example 2

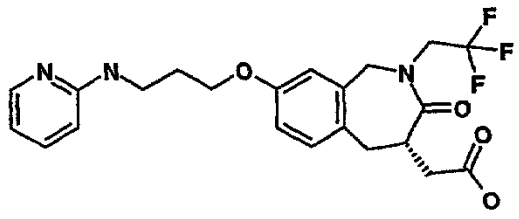
Preparation of N^4-(2,3-dimethyl-2*H*-indazol-6-yl)-N^4-methyl-N^2-{4-[(methylsulfonyl)methyl]phenyl}pyrimidine-2,4-diamine.



Example 2 was prepared according to the general procedure set forth above in Example 1 using Intermediate Example 4 and the appropriate aniline. The appropriate anilines were prepared using procedures similarly described for Intermediate Examples 5-10. ^{1}H NMR (300 MHz, d_6DMSO+$NaHCO_3$) δ 9.37 (bs, 1H), 7.88 (d, J = 6.1 Hz, 1H), 7.78 (m, 3H), 7.47 (s, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.91 (dd, J = 8.8, 1.5 Hz, 1H), 5.84 (d, J = 6.1 Hz, 1H), 4.37 (s, 2H), 4.09 (s, 3H), 3.51 (s, 3H), 2.88 (s, 3H), 2.65 (s, 3H). MS (ES+, m/z) 437 (M+H), 435 (M-H).

Example 3:

Preparation of 5-({4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl}amino)-2-methylbenzenesulfonamide monohydrochloride anhydrate.



Preparation 1

Preparation of methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

a) 3-[N-(tert-Butoxycarbonyl)-N-methylamino]methyl-4-bromoanisole

40% aqueous methylamine (49 mL, 563 mmole) was added rapidly to a solution of 4-bromo-3-bromomethylanisole (15.76 g, 56.29 mmole) in THF (280 mL) at RT. After 2.5 hr, the reaction was concentrated, and the residue was partitioned between Et_2O (560 mL) and 1.0 N NaOH (100 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated to a yellow oil: TLC (5% MeOH/$CHCl_3$) R_f 0.32. The oil was dissolved in $CHCl_3$ (280 mL), and di-tert-butyl dicarbonate (1.29 g, 56.29 mmole) was added. The reaction was stirred at RT for 45 min, then was concentrated. Silica gel chromatography (5% EtOAc/toluene) gave the title compound (16.81 g, 90%) as a light yellow oil: TLC (5% EtOAc/toluene) R_f 0.43; ^{1}H NMR (400, $CDCl_3$) mixture of rotamers; 7.42 (d, J=8.7 Hz, 1 H, 6.65-6.80 (m, 2 H), 4.40-4.55 (m, 2 H), 3.77 (s, 3 H), 2.81-2.97 (m, 3 H), 1.37-1.60 (m, 9 H); MS (ES) m/e 352/354 $(M+Na)^+$

b) Methyl (±)-3-carbomethoxy-4-[2-[N-(tert-butoxycarbonyl)-N-methylamino]methyl-4 -methoxypheny]butanoate

A solution of 3-[N-(tert-butoxycarbonyl)-N-methylamino]methyl-4-bromoanisole (4.95 g, 15 mmol), dimethyl itaconate (3.08 g, 19.5 mmol), palladium acetate (168 mg, 0.75 mmol), tri-o-tolylphosphine (457 mg, 1.5 mol), and diisopropylethylamine (5.2 mL, 30 mmol) in propionitrile (75 mL) was heated to reflux for 45 min, then was concentrated on the rotavap. The residue was diluted with Et_2O (150 mL), and the mixture was filtered through celite® to remove insoluble materials. The filtrate was concentrated, and the residue was reconcentrated from xylenes. Chromatography on silica gel (gradient: 20% EtOAc/hexanes, then 1:1 EtOAc/hexanes) removed the phosphine and baseline materials; all other materials with R_f 0.40-0.70 were collected together and concentrated to leave a cloudy, yellow oil: TLC (30% EtOAc/hexanes) R_f 0.41 (major product).

The oil was dissolved in MeOH (75 mL), and 10% Pd/C was added carefully. The mixture was shaken under hydrogen (50 psi) for 2.5 hr, then was filtered through celite®. to remove the catalyst. The filtrate was concentrated, and the residue was resubmitted to the reaction conditions. After another 2.5 hr, the mixture was filtered

through celite® to remove the catalyst, and the filtrate was concentrated to leave a light yellow oil. This was reconcentrated from $CHCl_3$/hexanes, then was chromatographed on silica gel (gradient: 20% EtOAc/hexanes, then 1:1 EtOAc/hexanes) to afford the title compound (4.53 g, 74%) as a light yellow oil: TLC (30% EtOAc/toluene) R_f 0.46; ^1H NMR (400, $CDCl_3$) mixture of rotamers; δ 7.03 (d, J=8.2 Hz, 1 H, 6.65-6.80 (m, 2 H), 4.46 (br s, 2 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 2.62-3.12 (m, 7 H), 2.35-2.50 (m, 1 H, 1.47 (br s, 9 H); MS (ES) m/e 432 $(M+Na)^+$.

c) Methyl (±)-3-carbomethoxy-4-[2-(methylamino)methyl-4-methoxyphenyl]butanoate

TFA (55 mL) was added all at once to a solution of methyl (±)-3-carbomethoxy-4-[2-[N-(tert-butoxycarbonyl)-N-(methylamino]methyl- 4-methoxyphenyl]butanoate (4.53 g, 11.06 mmole) in anhydrous CH_2Cl_2 (55 mL) at 0°C., and the reaction was warmed to RT. After 1 hr, the reaction was concentrated, and the residue was reconcentrated from toluene (2x100 mL) to leave the title compound (11.06 mmole, quantitative) as a light yellow oil: MS (ES) m/e 310 $(M+H)^+$.

d) Methyl (±)-8-methoxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acet ate

A solution of methyl (±)-3-carbomethoxy-4-[2-(methylamino)methyl-4-methoxyphenyl]butanoate (11.06 mmole) and diisopropylethylamine (5.8 mL, 33.18 mmole) in toluene (110 mL) was heated at reflux for 25 hr, stirred at RT for 4 days, then heated at reflux for another 24 hr. Concentration and silica gel chromatography (5% MeOH in 1:1 EtOAc/$CHCl_3$) gave the title compound (2.88 g, 94%) as a light yellow solid: TLC (5% MeOH in 1:1 EtOAc/$CHCl_3$) R_f 0.63; ^1H NMR (250, $CDCl_3$) δ 7.02 (d, J=8.4 Hz, 1 H, 6.78 (dd, J=8.4, 2.7 Hz, 1 H), 6.63 (d, J=2.7 Hz, 1 H), 5.29 (d, J=16.3 Hz, 1 H), 3.50-3.90 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.73-3.16 (m, 3 H), 3.04 (s, 3 H), 2.41 (dd, J=16.7, 5.4 Hz, 1 H; MS (ES) m/e 300 $(M+Na)^+$, 278 $(M+H)^+$.

e) Methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Anhydrous aluminum chloride (1.35 g, 10.15 mmole) was added all at once to a solution of methyl (±)-8-methoxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acet ate (562 mg, 2.03 mmole) and ethanethiol (0.75 mL, 10.15 mmole) in anhydrous CH_22 Cl_2 (20 mL) at 0°C. under argon. The mixture was warmed to RT and stirred for 4.5 hr, then was recooled to 0°C. Ice cold H_2O (20 mL) was added, and the mixture

was stirred briskly for 5 min, then was extracted with $CHCl_3$ (3x20 mL). The combined $CHCl_3$ layers were dried ($MgSO_4$) and concentrated to leave a residue. The aqueous layer was suction filtered to collect a solid precipitate. This precipitate and the residue from the $CHCl_3$ layer were combined in 1:1 MeOH/$CHCl_3$, and the solution was concentrated to leave an off-white solid. This was triturated with hot MeOH, and the mixture was allowed to cool to RT. The solid was collected by suction filtration and washed sequentially with cold MeOH and Et_2O. Drying in high vacuum at 40° C. gave the title compound (467.9 mg, 88%) as a colorless solid: TLC (5% MeOH/$CHCl_3$) R_f 0.17; ^1H NMR (250, DMSO-d_6) δ 9.29(s, 1 H), 6.89 (d, J=8.1 Hz, 1 H), 6.50-6.70 (m, 2 H), 5.16 (d, J=16.4 Hz, 1 H), 3.84 (d, J=16.4 Hz, 1 H), 3.60-3.85 (m, 1 H), 3.56 (s, 3 H), 2.30-3.00 (m, 4 H), 2.86 (s, 3 H); MS (ES) m/e 286 $(M+Na)^+$, 264 $(M+H)^+$.

Preparation 2

HPLC Separation of the Enantiomers of methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

a) Methyl (R)-(+)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate and methyl (S)-(-)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate was resolved into its enantiomers by chiral HPLC using the following conditions: Diacel Chiralpak AS® column (21.2x250 mm), EtOH mobile phase, 7 mL/min flowrate, uv detection at 254 nm, 70 mg injection; t_R for methyl (R)-(+)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate=21.5 min; t_R for methyl (S)-(-)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate=39.1 min.

Preparation 3

Preparation of (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2 ,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroeth yl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of methyl (S)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (19 g, 57.4 mmol) in dry THF (400 mL) and dry DMF (200 mL) under argon were added 2-(3-hydroxypropylamino)pyridine N-oxide (11.6 g, 69 mmol) and triphenylphosphine (18.0 g, 69 mmol). After all solids had completely dissolved (~30 minutes), the reaction was cooled to 0° C. in an ice bath and diisopropyl

azodicarboxylate (14.3 mL, 69 mmol) was added via syringe. The reaction was allowed to warm slowly to RT and was stirred for 18 h. Concentration and flash chromatography on silica gel (8:2:1 $CHCl_3$/EtOAc/EtOH) gave the title compound (20.83 g, 75%) as a solid foam. An additional 5.73 g of product can be obtained by recycling of the recovered starting material from the above reaction to give a total of 26.56 g (96%) of the title compound: MS (ES) m/e 482.2 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (dd, J=6.5, 1.3 Hz, 1H), 7.29 (t, 1H), 7.18 (t, 1H), 7.02 (d, J=9.2 Hz, 1H), 6.84-6.79 (m, 3H), 6.59 (t, 1H), 5.32 (d, J=16.5 Hz, 1H), 4.28-4.14 (m, 2H), 4.16 (d, J=16.5 Hz, 1H), 4.02 (t, 2H), 3.84 (m, 1H), 3.58 (s, 3H), 3.40 (dd, 2H), 3.01 (dd, 1H), 2.73 (dd, 1H), 2.70 (dd, 1H), 2.52 (dd, 1H), 2.02 (ddd, 2H).

b) Methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2 ,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (26.56 g, 55 mmol) in isopropanol (500 mL) were added 10% palladium on activated carbon (8 g, 7.5 mmol, carefully pre-wetted in isopropanol under Argon) and cyclohexene (55.7 mL, 550 mmol). The reaction was then heated to reflux under Argon in an oil bath set at 90°C. After 6 h an additional amount of 10% palladium on activated carbon (8 g, 7.5 mmol, carefully pre-wetted in isopropanol under Argon) and cyclohexene (55.7 mL, 550 mmol) were added. After an additional 18 h the reaction was hot-filtered through celite®, and the filter pad was washed with 1:1 MeOH/$CHCl_3$ (400 mL). The filtrate was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (95:5 $CHCl_3$/MeOH) to give the title compound (19.50 g, 76%) as a white sticky foam: TLC (silica, 5% MeOH in $CHCl_3$) R_f 0.52; MS (ES) m/e 466.3 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, 1H), 7.34 (t, 1H), 7.02 (d, J=9.2 Hz, 1H), 6.81 (m, 2H), 6.54 (t, 1H), 6.46 (m, 2H), 5.31 (d, J=16.5 Hz, 1H), 4.23-4.13 (m, 2H), 4.17 (d, J=16.5 Hz, 1H), 4.02 (t, 2H), 3.82 (m, 1H), 3.58 (s, 3H), 3.36 (m, 2H), 3.01 (dd, 1H), 2.72 (dd, 1H), 2.68 (dd, 1H), 2.50 (dd, 1H), 1.96 (ddd, 2H).

c) (S)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

To a stirred solution of methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (19.50 g, 42 mmol)

in dioxane (150 mL) was added aqueous 1 N NaOH (75 mL, 75 mmol). The cloudy reaction was stirred at RT for 2 h, then the resulting homogeneous solution was neutralized with aqueous 1 N HCl (75 mL, 75 mmol). The solution was concentrated to near dryness by rotary evaporation to precipitate out the product. The supernatant was decanted off and the remaining gummy solid was redissolved in methanol. The clear solution was then reconcentrated by rotary evaporation. The remaining solid was triturated with a small volume of water, filtered and dried under vacuum to give the title compound (16.38 g, 86%) as a white powder. HPLC (Hamilton PRP-1®, 25% CH_3CN/H_2O containing 0.1% TFA) k'=3.1; $[\alpha]_D$ -112.3° (c, 1.0, MeOH); MS (ES) m/e 452.3 $(M+H)^+$; . ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (dd, 1H), 7.34 (dt, 1H), 7.02 (d, J=9.2 Hz, 1H), 6.81 (m, 2H), 6.58 (t, 1H), 6.47 (m, 2H), 5.30 (d, J=16.5 Hz, 1H), 4.27-4.13 (m, 2H), 4.15 (d, J=16.5 Hz, 1H), 4.02 (t, 1H), 3.78 (m, 1H), 3.37 (m, 2H), 3.00 (dd, 1 H), 2.69 (dd, 1H), 2.65 (dd, 1H), 2.41 (dd, 1H), 1.96 (ddd, 2 H). Anal. Calcd for $C_{22}H_{24}F_3N_3O_4$: C, 58.53; H, 5.36; N, 9.31. Found: C, 58.37; H, 5.42; N, 9.20.

Biological Data: Effect of the compounds described in Examples 1 and 3 on choroidal neovascularization (CNV) in a mouse model for CNV.

The mice in the following examples were treated in compliance with the ARVO statement for the Use of Animals in Ophthalmic and Vision Research.

Example 4: Regression Model for CNV

Mice were anesthetized and the pupils were dilated. Burns of krypton laser photocoagulation were delivered to the retina. Administration of the compound described in Example 1 was initiated seven days after the laser-induced injury. Oral doses of either the vehicle alone or vehicle containing the compound of formula (I) (designated as VEGF R in Figure 1) at a dose or 4 mg/kg, 20 mg/kg, or 100 mg/kg were administered twice daily for seven days. After seven day of treatment, the mice were perfused with fluorescein-labeled dextran, and the area of choroidal neovascularization was quantitated. Pazopanib decreased the CNV area in a dose-specific manner. See Figure 1.

Example 5: Prevention Model for CNV

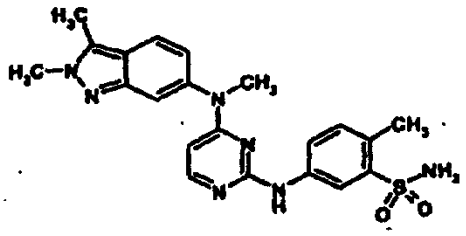
In this experiment, the compound described in Example 1 (Designated as VEGF R in Figure 2), Example 3 (designated as vitronectin in Figure 2), or a combination of the compounds described in Example 1 and Example 3 (designated as "both" in Figure

2) were administered to each mouse beginning one day before retinal burning was performed according to the methods described in Example 4. The compounds were administered orally twice daily at a dosage of 100 mg/kg for the compound of Example 1 or 45 mg/kg for the compound of Example 3. Fourteen days after the retinal burning, the CNV area was quantitated as described above. The results are shown in Figure 2.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

Claims

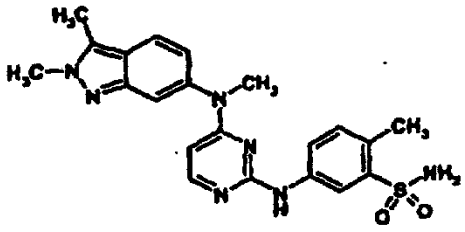
1. A topical pharmaceutical formulation comprising a compound of formula (I):



(I)

or salt or solvate thereof for use in the treatment of ocular neovascular disorders by direct administration to the eye.

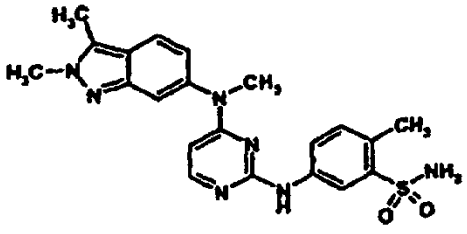
2. A topical formulation for use according to claim 1 wherein said compound is the compound of formula (I'):



HCl

(I').

3. A topical formulation for use according to claims 1 and 2 wherein said compound is the compound of formula (I''):



$HCl \cdot H_2O$ (I'').

4. A topical formulation for use according to claims 1-3 in the form of eye drops, wherein the compound of formula 1, 1'; or 1'' is dissolved or suspended in a suitable carrier.

5. A topical formulation for use according to claims 1-4 for administering in conjunction with one or more additional therapeutic agents for the treatment of neovascular disorders.

6. A topical formulation for use according to claim 5 wherein the one or more additional therapeutic agent is pegaptanib and/or ranibizumab.

7. A topical formulation for use according to claims 5-6 wherein the one or more additional therapeutic agents are administered separately.

8. A topical formulation for use according to claim 7 wherein the one or more additional therapeutic agents are administered by different means.

9. A topical formulation for use according o claims 1-8 wherein the ocular neovascular disorder is a choroidal neovascular disorder or a retinal neovascular disorders.

10. A topical formulation for use according to claim 9 wherein the ocular neovascular disorder is exudative age-related macular degeneration (AMD), angiod streaks, pathological myopia, ocular histoplasmosis syndrome, breaks in Bruch's membrane, macular edema (including diabetic macular edema), sarcoidosis, uveitis, atrophic AMD, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, proliferative vitreoretinopathy, retinopathy of prematurity, retinal degeneration, chronic glaucoma, retinal detachment, or sickle cell retinpathy.

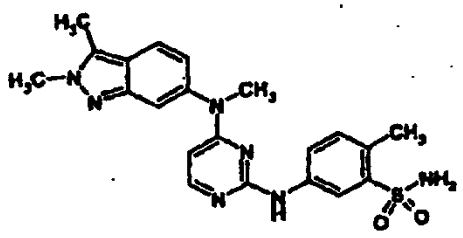
11. A topical formulation for use according to claim 10 wherein the ocular neovascular disorder is exudative age-related macular degeneration (AMD).

12. A topical formulation for use according to any of claims 1-11 for prevention of ocular neovascular disorders.

13. A topical formulation for use according to any of claims 1-11 for healing ocular neovascular disorders.

14. A topical formulation for use according to any of claims 1-11 for decreasing the rate of advancement of the disorder.

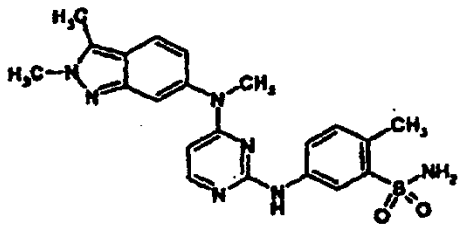
15. Use of a compound of formula (I):-



(I)

or a salt or solvate thereof in the manufacture of a medicament for treatment of ocular neovascular disorders by topical application direct to the eye.

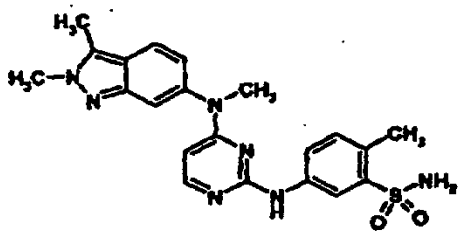
16. Use according to claim 15 wherein said compound is the compound of formula (I'):



HCl

(I').

17. Use according to claims 15-16 wherein said compound is the compound of formula (I"):



HCl • H_2O (I").

18. Use according to claims 15-17 wherein the medicament is in the form of eye drops, wherein the compound of formula 1 1' or 1" is dissolved or suspended in suitable solvent.

19. Use according to claims 15-18 wherein the medicament is administered in conjunction with one or more additional therapeutic agents for the treatment of neovascular disorders.

20. Use according to claim 19 wherein the one or more additional therapeutic agent is pegaptanib and/or ranibizumab.

21. Use according to claims 19-20 wherein the one or more additional therapeutic agents are administered separately.

22. Use according to claim 21 wherein the one or more additional therapeutic agents are administered by different means.

23. Use according to claims 15-22 wherein the ocular neovascular disorder is a choroidal neovascular disorder or a retinal neovascular disorder.

24. Use according to claim 23 wherein the ocular neovascular disorder is exudative age-related macular degeneration (AMD), angiod streaks, pathological myopia, ocular histoplasmosis syndrome, breaks in Bruch's membrane, macular edema (including diabetic macular edema), sarcoidosis, uveitis, atrophic AMD, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, proliferative vitreoretinopathy, retinopathy of prematurity, retinal degeneration, chronic glaucoma, retinal detachment, or sickle cell retinpathy.

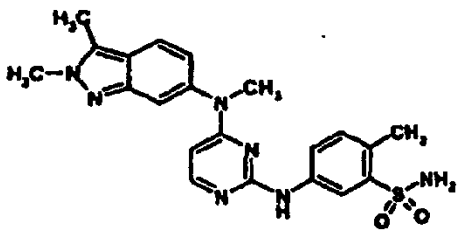
25. Use according to claim 24 wherein the ocular neovascular disorder is age-related macular degeneration (AMD).

26. Use according to any of claims 15-25 wherein the treatment is prevention of ocular neovascular disorders.

27. Use according to any of claims 15-25 wherein the treatment is healing ocular neovascular disorders.

28. Use according to any of claims 15-25 wherein the treatment is decreasing the rate of advancement of the disorder.

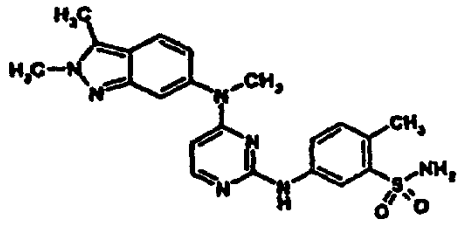
29. A compound of formula (I) or a salt or solvate thereof:



(I)

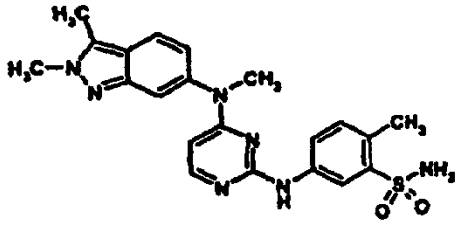
for use in the treatment of ocular neovascular disorders by topical administration directly to the eye.

30. A compound for use according to claim 29 of formula I':



HCl (I')

31. A compound for use according to claims 29-30 of formula I":



HCl • H_2O (I")