# 2-(1H-INDAZOL-6-YLAMINO)- BENZAMIDE COMPOUNDS AS PROTEIN KINASES INHIBITORS USEFUL FOR THE TREATMENT OF OPHTHALMIC DISEASES

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 60/434,902, filed December 19, 2002, herein incorporated by reference in its entirety for all purposes.

## FIELD OF THE INVENTION

This invention is directed to indazole compounds that mediate and/or inhibit ophthalmic diseases and the activity of certain protein kinases, and to pharmaceutical compositions containing such compounds. The invention is also directed to the therapeutic or prophylactic use of such compounds and compositions, and to methods of treating ophthalmic diseases and cancer as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, by administering effective amounts of such compounds.

## BACKGROUND OF THE INVENTION

Several diseases and conditions of the posterior segment of the eye threaten vision. Age related macular degeneration (ARMD or AMD), choroidal neovascularization (CNV), retinopathies (e.g., diabetic retinopathy, vitreoretinopathy, retinopathy of prematurity), retinitis (e.g., cytomegalovirus (CMV) retinitis), uveitis, macular edema, and glaucoma are several examples.

Age related macular degeneration (ARMD or AMD) is the leading cause of blindness in the elderly. ARMD attacks the center of vision and blurs it, making reading, driving, and other detailed tasks difficult or impossible. About 200,000 new cases of ARMD occur each year in the United States alone. Current estimates reveal that approximately forty percent of the population over age 75, and approximately twenty percent of the population over age 60, suffer from some degree of macular degeneration. "Wet" ARMD is the type of ARMD that most often causes blindness. In wet ARMD, newly formed choroidal blood vessels (choroidal neovascularization (CNV)) leak fluid and cause progressive damage to the retina. In the particular case of CNV in ARMD, two main methods of treatment are currently being developed, (a) photocoagulation and (b) the use of angiogenesis inhibitors.

However, photocoagulation can be harmful to the retina and is impractical when the CNV is in proximity of the fovea. Furthermore, photocoagulation often results in recurrent CNV over time. Oral administration of anti-angiogenic compounds is also being tested as a systemic treatment for ARMD. However, due to drug-specific metabolic restrictions, systemic administration usually provides sub-therapeutic drug levels to the

eye. Therefore, to achieve effective intraocular drug concentrations, either an unacceptably high dose or repetitive conventional doses are required. Various implants have also been developed for delivery of anti-angiogenic compounds locally to the eye. Examples of such implants are disclosed in U.S. Pat. Nos. 5,824,072 to Wong, U.S. Pat. No. 5,476,511 to Gwon et al., and U.S. Pat. No. 5,773,019 to Ashton et al., each of which is herein incorporated by reference in their entireties for all purposes.

Neovascular Diseases of the Eye

As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

Briefly, corneal neovascularization as a result of injury to the anterior segment is a significant cause of decreased visual acuity and blindness, and a major risk factor for rejection of corneal allografts. As described by Burger et al., Lab. Invest. 48:169-180, 1983, herein incorporated by reference in its entirety for all purposes, corneal angiogenesis involves three phases: a pre-vascular latent period, active neovascularization, and vascular maturation and regression. The identity and mechanism of various angiogenic factors, including elements of the inflammatory response, such as leukocytes, platelets, cytokines, and eicosanoids, or unidentified plasma constituents have yet to be revealed.

Currently no clinically satisfactory therapy exists for inhibition of corneal neovascularization or regression of existing corneal new vessels. Topical corticosteroids appear to have some clinical utility, presumably by limiting stromal inflammation.

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates.

Blood vessels can enter the cornea in a variety of patterns and depths, depending upon the process which incites the neovascularization. These patterns have been traditionally defined by ophthalmologists in the following types: pannus trachomatosus, pannus leprosus, pannus phylctenulosus, pannus degenerativus, and glaucomatous

pannus. The corneal stroma may also be invaded by branches of the anterior ciliary artery (called interstitial vascularization) which causes several distinct clinical lesions: terminal loops, a "brush-like" pattern, an umbel form, a lattice form, interstitial arcades (from episcleral vessels), and aberrant irregular vessels.

A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

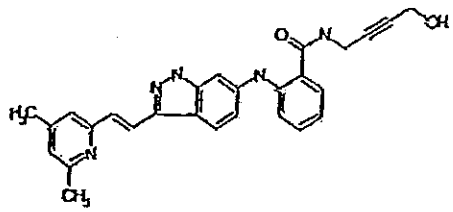
While the cause of corneal neovascularization may vary, the response of the cornea to the insult and the subsequent vascular ingrowth is similar regardless of the cause. Briefly, the location of the injury appears to be of importance as only those lesions situated within a critical distance of the limbus will incite an angiogenic response. This is likely due to the fact that the angiogenic factors responsible for eliciting the vascular invasion are created at the site of the lesion, and must diffuse to the site of the nearest blood vessels (the limbus) in order to exert their effect. Past a certain distance from the limbus, this would no longer be possible and the limbic endothelium would not be induced to grow into the cornea. Several angiogenic factors are likely involved in this process, many of which are products of the inflammatory response. Indeed, neovascularization of the cornea appears to only occur in association with an inflammatory cell infiltrate, and the degree of angiogenesis is proportional to the extent of the inflammatory reaction. Corneal edema further facilitates blood vessel ingrowth by loosening the corneal stromal framework and providing a pathway of "least resistance" through which the capillaries can grow.

Following the initial inflammatory reaction, capillary growth into the cornea proceeds in the same manner as it occurs in other tissues. The normally quiescent endothelial cells of the limbic capillaries and venules are stimulated to divide and migrate. The endothelial cells project away from their vessels of origin, digest the surrounding basement membrane and the tissue through which they will travel, and migrate towards the source of the angiogenic stimulus. The blind ended sprouts acquire a lumen and then anastomose together to form capillary loops. The end result is the establishment of a vascular plexus within the corneal stroma.

Anti-angiogenic factors and compositions of the present invention are useful by blocking the stimulatory effects of angiogenesis promoters, reducing endothelial cell division, decreasing endothelial cell migration, and impairing the activity of the proteolytic enzymes secreted by the endothelium.

## SUMMARY OF THE INVENTION

In a first aspect, there is provided a compound represented by the formula



or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided a pharmaceutical composition comprising:

a) a therapeutically effective amount of a compound or pharmaceutically acceptable salt as defined above; and

b) a pharmaceutically acceptable carrier, diluent, or vehicle therefor.

In a third aspect, there is provided a method of modulating the activity of a protein kinase receptor, comprising contacting the kinase receptor with an effective amount of a compound or pharmaceutically acceptable salt as defined above.

Within particularly preferred embodiments of the invention, an anti-angiogenic factor may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The anti-angiogenic factor solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea.

Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy.

Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the anti-angiogenic compositions described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. Asteroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Disclosed herein are methods for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic composition to the eye, such that the formation of blood vessels can be inhibited.

Briefly, neovascular glaucoma is a pathological condition wherein new capillaries develop in the iris of the eye. The angiogenesis usually originates from vessels located at the pupillary margin, and progresses across the root of the iris and into the trabecular

meshwork. Fibroblasts and other connective tissue elements are associated with the capillary growth and a fibrovascular membrane develops which spreads across the anterior surface of the iris. Eventually this tissue reaches the anterior chamber angle where it forms synechiae. These synechiae in turn coalesce, scar, and contract to ultimately close off the anterior chamber angle. The scar formation prevents adequate drainage of aqueous humor through the angle and into the trabecular meshwork, resulting in an increase in intraocular pressure that may result in blindness.

Neovascular glaucoma generally occurs as a complication of diseases in which retinal ischemia is predominant. In particular, about one third of the patients with this disorder have diabetic retinopathy and 28% have central retinal vein occlusion. Other causes include chronic retinal detachment, end-stage glaucoma, carotid artery obstructive disease, retrolental fibroplasia, sickle-cell anemia, intraocular tumors, and carotid cavernous fistulas. In its early stages, neovascular glaucoma may be diagnosed by high magnification slitlamp biomicroscopy, where it reveals small, dilated, disorganized capillaries (which leak fluorescein) on the surface of the iris. Later gonioscopy demonstrates progressive obliteration of the anterior chamber angle by fibrovascular bands. While the anterior chamber angle is still open, conservative therapies may be of assistance. However, once the angle closes surgical intervention is required in order to alleviate the pressure.

Therefore, within one embodiment of the invention anti-angiogenic factors (either alone or in an anti-angiogenic composition, as described above) may be administered topically to the eye in order to treat early forms of neovascular glaucoma.

Within other embodiments of the invention, anti-angiogenic compositions may be implanted by injection of the composition into the region of the anterior chamber angle. This can provide a sustained localized increase of anti-angiogenic factor, and can further prevent blood vessel growth into the area. Implanted or injected anti-angiogenic compositions which are placed between the advancing capillaries of the iris and the anterior chamber angle can "defend" the open angle from neovascularization. As capillaries will not grow within a significant radius of the anti-angiogenic composition, patency of the angle could be maintained. Within other embodiments, the anti-angiogenic composition may also be placed in any location such that the anti-angiogenic factor is continuously released into the aqueous humor. This would increase the anti-angiogenic factor concentration within the humor, which in turn bathes the surface of the iris and its abnormal capillaries, thereby providing another mechanism by which to deliver the medication. These therapeutic modalities may also be useful prophylactically and in combination with existing treatments.

Disclosed herein are methods for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a

therapeutically effective amount of an anti-angiogenic composition to the eyes, such that the formation of blood vessels is inhibited.

Briefly, the pathology of diabetic retinopathy is thought to be similar to that described above for neovascular glaucoma. In particular, background diabetic retinopathy is believed to convert to proliferative diabetic retinopathy under the influence of retinal hypoxia. Generally, neovascular tissue sprouts from the optic nerve (usually within 10 mm of the edge), and from the surface of the retina in regions where tissue perfusion is poor. Initially the capillaries grow between the inner limiting membrane of the retina and the posterior surface of the vitreous. Eventually, the vessels grow into the vitreous and through the inner limiting membrane. As the vitreous contracts, traction is applied to the vessels, often resulting in shearing of the vessels and blinding of the vitreous due to hemorrhage. Fibrous traction from scarring in the retina may also produce retinal detachment.

The conventional therapy of choice is panretinal photocoagulation to decrease retinal tissue, and thereby decrease retinal oxygen demands. Although initially effective, there is a high relapse rate with new lesions forming in other parts of the retina. Complications of this therapy include a decrease in peripheral vision of up to 50% of patients, mechanical abrasions of the cornea, laser-induced cataract formation, acute glaucoma, and stimulation of subretinal neovascular growth (which can result in loss of vision). As a result, this procedure is performed only when several risk factors are present, and the risk-benefit ratio is clearly in favor of intervention.

Therefore, within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection of an anti-angiogenic factor(s) (or anti-angiogenic composition) into the aqueous humor or the vitreous, in order to increase the local concentration of anti-angiogenic factor in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation. Within other embodiments of the invention, arteries which feed the neovascular lesions may be embolized (utilizing anti-angiogenic compositions, as described above).

Methods for treating retrolental fibroblasia, comprising the step of administering to a patient a therapeutically effective amount of an anti-angiogenic factor (or anti-angiogenic composition) to the eye, such that the formation of blood vessels can be inhibited are disclosed.

Briefly, retrolental fibroblasia is a condition occurring in premature infants who receive oxygen therapy. The peripheral retinal vasculature, particularly on the temporal side, does not become fully formed until the end of fetal life. Excessive oxygen (even levels which would be physiologic at term) and the formation of oxygen free radicals are thought to be important by causing damage to the blood vessels of the immature retina.

These vessels constrict, and then become structurally obliterated on exposure to oxygen. As a result, the peripheral retina fails to vascularize and retinal ischemia ensues. In response to the ischemia, neovascularization is induced at the junction of the normal and the ischemic retina.

In 75% of the cases these vessels regress spontaneously. However, in the remaining 25% there is continued capillary growth, contraction of the fibrovascular component, and traction on both the vessels and the retina. This results in vitreous hemorrhage and/or retinal detachment which can lead to blindness. Neovascular angle-closure glaucoma is also a complication of this condition.

As it is often impossible to determine which cases will spontaneously resolve and which will progress in severity, conventional treatment (i.e., surgery) is generally initiated only in patients with established disease and a well developed pathology. This "wait and see" approach precludes early intervention, and allows the progression of disease in the 25% who follow a complicated course. Therefore, within one embodiment of the invention, topical administration of anti-angiogenic factors (or anti-angiogenic compositions, as described above) may be accomplished in infants which are at high risk for developing this condition in an attempt to cut down on the incidence of progression of retrolental fibroplasia. Within other embodiments, intravitreous injections and/or intraocular implants of an anti-angiogenic composition may be utilized. Such methods are particularly preferred in cases of established disease, in order to reduce the need for surgery.

Protein Kinases

Protein kinases are a family of enzymes that catalyze phosphorylation of the hydroxyl group of specific tyrosine, serine, or threonine residues in proteins. Typically, such phosphorylation dramatically perturbs the function of the protein, and thus protein kinases are pivotal in the regulation of a wide variety of cellular processes, including metabolis m, cell proliferation, cell differentiation, and cell survival. Of the many different cellular functions in which the activity of protein kinases is known to be required, some processes represent attractive targets for therapeutic intervention for certain disease states. Two examples are angiogenesis and cell-cycle control, in which protein kinases play a pivotal role; these processes are essential for the growth of solid tumors as well as for other diseases.

Angiogenesis is the mechanism by which new capillaries are formed from existing vessels. When required, the vascular system has the potential to generate new capillary networks in order to maintain the proper functioning of tissues and organs. In the adult, however, angiogenesis is fairly limited, occurring only in the process of wound healing and neovascularization of the endometrium during menstruation. See Merenmies et al., *Cell Growth & Differentiation*, 8, 3-10 (1997), herein incorporated by reference in its entirety for

all purposes. On the other hand, unwanted angiogenesis is a hallmark of several diseases, such as retinopathies, psoriasis, rheumatoid arthritis, age-related macular degeneration (AMD), and cancer (solid tumors). Folkman, *Nature Med.*, 1, 27-31 (1995), herein incorporated by reference in its entirety for all purposes. Protein kinases which have been shown to be involved in the angiogenic process include three members of the growth factor receptor tyrosine kinase family: VEGF-R2 (vascular endothelial growth factor receptor 2, also known as KDR (kinase insert domain receptor) and as FLK-1); FGF-R (fibroblast growth factor receptor); and TEK (also known as Tie-2).

VEGF-R2, which is expressed only on endothelial cells, binds the potent angiogenic growth factor VEGF and mediates the subsequent signal transduction through activation of its intracellular kinase activity. Thus, it is expected that direct inhibition of the kinase activity of VEGF-R2 will result in the reduction of angiogenesis even in the presence of exogenous VEGF (see Strawn et al., *Cancer Research*, 56, 3540-3545 (1996)), as has been shown with mutants of VEGF-R2 which fail to mediate signal transduction. Millauer et al., *Cancer Research*, 56, 1615-1620 (1996). Furthermore, VEGF-R2 appears to have no function in the adult beyond that of mediating the angiogenic activity of VEGF. Therefore, a selective inhibitor of the kinase activity of VEGF-R2 would be expected to exhibit little toxicity.

Similarly, FGF-R binds the angiogenic growth factors aFGF and bFGF and mediates subsequent intracellular signal transduction. Recently, it has been suggested that growth factors such as bFGF may play a critical role in inducing angiogenesis in solid tumors that have reached a certain size. Yoshiji et al., *Cancer Research*, 57, 3924-3928 (1997). Unlike VEGF-R2, however, FGF-R is expressed in a number of different cell types throughout the body and may or may not play important roles in other normal physiological processes in the adult. Nonetheless, systemic administration of a small-molecule inhibitor of the kinase activity of FGF-R has been reported to block bFGF-induced angiogenesis in mice without apparent toxicity. Mohammad et al., *EMBO Journal*, 17, 5996-5904 (1998).

TEK (also known as Tie-2) is another receptor tyrosine kinase expressed only on endothelial cells which has been shown to play a role in angiogenesis. The binding of the factor angiopoietin-1 results in autophosphorylation of the kinase domain of TEK and results in a signal transduction process which appears to mediate the interaction of endothelial cells with peri-endothelial support cells, thereby facilitating the maturation of newly formed blood vessels. The factor angiopoietin-2, on the other hand, appears to antagonize the action of angiopoietin-1 on TEK and disrupts angiogenesis. Maisonpierre et al., *Science*, 277, 55-60 (1997).

As a result of the above-described developments, it has been proposed to treat angiogenesis by the use of compounds inhibiting the kinase activity of VEGF-R2, FGF-R, and/or TEK. For example, WIPO International Publication No. WO 97/34876 discloses certain cinnoline derivatives that are inhibitors of VEGF-R2, which may be used for the treatment of disease states associated with abnormal angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, arterial restinosis, autoimmune diseases, acute inflammation, and ocular diseases with retinal vessel proliferation.

Phosphorylase kinase activates glycogen phosphorylase, thus increasing glycogen breakdown and hepatic glucose release. Hepatic glucose production is disregulated in type 2 diabetes, and is the primary cause of fasting hyperglycemia, which results in many of the secondary complications afflicting these patients. Thus, reduction in glucose release from the liver would lower elevated plasma glucose levels. Inhibitors of phosphorylase kinase should therefore decrease phosphorylase activity and glycogenolysis, thus reducing hyperglycemia in patients.

Another physiological response to VEGF is vascular hyperpermeability, which has been proposed to play a role in the early stages of angiogenesis. In ischemic tissues, such as those occurring in the brain of stroke victims, hypoxia trigger VEGF expression, leading to increased vascular permeability and ultimately edema in the surrounding tissues. In a rat model for stroke, it has been shown by van Bruggen et al., *J. Clinical Invest.*, 104, 1613-20 (1999) that administration of a monoclonal antibody to VEGF reduces the infarct volume. Thus, inhibitors of VEGFR are anticipated to be useful for the treatment of stroke.

In addition to its role in angiogenesis, protein kinases also play a crucial role in cell-cycle control. Uncontrolled cell proliferation is the insignia of cancer. Cell proliferation in response to various stimuli is manifested by a de-regulation of the cell division cycle, the process by which cells multiply and divide. Tumor cells typically have damage to the genes that directly or indirectly regulate progression through the cell division cycle.

Cyclin-dependent kinases (CDKs) are serine-threonine protein kinases that play critical roles in regulating the transitions between different phases of the cell cycle. See, e.g., the articles compiled in *Science*, 274, 1643-1677 (1996). CDK complexes are formed through association of a regulatory cyclin subunit (e.g., cyclin A, B1, B2, D1, D2, D3, and E) and a catalytic kinase subunit (e.g., cdc2 (CDK1), CDK2, CDK4, CDK5, and CDK6). As the name implies, the CDKs display an absolute dependence on the cyclin subunit in order to phosphorylate their target substrates, and different kinase/cyclin pairs function to regulate progression through specific phases of the cell cycle.

It is CDK4 complexed to the D cyclins that plays a critical part in initiating the cell-division cycle from a resting or quiescent stage to one in which cells become committed to cell division. This progression is subject to a variety of growth regulatory mechanisms, both negative and positive. Aberrations in this control system, particularly those that affect the function of CDK4, have been implicated in the advancement of cells to the highly proliferative state characteristic of malignancies, particularly familial melanomas, esophageal carcinomas, and pancreatic cancers. See, e.g., Kamb, *Trends in Genetics*, 11, 136-140 (1995); Kamb et al., *Science*, 264, 436-440 (1994).

Myriad publications describe a variety of chemical compounds useful against a variety of therapeutic targets. For example, WIPO International Publication Nos. WO 99/23077 and WO 99/23076 describe indazole-containing compounds having phosphodiesterase type IV inhibitory activity produced by an indazole-for-catechol bioisostere replacement. U.S. Patent No. 5,760,028 discloses heterocycles including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2-(benzyloxycarbonylamino)propionic acid, which are useful as antagonists of the $\alpha_v\beta_3$ integrin and related cell surface adhesive protein receptors. WIPO International Publication No. WO 98/09961 discloses certain indazole derivatives and their use as inhibitors of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal. Recent additions to the virtual library of known compounds include those described as being anti-proliferative therapeutic agents that inhibit CDKs. For example, U.S. Patent No. 5,621,082 to Xiong et al. discloses nucleic acid encoding an inhibitor of CDK6, and European Patent Publication No. 0 666 270 A2 describes peptides and peptide mimetics that act as inhibitors of CDK1 and CDK2. WIPO International Publication No. WO 97/16447 discloses certain analogs of chromones that are inhibitors of cyclin-dependent kinases, in particular of CDK/cyclin complexes such as CDK4/cyclin D1, which may be used for inhibiting excessive or abnormal cell proliferation, and therefore for treating cancer. WIPO International Publication No. WO 99/21845 describes 4-aminothiazole derivatives that are useful as CDK inhibitors. Each of the above listed patents and/or application is herein incorporated by reference in their entireties for all purposes.

There is still a need, however, for small-molecule compounds that may be readily synthesized and are effective in inhibiting one or more CDKs or CDK/cyclin complexes. Because CDK4 may serve as a general activator of cell division in most cells, and complexes of CDK4 and D-type cyclins govern the early $G_1$ phase of the cell cycle, there is a need for effective inhibitors of CDK4, and D-type cyclin complexes thereof, for treating one or more types of tumors. Also, the pivotal roles of cyclin E/CDK2 and cyclin B/CDK1

kinases in the $G_1$/S phase and $G_2$/M transitions, respectively, offer additional targets for therapeutic intervention in suppressing deregulated cell-cycle progression in cancer.

Another protein kinase, CHK1, plays an important role as a checkpoint in cell-cycle progression. Checkpoints are control systems that coordinate cell-cycle progression by influencing the formation, activation and subsequent inactivation of the cyclin-dependent kinases. Checkpoints prevent cell-cycle progression at inappropriate times, maintain the metabolic balance of cells while the cell is arrested, and in some instances can induce apoptosis (programmed cell death) when the requirements of the checkpoint have not been met. See, e.g., O'Connor, *Cancer Surveys*, 29, 151-182 (1997); Nurse, *Cell*, 91, 865-867 (1997); Hartwell et al., *Science*, 266, 1821-1828 (1994); Hartwell et al., *Science*, 246, 629-634 (1989).

One series of checkpoints monitors the integrity of the genome and, upon sensing DNA damage, these "DNA damage checkpoints" block cell-cycle progression in $G_1$ and $G_2$ phases, and slow progression through S phase. O'Connor, *Cancer Surveys*, 29, 151-182 (1997); Hartwell et al., *Science*, 266, 1821-1828 (1994). This action enables DNA repair processes to complete their tasks before replication of the genome and subsequent separation of this genetic material into new daughter cells takes place. Importantly, the most commonly mutated gene in human cancer, the p53 tumor suppressor gene, produces a DNA damage checkpoint protein that blocks cell-cycle progression in $G_1$ phase and/or induces apoptosis (programmed cell death) following DNA damage. Hartwell et al., *Science*, 266, 1821-1828 (1994). The p53 tumor suppressor has also been shown to strengthen the action of a DNA damage checkpoint in $G_2$ phase of the cell cycle. See, e.g., Bunz et al., *Science*, 28, 1497-1501 (1998); Winters et al., *Oncogene*, 17, 673-684 (1998); Thompson, *Oncogene*, 15, 3025-3035 (1997).

Given the pivotal nature of the p53 tumor suppressor pathway in human cancer, therapeutic interventions that exploit vulnerabilities in p53-defective cancer have been actively sought. One emerging vulnerability lies in the operation of the $G_2$ checkpoint in p53 defective cancer cells. Cancer cells, because they lack $G_1$ checkpoint control, are particularly vulnerable to abrogation of the last remaining barrier protecting them from the cancer-killing effects of DNA-damaging agents: the $G_2$ checkpoint. The $G_2$ checkpoint is regulated by a control system that has been conserved from yeast to humans. Important in this conserved system is a kinase, CHK1, which transduces signals from the DNA-damage sensory complex to inhibit activation of the cyclin B/Cdc2 kinase, which promotes mitotic entry. See, e.g., Peng et al., *Science*, 277, 1501-1505 (1997); Sanchez et al., *Science*, 277, 1497-1501 (1997). Inactivation of CHK1 has been shown to both abrogate $G_2$ arrest induced by DNA damage inflicted by either anticancer agents or endogenous DNA damage, as well as result in preferential killing of the resulting checkpoint defective

cells. See, e.g., Nurse, *Cell*, 91, 865-867 (1997); Weinert, *Science*, 277, 1450-1451 (1997); Walworth et al., *Nature*, 363, 368-371 (1993); and Al-Khodairy et al., *Molec. Biol. Cell*, 5, 147-160 (1994).

Selective manipulation of checkpoint control in cancer cells could afford broad utilization in cancer chemotherapeutic and radiotherapy regimens and may, in addition, offer a common hallmark of human cancer "genomic instability" to be exploited as the selective basis for the destruction of cancer cells. A number of factors place CHK1 as a pivotal target in DNA-damage checkpoint control. The elucidation of inhibitors of this and functionally related kinases such as Cds1/CHK2, a kinase recently discovered to cooperate with CHK1 in regulating S phase progression (see Zeng et al., *Nature*, 395, 507-510 (1998); Matsuoka, *Science*, 282, 1893-1897 (1998)), could provide valuable new therapeutic entities for the treatment of cancer.

Integrin receptor binding to ECM initiates intracellular signals mediated by FAK (Focal Adhesion Kinase) that are involved in cell motility, cellular proliferation, and survival. In human cancers, FAK overexpression is implicated in tumorigenesis and metastatic potential through its role in integrin mediated signaling pathways.

Tyrosine kinases can be of the receptor type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular). At least one of the non-receptor protein tyrosine kinases, namely, LCK, is believed to mediate the transduction in T-cells of a signal from the interaction of a cell-surface protein (Cd4) with a cross-linked anti-Cd4 antibody. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, *Oncogene*, 8, 2025-2031 (1993), which is incorporated herein by reference in its entirety for all purposes.

In addition to the protein kinases identified above, many other protein kinases have been considered to be therapeutic targets, and numerous publications disclose inhibitors of kinase activity, as reviewed in the following: United States Patent No. 6,534,524, issued March 18, 2003, United States Patent No. 6,531,491, issued March 11, 2003, PCT international patent application publication number WO 00/38665 (published July 6, 2001), PCT international patent application publication number WO 97/49688 (published December 31, 1997), PCT international patent application publication number WO 98/23613 (published June 4, 1998), United States Patent No. 6,071,935 issued June 6, 2000, PCT international patent application publication number WO 96/30347 (published October 3, 1996), PCT international patent application publication number WO 96/40142 (published December 19, 1996), PCT international patent application publication number WO 97/13771 (published April 17, 1997), PCT international patent application publication number WO 95/23141 (published August 31, 1995), PCT international patent application publication number WO 03/006059 (published January 23, 2003), PCT international

patent application publication number WO 03/035047 (published May 1, 2003), PCT international patent application publication number WO 02/064170 (published August 22, 2002), PCT international patent application publication number WO 02/41882 (published May 30, 2002), PCT international patent application publication number WO 02/30453 (published April 18, 2002), PCT international patent application publication number WO 01/85796 (published November 15, 2001), PCT international patent application publication number WO 01/74360 (published October 11, 2001), PCT international patent application publication number WO 01/74296 (published October 11, 2001), PCT international patent application publication number WO 01/70268 (published September 27, 2001), European patent application publication number EP 1086705 (published March 28, 2001), and PCT international patent application publication number WO 98/51344 (published November 19, 1998). The foregoing patents and applications are each incorporated herein by reference in their entirety for all purposes.

There is still a need, however, for effective inhibitors of protein kinases. Moreover, as is understood by those skilled in the art, it is desirable for kinase inhibitors to possess both high affinity for the target kinase or kinases as well as high selectivity versus other protein kinases.

Thus, disclosed herein are potent agents for the treatment of ophthalmic diseases, such as age related macular degeneration (ARMD), choroidal neovascularization (CNV), retinopathies (e.g., diabetic retinopathy, vitreoretinopathy, retinopathy of prematurity), retinitis (e.g., cytomegalovirus (CMV) retinitis), uveitis, macular edema, and glaucoma.

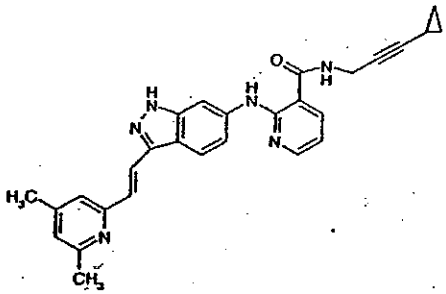
Disclosed further herein are potent inhibitors of protein kinases.

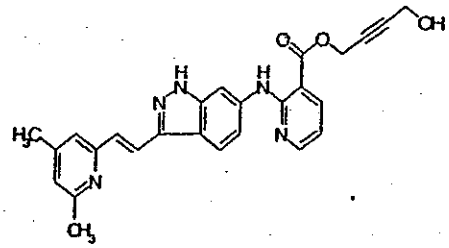
Disclosed yet further herein are kinase inhibitors having a strong and selective affinity for one or more particular kinases.

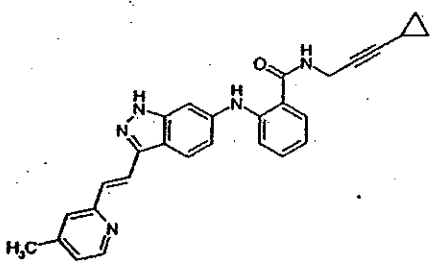
The above can be achieved by the discovery of the indazole compounds, pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts thereof (such compounds, prodrugs, metabolites and salts are collectively referred to as "agents") described below, which modulate and/or inhibit the activity of protein kinases. Pharmaceutical compositions containing such agents are useful in treating diseases mediated by kinase activity, such as cancer, as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis. Further, the agents may have advantageous properties relating to the

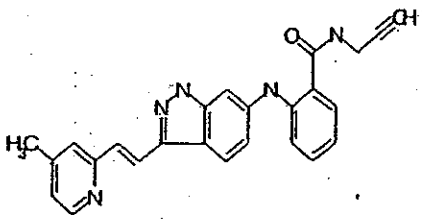
modulation and/or inhibition of the kinase activity associated with VEGF-R, FGF-R, CDK complexes, CHK1, LCK, TEK, FAK, and/or phosphorylase kinase.

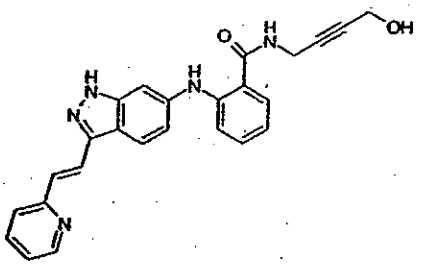
Disclosed herein are compounds having the following structures:

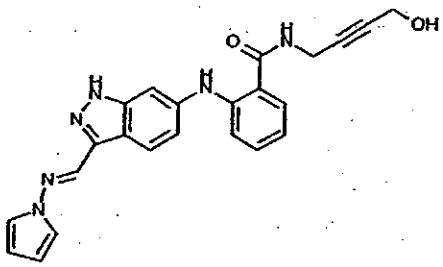


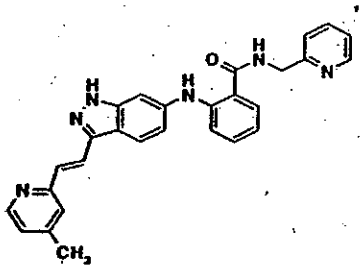


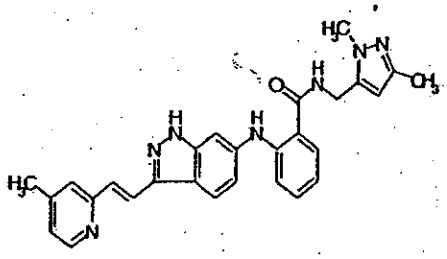


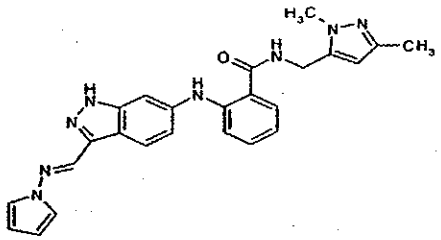


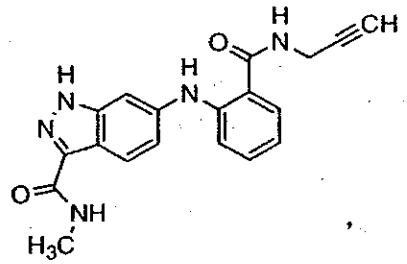


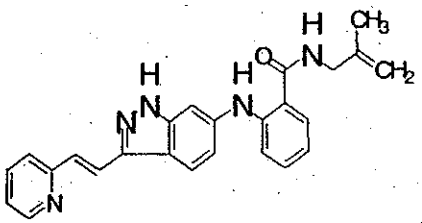


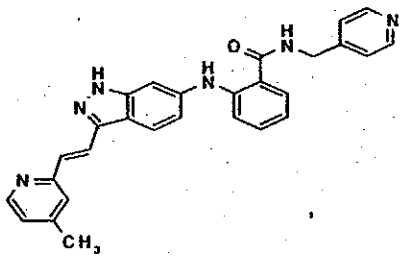


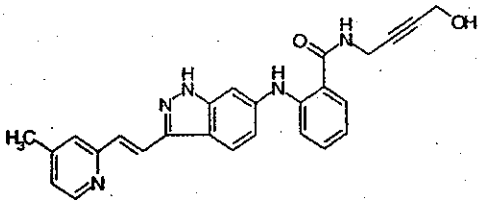


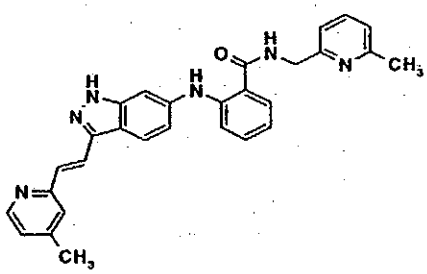


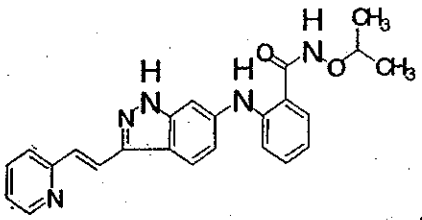


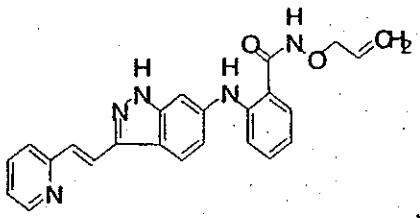


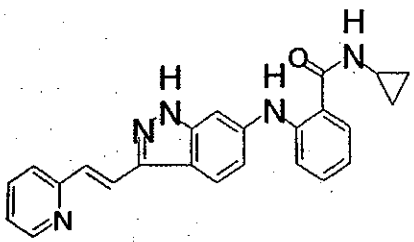


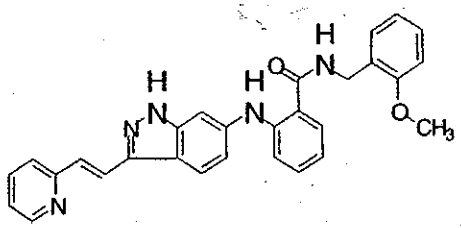


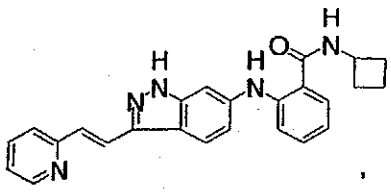


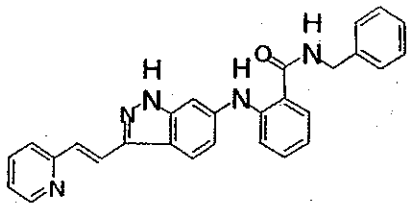


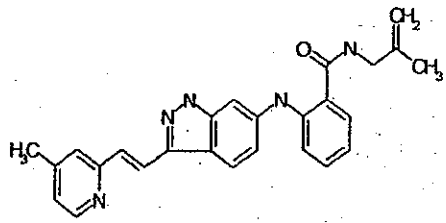


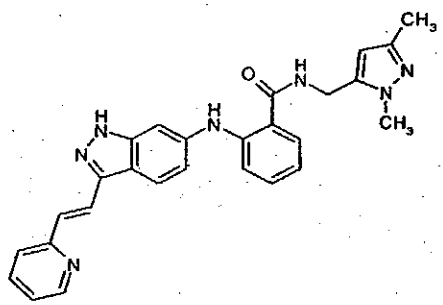


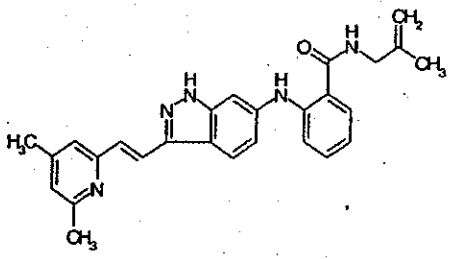


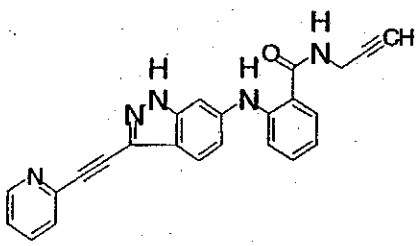


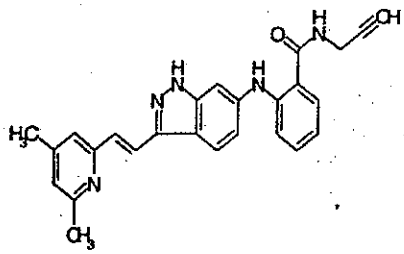


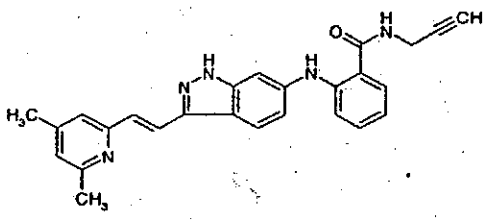


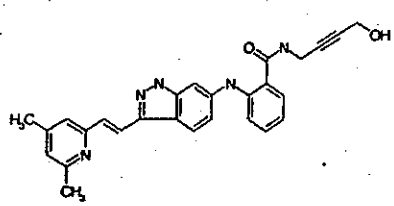


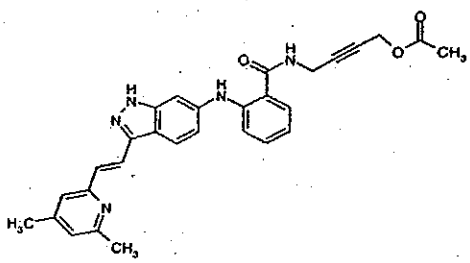


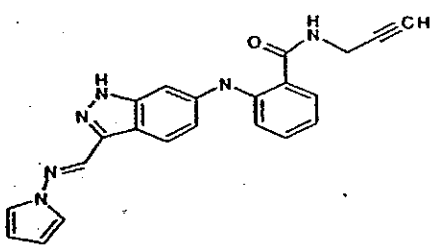


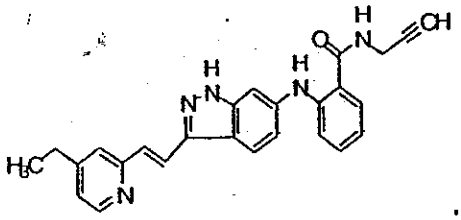


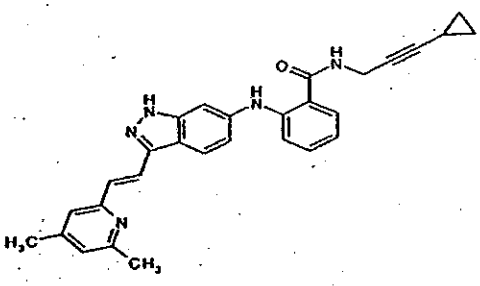


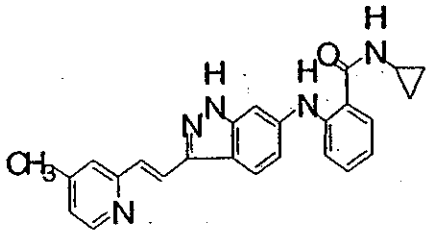


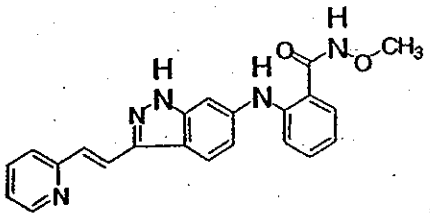


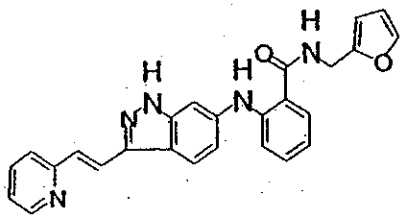


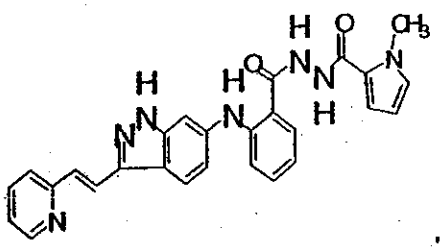


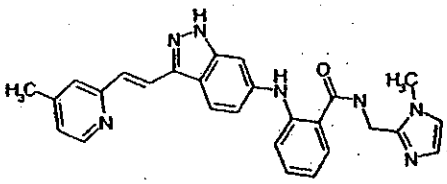


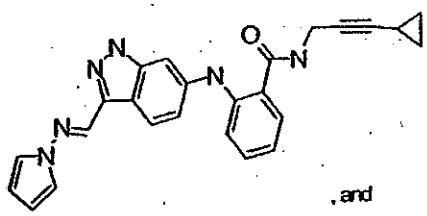












, and

Disclosed further is a method of modulating and/or inhibiting the kinase activity of VEGF-R, FGF-R, a CDK complex, CHK1, LCK, TEK, FAK, and/or phosphorylase kinase by administering a compound of Formula I or a

pharmaceutically acceptable prodrug, pharmaceutically active metabolite, or pharmaceutically acceptable salt thereof. Preferred compounds of the present invention that have selective kinase activity - i.e., they possess significant activity against one or more specific kinases while possessing less or minimal activity against one or more different kinases. In one preferred embodiment of the invention, compounds of the present invention are those of Formula I possessing substantially higher potency against VEGF receptor tyrosine kinase than against FGF-R1 receptor tyrosine kinase. The

In one embodiment there are provided

methods of modulating VEGF receptor tyrosine kinase activity

without significantly modulating FGF receptor tyrosine kinase activity.

The compounds disclosed may be used advantageously in combination with other known therapeutic agents. For example, compounds of Formula I, II, III, or IV which possess antiangiogenic activity may be co-administered with cytotoxic chemotherapeutic agents, such as taxol, taxotere, vinblastine, cis-platin, doxorubicin, adriamycin, and the like, to produce an enhanced antitumor effect. Additive or synergistic enhancement of therapeutic effect may also be obtained by co-administration of compounds of Formula I, II, III, or IV which possess antiangiogenic activity with other antiangiogenic agents, such as combretastatin A-4, endostatin, prinomastat, celecoxib, rofocoxib, EMD121974, IM862, anti-VEGF monoclonal antibodies, and anti-KDR monoclonal antibodies. Additional combinations are exemplified in WO 0038716, WO 00387171, WO 0038715, WO 0038730, WO 0038718, Wo 0038665, WO 0037107, WO 0038786, WO 0038719, all concurrently filed on December 22, 1999, herein incorporated by reference in their entireties for all purposes.

Disclosed herein are pharmaceutical compositions, each comprising

an effective amount of an agent selected from compounds of Formula I and pharmaceutically acceptable salts, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs thereof; and a pharmaceutically acceptable carrier or vehicle for such agent. Disclosed further herein are methods of treating ophthalmic diseases/conditions and cancer as well as other disease states associated with unwanted angiogenesis and/or cellular proliferation, comprising administering effective amounts of such an agent to a patient in need of such treatment.

The compounds of the Formula 1 can be useful for treating

ophthalmic diseases and mediating the activity of protein kinases. More particularly, the compounds are useful as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for ophthalmic diseases and cancer or other diseases associated with cellular proliferation mediated by protein kinases.

The term "alkyl" as used herein refers to straight- and branched-chain alkyl groups having one to twelve carbon atoms. Exemplary alkyl groups include methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (t-Bu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like. The term "lower alkyl" designates an alkyl having from 1 to 8 carbon atoms (a $C_{1-8}$-alkyl). Suitable substituted alkyls include fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and the like.

The term "alkylidene" refers to a divalent radical having one to twelve carbon atoms. Illustrative alkylidene groups include $CH_2$, $CHCH_3$, $(CH_3)_2$, and the like.

The term "alkenyl" refers to straight- and branched-chain alkenyl groups having from two to twelve carbon atoms. Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and the like.

The term "alkynyl" refers to straight- and branched-chain alkynyl groups having from two to twelve carbon atoms.

The term "cycloalkyl" refers to saturated or partially unsaturated carbocycles having from three to twelve carbon atoms, including bicyclic and tricyclic cycloalkyl structures. Suitable cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

A "heterocycloalkyl" group is intended to mean a saturated or partially unsaturated monocyclic radical containing carbon atoms, preferably 4 or 5 ring carbon atoms, and at least one heteroatom selected from nitrogen, oxygen and sulfur.

The terms "aryl" and "heteroaryl" refer to monocyclic and polycyclic unsaturated or aromatic ring structures, with "aryl" referring to those that are carbocycles and "heteroaryl" referring to those that are heterocycles. Examples of aromatic ring structures include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, furyl, thienyl, pyrrolyl, pyridinyl, pyrazolyl, imidazolyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1-H-tetrazol-5-yl, indolyl, quinolinyl, benzofuranyl, benzothiophenyl (thianaphthenyl), and the like. Such moieties may be optionally substituted by a fused-ring structure or bridge, for example $OCH_2O$.

The term "alkoxy" is intended to mean the radical –O-alkyl. Illustrative examples include methoxy, ethoxy, propoxy, and the like.

The term "aryloxy" respresents –O—aryl, wherein aryl is defined above.

The term "cycloalkoxyl" represents –O—cycloalkyl, wherein cycloalkyl is defined above.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

In general, the various moieties or functional groups for variables in the formulae may be optionally substituted by one or more suitable substituents. Exemplary substituents include

a halogen (F, Cl, Br, or I), lower alkyl, -OH, $-NO_2$, -CN, $-CO_2H$, -O-lower alkyl, -aryl, -aryl-lower alkyl, $-CO_2CH_3$, $-CONH_2$, $-OCH_2CONH_2$, $-NH_2$, $-SO_2NH_2$, haloalkyl (e.g., $-CF_3$, $-CH_2CF_3$), -O-haloalkyl (e.g., $-OCF_3$, $-OCHF_2$), and the like.

The terms "comprising" and "including" are used in an open, non-limiting sense.

It is understood that while a compound of Formula I may exhibit the phenomenon of tautomerism, the formula drawings within this specification expressly depict only one of the possible tautomeric forms. It is therefore to be understood that within the invention the formulae are intended to represent any tautomeric form of the depicted compound and is not to be limited merely to a specific tautomeric form depicted by the formula drawings.

Some of the compounds disclosed may exist as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the inventive compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

Additionally, the formulas are intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

In addition to compounds of Formula 1, disclosed herein are pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound.

"A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof.

Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein.

Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. See, e.g., Bertolini, G. et al., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan, D. et al., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe K., *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, N., *Advances in Drug Res.*, 13, 224-331 (1984); Bundgaard, H., *Design of Prodrugs* (Elsevier Press 1985); and Larsen, I. K., *Design and Application of Prodrugs*, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an

inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

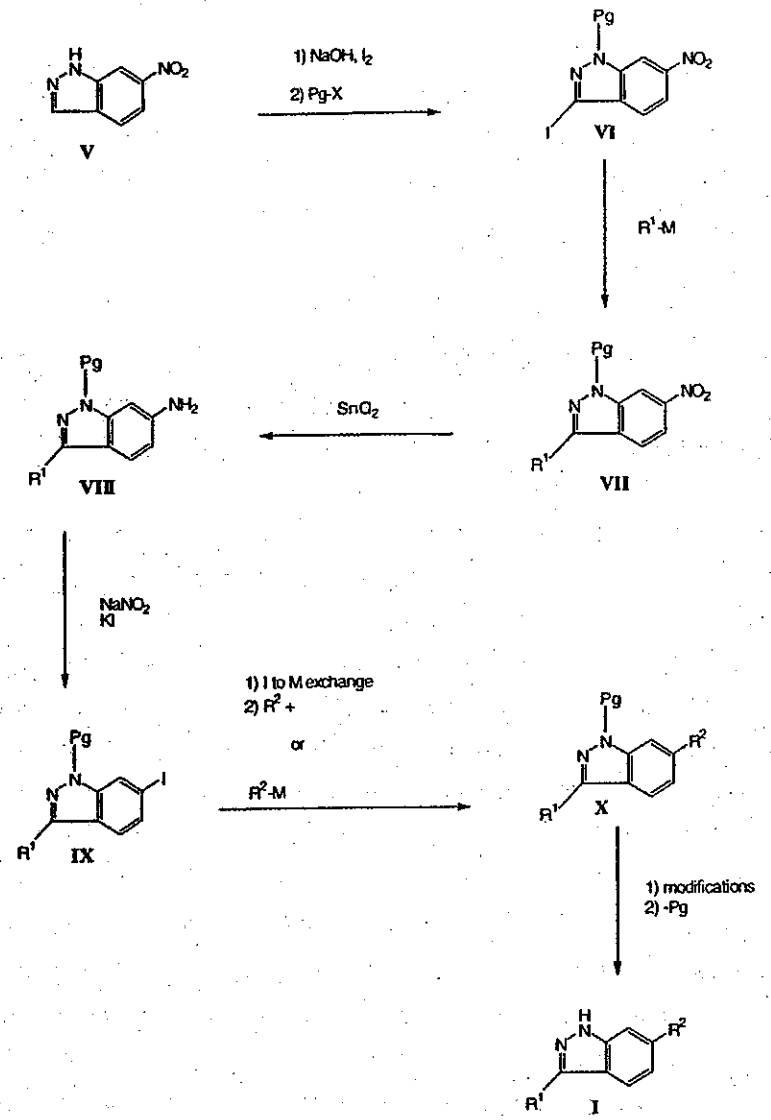
In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

Therapeutically effective amounts of the agents disclosed may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of an agent that, when administered to a mammal in need of such treatment, is sufficient to effect treatment for a disease mediated by the activity of one or more protein kinases, such as tryosine kinases. Thus, e.g., a therapeutically effective amount of a compound of the Formula I, salt, active metabolite or prodrug thereof is a quantity sufficient to modulate, regulate, or inhibit the activity of one or more protein kinases such that a disease condition which is mediated by that activity is reduced or alleviated.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. "Treating" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is affected, at least in part, by the activity of one or more protein kinases, such as tyrosine kinases, and includes: preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

The agents may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available.

In one general synthetic process, compounds of Formula I are prepared according to the following reaction scheme:

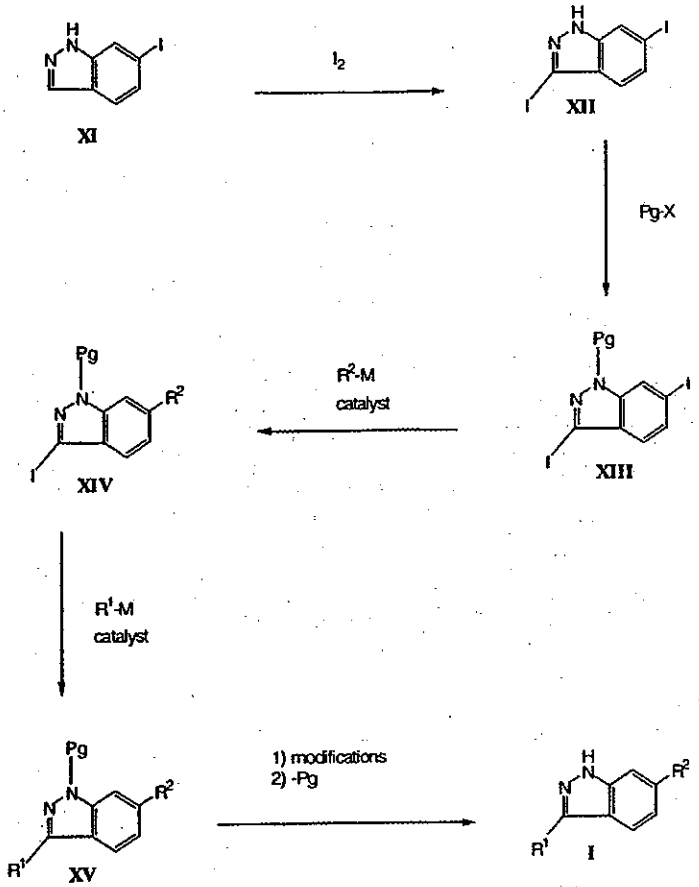



6-Nitroindazole (compound **V**) is treated with iodine and base, e.g., NaOH, in an aqueous/organic mixture, preferably with dioxane. The mixture is acidified and the product isolated by filtration. To the resulting 3-iodo-6-nitroindazole in dichloromethane-50% aqueous KOH at 0 °C is added a protecting group ("Pg") reagent (wherein X = halo), preferably trimethylsilylethoxymethyl chloride (SEM-Cl), and a phase transfer catalyst, e.g., tetrabutylammonium bromide (TBABr). After 1-4 hours, the two phases are diluted, the organics are separated, dried with sodium sulfate, filtered and concentrated. The crude product is purified by silica gel chromatography to give compounds of formula **VI**. Treatment of compounds of formula **VI** in a suitable organic solvent with a suitable $R^1$-organometallic reagent, preferably an $R^1$-boronic acid, in the presence of aqueous base,

e.g., sodium carbonate, and a suitable catalyst, preferably $Pd(PPh_3)_4$ gives, after extractive work-up and silica gel chromatography, compounds of formula **VII**. The $R^1$ substituent may be exchanged within compounds of formula **VII** or later intermediates throughout this scheme by oxidative cleavage (e.g., ozonolysis) followed by additions to the resulting aldehyde functionality with Wittig or condensation transformations (typified in Example 42(a-e)). Treatment of compounds of formula **VII** with a reducing agent, preferably $SnCl_2$, provides, after conventional aqueous work up and purification, compounds of formula **VIII**. For the series of derivatives where Y = NH or N-lower alkyl, compounds of formula **VIII** may be treated with aryl or heteroaryl chlorides, bromides, iodides or triflates in the presence of a base, preferably $Cs_2CO_3$, and catalyst, preferably Pd-BINAP, (and where Y = N-lower alkyl, with a subsequent alkylation step) to provide compounds of formula **X**. To produce other Y linkages, sodium nitrite is added to compounds of formula **VIII** under chilled standard aqueous acidic conditions followed by the addition of potassium iodide and gentle warming. Standard work-up and purification produces iodide compounds of formula **IX**.

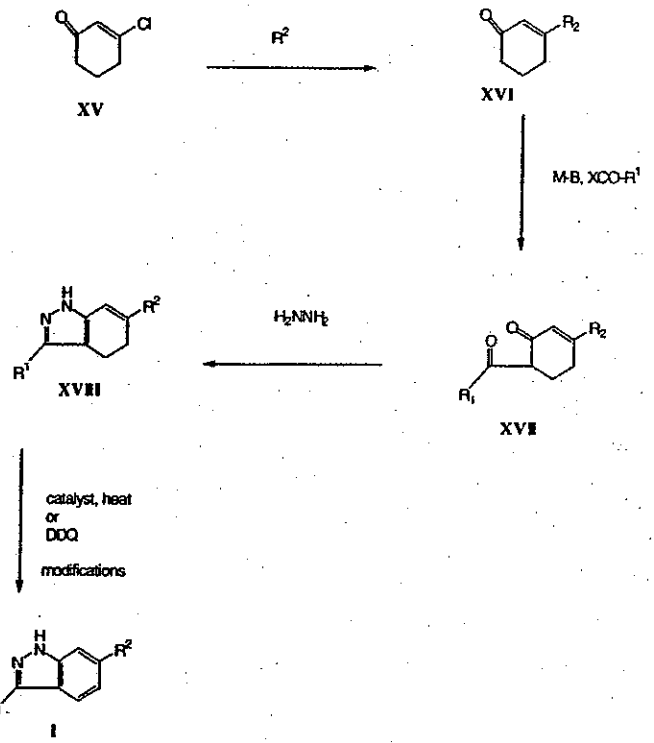
Treatment of compounds of formula **IX** with an organometallic reagent, e.g., butyllithium, can promote lithium halogen exchange. This intermediate can be then reacted with an $R^2$ electrophile, e.g., a carbonyl or triflate, through the possible mediation of additional metals and catalysts, preferably zinc chloride and $Pd(PPh_3)_4$ to provide compounds of formula **X**. Alternatively, compounds of formula **IX** may be treated with an organometallic reagent such as an organoboronic acid in the presence of a catalyst, e.g., $Pd(PPh_3)_4$, under a carbon monoxide atmosphere to give compounds of formula **X**. Alternatively, for derivatives where Y = NH or S, compounds of formula **IX** may be treated with appropriate amines or thiols in the presence of base, preferably $Cs_2CO_3$ or $K_3PO_4$ and a catalyst, preferably Pd-BINAP or Pd-(bis-cyclohexyl)biphenylphosphine to provide compounds of formula **X**. Conventional functional group interchanges, such as oxidations, reductions, alkylations, acylations, condensations, and deprotections may then be employed to further derivatize this series giving final compounds of Formula **I**.

The compounds of Formula 1 may also be prepared according general procedure shown in the following scheme:



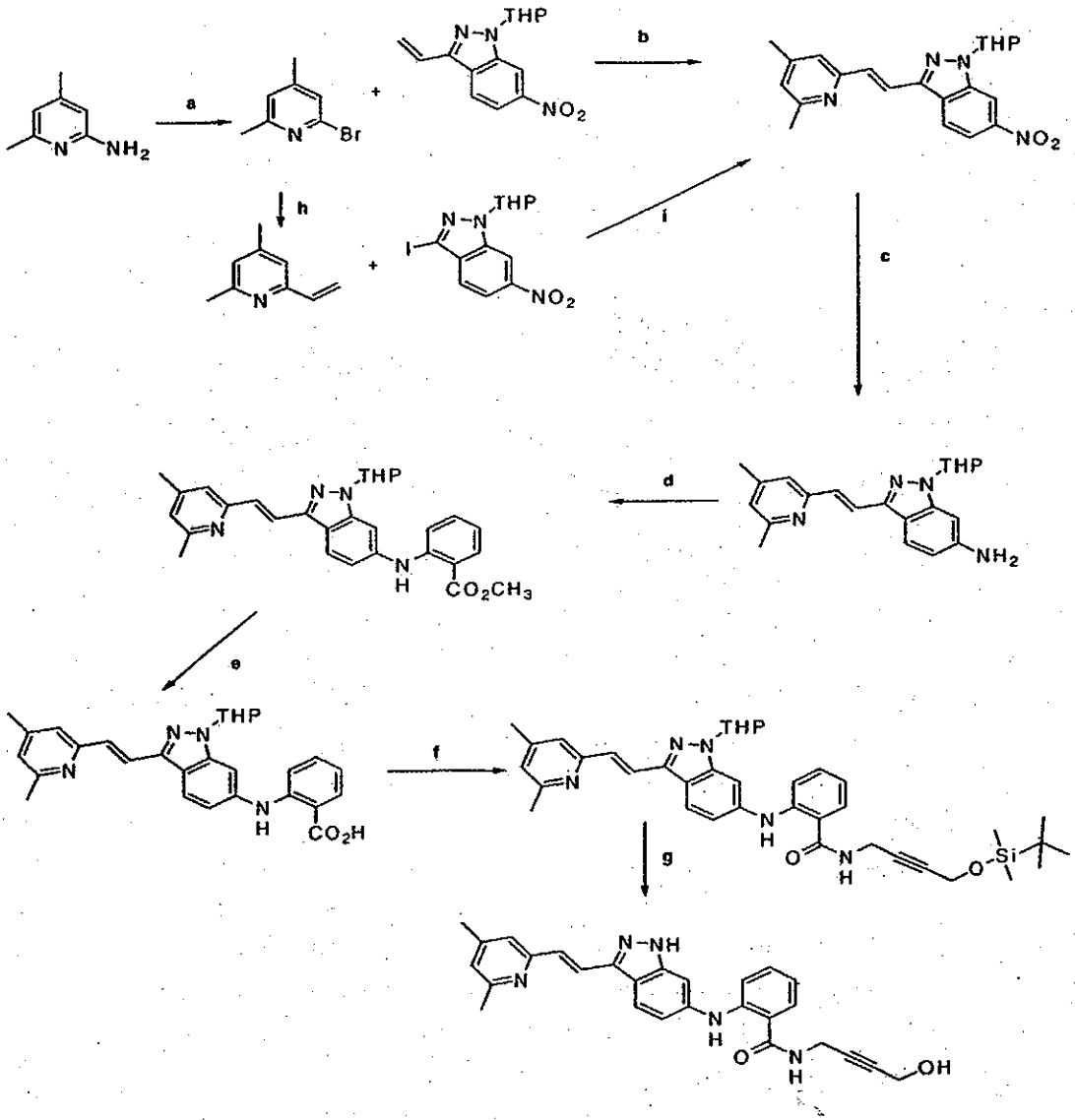

6-Iodoindazole (**XI**) is treated with iodine and base, e.g., NaOH, in an aqueous/organic mixture, preferably with dioxane. The mixture is acidified and the product **XII** is isolated by filtration. To the resulting 3,6 di-iodoindazole in dichloromethane-50% aqueous KOH at 0 °C is added a protecting group reagent, preferably SEM-Cl, and a phase transfer catalyst, e.g., TBABr. The two phases are diluted, the organics separated, dried with sodium sulfate, filtered and concentrated. The crude product is purified by silica gel chromatography to give compounds of the formula **XIII**. Treatment of compounds of formula **XIII** in a suitable organic solvent with a suitable $R^2$-organometallic reagent, e.g., $R^2$-ZnCl or boron $R^2$-boron reagent and a suitable catalyst, preferably $Pd(PPh_3)_4$ gives, after extractive work-up and silica gel chromatography, compounds of formula **XIV**. Treatment of compounds of formula **XIV** in a suitable organic solvent with a suitable $R^1$-organometallic reagent (e.g., boron $R^1$-boron reagent or $R^1$-ZnCl), in the presence of aqueous base, sodium carbonate, and a suitable catalyst, preferably $Pd(PPh_3)_4$ gives, after extractive work-up and silica gel chromatography, compounds of formula **XV**. Conventional functional group interchanges, such as oxidations, reductions, alkylations, acylations, condensations and deprotections may then be employed to further derivatize this series giving final compounds of Formula I.

Alternatively, compounds of Formula I where $R^2$ is a substituted or unsubstituted Y-Ar, where Y is O or S may be prepared according to the following general scheme:




A stirred acetone solution of 3-chloro-cyclohex-2-enone (**XV**), H-$R^2$, and anhydrous potassium carbonate is refluxed for 15-24 hours, cooled, and filtered. Concentrating and chromatographing the filtrate on silica gel gives 3-$R^2$-cyclohex-2-enone (**XVI**).

The ketones of formula **XVI** may be reacted with a suitable base (M-B), preferably lithium bis(trimethylsily)amide, and reacted with $R^1$-CO-X (where X = halogen), which after standard acid work up and purification provides compounds of the formula **XVII**. This product, in HOAc/EtOH, combined with hydrazine monohydrate, is heated at a suitable temperature for an appropriate time period, preferably at 60-80 $^0$C for 2-4 hours. After cooling, the mixture is poured into saturated sodium bicarbonate solution, extracted with an organic solvent, concentrated, and purified on silica gel to give compounds of formula **XVIII**. Compounds of formula **XVIII** may be oxidized using a variety of known methods to give compounds of the Formula I.



An alternative process for synthesizing the compounds of the present invention follows:

Whereby the conditions of the steps a) through i) are as follows:

a) $NaNO_2$, $Br_2$, HBr, 0°C- -5°C; 48% yield;

b) $Pd(OAc)_2$, Pd(o-tolyl)$_3$, Di-isopropyl ethyl amine (DIEA), DMF, $H_2O$, degassed, microwave, 110°C, 1 hr; 68% yield;

c) iron powder, saturated aqueous $NH_4OH$, EtOH, 45C; 72% yield;

d) Methyl-2-bromobenzoate, R-BINAP, $Pd_2(dba)_3$, $Cs_2CO_3$, toluene, degassed, 110°C overnight; 74% yield;

e) KOH, MeOH:THF:$H_2O$ (3:1:1) 70°C, 2-3 hr; quantitative;

f) Protected amine, HATU, $NEt_3$, DMF, room temperature for 2 hours; 80% yield;

g) TsOH (12% TsOH in HOAc), EtOH (10% aqueous); 44% yield;

h) Tributylvinyltin, $Pd(PPh_3)_4$, 2,6-Di-t-butyl-4-methylphenol, toluene, degassed, 105°C; 31% yield;

i) $Pd(OAc)_2$, Pd(o-tolyl)$_3$, DIEA, DMF, degassed, 100°C; approximately 70% yield.

Other compounds of Formula I may be prepared in manners analogous to the general procedures described above or the detailed procedures described in the examples herein. The affinity of the compounds for a receptor may be enhanced by providing multiple copies of the ligand in close proximity, preferably using a scaffolding provided by a carrier moiety. It has been shown that provision of such multiple valence compounds with optimal spacing between the moieties dramatically improves binding to a receptor. See, e.g., Lee et al., *Biochem*, 23, 4255 (1984). The multivalency and spacing can be controlled by selection of a suitable carrier moiety or linker units. Such moieties include molecular supports which contain a multiplicity of functional groups that can be reacted with functional groups associated with the compounds of the invention. Of course, a variety of carriers can be used, including proteins such as BSA or HAS, a multiplicity of peptides including, for example, pentapeptides, decapeptides, pentadecapeptides, and the like. The peptides or proteins can contain the desired number of amino acid residues having free amino groups in their side chains; however, other functional groups, such as sulfhydryl groups or hydroxyl groups, can also be used to obtain stable linkages.

Compounds that potently regulate, modulate, or inhibit the protein kinase activity associated with receptors VEGF, FGF, CDK complexes, TEK, CHK1, LCK, FAK, and phosphorylase kinase among others, and which inhibit angiogenesis and/or cellular profileration is desirable and is one preferred embodiment of the present invention.

Disclosed further are methods of modulating or inhibiting protein kinase activity, for example in mammalian tissue, by administering an agent. The activity of the compounds as modulators of protein kinase activity, such as the activity of kinases, may be measured by any of the methods available to those skilled in the art, including *in vivo* and/or *in vitro* assays. Examples of suitable assays for activity measurements include those described in Parast C. et al., *BioChemistry*, 37, 16788-

16801 (1998); Jeffrey et al., *Nature*, 376, 313-320 (1995); WIPO International Publication No. WO 97/34876; and WIPO International Publication No. WO 96/14843. These properties may be assessed, for example, by using one or more of the biological testing procedures set out in the examples below.

The active agents as disclosed may be formulated into pharmaceutical compositions as described below. Pharmaceutical compositions as disclosed comprise an effective modulating, regulating, or inhibiting amount of a compound of Formula I and an inert, pharmaceutically acceptable carrier or diluent. In one embodiment of the pharmaceutical compositions, efficacious levels of the inventive agents are provided so as to provide therapeutic benefits involving modulation of protein kinases. By "efficacious levels" is meant levels in which the effects of protein kinases are, at a minimum, regulated. These compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

An inventive agent is administered in conventional dosage form prepared by combining a therapeutically effective amount of an agent (e.g., a compound of Formula I) as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, drop, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent is dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, gylcerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with

water. The composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

It will be appreciated that the actual dosages of the agents used in the compositions as disclosed will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for an agent. For oral administration, an exemplary daily dose generally employed is from about 0.001 to about 1000 mg/kg of body weight, more preferably from about 0.001 to about 50 mg/kg body weight, with courses of treatment repeated at appropriate intervals. Administration of prodrugs are typically dosed at weight levels which are chemically equivalent to the weight levels of the fully active form.

The compositions as disclosed may be manufactured in manners generally known for preparing pharmaceutical compositions, e.g., using conventional techniques such as mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically.

Proper formulation is dependent upon the route of administration chosen. For injection, the agents may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP).

If desired, disintegrating agents may be added, such as crosslinked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active agents.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration intranasally or by inhalation, the compounds for use as disclosed may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents

which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For administration to the eye, a compound of Formula I; is delivered in a pharmaceutically acceptable ophthalmic vehicle such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the cornea and/or sclera and internal regions of the eye, including, for example, the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/cilary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may be an ointment, vegetable oil, or an encapsulating material. A compound of the invention may also be injected directly into the vitreous humor or aqueous humor.

Further, a compound may be also be administered by well known, acceptable methods, such as subtebnon and/or subconjunctival injections. As is well known in the ophthalmic art, the macula is comprised primarily of retinal cones and is the region of maximum visual acuity in the retina. A Tenon's capsule or Tenon's membrane is disposed on the sclera. A conjunctiva 36 covers a short area of the globe of the eye posterior to the limbus (the bulbar conjunctiva) and folds up (the upper cul-de-sac) or down (the lower cul-de-sac) to cover the inner areas of the upper eyelid and lower eyelid, respectively. The conjunctiva is disposed on top of Tenon's capsule.

The sclera and Tenon's capsule define the exterior surface of the globe of the eye. For treatment of ARMD, CNV, retinopathies, retinitis, uveitis, cystoid macular edema (CME), glaucoma, and other diseases or conditions of the posterior segment of the eye, it is preferable to dispose a depot of a specific quantity of an ophthalmically acceptable pharmaceutically active agent directly on the outer surface of the sclera and below Tenon's capsule. In addition, in cases of ARMD and CME it is most preferable to dispose the depot directly on the outer surface of the sclera, below Tenon's capsule, and generally above the macula. In a study using New Zealand White rabbits, a drug depot of 4,9(11)-Pregnadien-17.alpha.,21-diol-3,20-dione-21-acetate, an angiostatic steroid available from Steraloids, Inc. of Wilton, New Hampshire, was disposed directly on the outer surface of the sclera, below the Tenon's capsule, and slightly posterior of the equator of the rabbit eyes. Such a drug depot resulted in a concentration of the angiostatic steroid, averaged over the entire retina and measured the day after the injection, about ten times greater than a similar concentration delivered by a depot located below the conjunctiva but above the Tenon's capsule of the rabbit eyes. Given the fact that the Tenon's capsule of a New Zealand White rabbit is very thin, these beneficial results are highly unexpected. It is important to note that Tenon's capsule of the human eye is also very thin. 4,9(11)Pregnadien-17.alpha.,21-diol-3,20-dione-21-acetate, and the related compound 4,9(11)-Pregnadien-17.alpha.,21-diol-3,20-dione, are more fully

described in U.S. Pat. Nos. 5,770,592 and 5,679,666, which are incorporated herein in their entirety by reference.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) intramuscular injection or by the above mentioned subtenon or intravitreal injection.

Within particularly preferred embodiments of the invention, the compounds may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The anti-angiogenic factor solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea.

Within preferred embodiments, the composition is prepared with a muco-adhesive polymer which binds to cornea. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy.

A pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds as disclosed may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The preparation of preferred compounds as disclosed is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other protein kinase inhibitors.

For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds as disclosed.

## DETAILED DESCRIPTION OF INVENTION AND PREFERRED EMBODIMENTS

## EXAMPLES

In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane, toluene, and dioxane were purchased from Aldrich in Sure seal bottles and used as received. All solvents

were purified using standard methods readily known to those skilled in the art, unless otherwise indicated.

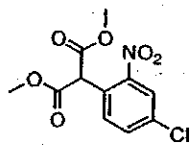
The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate solvent ratios (v/v), and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20 wt % in ethanol) and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were dried over anhydrous $Na_2SO_4$ prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Flash column chromatography (Still et al., *J. Org. Chem.*, 43, 2923 (1978)) was done using Baker grade flash silica gel (47-61 μm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated. Hydrogenolysis was done at the pressure indicated in the examples or at ambient pressure.

$^1$H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and $^{13}$C-NMR spectra were recorded operating at 75 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or $CD_3OD$ (3.4 and 4.8 ppm and 49.3 ppm), or internally tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

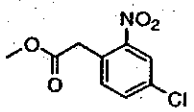
Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when given are reported in wave numbers ($cm^{-1}$). The mass spectra were obtained using LSIMS or electrospray. All melting points (mp) are uncorrected.

**Example 1(a) 2-(4-Chloro-2-nitro-phenyl)-malonic acid dimethyl ester**



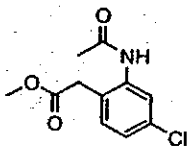
To a stirred slurry of NaH (36.0 g, 1500 mmol) in NMP (1.0 L) was added dimethyl malonate (137.4 mL, 1200 mmol) drop wise. The reaction was cooled as needed to keep the internal temperature below 30 degrees Celsius. After gas evolution ceased, 2,4-dichloronitrobenzene (192 g, 1000 mmol) was added to the reaction. It was carefully heated to 65 degrees Celsius until the reaction was complete as determined by HPLC. The reaction was cooled to room temperature, and then poured over 500 mL ice mixed with 150 mL conc. HCl. The pH of the aqueous layer was adjusted to neutral using 1 N NaOH. The solids were removed by filtering through a coarse fritted filter, and rinsed with water (3 L). The yellow solids were allowed to dry overnight. Yield 261.5 g, 91%.

**Example 1(b) (4-Chloro-2-nitro-phenyl)-acetic acid methyl ester**



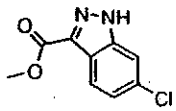
A solution of 2-(4-Chloro-2-nitro-phenyl)-malonic acid dimethyl ester (195 g, 679.4 mmol) in water (100 mL) and NMP (1000 mL) was heated to reflux for 3.5 hours. The solvent was removed by rotary evaporation to an oil. The oil was dissolved in EtOAc, and then washed with water (5 x 300 mL). The aqueous layer was then extracted with EtOAc (4 x 300 mL). The organic was washed with water. The organic layers were combined and dried over $MgSO_4$. After removing the solids by filtration, the solvent was evaporated to yield the desired product as a orange/brown solid (160.0 g, 95%).

**Example 1(c) (2-Acetylamino-4-chloro-phenyl)-acetic acid methyl ester**



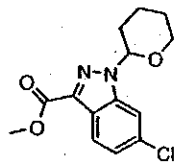
An argon filled flask was charged with (4-Chloro-2-nitro-phenyl)-acetic acid methyl ester (40 g, 175 mmol), 10% Pd/C (2.5 g), acetic anhydride (64 mL, 677 mmol), water (9 mL) and acetic acid (150 mL). The flask was vacuum flushed with hydrogen gas at 30 PSI and shook vigorously. After 2 hours, more 10% Pd/C (2 g) was added, and the reaction was complete after a total of 4 hours reaction time. The 10 % Pd/C was removed by filtration, and the solvent was removed by rotary evaporation.

**Example 1(d) 6-Chloro-1H-indazole-3-carboxylic acid methyl ester**



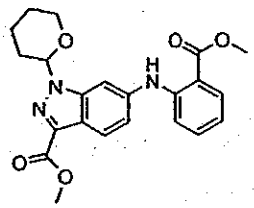
To a solution of (2-Acetylamino-4-chloro-phenyl)-acetic acid methyl ester (32.0 g, 133 mmol) in acetic acid (200 mL) stirred at 90 degree Celsius was added *tert*-butyl nitrite (20.5 mL, 172.3 mmol) over 1 hour. The reaction was poured into water (1.4 L) and the solids were recovered by filtration. The yellow precipitate was dissolved in EtOAc, then washed with saturated NaCl. The organic was dried over $MgSO_4$, filtered, and concentrated to a solid. The solids were triturated with hexanes and filtered to afford the desired material (21.63 g, 77%).

**Example 1(e) 6-Chloro-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid methyl ester**



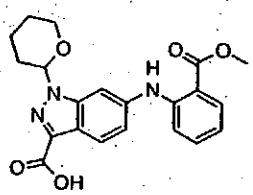
To a slurry of 6-Chloro-1H-indazole-3-carboxylic acid methyl ester (8.3 g, 39.5 mmol) in MeCN (200 mL) was added 3,4-Dihydro-2H-pyran (5.4 mL, 59.3 mmol) and *p*-toluenesulfonic acid (237 mg, 1.25 mmol). After letting the reaction stir for 10 minutes, saturated $NaHCO_3$ (1 mL) was added and the solvent was removed by rotary evaporation to a volume of 100 mL. The mixture was diluted with EtOAc and washed with water (50 mL) and then with saturated NaCl (50 mL). The organic layer was then dried over $Na_2SO_4$. After the solids were removed by filtration, the organic layer was concentrated to an oil by rotary evaporation. The product was precipitated from the oil using hexanes to yield the desired product (7.667 g, 66% yield).

**Example 1(f) 6-(2-Methoxycarbonyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid methyl ester**



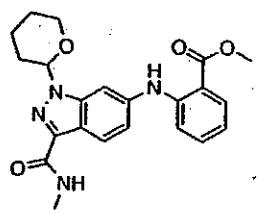
To a solution of 6-Chloro-1H-indazole-3-carboxylic acid methyl ester (2.94g, 10.0 mmol) in 1,2-dimethoxyethane (30 mL) was added $K_3PO_4$ (5.32g, 25.0 mmol), tris(dibenzylideneacetone)dipalladium (459 mg, 0.05 mmol), 2-(dicyclohexylphosphino) biphenyl (701 mg, 2.0 mmol), and methyl anthranilate (2.59 mL, 20.0 mmol). The solution was vacuum flushed with argon three times before being heated to 80 degrees Celsius for 18 hours. The reaction was cooled to room temperature and the solids were removed by filtration. After washing the solids with ethyl acetate, the solvent was removed by rotary evaporation. The residual oil was chromatographed (150 g silica gel, 10 – 30% EtOAc/Hex) to yield 1.23 g (51%) of the desired product.

**Example 1(g)6-(2-Methoxycarbonyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid**



To a solution of 6-(2-Methoxycarbonyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid methyl ester (2.05 g, 5 mmol) in methanol (18 mL) and tetrahydrofuran (8 mL), was added a solution of sodium hydroxide (0.30g, 7.5 mmol) in water (2.7 mL). The reaction was stirred at room temperature for 3 hours and was then neutralized with 1 N HCl to a pH of 1. The mixture was diluted with EtOAc (25 mL) and water (25 mL). After separating the layers, the aqueous layer was washed with $CH_2Cl_2$ (3 x 25 mL). The combined organic extracts were washed with saturated NaCl (100 mL) and then dried over $Na_2SO_4$. The solids were filtered and the liquid was concentrated to an oil. The product was crystallized from EtOAc and Hexanes to yield the desired product (1.616 g, 82%).

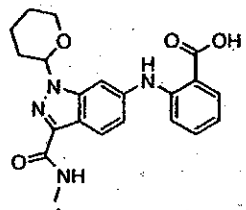
**Example 1(h) 2-[3-Methylcarbamoyl-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester**



To a solution of 6-(2-Methoxycarbonyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid (0.50g, 1.27 mmol) in DMF was added triethylamine (0.42 mL,

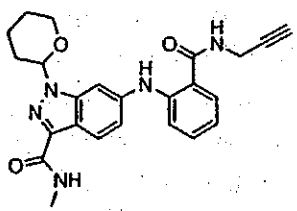
3.04 mmol), methylamine (1.9 mL, 3.81 mmol), and HATU (0.578 g, 1.52 mmol). The reaction was stirred for 3 hours and then concentrated by rotary evaporation. The crude oil was chromatographed (50 g silica gel, 25 – 50% EtOAc/hexanes) to yield the desired product (214 mg, 42 %).

**Example 1(i) 2-[3-Methylcarbamoyl-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid**



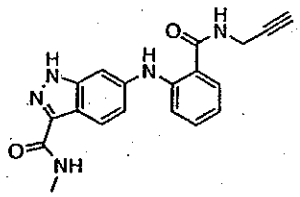
To a solution of 2-[3-Methylcarbamoyl-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester (0.20g, 0.49 mmol) in methanol (1.4 mL) and tetrahydrofuran (0.6 mL) was added a solution of sodium hydroxide (59 mg, 1.47 mmol) in water (0.3 mL). The reaction was heated to 60 degrees Celsius for 1 hour and then was cooled to room temperature. The pH was adjusted with 2 N HCl to a pH of 2. EtOAc (30 mL) and water (30 mL) was added and the layers were separated. The aqueous was extracted with EtOAc (3 x 20 mL) and the organic layers were combined. After washing with water (15 mL), the organic layer was dried over $Na_2SO_4$. The solids were filtered away, and the organic was evaporated to yield a yellow solid (193 mg, 100%).

**Example 1(j) 6-(2-Prop-2-ynylcarbamoyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid methylamide**



To a solution of 2-[3-Methylcarbamoyl-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid (150 mg, 0.381 mmol) in DMF (3.6 mL) was added propargylamine (0.052 mL, 0.761 mmol), TEA (0.264 mL, 1.90 mmol), and HATU (217 mg, 0.571 mmol). The reaction was stirred for 4 hours, and then diluted with EtOAc (30 mL) and water (30 mL). The layers were separated, and the aqueous was extracted with EtOAc (2 x 20 mL). The combined organics were washed with saturated NaCl (15 mL) and then dried over $Na_2SO_4$. The solids were removed by filtration, and the liquid was concentrated by rotary evaporation to a yellow oil (164 mg, 100%).

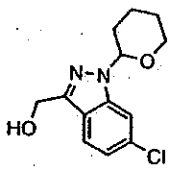
**Example 1(k) 6-(2-Prop-2-ynylcarbamoyl-phenylamino)-1H-indazole-3-carboxylic acid methylamide**



Dissolved 6-(2-Prop-2-ynylcarbamoyl-phenylamino)-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carboxylic acid methylamide (30 mg) in 1.5 mL of a 90:10:1 mixture of $CH_2Cl_2$:TFA:triethyl silane and heat to reflux for 2 hours. Diluted the solution with toluene (40 mL) and concentrate by rotary evaporation to an oil. Dissolved the oil in DMF (1 mL), and filter using a 0.2-micron syringe filter. Used prep-HPLC to isolate the desired compound (12 mg, 50%). $^1$H NMR ($CDCl_3$-d) δ 9.96 (1H, s), □□□□s),??? 8.28 (1H, d, J = 8.85 Hz), 7.47 (1H, m), 7.34 (1H, m), 7.22 (1H, m), 7.15 (1H, dd, J1 = 8.76 Hz, J2 = 1.79 Hz), 6.99 (1H, m), 6.86 (1H, t, J = 6.97Hz), 6.31 (1H, m), 4.23 (2H, dd, J1 = 5.18 Hz, J2 = 2.54 Hz), 3.49 (3H, s), 2.29 (s, 1H).

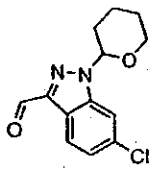
*Anal.* Calcd. For $C_{19}H_{17}N_5O_2$•1.0 MeOH•0.1 TFA: C, 62.08; H, 5.44; N, 17.92. Found: C, 61.78; H, 5.45; N, 18.04.

**Example 2(a) [6-Chloro-1-(tetrahydro-pyran-2-yl)-1H-indazol-3-yl]-methanol**



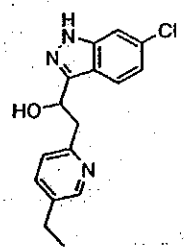
To a solution of 6-Chloro-1H-indazole-3-carboxylic acid methyl ester (2.94 g, 10.0 mmol) in dry $CH_2Cl_2$ (50 mL) cooled to –78 degrees Celsius was added DIBAL-H (3.56 mL, 20.0 mmol) slowly. After the addition was complete, the reaction was allowed to warm to room temperature, where HPLC showed that there was a remaining 10% starting material. Extra DIBAL-H (0.35 mL) was then added and stirred for 10 minutes. The reaction was diluted with EtOAc (1000 mL) and washed with 1 N HCl (2 x 100 mL). It was further washed with 1 N $NaHCO_3$ (100 mL), and then with saturated NaCl (100 mL). The organic was dried over Mg $SO_4$, filtered, and then concentrated to a white solid (2.65 g, 99.5 %).

**Example 2(b) 6-Chloro-1-(tetrahydro-pyran-2-yl)-1H-indazole-3-carbaldehyde**



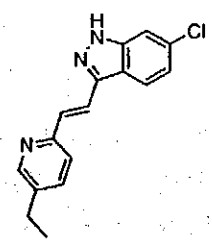
A solution of [6-Chloro-1-(tetrahydro-pyran-2-yl)-1H-indazol-3-yl]-methanol (1.75 g, 6.58 mmol), IBX (2.76 g, 9.87 mmol) and DMSO (27 mL) was stirred overnight. The reaction was diluted in EtOAc and water. The layers were separated, and the aqueous was extracted with EtOAc (3 x 100 mL). The organics were combined and washed with saturated NaCl (100 mL). The organic was dried over $MgSO_4$, filtered, and then concentrated to a solid. The solid was dissolved in $CH_2Cl_2$, and filtered. The organic was evaporated to yield the desired product (1.707g, 92%).

**Example 2(c) 1-(6-Chloro-1H-indazol-3-yl)-2-(5-ethyl-pyridin-2-yl)-ethanol**



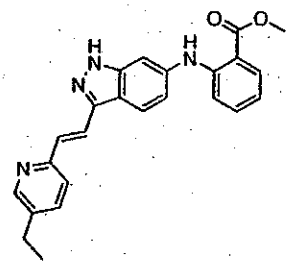
To a stirred solution of 4-ethyl-2-methylpyridine (0.458 g, 3.79 mmol) in THF (4mL) at –50 degrees Celsius, add butyl lithium (1.5 mL, 2.5 M, 3.79 mmol) slowly and stir for 10 minutes. To the reaction, slowly add a solution of 6-Chloro-1H-indazole-3-carbaldehyde (0.5 g, 1.89 mmol) in THF (4 mL). After stirring for 10 minutes, the reaction was quenched with 1 N citric acid (10 mL). The mixture was diluted with EtOAc (50 mL), water (20 mL), and saturated NaCl (10 mL). The layers were separated, and the aqueous was extracted with EtOAc (3 x 15 mL). The organics were combined and washed with saturated NaCl (20 mL). After drying the organic layer over $Na_2SO_4$, the solids were removed by filtration and the liquid was concentrated to an oil by rotary evaporation. Chromatography (40 g silica gel, 60 – 100% EtOAc/hex) yields the desired product (142 mg, 32%) and recovered 6-Chloro-1H-indazole-3-carbaldehyde (348 mg).

**Example 2(d) 6-Chloro-3-[2-(5-ethyl-pyridin-2-yl)-vinyl]-1H-indazole**



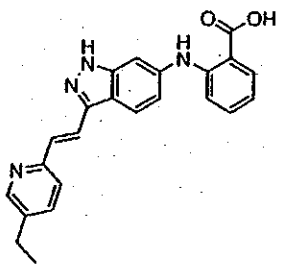
To a stirred solution of 1-(6-Chloro-1H-indazol-3-yl)-2-(5-ethyl-pyridin-2-yl)-ethanol (232 mg, 0.60 mmol) in $CH_2Cl_2$ was added TEA (0.25 mL, 1.81 mmol) and mesyl chloride (0.070 mL, 0.90 mmol). The reaction was stirred for 30 minutes, and then DBU (2 mL) was added. The reaction was refluxed for 18 hours and then quenched with 40 mL of 1 N citric acid. The layers were separated, and the aqueous was extracted with 20 mL $CH_2Cl_2$. The combined organics were dried over $Na_2SO_4$, filtered, and concentrated by rotary evaporation. Purification by chromatography (12 g silica gel, 50 – 70% EtOAc/hexanes) yielded the desired compound (135 mg, 71 %).

**Example 2(e) 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid methyl ester**



1,2-Dimethoxymethane (2 mL) was added to 6-Chloro-3-[2-(5-ethyl-pyridin-2-yl)-vinyl]-1H-indazole (130 mg, 0.354 mmol), tris(dibenzylideneacetone)dipalladium (16 mg, 0.018 mmol), -(dicyclohexylphosphino)biphenyl (25 mg, 0.071 mmol), $K_3PO_4$ (0.188 g, 0.885 mmol), and methyl anthranilate (0.092 mL, 0.71 mmol). The reaction was vacuum flushed with argon (4x) and then heated to 80 degrees Celsius for 19 hours. The reaction was diluted with EtOAc (20 mL) and filtered through a silica gel plug. After washing with EtOAc (50 mL), the solvent was removed by rotary evaporation. The crude oil was purified by chromatography (40 g silica gel, 30 – 40% EtOAc/hexanes) to yield the desired product (54 mg, 32%).

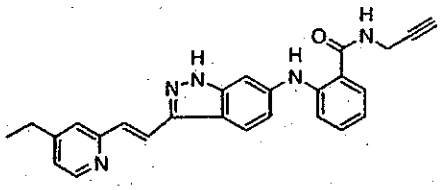
**Example 2(f) 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid**



To a solution of 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid methyl ester (50 mg, 0.104 mmol) in methanol (0.42 mL) and THF (0.10 mL) was added a solution of sodium hydroxide (12 mg, 0.311 mmol) in water (0.05 mL). The solution was heated to 60 degrees Celsius for 3.5 hours and then neutralized with

saturated $NH_4Cl$. The reaction was diluted with water (20 mL), and then extracted with EtOAc (2 x 20 mL). The combined extracts were first dried over $Na_2SO_4$, and then the solids were removed by filtration. The desired product (48.7 mg, 100%) was recovered after rotary evaporation to remove the solvents.

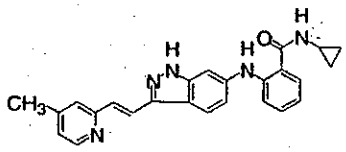
**Example 2(g) 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-prop-2-ynyl-benzamide**



To 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid (49 mg, 0.105 mmol) was added 2 mL of a 90:10:1 mixture of $CH_2Cl_2$:TFA:TES. The reaction was stirred at reflux for 1 hour, and then diluted with toluene (20 mL). The solvent was removed by rotary evaporation to yield a thick oil. The oil was dissolved in DMF (1 mL) and to this solution was added TEA (0.072 mL, 0.52 mmol), propargyl amine (0.014 mL, 0.208 mmol), and HATU (59 mg, 0.156 mmol). The reaction was stirred for 3 hours, and then purified by preparatory HPLC to yield the desired product (29 mg, 66%). $^1$H NMR ($CDCL_3$-d): δ 9.83 (1H, s), 8.63 (2H, s), 8.04 (2H, m), 7.68 (2H, s), 7.47 (1H, m), 7.32 (1H, d, J = 1.51 Hz), 7.10 (1H, dd, J1 = 8.67 Hz, J2 = 1.88 Hz), 6.93 (1H, m), 6.07 (2H, dd, J1 = 5.09 Hz, J2 = 2.26 Hz), 3.15 (1H, t, J = 2.35 Hz), 2.97 (2H, s), 2.74 (1H, s), 2.29 (1H, s), 1.27 (3H, t, J = 7.44 Hz)

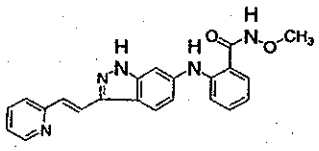
*Anal.* Calcd. for $C_{26}H_{23}N_5O \cdot 0.3\ H_2O \cdot 1.2$ TFA: C, 60.51; H, 4.43; N, 12.42. Found: C, 60.38; H, 4.73; N, 12.44.

**Example 2(h) N-Cyclopropyl-2-{3-[(E)-2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



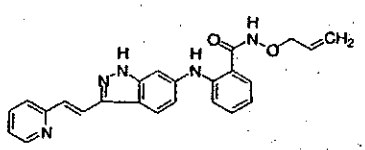
The title compound was prepared analogously to 2-{3-[2-(5-Ethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-prop-2-ynyl-benzamide described above, substitutiting 2,4-dimethyl-pyridine for 4-ethyl-2-methyl-pyridine in the step where 1-(6-Chloro-1H-indazol-3-yl)-2-(5-ethyl-pyridin-2-yl)-ethanol was prepared, and substituting cyclopropyl amine in place of propargyl amine in the final step of the sequence. $^1$H NMR (DMSO-$d_6$): δ 9.85 (1H, s), 8.56 (2H, m), 8.20 (3H, m), 7.53 (5H, m), 7.35 (1H, s), 7.2 (1H, d, J = 6.5 Hz), 7.0 (1H, s), 2.83 (1H, m), 0.70 (2H, m), 0.56 (2H, m). ESIMS ($M+H^+$): 410.3.

**Example 3(a) N-Methoxy-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



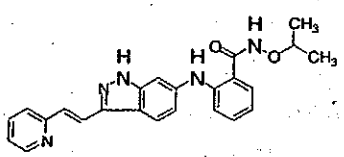
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), O-methyl-hydroxylamine hydrochloride (15 mg, 0.17 mmol), triethylamine(58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 21.6 mg (67%) of the title compound as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 9.23 (1H, s), 8.71 (1H, d, J=2.2), 8.05 (4H, m), 7.51 (5H, m), 7.25 (1H, s), 7.10 (1H, d, J = 7.7 Hz), 6.91 (1H, m), 5.98 (1H, m), 4.31 (1H, d, J= 14.3), 7.20 (1H, d, J=7.3),4.42 (2H, d, J=3.2). ESIMS (M+H$^+$): 412.1.

**Example 3(b) N-Allyloxy-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



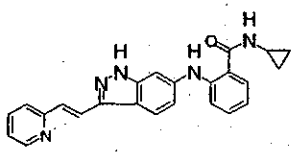
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), O-allyl-hydroxylamine hydrochloride (18.3 mg, 0.17 mmol), triethylamine(58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 25.5 mg (74%) of the title compound as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 9.28 (1H, s), 8.67 (2H, d, J=3.4), 8.05 (4H, m), 7.48 (5H, m), 7.23 (1H, s), 7.04 (1H, d, J = 7.6 Hz), 6.91 (1H, m), 3.69 (3H, s). ESIMS (M+H$^+$): 386.1.

**Example 3(c) N-Isopropoxy-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



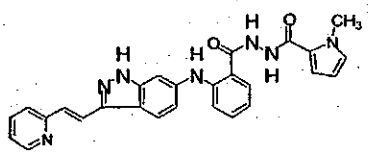
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), O-isopropyl-hydroxylamine hydrochloride (18.7 mg, 0.17 mmol), triethylamine(58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 17.4 mg (50%) of the title compound as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 9.23 (1H, s), 8.69 (H, d, J=2.1), 8.03 (4H, m), 7.50 (5H, m), 7.23 (1H, s), 7.04 (1H, d, J = 6.7 Hz), 6.92 (1H, m), 5.98 (1H, m), 4.13 (1H, m), 1.29 (6H, d, J=8.1). ESIMS ($M+H^+$): 414.1.

**Example 3(d) N-Cyclopropyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



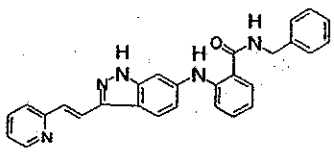
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), cyclopropyl amine (11.6 µL, 0.17 mmol), triethylamine (58 µl, 0.25 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 11.7 mg (35%) of the title compound as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 9.81 (1H, s), 8.68 (1H, d, J=1.7), 8.51 (1H, s), 8.01 (4H, m), 7.50 (5H, m), 7.24 (1H, s), 7.03 (1H, d, J=5.3), 6.89 (1H, t, J=4.2), 2.84 (1H, m), 0.72 (2H, m), 0.56 (2H, m). ESIMS ($M+H^+$): 396.1.

**Example 3(f) 1-Methyl-1H-pyrrole-2-carboxylic acid N'-(1-{2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-phenyl}-methanoyl)-hydrazide**



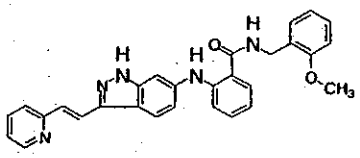
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), 1-methyl-1H-pyrrole-2-carboxylic acid hydrazide (23.3 mg, 0.17 mmol), triethylamine(58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 16.1 mg (40%) of the title compound as a yellow solid. $^1$H NMR (DMSO-$d_6$): δ 10.39 (1H, s), 10.00 (1H, s), 9.52 (1H, s), 8.67 (1H, d, J=2.4), 8.07 (4H, m), 7.77 (1H, d, J=5.2), 7.51 (4H, m), 7.32 (1H, s), 7.09 (1H, d, J=6.3), 6.98 (3H, m), 6.13 (1H, m), 3.87 (3H, s). ESIMS ($M+H^+$): 478.1.

**Example 3(g)N-Benzyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



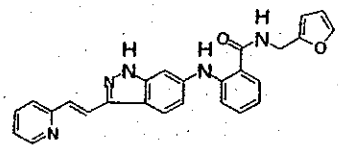
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), benzylamine (18.2 µL, 0.17 mmol), triethylamine (58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 45.2 mg (76%) of the title compound as a TFA salt (1.5 $H_2O$, 2.1 TFA, effective MW=711.98). $^1H$ NMR (DMSO-$d_6$): δ 9.86 (1H, s), 9.14 (1H, t, J=5.4), 8.73 (1H, d, J=4.8), 8.29 (4H, m), 7.56 (1H, d, J=7.0), 7.74 (2H, m), 7.89 (2H, m), 7.31 (5H, m), 7.16 (1H, d, J=7.8), 6.93 (1H, t, J=7.3), 4.46 (2H, d, J=6.1). ESIMS ($M+H^+$): 446.5.

**Example 3(h)N-(2-Methoxy-benzyl)-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



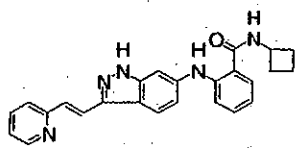
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), *o*-methoxybenzylamine (21.8 µL, 0.17 mmol), triethylamine (58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 46 mg (81%) of the title compound as a TFA salt (1.5 $H_2O$, 1.5 TFA, effective MW=673.59). $^1H$ NMR (DMSO-$d_6$): δ 9.83 (1H, s), 9.03 (1H, t, J=3.4), 8.70 (1H, d, J=3.7), 8.08 (4H, m), 7.82 (1H, d, J=7.4), 7.49 (4H, m), 7.21 (3H, m), 6.96 (4H, m), 4.48 (2H, d, J=6.3). ESIMS ($M+H^+$): 476.1.

**Example 3(i) N-Furan-2-ylmethyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



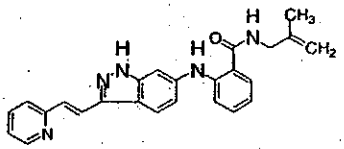
A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), C-furan-2-yl-methylamine (19 µL, 0.17 mmol), triethylamine (58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 45 mg (85%) of the title compound as a TFA salt (1.5 $H_2O$, 1.5 TFA, effective MW=633.52). $^1$H NMR (DMSO-$d_6$): δ 9.82(1H, s), 9.05 (1H, t, J=2.6), 8.73 (1H, d, J=3.7), 8.13 (4H, m), 7.73 (1H, d, J=6.8), 7.57 (2H, m), 7.26 (1H, s), 7.03 (1H, d, J=7.5), 6.40 (1H, m), 6.28 (1H, m), 4.48 (2H, d, J=6.5). ESIMS ($M+H^+$): 436.1.

**Example 3(j) N-Cyclobutyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), cyclobutylamine (18.2 µL, 0.17 mmol), triethylamine (58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 43.2 mg (92%) of the title compound as a TFA salt (1.5 H2O, 1.1 TFA, effective MW=561.92). $^1$H NMR (DMSO-$d_6$): δ 9.78 (1H, s), 8.72 (2H, m), 8.13 (4H, m), 7.70 (1H, d, J=7.1), 7.58 (2H, m), 7.41 (2H, m), 7.27 (1H, s), 6.89 (1H, t, J=4.2), 2.84 (1H, m), 0.72 (2H, m), 0.56 (2H, m). ESIMS ($M+H^+$): 396.1.

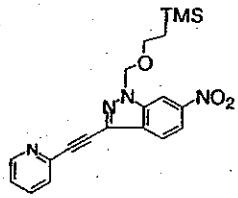
**Example 3(k) N-(2-Methyl-allyl)-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



A solution of 2-[3-(2-Pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzoic acid (50.0 mg, 0.084 mmol), 2-methyl-allylamine (16.4 µL, 0.17 mmol), triethylamine (58 µl, 0.42 mmol), dissolved in DMF (0.8 mL), was treated with HATU (48 mg, 0.13 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 45 mg (91%) of the title compound as a TFA salt (1.6 $H_2O$, 1.3 TFA, effective MW=586.53). $^1$H NMR (DMSO-$d_6$): δ 9.78 (1H, s), 8.72 (2H, m), 8.13 (4H, m), 7.70 (1H, d, J=7.1), 7.58 (2H, m),

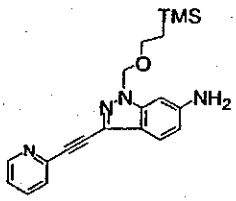
7.41 (2H, m), 7.27 (1H, s), 7.06 (1H, d, J=7.1), 6.91 (1H, t, J=7.5), 4.42 (1H, m), 2.22 (2H, m), 2.08 (2H, m), 1.68 (2H, m). ESIMS ($M+H^+$): 410.1.

**Example 3(l) 6-Nitro-3-pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole**



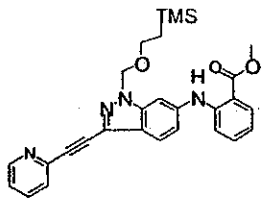

A mixture of 3-Iodo-6-nitro-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole (838mg, 2.0 mmol), 2-ethynyl-pyridine (242 µL, 2.4 mmol), and triethylamine (6.0 mL), were degassed and flushed with argon, then treated with CuI (8 mg, 0.042 mmol), and $Pd(PPh_3)_2Cl_2$ (16 mg, 0.023mmol). The resulting mixture was stirred overnight at room temperature, at which time HPLC indicated all starting material had been consumed. The mixture was purified by stripping of volatiles under high vacuum, then passing through a plug of silica eluted with ethyl acetate. The resulting product was used in the next step without further purification. ESIMS ($M+H^+$): 395.1.

**Example 3(m) 3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamine**



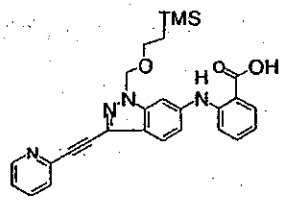

A mixture of 6-Nitro-3-pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole (2 mmol), $SnCl_2$ (1.37g, 6.0 mmol), water (0.5 mL), and MeOH (10 mL), were stirred in a 60 deg C oil bath for 30 min at which time HPLC indicated complete reduction. The resulting mixture was stripped of methanol, suspended in EtOAc (50 mL) and diluted with 1M NaOH (18 mL). The resulting emulsion was gently extracted EtOAc (10 x 25 ml). The combined organics were extracted with 1M $Na_2CO_3$, brine, dried over $MgSO_4$, concentrated and filtered through a pad of silica eluted with EtOAc. The yield of crude product for two steps was 701 mg, 96% mass recovery. ESIMS ($M+H^+$): 365.1.

**Example 3(n) 2-[3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid methyl ester**



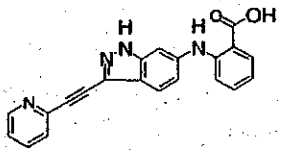
A mixture of 3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamine (560 mg, 1.54 mmol), 2-bromomethylbenzoate (647.5 µL, 4.61 mmol), biphenyl-2-yl-dicyclohexyl-phosphane (107.8 mg, 0.308 mmol), $Pd_2(dba)_3$ (70.5 mg, 0.0768 mmol), $K_3PO_4$ (816 mg, 3.844 mmol), and dimethoxyethane (1.7 ml), were vacuum flushed with nitrogen, then heated in an oil bath at 70 deg C for 24h. The black mixture was diluted with methylene chloride, and filtered, concentrated, and chromatographed (20% to 40% ethylacetate/hexanes). Yield of yellow/orange oil was 260 mg, 35% for three steps.

**Example 3(o) 2-[3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid**



2-[3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid methyl ester (253mg, 0.517 mmol), was added to a solution of NaOH (62 mg, 1.55 mmol), dissolved in THF (1.0 mL), MeOH (2.25 mL), and water (0.5 mL). The reaction was stirred at room temperature for 1h, at which time HPLC indicated that all starting material had been consumed. The reaction was neutralized with 1N HCL, extracted with ethylacetate, which was then washed with brine and dried with $MgSO_4$. After concentrating under vacuum, 249 mg of yellow solid was obtained (99% mass recovery). This material was used without further purification. ESIMS (M-H): 483.0.

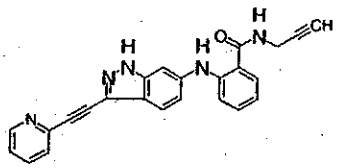
**Example 3(p) 2-[3-Pyridin-2-ylethynyl-1H-indazol-6-ylamino]-benzoic acid**



A solution of 2-[3-Pyridin-2-ylethynyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid (231 mg, 0.477), 1M tetrabutylammonium fluoride in THF (3.8 mL, 3.816 mmol), and ethylenediamine (127 µL, 1.908 mmol), were stirred in an oil bath at 80 deg C for 6h. The reaction was quenched with acetic acid (218 µL, 3.816 mmol), diluted with water, and extracted with EtOAc (10 x 50 mL). The combined organics

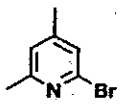
were washed with brine and dried over $MgSO_4$. After concentrating a solid forms which was triturated with $CH_2Cl_2$, giving the product as a yellow powder (124 mg, 73%). ESIMS ($M-H^-$): 353.0.

**Example 3(q) N-Prop-2-ynyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylamino]-benzamide**



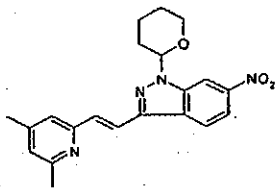
A solution of 2-(3-Pyridin-2-ylethynyl-1H-indazol-6-ylamino)-benzoic acid (41 mg, 0.117 mmol), propargylamine (24 µL, 0.35 mmol), triethylamine (81 µl, 0.58 mmol), dissolved in DMF (0.5 mL), was treated with HATU (89 mg, 0.233 mmol). The mixture was stirred overnight, then purified by reverse phase HPLC yielding 27 mg (59%) of the title compound as a yellow solid. $^1H$ NMR (DMSO-$d_6$): δ 9.78 (1H, s), 8.99 (1H, m), 8.61 (1H, d, J=2.1), 7.88 (1H, s), 7.72 (3H, m), 7.43 (4H, m), 7.29 (1H, s), 7.04 (1H, d, J=7.3), 6.91 (1H, t, J=5.2), 4.04 (2H, s), 3.04 (1H, s). ESIMS ($M+H^+$): 392.1.

**Example 4(a): 2-Bromo-4,6-dimethyl-pyridine.**



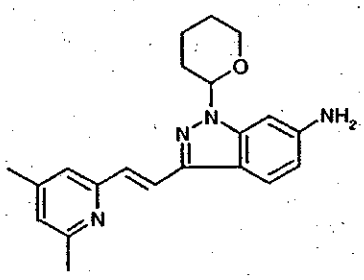
A solution of 48% HBr (aq) (Aldrich, 65 mL, 1.2 mol, 10 eq) was cooled to –5°C and treated with 4,6-dimethyl-pyridin-2-ylamine (Aldrich, 15.0 g, 0.12 mol. 1.0 eq). The thick white salt mixture was stirred with a mechanical stirrer while bromine (Aldrich, 19.7 mL, 0.38 mol, 3.1 eq) was added dropwise. The resultant red mixture was treated with an aqueous solution (32 mL $H_2O$) of $NaNO_2$ (Aldrich, 22.1 g, 0.32 mol, 2.6 eq) over one hour. The temperature was maintained below 5°C during the nitrite addition, and then gradually warmed to 20°C over 2 hours. The reaction mixture was adjusted to pH 14 with NaOH (aq), and extracted with MTBE. The organic extracts were washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product (29 g of a red oil) was purified by flash chromatography (silica, 350 g) and eluted with 2-7% ethyl acetate-cyclohexane, which gave an orange oil (11.0 g, 48%). $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 7.30 (1H, s), 7.13 (1H, s), 2.39 (3H, s), 2.26 (3H, s). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 159.4, 151.3, 140.9, 125.7, 124.0, 23.7, 20.3. ESI m/z 186/188 $(M + H)^+$.

**Example 4(b): 3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-6-nitro-1-(tetrahydro-pyran-2-yl)-1*H*-indazole**



A suspension of 2-bromo-4,6-dimethylpyridine (2.42g, 13 mmol), 3-vinyl-6-nitro-1-(tetrahydro-pyran-2-yl)-1*H*-indazole (2.37g, 8.67 mmol), palladium acetate (0.145g, 0.65mmol), tri-ortho-tolylphosphine (0.791g, 2.6 mmol), and diisopropylethylamine (2.4 mL, 13.8mmol) in aqueous DMF (85%, 34.5 mL) was degassed with Argon bubbling for 5 minutes followed by sonication for 5 minutes before heating in microwave apparatus (300 watts, 10% power) at 110°C for 40 minutes. After cooling, the mixture was dropped into cold water. The resulting yellow ppt was collected by filtration. The solids were dissolved in ethyl acetate, dried (sodium sulfate), and concentrated under reduced pressure. The residue was purified on silica gel using a gradient of 0 to 20% ethyl acetate in a mixture of chloroform and hexanes (1:1) as eluent. Product from chromatography was triturated with MTBE/hexanes to obtain clean product as yellow solid. Mother liquor was repurified in a similar fashion on silica gel followed by trituration to obtain more clean product in a 68% yield. $^1$H NMR ($CDCl_3$): δ 8.54 (1H, s), 8.15 (1H, d, J=9.4 Hz), 8.08 (1H, dd, J = 9.04, 1.9 Hz), 7.87 (1H, d, J=16.6 Hz), 7.55 (1H, d, J=16.6 Hz), 7.14 (1H, s), 6.90 (1H, s), 5.82 (1H, dd, J = 9.0, 3.0 Hz), 4.08-4.01 (1H, m), 3.84-3.76 (1H, m), 2.56 (3H, s), 2.62-2.54 (1H, m), 2.34 (3H, s), 2.24-2.10 (2H, m), 1.88-1.68 (3H, m).

**Example 5: 3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamine**

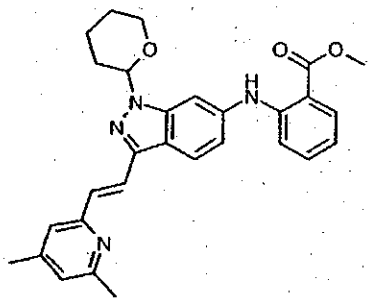


A suspension of 3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-6-nitro-1-(tetrahydro-pyran-2-yl)-1H-indazole (4.22g, 11.16mmol), iron powder (2.71g, 48.51mmol) and sat. aq. $NH_4Cl$ (25ml) in 25 ml of ethanol was heated at 45°C for 18hr. The reaction was cooled and

filtered through filter paper washing with methanol. The solvents were removed under reduced pressure and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 4.02g (quantitative) of a rust colored solid and was used without further purification.

$^1$H NMR (DMSO-d6) δ 7.79 (1H, s), 7.74 (1H, d, J = 16.4 Hz), 7.35 (1H, d, J = 16.4 Hz), 7.29 (1H, s), 6.96 (1H, s), 6.63 (2H, m), 5.57 (1H, dd, J = 2.4, 9.5 Hz), 5.44 (2H, broad s), 3.88 (1H, m), 3.67 (1H, m), 2.45 (3H, s), 2.37 (1H, m), 2.29 (3H, s), 1.99 (2H, m), 1.73 (1H, m), 1.57 (2H, m).

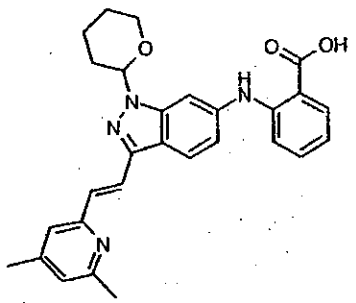
**Example 6: 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester**



A stirred suspension of 3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamine (870mg, 2.5mmol), 2-Bromo-benzoic acid methyl ester (0.44ml, 3.12mmol), R-BINAP (78mg, 0.125mmol), $Pd_2(dba)_3$ (29mg, 0.03mmol) and Cesium Carbonate (1.22g, 3.75mmol) in toluene( 6ml) was degassed and heated at 100°C for 18hr. The reaction mixture was cooled, poured into sat. $NaHCO_3$ and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was flash chromatographed on silica gel eluting a gradient of 5-10% EtOAc in$CH_2Cl_2$ to give 964mg (80%) of a yellow foam.

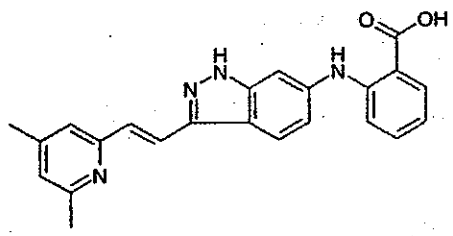
$^1$H NMR (DMSO-$d_6$) δ 9.49 (1H, s), 8.13 (1H, d, J = 8.7 Hz), 7.94 (1H, dd, J = 1.5, 8.0 Hz), 7.85 (1H, d, J = 16.4 Hz), 7.58 (1H, d, J = 1.5 Hz), 7.48 (1H, d, J = 16.4 Hz), 7.47 (1H, m), 7.37 (1H, d, J = 7.7 Hz), 7.34 (1H, s), 7.19 (1H, dd, J = 1.7, 8.7 Hz), 6.99 (1H, s), 6.89 (1H, t, J = 8.1 Hz), 5.83 (1H, d, J = 7.2 Hz), 3.88 (3H, s), 3.75 (1H, m), 2.48 (3H, s), 2.41 (2H, m), 2.31 (3H, s), 2.02 (2H, m), 1.75 (1H, m), 1.59 (2H, m). *Anal.* Calcd for $C_{29}H_{30}N_4O_3$ • 0.15 EtOAc: C, 71.71; H, 6.34; N, 11.30. Found: C, 71.60; H, 6.14; N, 11.37.

**Example 7: 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid**



To a stirred solution of 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester (1.98g, 4.11mmol) in THF:MeOH (12ml, 3:1) was added Potassium hydroxide (1.15g, 20.5mmol) dissolved in $H_2O$ (3ml). The reaction was heated at 70°C for 2hr, cooled, concentrated under reduced pressure to about 5ml and diluted with more water. The solution was neutralized with 2N HCl and the precipitate was collected by filtration and washed with water to give 2.00g (quantitative) of a bright yellow solid. $^1$H NMR (DSMO-$d_6$) δ13.12 (1H, broad s), 9.82 (1H, s), 8.13 (1H, d, J = 8.7 Hz), 7.95 (1H, dd, J = 1.5, 8.0 Hz), 7.89 (1H, d, J = 16.4 Hz), 7.60 (1H, s), 7.50 (1H, d, J = 16.4 Hz), 7.46 (1H, d, J = 6.9 Hz), 7.37 (1H, d, J = 7.7 Hz), 7.20 (1H, d, J = 8.7 Hz), 7.06 (1H, s), 6.86 (1H, t, J = 6.9 Hz), 5.85 (1H, d, J = 7.3 Hz), 3.82 (2H, m), 2.50 (3H, s, obscured by dmso), 2.48 (2H, m), 2.34 (3H, s), 2.03 (2H, m), 1.76 (1H, m), 1.59 (2H, m). *Anal.* Calcd for $C_{28}H_{26}N_4O_3 \bullet 0.5$ KOH: C, 67.72; H, 5.79; N, 11.28. Found: C, 67.65; H, 5.88; N, 11.07.

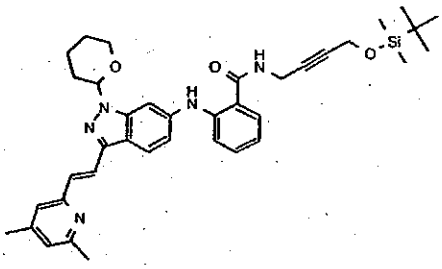
**Example 8: 2-{3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid p-toluene sulfonate**



A mixture of 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid (2 mmol) and p-toluene sufonic acid (10 mmol) in aqueous methanol (90%, 20mL) was stirred at 70C for 18 hr. After cooling, the resulting thick yellow slurry was filtered and the solids washed with methanol to give 2-{3-[2-(4,6-

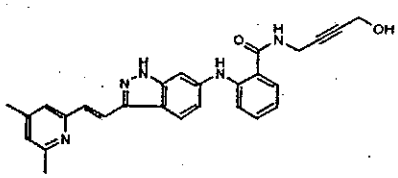
Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzoic acid as the tosylate salt in 85% yield as a pale yellow solid. $^1$H NMR (DMSO-$d_6$): δ 13.43 (1H, s), 9.78 (1H, s), 8.24-8.19 (2H, m), 8.09 (1H, d, J = 9.04 Hz), 7.95 (1H, dd, J = 7.9, 1.1 Hz), 7.62-7.55 (2H, m), 7.49-7.38 (5H, m), 7.20 (1H, dd, J=9.0, 1.9 Hz ), 7.09 (2H, d, J= 8.3 Hz), 6.86 (1H, dt, J = 7.9, 1.1 Hz), 2.67 (3H, s), 2.54 (3H, s), 2.27 (3H, s).

**Example 9: N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 33(a) step (v), in US Patent Application Serial Number 09/609,335, filed June 30, 2000, herein incorporated by reference in its entirety for all purposes, except using 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynylamine and 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid. $^1$H NMR (DMSO-$d_6$) δ 9.56 (1H, s), 9.01 (1H, t, J = 5.7 Hz), 8.06 (1H, d, J =8.7 Hz), 7.81 (1H, d, J = 16.4 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.41 (4H, m), 7.32 (1H, s), 7.09 (1H, dd, J = 1.8, 8.7 Hz), 6.98 (1H, s), 6.89 (1H, t, J = 8.0 Hz), 5.79 (1H, dd, J = 2.4, 9.2 Hz), 4.28 (2H, s), 4.09 (2H, m), 3.86(1H,m), 3.72 (1H, m), 2.46 (3H, s), 2.42 (1H, m), 2.30 (3H, s), 2.08 (2H, m), 1.74 (1H, m), 1.57 (2H, m), 0.80 (9H, s), 0.03 (6H, s). *Anal.* Calcd for $C_{38}H_{47}N_5O_3Si \bullet 0.7\ H_2O$: C, 68.89; H, 7.36; N, 10.57. Found: C, 68.99; H, 7.36; N, 10.21.

**Example 10: 2-{3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-(4-hydroxy-but-2-ynyl)-benzamide**

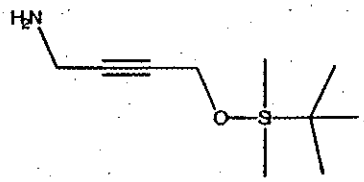


A stirred solution of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide (737mg, 1.13mmol) and p-Toluene-sulfonic acid (8.2ml, 12% in HOAc) was heated at

70°C for 2hr. The reaction was cooled, and cautiously poured into sat. $NaHCO_3$ and extracted with EtOAc (2x). The combined organic layers were washed with brine (2x), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was flash chromatographed on silica gel eluting $CH_2Cl_2$:EtOAc: MeOH (1:1:0.1) to give 225mg (44%) of a white solid. $^1H$ NMR (DMSO-$d_6$) δ 12.91 (1H, s), 9.84 (s, 1H), 9.01 (1H, t, J = 5.3 Hz), 8.07 (1H, d, J =8.7 Hz), 7.84 (1H, d, J = 16.4 Hz), 7.70 (1H, d, J = 7.2 Hz), 7.43 (3H, m), 7.31 (1H, s), 7.26 (1H, s), 7.02 (1H, dd, J = 1.6, 8.7 Hz), 6.97 (1H, s), 6.89 (1H, t, J = 6.7 Hz), 5.12 (1H, t, J = 5.8 Hz), 4.10 (2H, d, J = 5.3 Hz), 4.07 (2H, d, J = 5.8 Hz), 2.47 (3H, s), 2.31 (3H, s).

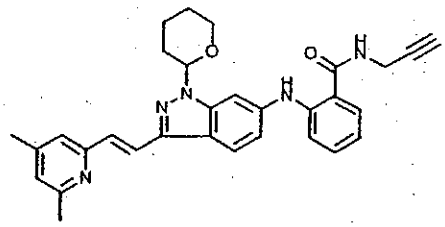
*Anal.* Calcd for $C_{27}H_{25}N_5O_2 \bullet 1.1\ H_2O$: C, 68.80; H, 5.82; N, 14.86. Found: C, 68.72; H, 5.81; N, 14.65.

**Example 11: 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynylamine**




To an ice cold, stirred solution of the known 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-yn-1-ol (3.14g, 15.7mmol) in THF (50ml) was added DBU (2.6ml, 17.4mmol) and DPPA (3.8ml, 17.6mmol). The solution was warmed to room temperature and stirred under an inert atmosphere overnight. The reaction was poured into sat. $NaHCO_3$ and the layers separated. The aqueous layer was re-extracted with EtOAc (2x) and the combined organic layers were dried ($Na_2SO_4$), and concentrated under vacuum. Triphenylphosphine (4.61g, 17.6mmol) was added to this crude azide dissolved in THF (50ml), followed by addition of $H_2O$ (0.44ml). The resultant solution was stirred overnight at room temperature, concentrated under reduced pressure and the residue was slurried in a 1:1 mixture of $Et_2O$/pet ether. The solids were removed and the filtrate was concentrated and purified by flash chromatography on silica gel eluting $CH_2Cl_2$/MeOH (19:1) to give an amber oil. $^1H$ NMR ($CDCl_3$) δ 4.19 (2H, t, J = 1.9Hz), 3.33 (2H, t, J = 1.9Hz), 0.79 (9H, s), 0.00 (6H, s).

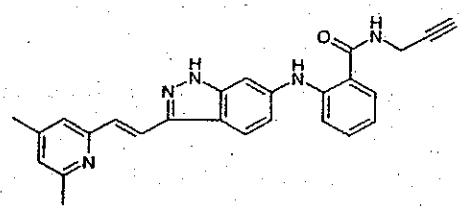
**Example 12: 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-N-prop-2-ynyl-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid and propargyl amine. $^1$H NMR (DMSO-$d_6$) δ 9.87 (1H, s), 9.04 (1H, t, J = 5.8 Hz), 8.08 (1H, d, J = 8.7 Hz), 7.83 (1H, d, J = 16.4 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.44 (4H, m), 7.34 (1H, s), 7.12 (1H, dd, J = 1.7, 8.7 Hz), 6.99 (1H, s), 6.91 (1H, t, J = 5.8 Hz), 5.81 (1H, dd, J = 2.4, 9.2 Hz), 4.07 (2H, dd, J = 2.5, 5.7 Hz), 3.88 (1H,m), 3.74 (1H, m), 3.12 (1H, t, J = 2.5 Hz), 2.48 (3H, s), 2.43 (1H, m), 2.31 (3H, s), 2.01 (2H, m), 1.74 (1H, m), 1.58 (2H, m).

*Anal.* Calcd for $C_{31}H_{31}N_5O_2 \bullet 1.1\ H_2O \bullet 0.3$ TBME: C, 70.73; H, 6.72; N, 12.69. Found: C, 70.56; H, 6.45; N, 12.49.

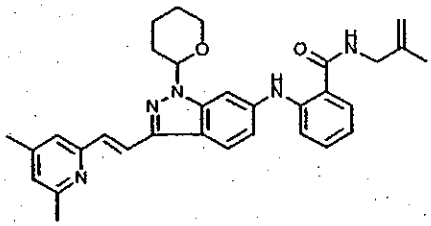
**Example 13: N-(prop-2-ynyl)-2-{3-[(E)-2-(2,4-dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



Prepared in a similar manner to that described for Example 7 except using *N*-(3-Cyclopropyl-prop-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$): δ 12.90 (1H, s), 9.78 (1H, s), 9.01 (1H, t, J = 5.3 Hz), 8.06 (1H, d, J = 8.3 Hz), 7.84 (1H, d, J = 16.2 Hz), 7.68 (1H, dd, J = 7.9, 1.1 Hz), 7.45-7.36 (3H, m), 7.30 (1H, s), 7.25 (1H, d, J = 1.5 Hz), 7.01 (1H, dd, J = 8.7, 1.9 Hz),

6.96 (1H, s), 6.88 (1H, dt, J = 6.8, 1.9 Hz), 4.04 (2H, dd, J = 5.6, 2.6 Hz), 3.11 (1H, t, J = 2.6 Hz), 2.46 (3H, s), 2.29 (3H, s).

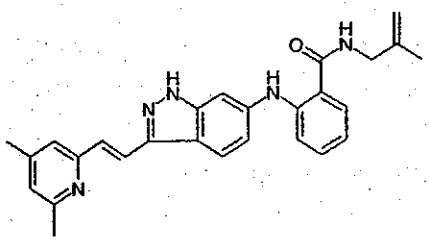
**Example 14: 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-N-(2-methyl-allyl)-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid and 2-Methyl-allylamine. $^1$H NMR (DMSO-$d_6$) δ 9.87 (1H, s), 8.82 (1H, t, J = 5.8 Hz), 8.07 (1H, d, J = 8.7 Hz), 7.82 (1H, d, J = 16.4 Hz), 7.74 (1H, d, J = 7.3 Hz), 7.43 (4H, m), 7.33 (1H, s), 7.10 (1H, d, J = 8.7 Hz), 6.99 (1H, s), 6.92 (1H, t, J = 7.8 Hz), 5.80 (1H, dd, J = 2.2, 9.2 Hz), 4.83 (2H, d, J = 11.8 Hz), 3.83 (4H,m), 2.47 (3H, s), 2.44 (1H, m), 2.31 (3H, s), 2.00 (2H, m), 1.75 (1H, m), 1.73 (3H, s), 1.58 (2H, m).

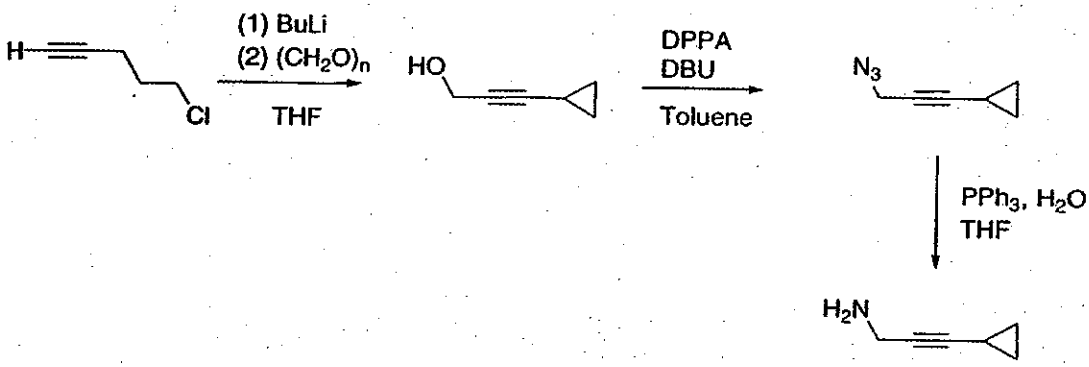
*Anal.* Calcd for $C_{32}H_{35}N_5O_2 \bullet 1.09\ H_2O$: C, 71.00; H, 6.92; N, 12.94. Found: C, 71.40; H, 6.89; N, 12.54.

**Example 15: 2-{3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-(2-methyl-allyl)-benzamide**

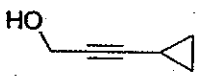


Prepared in a similar manner to that described for Example 7 except using *N*-(2-Methyl-allyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ 12.89 (1H, s), 9.75 (1H, s), 8.79 (1H, t, J=5.6 Hz), 8.05 (1H, d, J = 8.7 Hz), 7.85 (1H, d, J=16.2 Hz), 7.74 (1H, d, J=7.9 Hz), 7.45-7.33 (4H, m), 7.23 (1H, d, J= 1.5 Hz), 7.00-6.97 (2H, m), 6.90 (1H, dt, J = 7.9, 1.1 Hz), 4.81 (2H, d, J= 11.3 Hz), 3.81 (2H, d, J=5.6 Hz), 2.47 (3H, s), 2.30 (3H, s), 1.71 (3H, s).

Alternative Synthetic Scheme

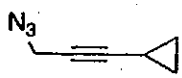



**Example 16(a):Cyclopropyl-prop-2-yn-1-ol**




To a round bottom flask containing 70 mL anhydrous THF cooled in –10°C ice bath was added 65.6 mL 1.6M BuLi in hexanes (105 mmol). 5-Chloro-pent-1-yne (5.13 g, 50 mmol) was introduced slowly while maintaining temperature at –10 to 0°C. The mixture was stirred at 0°C for two hours under argon. Paraformaldehyde (3 g, 100 mmol) was added as a solid. The mixture was warmed up slowly to room temperature and stirred overnight under argon. The next day, water was added and c.a. 50 mL 1 N aqueous HCl was added. The mixture was extracted with ethyl acetate and the combined organic layers was washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The crude product was purified by column eluting with 20% $Et_2O$ in hexanes to give 3 g 3-cyclopropyl-prop-2-yn-1-ol as an oil (62% yield). $^1H$ NMR ($CDCl_3$) δ 4.22 (dd, 2H, $J$ = 6.04, 2.01 Hz), 1.46 (t, 1H, $J$ = 6.04 Hz), 1.26 (m, 1H), 0.77 (m, 2H), 0.70 (m, 2H).

**Example 16(b): 3-Cyclopropyl-prop-2-ynylazide**




3-Cyclopropyl-prop-2-yn-1-ol (3.28 g, 34.1 mmol) was dissolved in 40 mL toluene, DPPA (11.26 g, 40.9 mmol) was added, followed with DBU (6.24 g, 40.9 mmol) while maintaining temperature with a water bath. The mixture was stirred at room temperature for one hour and was diluted with 100 mL hexane and 15 mL $CH_2Cl_2$. The mixture was washed with water four times and once with brine, dried over $Na_2SO_4$, filtered and

concentrated under rotvap with cold water bath to remove most of organic solvent leaving some toluene (product volatile). The residual oil was used for the next step.

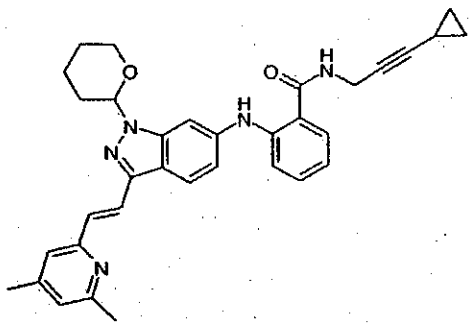
$^1$H NMR ($CDCl_3$) δ 3.85 (s, 2H), 1.26 (m, 1H), 0.80 (m, 2H), 0.72 (m, 2H).

**Example 16(c): 3-Cyclopropyl-prop-2-ynylamine**



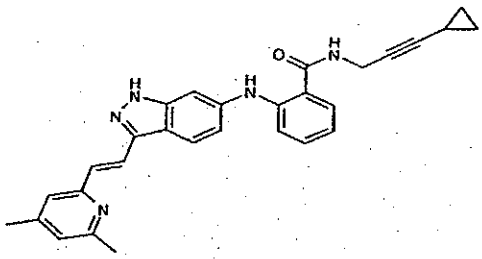
3-Cyclopropyl-prop-2-ynylazide (c.a. 34 mmol) was dissolved in 100 mL THF, 1 mL water was added, followed with addition of $PPh_3$ (13.37 g, 51 mmol) as a solid while maintaining temperature with a water bath. The mixture was stirred at room temperature for one hour. 150 mL 1N aqueous HCl was added to the mixture. The mixture was washed with methylene chloride three times. The aqueous layer was basified with 5 N NaOH to pH 10~12. The mixture was extracted with ethyl acetate. The aqueous layer was checked with TLC staining to monitor progress of extraction of amine to the organic phase. The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated to give 1.62 g desired product (product volatile, contains residual EtOAc solvent) (50 % yield for two steps). $^1$H NMR ($CDCl_3$) δ 3.37 (d, 2H, $J$ = 2 Hz), 1.22 (m, 1H), 0.74 (m, 2H), 0.65 (m, 2H).

**Example 17: *N*-(3-Cyclopropyl-prop-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide**



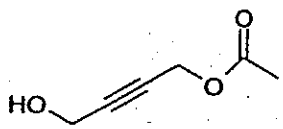
Was prepared in a similar manner to that described for Example 6 above, except using 2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid E and 3-Cyclopropyl-prop-2-ynylamine. $^1$H NMR ($CDCl_3$): δ 9.51 (1H, s), 7.97 (1H, d, J = 8.7 Hz), 7.81 (1H, d, J = 16.6 Hz), 7.51-7.42 (3H, m), 7.34-7.29 (2H, m), 7.16 (1H, s), 7.11 (1H, dd, J = 9.0, 1.9 Hz), 6.85 (1H, s), 6.81 (1H, dt, J = 7.2, 1.1 Hz), 6.23 (1H, t, J = 7.2 Hz), 5.61 (1H, dd, J = 9.0, 2.6 Hz), 4.17 (2H, dd, J = 5.3, 2.3 Hz), 4.07-4.00 (1H, m), 3.75-3.66 (1H, m), 2.63-2.50 (1H, m), 2.54 (3H, s), 2.32 (3H, s), 2.20-2.02 (2H, m), 1.79-1.62 (3H, m), 1.29-1.19 (1H, m), 0.77-0.67 (4H, m).

**Example 18: N-(3-Cycloprop-2-ynyl)-2-{3-[(E)-2-(4,6-dimethyl-pyridin-2-yl)--vinyl]-1H-indazol-6-ylamino}-benzamide**



Prepared in a similar manner to that described for Example 7 above, except using 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-N-prop-2-ynyl-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$): δ 12.90 (1H, s), 9.79 (1H, s), 8.91 (1H, t, J = 5.6 Hz), 8.06 (1H, d, J = 8.7 Hz), 7.83 (1H, d, J = 16.2 Hz), 7.68 (1H, dd, J = 7.9, 1.1 Hz), 7.49-7.38 (3H, m), 7.29 (1H, s), 7.25 (1H, d, J = 1.9 Hz), 6.99 (1H, dd, J = 9.0, 2.3 Hz), 6.96 (1H, s), 6.88 (1H, dt, J = 7.9, 1.5 Hz), 4.00 (2H, dd, J = 5.6, 1.9 Hz), 2.46 (3H, s), 2.29 (3H, s), 1.31-1.23 (1H, m), 0.75-0.70 (2H, m), 0.57-0.52 (2H, m).

**Example 19(a): 2-Butyne-1,4-diol, monoacetate**



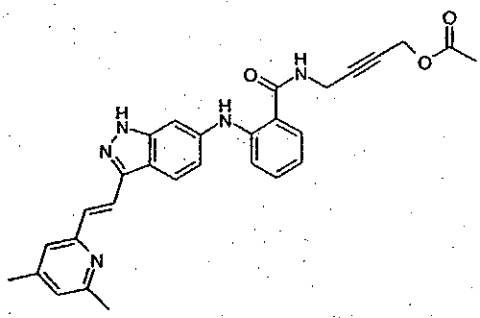
To a solution of butyne-1,4-diol (5g, 58 mmol) in dry THF at RT was added portion-wise sodium hydride (60% dispersion in oil, 2.32g, 58mmol). After 4.3 hr, acetyl chloride (4.12 mL, 58 mmol) was added. After stirring at RT for 22 hr, the mixture was concentrated under reduced pressure. The residue was concentrated twice from toluene before purification on silica gel using ethyl acetate/dichloromethane (1:3) as eluent to give 2-Butyne-1,4-diol, monoacetate as an oil in 49% yield. $^1$H NMR (DMSO-$d_6$) δ 5.23 (1H, bs), 4.70 (2H, t, J= 1.8 Hz), 4.09 (2H, s), 2.03 (3H, s).

**Example 19(b): Acetic acid 4-amino-but-2-ynyl ester**



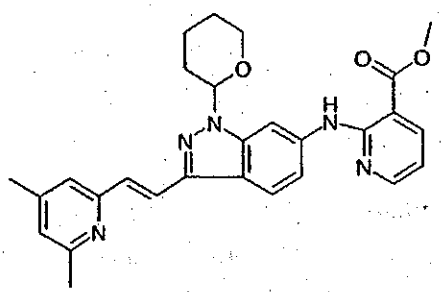
Prepared in a similar manner as described in Example 8 except 2-Butyne-1,4-diol monoacetate was used instead of 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-yn-1-ol. $^1$H NMR (DMSO-$d_6$) δ 4.77 (2H, s), 4.20 (2H, s), 2.04 (3H, s).

**Example 20: Acetic acid 4-(2-{3-[(E)-2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1*H*-indazol-6-ylamino}-benzoylamino)-but-2-ynyl ester**



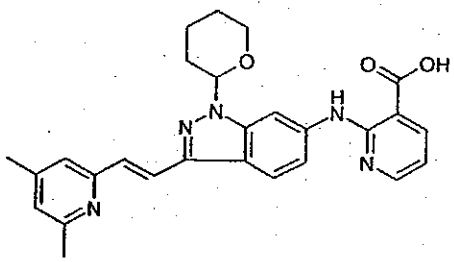
Prepared in a similar manner to that described for Example 6 above, except using 2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl] 1*H*-indazol-6-ylamino]-benzoic acid p-toluene sulfonate and Acetic acid 4-amino-but-2-ynyl ester. $^1$H NMR ($CD_3CN$): δ 11.00 (1H, bs), 9.59 (1H, s), 7.99 (1H, d, J = 8.6 Hz), 7.86 (1H, d, J = 16.4 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.49-7.37 (4H, m), 7.32 (1H,s ), 7.21 (1H, s), 7.06 (1H, dd, J = 8.8, 1.8 Hz), 6.96 (1H, s), 6.90 (1H, t, J = 7.8 Hz), 4.63 (2H, s), 4.16 (2H, d, J = 5.6 Hz), 2.49 (3H, s), 2.32 (3H, s), 2.01 (3H, s).

**Example 21: 2-[3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinic acid methyl ester**



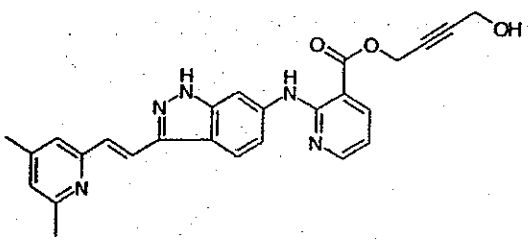
Prepared in a similar manner to that described for Example 3 above except using 2-Bromo-nicotinic acid methyl ester instead of 2-bromo-benzoic acid methyl ester. $^1$H NMR (DMSO-$d_6$): δ 10.36 (1H, s), 8.50 (1H, dd, J = 4.7, 1.9 Hz), 8.36 (1H, d, J=1.4 Hz), 8.30 (1H, dd, J = 7.8, 2.0 Hz), 8.08 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J=16.4 Hz), 7.48 (1H, d, J = 7.5 Hz), 7.44 (1H, s), 7.33 (1H, s), 6.98-6.93 (2H, m), 5.80 (1H, d, J = 7.0 Hz), 2.93 (3H, s), 3.93-3.90 (1H, m), 3.80-3.75 (1H, m), 2.46 (3H, s), 2.30 (3H, s), 2.10-1.97 (2H, m), 1.89-1.60 (3H, m).

**Example 22: 2-[3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-nicotinic acid**



Prepared in a similar manner to that described for Example 4 except using 2-[3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinic acid methyl ester instead of 2-[3-[2-(4,6-dim ethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester. $^1$H NMR (DMSO-$d_6$): δ 10.73 (1H, s), 8.49 (1H, d, J = 1.9 Hz), 8.45 (1H, s), 8.31 (1H, dd, J = 7.7, 1.8 Hz), 8.16-7.97 (3H, m), 7.70 (1H, d, J = 16.4 Hz), 7.50 (1H, d, J=8.6 Hz ), 7.37 (1H, s), 6.96 (1H, dd, J = 7.7, 4.8 Hz), 5.87 (1H, d, J = 8.4 Hz ), 3.95-3.90 (1H, m), 3.79-3.70 (1H, m), 2.63 (3H, s), 2.47 (3H, s), 2.07-1.99 (2H, m), 1.81-1.62 (3H, m).

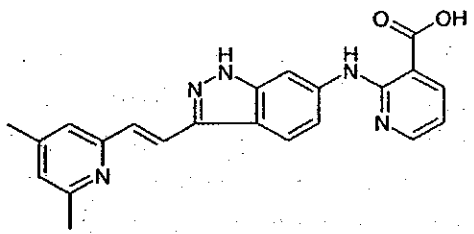
**Example 23: 2-{3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-(4-hydroxy-but-2-ynyl)-nicotinamide**



A crude mixture of *N*-(4-Hydroxy-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinamide and *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-

pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinamide was prepared from 2-[3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-nicotinic acid and 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynylamine in a similar fashion to that described for Example 6 above and subsequently converted to 2-{3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-(4-hydroxy-but-2-ynyl)-nicotinamide in a similar fashion to that described for Example 7 except using a mixture of *N*-(4-Hydroxy-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinamide and *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-nicotinamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$): δ 12.99 (1H, s), 11.21 (1H, s), 9.26 (1H, t, J = 5.3 Hz), 8.50 (1H, d, J = 1.9 Hz), 8.41 (1H, dd, J = 4.9, 1.9 Hz), 8.16 (1H, dd, J = 8.3, 1.9 Hz), 8.04 (1H, d, J = 9.0 Hz), 7.85 (1H, d, J = 16.6 Hz), 7.42 (1H, d, J = 16.6 Hz), 7.31 (1H,s ), 7.06 (1H, dd, J = 8.7, 1.5 Hz), 6.96 (1H, s), 6.93 (1H, dd, J = 7.5, 4.9 Hz), 5.14 (1H, t, J = 5.6 Hz), 4.16 (2H, d, J = 5.6 Hz), 4.08 (2H, d, J = 7.2 Hz), 2.46 (3H, s), 2.30 (3H, s).

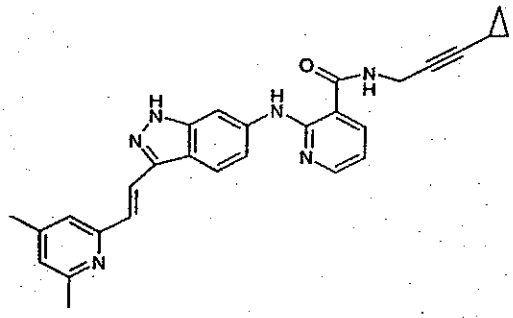
**Example 24: 2-{3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1*H*-indazol-6-ylamino}-nicotinic acid p-toluene sulfonate**



Prepared in a similar manner to that described for Example 5 except using 2-[3-[(E)-2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-nicotinic acid instead of 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid.

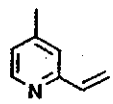
$^1$H NMR (DMSO-$d_6$): δ 13.49 (1H, s), 10.80 (1H, s), 8.63 (1H, d, J = 1.5 Hz), 8.49 (1H, dd, J = 4.8, 1.9 Hz), 8.31 (1H, dd, J = 7.7, 1.9 Hz), 8.24-8.19 (2H, m), 8.06 (1H, d, J = 8.8 Hz), 7.60-7.55 (2H, m), 7.46 (2H, d, J = 8.1 Hz), 7.22 (1H, dd, J = 8.8, 1.7 Hz ), 7.09 (2H, d, J= 7.9 Hz), 6.95 (1H, dd, J = 7.7, 4.7Hz), 2.66 (3H, s), 2.54 (3H, s), 2.27 (3H, s).

**Example 25: *N*-(3-Cyclopropyl-prop-2-ynyl)-2-{3-[(E)-2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1*H*-indazol-6-ylamino}-nicotinamide**



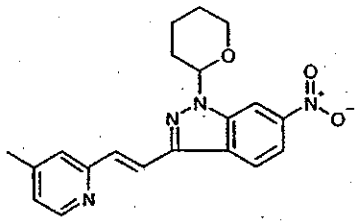
Prepared in a similar manner to that described for Example 6 above, except using 2-{3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1*H*-indazol-6-ylamino)-nicotinic acid p-toluene sulfonate and 3-Cyclopropyl-prop-2-ynylamine. $^1$H NMR (DMSO-$d_6$): δ13.01 (1H, s), 11.20 (1H, s), 9.19 (1H, bt), 8.51 (1H, s), 8.40 (1H, d, J = 4.9 Hz), 8.15 (1H, d, J = 7.5 Hz), 8.05 (1H, d, J = 8.7 Hz), 7.83 (1H, d, J = 16.4 Hz), 7.42 (1H, d, J = 16.4 Hz), 7.31 (1H, s), 7.05 (1H, d, J = 8.3 Hz), 6.96 (1H, s), 6.92 (1H, dd, J = 7.5, 4.9 Hz), 4.06 (2H, d, J = 4.14 Hz), 2.46 (3H, s), 2.29 (3H, s), 1.33-1.28 (1H, m), 0.77-0.72 (2H, m), 0.60-0.55 (2H, m).

**Example 26: 4-Methyl-2-vinyl-pyridine**



A yellow mixture of 2-bromo-4-methyl-pyridine (Aldrich, 5.2 g, 30.5 mmol, 1.0 eq), 2,6-di-tert-butyl-4-methyl-phenol (Aldrich, 67 mg, 0.3 mmol, 1mol%), tributyl-vinyl-stannane (Aldrich, 26.8 mL, 91.5 mmol, 3.0 eq) and tetrakis(triphenylphosphine) palladium (0) (Strem, 1.8 g, 1.5 mmol, 5mol%) in toluene (100 mL) was degassed and purged with argon. An amber solution was obtained after the mixture was warmed to 100 °C. The reaction mixture was quenched after 18 hours by the addition of 1.0 M HCl. The acidic extract was washed with ether, adjusted to pH 9 with solid sodium bicarbonate, and extracted with ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product (3.7 g of a brown oil) was purified by flash chromatography (silica) and eluted with 0-5% ethyl acetate-dichloromethane, which gave a clear oil (1.9 g, 53%). $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 8.39 (1H, d, J = 4.9 Hz), 7.33 (1H, s), 7.10 (1H, dd, J = 5.0, 0.8 Hz), 6.77 (1H, dd, 17.5, 10.8 Hz), 6.20 (1H, dd, J = 17.5, 1.7 Hz), 5.44 (1H, dd, J = 10.8, 1.8 Hz), 2.31 (3H, s). ESIMS m/z 120 $(M + H)^+$.

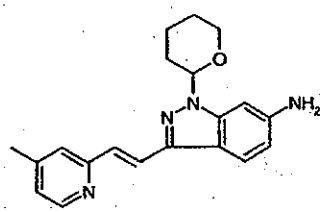
**Example 27: 3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-6-nitro-1-(tetrahydro-pyran-2-yl)-1H-indazole**



A suspension of 4-Methyl-2-vinyl-pyridine (Example 23) (1.9g, 15.97mmol), 6-Nitro-1-(tetrahydro-pyran-2-yl)-3-vinyl-1H-indazole (4.96g, 13.3mmol), $Pd(OAc)_2$ (149mg, 0.66mmol), $P(o\text{-}tolyl)_3$, and DIEA(3.5ml, 19.96mmol) in degassed DMF (50ml) was heated under argon at 100°C for 18hr. The reaction mixture was cooled and the solids removed by filtration washing with EtOAc. The filtrate was diluted wih EtOAc and washed with brine (2x), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel eluting Hexanes: EtOAc (3:1) to give 3.40g (70%) of a bright yellow solid.

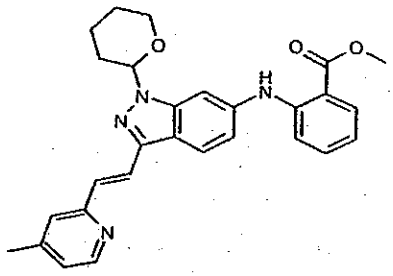
$^1H$ NMR ($CDCl_3$) δ 8.56 (1H, s), 8.50 (1H, d, J = 5.0 Hz), 8.11 (2H, m), 7.89 (1H, d, J = 16.3 Hz), 7.61 (1H, s), 7.03 (1H, d, J = 4.3 Hz), 5.83 (1H, dd, J = 2.6, 9.0 Hz), 4.06 (1H, m), 3.82 (1H, m), 2.58 (1H, m), 2.39 (3H, s), 2.18 (2H, m), 1.78 (3H, m). *Anal.* Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.80; H, 5.52; N, 15.15.

**Example 28: 3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamine**



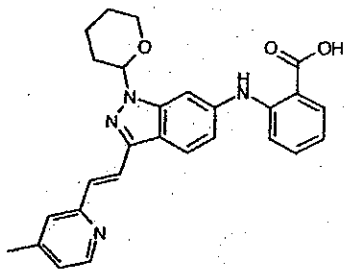
Prepared in a similar manner to that described for Example 2 except using [2-(4-Methyl-pyridin-2-yl)-vinyl]-6-nitro-1-(tetrahydro-pyran-2-yl)-1H-indazole (Example 24) instead of 3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-6-nitro-1-(tetrahydro-pyran-2-yl)-1H-indazole. $^1H$ NMR (DMSO-$d_6$): δ 8.43 (1H, d, J=4.8 Hz), 7.79-7.73 (2H, m), 7.50 (1H, s), 7.39 (1H, d, J=16.4 Hz), 7.09 (1H, d, J=4.8 Hz), 6.64-6.62 (2H, m), 5.57 (1H, dd, J = 9.8, 2.5 Hz), 5.48 (2H, bs), 3.92-3.85 (1H, m), 3.72-3.64 (1H, m), 2.43-2.34 (1H, m), 2.33 (3H, s), 2.07-2.00 (1H, m), 1.96-1.90 (1H, m), 1.79-1.66 (1H, m), 1.60-1.53 (2H, m).

**Example 29: 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester**



Prepared in a similar manner to that described for Example 3 except using 3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamine instead of 3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamine. $^1$H NMR (DMSO-$d_6$): δ 9.48 (1H, s), 8.45 (1H, d, J = 4.9 Hz), 8.13 (1H, d, J=8.7 Hz), 7.93 (1H, dd, J = 8.3, 1.9 Hz), 7.86 (1H, d, J = 16.2 Hz), 7.58 (1H, d, J=1.9 Hz), 7.54-7.44 (3H, m), 7.36 (1H, d, J = 7.5 Hz), 7.18 (1H, dd, J = 8.7, 1.9 Hz), 7.11 (1H, d, J = 4.9 Hz), 6.87 (1H, t, J = 8.3 Hz), 5.83 (1H, dd, J = 9.4, 2.3 Hz), 3.87 (3H, 1H), 3.93-3.84 (1H, m), 3.77-3.69 (1H, m), 2.46-2.37 (1H, m), 2.34 (3H, s), 2.10-1.94 (2H, m), 1.81-1.53 (3H, m).

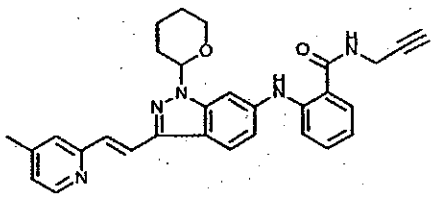
**Example 30: 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid**



Prepared in a similar manner to that described for Example 4 above except that 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester was used instead of 2-[3-[2-(4,6-Dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid methyl ester (Example 3). $^1$H NMR (DMSO-$d_6$) δ 13.17 (1H, broad s), 9.83 (1H, s), 8.51 (1H, d, J = 5.2 Hz), 8.14 (1H, d, J = 8.7 Hz), 7.95 (1H, d, J = 16.4 Hz), 7.94 (dd, 1H, J = 1.5, 8.0 Hz), 7.73 (1H, s), 7.60 (1H, d, J = 1.5 Hz), 7.59 (1H, s), 7.54 (1H, s), 7.46 (1H, m), 7.37 (1H, d, J = 7.6 Hz), 7.23

(2H, m), 6.86 (1H, t, J = 6.9 Hz), 5.87 (1H, d, J = 7.6 Hz), 3.90 (1H, m), 3.76 (1H,m), 2.45 (1H,m), 2.41 (3H, s), 2.03 (2H, m), 1.77 (1H, m), 1.59 (2H, m).

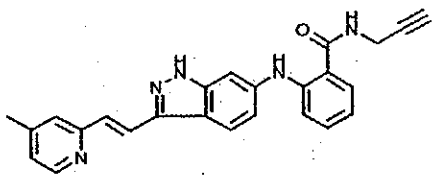
**Example 31: 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-N-prop-2-ynyl-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using propargyl amine and 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid. $^1$H NMR (DMSO-$d_6$) δ 9.87 (1H, s), 9.03 (1H, t, J = 5.5 Hz), 8.46 (1H, d, J = 4.9 Hz), 8.08 (1H, d, J = 8.7 Hz), 7.86 (1H, d, J = 16.4 Hz), 7.69 (1H, d, J = 7.3Hz), 7.53 (1H, s), 7.44 (4H, m), 7.13 (2H, m), 6.91 (1H, t, J = 7.9 Hz), 5.81 (1H, dd, J = 2.2, 9.6 Hz), 4.07 (2H, dd, J =2.5, 5.5 Hz), 3.89 (1H,m), 3.75 (1H, m), 3.12 (1H, t, J = 2.5 Hz), 2.42 (1H, m), 2.36 (3H, s), 2.00 (2H, m), 1.75 (1H, m), 1.58 (2H, m).

*Anal.* Calcd for $C_{30}H_{29}N_5O_2 \bullet 0.25$ TBME: C, 73.07; H, 6.28; N, 13.64. Found: C, 72.95; H, 6.30; N, 13.64.

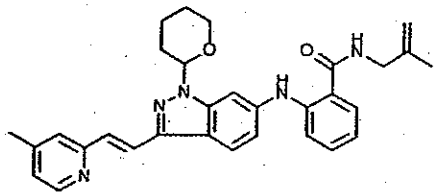
**Example 32: 2-{3-[(E)-2-(4-Methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-prop-2-ynyl-benzamide**



Prepared in a similar manner to that described for Example 7 except that 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-N-prop-2-ynyl-benzamide was used instead of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ 12.93,,s), 9.79 (1H, s), 9.02 (1H, t, J = 5.4 Hz), 8.45 (1H, d, J = 4.9 Hz), 8.08 (1H, d, J = 8.7 Hz), 7.88 (1H, d, J = 16.4 Hz), 7.69 (1H, d, J = 7.7 Hz), 7.45 (4H, m), 7.27 (1H, s), ), 7.10 (1H, d, J = 4.9 Hz), 7.03 (1H, d, J = 8.8 Hz), 6.90 (1H, t, J = 7.9 Hz), 4.06 (2H, dd, J = 2.4, 5.4 Hz), 3.12 (1H, t, J = 2.4 Hz), 2.35 (3H, s).

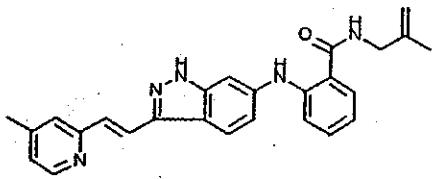
*Anal.* Calcd for $C_{25}H_{21}N_5O \bullet 0.35\ CH_2Cl_2$: C, 69.64; H, 5.00; N, 16.02. Found: C, 69.65; H, 5.15; N, 15.80.

**Example 33: N-(2-Methyl-allyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using 2-Methyl-allylamine and 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid. $^1$H NMR (DMSO-$d_6$) δ 9.86 (1H, s), 8.81 (1H, t, J = 5.5 Hz), 8.46 (1H, d, J = 4.9 Hz), 8.07 (1H, d, J = 8.9 Hz), 7.86 (1H, d, J = 16.4 Hz), 7.75 (1H, d, J = 7.7 Hz), 7.54 (1H, s), 7.50 (1H, d, J = 16.4 Hz), 7.43 (3H, m), 7.11 (2H, m), 6.92 (1H, t, J = 8.1 Hz), 5.81 (1H, dd, J = 2.5, 9.8 Hz), 4.83 (2H, d, J = 11.5 Hz), 3.81 (4H, m), 2.41 (1H, m), 2.35 (3H, s), 2.00 (2H, m), 1.76 (1H, m), 1.73 (3H, s), 1.58 (2H, m). *Anal.* Calcd for $C_{31}H_{33}N_5O_2 \bullet 0.80$ TBME: C, 72.71; H, 7.43; N, 12.11. Found: C, 72.43; H, 7.57; N, 12.02.

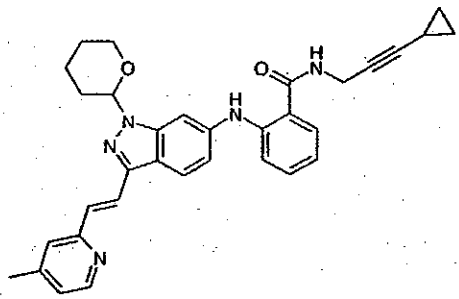
**Example 34: N-(2-Methyl-allyl)-2-{[(E)-2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



Prepared in a similar manner to that described for Example 7 except that N-(2-Methyl-allyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide was used instead of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ 12.90 (1H, s), 9.76 (1H, s), 8.80 (1H, t, J = 5.5 Hz), 8.45 (1H, d, J = 5.1 Hz), 8.07 (1H, d, J = 8.9 Hz), 7.88 (1H, d, J = 16.4 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.51 (1H, s), 7.48 (1H, d, J = 16.4 Hz), 7.43 (2H, m), 7.24 (1H, s), 7.10 (1H, d, J = 4.9 Hz), 7.00 (1H, dd, J = 1.9, 8.9 Hz), 6.91 (1H, t, J = 8.1 Hz), 4.82 (2H, d, J = 11.3 Hz), 3.83 (2H, d, J = 5.8 Hz), 2.35 (3H, s), 1.73 (3H, s).

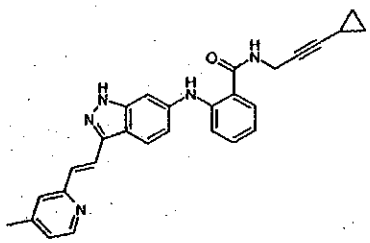
*Anal.* Calcd for $C_{26}H_{25}N_5O \bullet 0.20\ H_2O$: C, 73.11; H, 5.99; N, 16.40. Found: C, 73.13; H, 6.03; N, 16.13.

**Example 35: *N*-(3-Cyclopropyl-prop-2-ynyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide**



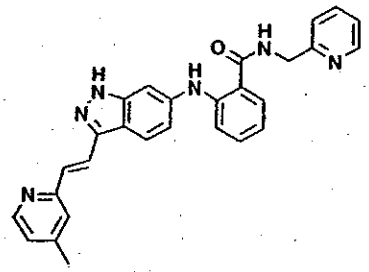
Prepared in a similar manner to that described for Example 6 above, except using 2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid and 3-Cyclopropyl-prop-2-ynylamine. $^1$H NMR (DMSO-$d_6$): δ 9.88 (1H, bs), 8.93 (1H, bt), 8.46 (1H, d, J = 4.9 Hz), 8.08 (1H, d, J = 8.7 Hz), 7.85 (1H, d, J = 16.4 Hz), 7.69 (1H, d, J = 7.6 Hz), 7.54-7.40 (5H, m), 7.14-7.11 (2H, m), 6.90 (1H, t, J = 6.1 Hz), 5.81 (1H, d, J = 7.5 Hz), 4.02 (2H, d, J = 3.6 Hz), 3.95-3.85 (1H, m), 3.79-3.72 (1H, m), 2.49-2.35 (1H, m), 2.35 (3H, s), 2.15-2.01 (2H, m), 1.87-1.55 (3H, m), 1.30-1.25 (1H, m), 0.77-0.70 (2H, m), 0.59-0.54 (2H, m).

**Example 36: N-(3-Cycloprop-2-ynyl)-2-{3-[(E)-2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



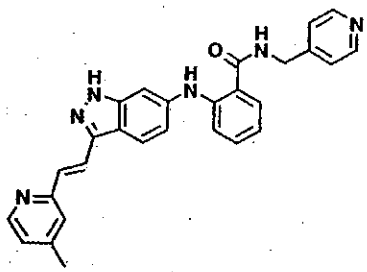
Prepared in a similar manner to that described for Example 7 above except using *N*-(3-cycloprop-2-ynyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$): δ 12.91 (1H, s), 9.79 (1H, s), 8.91 (1H, t, J = 5.6 Hz), 8.44 (1H, d, J = 4.9 Hz), 8.06 (1H, d, J = 8.7 Hz), 7.87 (1H, d, J = 16.6 Hz), 7.67 (1H, dd, J = 7.9, 1.5 Hz), 7.50-7.35 (4H, m), 7.24 (1H, d, J = 1.9 Hz), 7.09 (1H, d, J = 4.9 Hz), 7.00 (1H, dd, J = 8.7, 1.5 Hz), 6.88 (1H, dt, J = 4.1, 1.5 Hz), 4.00 (2H, dd, J = 5.3, 1.9 Hz), 2.34 (3H, s), 1.31-1.23 (1H, m), 0.75-0.69 (2H, m), 0.56-0.52 (2H, m).

**Example 37: 2-{3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-pyridin-2-ylmethyl-benzamide**



Prepared in a similar manner to that described for Example 6 and Example 7 above except using 2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid and C-Pyridin-2-yl-methylamine. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 12.91 (1H, s), 9.77 (1H, s), 9.19 (1H, t, J = 5.8 Hz), 8.50 (1H, d, J = 4.1 Hz), 8.45 (1H, d, J = 5.0Hz), 8.06 (1H, d, J = 8.8 Hz), 7.88 (1H, d, J = 16.4 Hz), 7.82-7.70 (2H, m), 7.51-7.25 (7H, m), 7.10 (1H, d, J = 4.6 Hz), 6.98 (1H, dd, J = 8.8, 1.8 Hz), 6.96-6.91 (1H, m), 4.58 (2H, d, J = 5.9 Hz), 2.35 (3H, s). ESIMS m/z 461 $(M + H)^+$. Anal. Calcd. for $C_{28}H_{24}N_6O$ x 0.3 MTBE: C, 72.71; H, 5.77; N, 17.25. Found: C, 72.38; H, 5.80; N, 16.88.

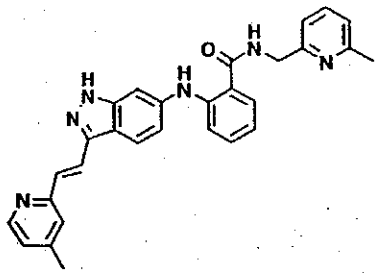
**Example 38: 2-{3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-pyridin-4-ylmethyl-benzamide**



Prepared in a similar manner to that described for Examples 6 and 7 above except using 2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid and C-Pyridin-4-yl-methylamine.

$^1$H NMR (DMSO-$d_6$, 300 MHz) δ 12.90 (1H, s), 9.73 (1H, s), 9.21 (1H, t, J = 5.9 Hz), 8.49-8.44 (3H, m), 8.06 (1H, d, J = 8.7 Hz), 7.88 (1H, d, J = 16.4 Hz), 7.81 (1H, d, J = 7.5 Hz), 7.51-7.40 (4H, m), 7.31 (2H, d, J = 5.9 Hz), 7.24 (1H, s), 7.11 (1H, d, J = 4.4 Hz), 7.00 (1H, dd, J = 8.7, 1.7Hz), 6.97-6.92 (1H, m), 4.50 (2H, d, J = 5.9 Hz), 2.35 (3H, s). ESIMS m/z 461 $(M + H)^+$. Anal. Calcd. for $C_{28}H_{24}N_6O$ x 0.4 $H_2O$ x 0.7 MTBE: C, 71.36; H, 6.45; N, 15.85. Found: C, 71.27; H, 6.29; N, 15.53.

**Example 39: N-(6-Methyl-pyridin-2-ylmethyl)-2-{3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**

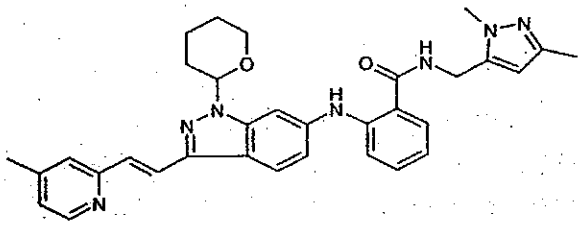


Prepared in a similar manner to that described for Examples 6 and 7 above except using 2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid and C-(6-Methyl-pyridin-2-yl)-methylamine.

$^1$H NMR (DMSO-$d_6$, 300 MHz) δ12.92 (1H, s), 9.76 (1H, s), 9.20 (1H, t, J = 5.8 Hz), 8.44 (1H, d, J = 4.9 Hz), 8.05 (1H, d, J = 8.6 Hz), 7.86 (1H, d, J = 16.4 Hz), 7.81 (1H, d, J = 7.7 Hz), 7.59 (1H, t, J = 7.7 Hz), 7.49-7.37 (4H, m), 7.23 (1H, s), 7.11-7.08 (3H, m), 6.99 (1H, dd, J = 8.7, 1.6 Hz), 6.95-6.90 (1H, m), 4.51 (2H, d, J = 5.9 Hz), 2.42 (3H, s), 2.33 (3H, s). ESIMS m/z 475 $(M + H)^+$. Anal. Calcd. for $C_{29}H_{26}N_6O$ x 0.4 DCM: C, 68.98; H, 5.29; N, 16.39. Found: C, 68.84; H, 5.42; N, 16.20.

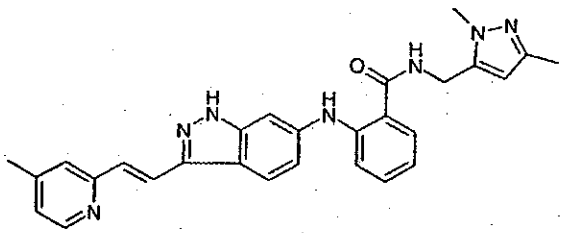
**Example 40: *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[(E)-3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide**

Prepared in a similar manner to that described for Example 6 above, except using



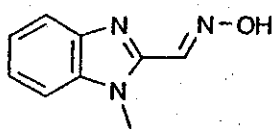
2-{3-[2-(4-methyl-pyridin-2-yl-vinyl)-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid and *C*-(2,5-Dimethyl-2*H*-pyrazol-3-yl)-methylamine. $^1$H NMR (DMSO-$d_6$) δ 9.81(1H, s), 9.05 (1H, bt), 8.46 8.7 Hz), 7.85 (1H, d, J=16.4 Hz), 7.71 (1H, d, J=7.5 Hz), 7.54-7.40 (5H, m), 7.11-7.09 (2H, m), 6.91 (1H, t, J = 6.9 Hz), 5.94 (1H, s), 5.80 (1H, d, J=7.3Hz), 4.45 (2H, d, J=5.5 Hz), 3.93-3.85 (1H, m), 3.78-3.69 (1H, m), 3.73 (3H, s), 2.45-2.35 (1H, m), 2.35 (3H, s), 2.07 (3H, s), 2.06-1.95 (2H, m), 1.85-1.53 (m, 3H).

**Example 41: N-(2,5-Dimethyl-2H-pyrazol-3-ylmethyl)-2-{3-[(E)-2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



Prepared in a similar manner to that described for Example 7 except using *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[(E)-3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ 12.90 (1H, s), 9.70 (1H, s), 9.03 (1H, t, J=6.0 Hz), 8.44 (1H, d, J = 4.9 Hz), 8.06 (1H, d, J = 9.0 Hz), 7.87 (1H, d, J=16.2 Hz), 7.70 (1H, d, J=7.5 Hz), 7.50-7.38 (4H, m), 7.22 (1H, s), 7.1 (1H, d, J = 5.6 Hz), 6.99 (1H, dd, J = 8.7, 1.5 Hz), 6.90 (1H, dt, J=7.9, 1.9 Hz), 5.91 (1H, s), 4.43 (2H, d, J=5.6Hz), 3.72 (3H, s), 2.34 (3H, s), 2.05 (3H, s).

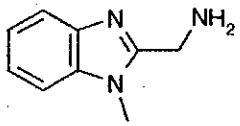
**Example 42: 1-Methyl-1H-benzoimidazole-2-carbaldehyde oxime**



To a stirred suspension of 1-Methyl-1H-benzoimidazole-2-carbaldehyde (980mg, 6.61mmol) in $H_2O$ (10ml) was added a solution of Sodium Acetate (3.25g, 39.68mmol) and Hydroxylamine hydrochloride (1.38g, 19.84mmol) in 10ml of $H_2O$. The reaction was stirred at rt for 2hr and the thick precipitate was collected by filtration, washed with water and dried under vacuum to give 1.02g (94%) of a white solid. $^1$H NMR (DMSO-$d_6$) δ 12.06 (1H, s), 8.28 (1H, s), 7.65 (1H, d, J = 7.5 Hz), 7.60 (1H, d, J = 6.8Hz), 7.32 (1H, t, J = 7.2 Hz), 7.23 (1H, t, J = 6.8 Hz), 4.00 (3H, s).

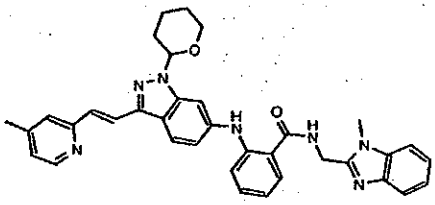
*Anal.* Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.80; H, 5.23; N, 23.98.

**Example 43: C-(1-Methyl-1H-benzoimidazol-2-yl)-methylamine dihydrochloride**



A Parr pressure bottle was charged with 1-Methyl-1H-benzoimidazole-2-carbaldehyde oxime M (267mg, 1.6mmol), 10% Palladium on Carbon (75mg), con HCl (2drops) and EtOH (25ml). The reaction mixture was shaken under 45psi $H_2$ for 2hr before the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was triturated with $Et_2O$ to give 340mg (90%) of a white solid as the dihydrochloride salt and was used without further purification. $^1$H NMR (DSMO-$d_6$): δ 8.87 (2H, broad s), 7.72 (2H, m), 7.38 (2H, m), 4.50 (2H, s), 3.89 (3H, s).

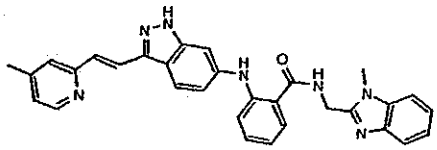
**Example 44: N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using C-(1-Methyl-1H-benzoimidazol-2-yl)-methylamine hydrochloride N and 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid. $^1$H NMR (DMSO-$d_6$) δ 9.82 (1H, s), 9.20 (1H, t, J = 5.3 Hz), 8.46 (1H, d, J = 4.9 Hz), 8.07 (1H, d, J = 8.9 Hz), 7.85 (1H, d, J = 16.4 Hz), 7.74 (1H, d, J = 7.3 Hz), 7.58 (1H, d, J = 7.2 Hz), 7.50 (6H, m), 7.19 (4H, m), 6.92 (1H, t, J = 8.1 Hz), 5.78 (1H, dd, J = 2.5, 9.5 Hz), 4.79 (2H, d, J = 5.5 Hz), 3.89 (1H,m), 3.83 (3H, s), 3.71 (1H, m), 2.41 (1H, m), 2.35 (3H, s), 2.00 (2H, m), 1.74 (1H, m), 1.57 (2H, m).

*Anal.* Calcd for $C_{36}H_{35}N_7O_2 \bullet 0.65$ Hexanes: C, 73.31; H, 6.80; N, 15.00. Found: C, 72.92; H, 6.90; N, 14.71.

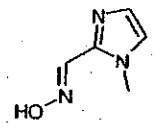
**Example 45: N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-2-{3-[(E)2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



Prepared in a similar manner to that described for Example 7 except that N-(1-Methyl-1H-benzoimidazol-2-ylmethyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide was used instead of of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ12.93 (1H, s), 9.73 (1H, s), 9.19 (1H, t, J = 5.3 Hz), 8.45 (1H, d, J = 4.9 Hz), 8.06 (1H, d, J = 8.5 Hz), 7.88 (1H, d, J = 16.4 Hz), 7.74 (1H, d, J = 7.9 Hz), 7.60-7.36 (6H, m), 7.29-7.14 (3H, m), 7.10 (1H, d, J = 4.7 Hz), 7.04 (1H, dd, J = 1.8, 8.9 Hz), 6.91 (1H, t, J = 7.3 Hz), 4.79 (2H, d, J = 5.3 Hz), 3.83 (3H, s), 2.35 (3H, s).

*Anal.* Calcd for $C_{31}H_{27}N_7O \bullet 1.80H_2O \bullet 0.40CH_2Cl_2$: C, 65.02; H, 5.46; N, 16.91. Found: C, 64.97; H, 5.82; N, 17.09.

**Example 46: 1-Methyl-1H-imidazole-2-carbaldehyde oxime**

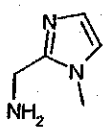


Prepared in a similar manner to that described for Example 39 except that 1-Methyl-1H-imidazole-2-carbaldehyde was used instead of 1-Methyl-1H-benzoimidazole-2-carbaldehyde.

$^1$H NMR (DMSO-$d_6$): δ11.50 (1H, s), 8.05 (1H, s), 7.28 (1H, s), 6.95 (1H, s), 3.80 (3H, s).

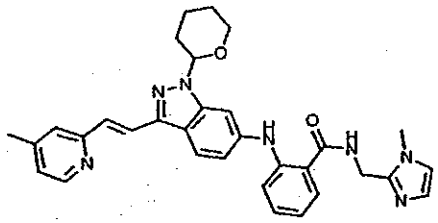
*Anal.* Calcd for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.22; H, 5.58; N, 33.45.

**Example 47: C-(1-Methyl-1H-imidazol-2-yl)-methylamine dihydrochloride**



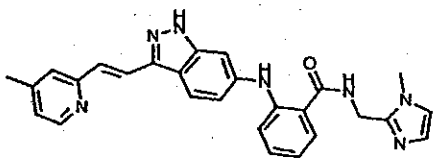
Prepared in a similar manner to that described for Example 40 except that 1-Methyl-1H-imidazole-2-carbaldehyde oxime was used instead of 1-Methyl-1H-benzoimidazole-2-carbaldehyde oxime. $^1$H NMR (DMSO-$d_6$): δ 7.45 (1H, s), 7.29 (1H, s), 4.25 (21H, s), 3.79 (3H, s).

**Example 48: N-(1-Methyl-1H-imidazol-2-ylmethyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide**



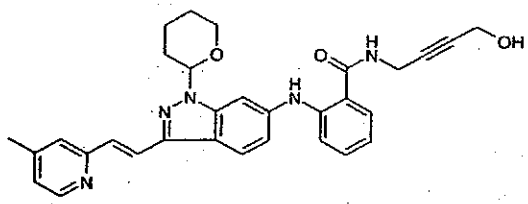
Prepared in a similar manner to that described for Example 6 above except using C-(1-Methyl-1H-imidazol-2-yl)-methylamine hydrochloride and 2-[3-[2-(4-Methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzoic acid. $^1$H NMR (DMSO-$d_6$) δ 9.83 (1H, s 9.03 (1H, t, J = 5.5 Hz), 8.45 (1H, d, J = 4.7 Hz), 8.09 (1H, d, J = 8.5 Hz), 7.85 (1H, d , J = 16.5 Hz), 8.67 (1H, d , J = 7.3 Hz), 7.53-7.39 (4H, m), 7.11 (3H, m), 6.90 (1H, d , J = 6.9 Hz), 6.86 (1H, s), 5.79 (1H, d , J = 8.9 Hz), 5.75 (1H, s), 4.54 (1H, d , J = 5.5 Hz), 3.85 - 3.70 (2H, m), 3.66 (3H, s), 2.35 (3H, s), 2.10 (2H, m), 1.70 (2H, m), 1.60 (3H, m). *Anal.* Calcd for $C_{32}H_{33}N_7O_2 \bullet 0.8\ CH_2Cl_2$: C, 63.99; H, 5.672; N, 15.93. Found: C, 63.95; H, 5.72; N, 16.01.

**Example 49: N-(1-Methyl-1H-imidazol-2-ylmethyl)-2-{3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-benzamide**



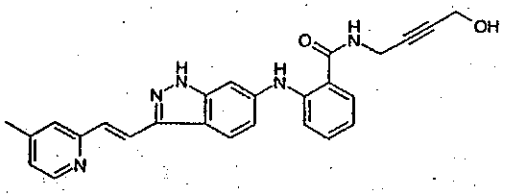
Prepared in a similar manner to that described for Example 7 except that N-(1-Methyl-1H-imidazol-2-ylmethyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide was used instead of of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1H-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$) δ 12.89 (1H, s 9.72 (1H, s 8.99 (1H, t, J = 5.6 Hz), 8.44 (1H, d, J = 4.9 Hz), 8.05 (1H, d, J = 8.7 H), 7.86 (1H, d , J = 16.4 Hz), 7.66 (1H, d , J = 6.7 Hz), 7.49-7.36 (4H, m), 7.24 (1H, m), 7.09 (2H, d, J = 8.1Hz), 7.02 (1H, d, J = 8.8 Hz), 6.88 (1H, t, J = 6.9 Hz), 6.81 (1H, s), 4.52 (2H, d , J = 5.5 Hz), 3.29 (3H, s), 2.34 (3H, s). *Anal.* Calcd for $C_{27}H_{25}N_7O \bullet 0.35CH_2Cl_2$: C, 66.59; H, 5.25; N, 19.88. Found: C, 66.48; H, 5.65; N, 19.56.

**Example 50: *N*-(4-Hydroxy-but-2-ynyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide**



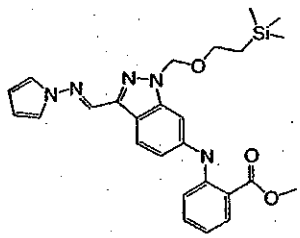
Prepared in a similar manner to that described for Example 6 except using 2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzoic acid and 4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-ynylamine. $^1$H NMR ($CDCl_3$): δ 9.48 (H, s), 8.46 (1H, d, J = 5.3 Hz), 7.92 (1H, d, J = 9.0 Hz), 7.83 (1H, d, J = 16.2 Hz), 7.52 (1H, d, J = 16.6 Hz), 7.46-7.41 (2H, m), 7.34-7.31 (3H, m), 7.12 (1H, dd, J = 8.7, 1.9 Hz), 6.99 (1H, d, J = 4.9 Hz), 6.81 (1H, t, J = 6.8 Hz), 6.40 (1H, t, J = 4.9 Hz), 5.62 (1H, dd, J = 9.4, 3.0 Hz), 4.28-4.23 (4H, m), 4.08-4.01 (1H, m), 3.76-3.67 (1H, m), 2.63-2.49 (1H, m), 2.38 (3H, s), 2.22-2.06 (2H, m), 1.80-1.60 (3H, m).

**Example 51: 2-{3-[(E)-2-(4-Methyl-pyridin-2-yl)-vinyl]-1H-indazol-6-ylamino}-N-(4-hydroxy-but-2-ynyl)-benzamide**



Prepared in a similar manner to that described for Example 7 except using a mixture of *N*-(4-Hydroxy-but-2-ynyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide and *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4-methyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide instead of *N*-[4-(tert-butyl-dimethyl-silanyloxy)-but-2-ynyl)-2-[3-[2-(4,6-dimethyl-pyridin-2-yl)-vinyl]-1-(tetrahydro-pyran-2-yl)-1*H*-indazol-6-ylamino]-benzamide. $^1$H NMR (DMSO-$d_6$): δ 12.92 (1H, s), 9.83 (1H, s), 9.00 (1H, t, J = 5.3 Hz), 8.44 (1H, d, J = 4.9 Hz), 8.06 (1H, d, J = 9.0 Hz), 7.87 (1H, d, J = 16.6 Hz), 7.68 (1H, d, J = 7.9 Hz), 7.50-7.38 (4H, m), 7.26 (1H, s), 7.09 (1H, d, J = 5.3 Hz), 7.01 (1H, dd, J = 8.7, 1.5 Hz), 6.88 (1H,dt, J = 6.8, 1.5 Hz), 5.11 (1H, t, J = 3.0 Hz), 4.10-4.04 (4H, m), 2.34 (3H, s).

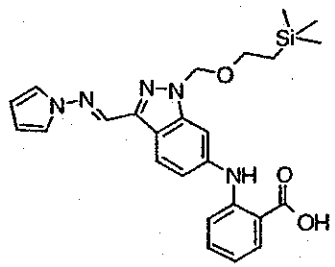
**Example 52: 2-[3-(Pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid methyl ester**



Prepared in a similar manner to that described for Examples 2 and 3 above except starting with 6-Nitro-3-styryl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole instead of 6-Iodo-3-styryl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazole.

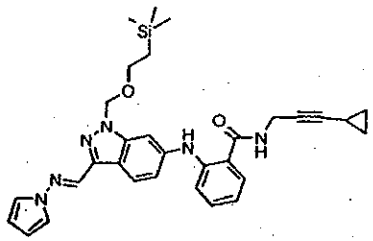
This material was taken on as a crude mixture of poduct and 2-Amino-benzoic acid methyl ester in the next step.

**Example 53: 2-[3-(Pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid**



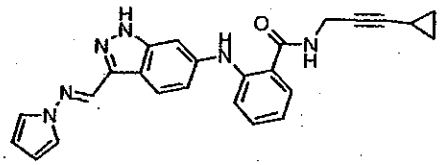
Isolated as a byproduct from reaction of N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide and TBAF using a procedure similar to Example 11 in US Serial Number 09/609,335, filed June 30, 2000, hereby incorporatd in its entirety for all purposes. $^1$H NMR (DMSO-$d_6$) δ 13.19 (1H, broad s 10.00 (1H, s, 9.13 (1H, s), 8.37 (1H, d, J = 8.7 Hz), 8.06 (1H, d, J = 7.5 Hz), 7.75 (1H, s), 7.64 (2H, t, J = 2.3 Hz), 7.54 (2H, m), 7.35 (1H, dd, J = 1.9, 8.7 Hz), 6.99 (1H, m), 6.33 (2H, t, J = 2.3 Hz), 5.89 (2H, s), 3.68 (2H, t, J = 8.1 Hz), 0.94 (2H, t , J = 8.1 Hz), 0.00 (9H, s).

**Example 54: N-(3-Cyclopropyl-prop-2-ynyl)-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using 2-[3-(Pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid and 3-Cyclopropyl-prop-2-ynylamine. $^1$H NMR (DMSO-$d_6$) δ 9.93 (1H, s 8.99 (1H,s), 8.95 (1H, d, J = 5.6 Hz), 8.20 (1H, d, J = 8.9 Hz), 7.68 (1H, d , J = 8.1 Hz), 7.51 (4H, m), 7.37 (1H, t , J = 6.8 Hz), 7.14 (1H, d, J = 9.0 Hz), 6.91 (1H, t, J = 7.5 Hz), 6.21 (2H, t, J = 2.3 Hz), 5.74 (2H, s), 4.00 (2H, dd, J = 2.0, 5.6 Hz), 3.55 (2H, t, J = 7.9 Hz), 1.26 (1H, m), 0.82 (2H, t, J = 7.9 Hz), 0.72 (2H, m) 0.54 (2H, m), -0.12 (9H, s).

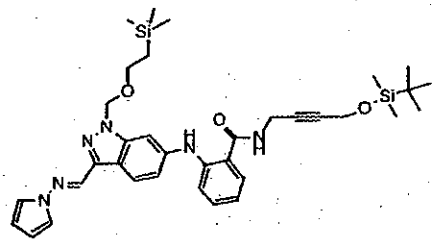
**Example 55: N-(3-Cyclopropyl-prop-2-ynyl)-2-[3-(pyrrol-1-yliminomethyl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 11 in US Patent Application Serial Number 09/609,335, filed June 30, 2000, herein incorporated by reference in its entirety for all purposes, except that N-(3-Cyclopropyl-prop-2-ynyl)-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide was used instead of N-methyl-N-[3-styryl-1-[2-trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-benzene-1,3-diamine. $^1$H NMR (DMSO-$d_6$) δ 13.29 (1H, s), 9.83 (1H, s 8.98 (1H, s), 8.95 (1H, t, J = 5.5 Hz), 8.19 (1H, d, J = 8.9 Hz), 7.68 (1H, d, J = 7.5 Hz), 7.52 (2H, t, J = 2.3 Hz), 7.43 (2H, m), 7.29 (1H, s), 7.07 (1H, dd, J = 1.9, 8.7 Hz), 6.91 (1H, t, J = 7.4 Hz), 6.21 (2H, t, J = 2.3 Hz), 4.01 (2H, dd, J = 1.7, 5.5 Hz), 1.27 (1H, m),

0.73 (2H, m), 0.55 (2H, m). *Anal.* Calcd for $C_{25}H_{22}N_6O$ • 0.05Hexanes • 0.30 $H_2O$: C, 70.31; H, 5.43; N, 19.45. Found: C, 70.63; H, 5.38; N, 19.18.

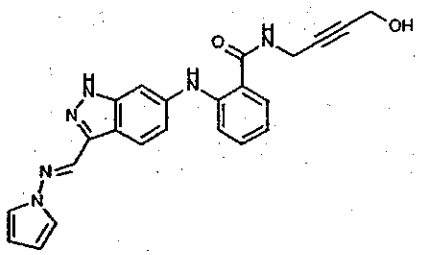
**Example 56: N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-**



**benzamide**

Prepared in a similar manner to that described for Example 6 above except using 2-[3-(Pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid and 4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynylamine. $^1$H NMR (DMSO-$d_6$) δ 10.04 (1H, s 9.16 (1H, t, J = 5.3 Hz), 9.10 (1H,s), 8.31 (1H, d, J = 8.7 Hz), 7.78 (1H, d, J = 7.9 Hz), 7.67 (4H, m), 7.49 (1H, t , J = 8.5 Hz), 7.24 (1H, dd, J = 1.7, 8.7 Hz), 7.03 (1H, t, J = 7.4 Hz), 6.33 (2H, t, J = 2.3 Hz), 5.85 (2H, s), 4.83 (2H, s), 4.19 (2H, d, J = 5.5 Hz), 3.66 (2H, t, J = 7.9 Hz), 0.94 (2H, m), 0.89 (9H, s), 0.13 (6H, s), 0.00 (9H, s).

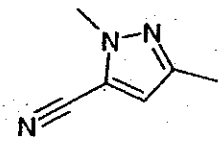
**Example 57: N-(4-Hydroxy-but-2-ynyl)-2-[3-(pyrrol-1-yliminomethyl)-1H-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 11, in US Patent Application Serial Number 09/609,335, filed June 30, 2000, herein incorporated by reference in its entirety for all purposes, except that N-[4-(tert-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide was used instead of N-methyl-N-{3-styryl-1-[2-trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-benzene-1,3-diamine. $^1$H NMR (DMSO-$d_6$) δ 13.30 (1H,

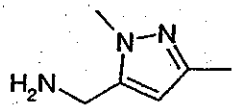
s), 9.87 (1H, s 9.04 (1H, t, J = 5.3 Hz), 8.99 (1H, s), 8.19 (1H, d, J = 8.5 Hz), 7.70 (1H, d , J = 7.3 Hz), 7.46 (4H, m), 7.31 (1H, s), 7.08 (1H, dd, J = 1.7, 8.7 Hz), 6.91 (1H, t, J = 7.3 Hz), 6.21 (2H, t, J = 2.1 Hz), 5.14 (1H, t, J = 5.8 Hz), 4.10 (2H, d , J = 5.5 Hz), 4.06 (2H, d , J = 5.8 Hz). *Anal.* Calcd for $C_{23}H_{20}N_6O_2 \bullet 0.35$Hexanes $\bullet 0.20\ H_2O$: C, 67.45; H, 5.86; N, 18.81. Found: C, 67.70; H, 5.73; N, 18.56.

**Example 58: 2,5-Dimethyl-2H-pyrazole-3-carbonitrile**



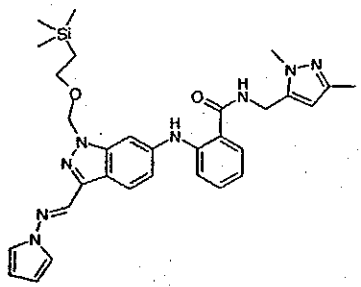
2,5-Dimethyl-2H-pyrazole-3-carbonitrile was prepared from ethyl 1,3-dimethylpyrazole-5-carboxlate according to procedures published for 1-methyl-pyrazol-5-carbonitrile by Castellanos, Maria and Montserrat, Llinas; JCS Perkins Trans I (1985) 1209-1215. $^1$H NMR ($CDCl_3$) δ 6.52 (1H, s), 3.96 (3H, s), 2.27 (3H, s).

**Example 59: *C*-(2,5-Dimethyl-2*H*-pyrazol-3-yl)-methylamine**



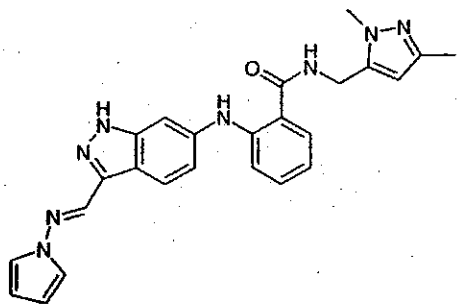
A suspension of 2,5-Dimethyl-2H-pyrazole-3-carbonitrile (654 mg, 5.4 mmol) and 10% palladium on carbon (200 mg) in ethanol (15 mL) was shaken in a Parr hydrogenation apparatus under 45 psi $H_2$ for 17 hr. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure to give 608 mg of an oil which was used without any further purification. $^1$H NMR ($CDCl_3$) δ 5.91 (1H, s), 3.81, 3.73 (2H,2s), 3.75 (3H, s), 2.21 (3H, s).

**Example 60: *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide**



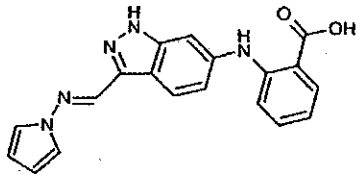
Prepared in a similar manner to that described for Example 6 above except using 2-[3-(Pyrrol-1-yliminomethyl)- 1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid and *C*-(2,5-Dimethyl-2*H*-pyrazol-3-yl)-methylamine. $^1$H NMR ($CDCl_3$) δ 9.56 (1H, s), 8.68 (1H, s), 8.30 (1H, d, J = 8.7 Hz), 7.49 (1H, d, J=8.3 Hz), 7.43 (1H, dd, J = 7.9, 1.5 Hz), 7.36-7.31 (2H, m), 7.23 (2H, t, J=2.6 Hz), 7.17 (1H, dd, J = 8.7, 1.9 Hz), 6.83 (1H, t, J=7.2 Hz), 6.32 (1H, bt), 6.29 (2H, t, J=2.3 Hz), 6.01 (1H, s), 5.67 (2H, s), 4.61 (2H, d, J=5.6 Hz), 3.60 (3H, s), 3.58 (2H, t, J=8.3 Hz), 2.22 (3H, s), 0.90 (2H, t, J=8.7 Hz), 0.06 (9H, s).

**Example 61: *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[3-(pyrrol-1-yliminomethyl)-1*H*-indazol-6-ylamino]-benzamide**



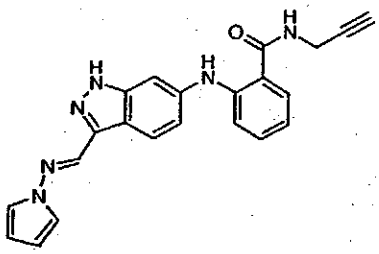
Prepared in a similar manner to that described for Example 11 in US Patent Application Serial Number 09/609,335, filed June 30, 2000, herein incorporated by reference in its entirety for all purposes, except that *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[3-(pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzamide was used instead of N-methyl-N-{3-styryl-1-[2-trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-benzene-1,3-diamine. $^1$H NMR (DMSO-$d_6$) δ 13.27 (1H, s), 9.72 (1H, s), 9.05 (1H, t, J= 5.3 Hz), 8.97 (1H, s), 8.16 (1H, d, J = 8.7 Hz), 7.68 (1H, dd, J=8.3, 1.9 Hz), 7.50 (2H, t, J=2.6 Hz), 7.46-7.38 (2H, m), 7.25 (1H, s), 7.05 (1H, dd, J = 8.7, 1.9 Hz), 6.91 (1H, t, J=6.80 Hz), 6.20 (2H, t, J=2.3 Hz), 5.91 (1H, s), 4.43 (2H, d, J=5.6 Hz), 3.71 (3H, s), 2.04 (3H, s).

**Example 62: 2-[3-(Pyrrol-1-yliminomethyl)-1H-indazol-6-ylamino]-benzoic acid**



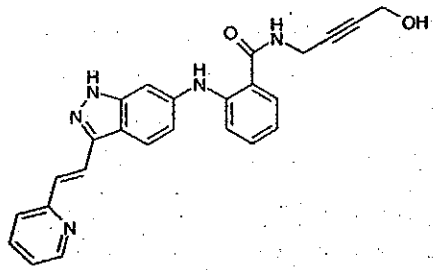
Prepared in a similar manner to that described for Example 11 in US Patent Application Serial Number 09/609,335, filed June 30, 2000, herein incorporated by reference in its entirety for all purposes, except using 2-[3-(Pyrrol-1-yliminomethyl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-indazol-6-ylamino]-benzoic acid instead of N-methyl-N-{3-styryl-1-[2-trimethyl-silanyl)-ethoxymethyl]-1H-indazol-6-yl}-benzene-1,3-diamine. $^1$H NMR (DMSO-$d_6$) δ 13.12 (1H, s), 12.70 (1H, s), 8.94 (1H, s), 8.10 (1H, d, J = 8.7 Hz), 7.91 (1H, dd, J = 1.7, 7.7 Hz), 7.50 (2H, t, J = 2.3 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.27 (1H, d, J = 1.5 Hz), 7.16 (1H, t, J = 7.5 Hz), 6.94 (1H, dd, J = 1.7, 8.7 Hz), 6.68 (1H, t, J = 7.5 Hz), 6.19(2H, t, J = 2.3 Hz).

**Example 63: N-Prop-2-ynyl-2-[3-(pyrrol-1-yliminomethyl)-1H-indazol-6-ylamino]-benzamide**



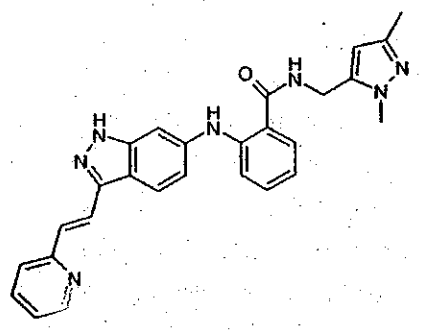
Prepared in a similar manner to that described for Example 6 above, except using 2-[3-(Pyrrol-1-yliminomethyl)-1H-indazol-6-ylamino]-benzoic acid and propargylamine. $^1$H NMR (DMSO-$d_6$) δ 13.30 (1H, s), 9.82 (1H, s), 9.04 (1H, t, J = 5.6 Hz), 8.98 (1H, s), 8.19 (1H, d, J = 8.6 Hz), 7.69 (1H, d, J = 7.9 Hz), 7.45(4H, m), 7.31 (1H, s), 7.08 (1H, d, J = 8.6 Hz), 6.91 (1H, t, J = 7.6 Hz), 6.21 (2H, s), 4.05 (2H, s), 3.13 (1H, s). *Anal.* Calcd for $C_{22}H_{18}N_6O \bullet 0.40H_2O \bullet 0.05$ Hexanes: C, 67.97; H, 5.01; N, 21.33. Found: C, 67.91; H, 4.78; N, 21.00.

**Example 64: *N*-(4-Hydroxy-but-2-ynyl)-2-[3-(2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using tetrabutyl ammonimum 2-[3-(2-Pyridin-2-yl-vinyl)-1*H*-indazol-6-ylamino]-benzoate and 4-Amino-but-2-yn-1-ol. $^1$H NMR (DMSO-$d_6$): δ 12.95 (1H, s), 9.84 (1H, s), 9.02 (1H, t, J = 5.6 Hz), 8.59 (1H, d, J = 4.9 Hz), 8.08 (1H, d, J = 8.7 Hz), 7.90 (1H, d, J = 16.2 Hz), 7.80 (1H, t, J = 7.2 Hz), 7.70-7.64 (2H, m), 7.51 (1H, d, J = 16.2 Hz), 7.45-7.36 (2H, m), 7.27-7.24 (2H, m), 7.02 (1H, d, J = 9.0 Hz), 6.88 (1H, t, J = 7.2 Hz), 5.13 (1H, t, J = 5.6 Hz), 4.10-4.04 (4H, m).

**Example 65: *N*-(2,5-Dimethyl-2*H*-pyrazol-3-ylmethyl)-2-[3-(2-pyridin-2-yl-vinyl)-1*H*-indazol-6-ylamino]-benzamide**



Prepared in a similar manner to that described for Example 6 above, except using tetrabutyl ammonimum 2-[3-(2-Pyridin-2-yl-vinyl)-1*H*-indazol-6-ylamino]-benzoate and *C*-(2,5-Dimethyl-2*H*-pyrazol-3-yl)-methylamine. $^1$H NMR (DMSO-$d_6$) δ 12.93 (1H, s), 9.70 (1H, s), 9.04 (1H,bt), 8.58 (1H, d, J = 4.0 Hz), 8.07 (1H, d, J = 8.8 Hz), 7.88 (1H, d, J=16.4 Hz), 7.79 (1H, t, J=8.6 Hz), 7.71-7.64 (2H, m), 7.50 (1H, d, J = 16.4 Hz), 7.44-7.39 (2H, m), 7.28-7.23 (2H, m), 7.00 (1H, d, J = 8.8 Hz), 6.90 (1H, t, J=8.0 Hz), 5.91 (1H, s), 4.43 (2H, d, J=5.5 Hz), 3.71 (3H, s), 2.04 (3H, s).

The exemplary compounds described above may be tested for their activity using the tests described below.

BIOLOGICAL TESTING: ENZYME ASSAYS

The stimulation of cell proliferation by growth factors such as VEFG, FGF, and others is dependent upon their induction of autophosphorylation of each of their respective receptor's tyrosine kinases. Therefore, the ability of a protein kinase inhibitor to block autophosphorylation can be measured by inhibition of the peptide substrates. To measure the protein kinase inhibition activity of the compounds, the following constructs were devised.

VEGF-R2 Construct for Assay: This construct determines the ability of a test compound to inhibit tyrosine kinase activity. A construct (VEGF-R2Δ50) of the cytosolic domain of human vascular endothelial growth factor receptor 2 (VEGF-R2) lacking the 50 central residues of the 68 residues of the kinase insert domain was expressed in a baculovirus/insect cell system. Of the 1356 residues of full-length VEGF-R2, VEGF-R2Δ50 contains residues 806-939 and 990-1171, and also one point mutation (E990V) within the kinase insert domain relative to wild-type VEGF-R2. Autophosphorylation of the purified construct was performed by incubation of the enzyme at a concentration of 4 μM in the presence of 3 mM ATP and 40 mM $MgCl_2$ in 100 mM HEPES, pH 7.5, containing 5% glycerol and 5 mM DTT, at 4 °C for 2 h. After autophosphorylation, this construct has been shown to possess catalytic activity essentially equivalent to the wild-type autophosphorylated kinase domain construct. See Parast et al., *Biochemistry*, 37, 16788-16801 (1998).

FGF-R1 Construct for Assay: The intracellular kinase domain of human FGF-R1 was expressed using the baculovirus vector expression system starting from the endogenous methionine residue 456 to glutamate 766, according to the residue numbering system of Mohammadi et al., *Mol. Cell. Biol.*, 16, 977-989 (1996). In addition, the construct also has the following 3 amino acid substitutions: L457V, C488A, and C584S.

LCK Construct for Assay: The LCK tyrosine kinase was expressed in insect cells as an N-terminal deletion starting from amino acid residue 223 to the end of the protein at residue 509, with the following two amino acid substitutions at the N-terminus: R233M and C224D.

CHK1 Construct for Assay: C-terminally His-tagged full-length human CHK1 (FL-CHK1) was expressed using the baculovirus/insect cell system. It contains 6 histidine residues (6 x His-tag) at the C-terminus of the 476 amino acid human CHK1. The protein was purified by conventional chromatographic techniques.

CDK2/Cyclin A Construct for Assay: CDK2 was purified using published methodology (Rosenblatt et al., *J. Mol. Biol.*, 230, 1317-1319 (1993)) from insect cells that had been infected with a baculovirus expression vector. Cyclin A was purified from *E. coli* cells expressing full-length recombinant cyclin A, and a truncated cyclin A construct was generated by limited proteolysis and purified as described previously (Jeffrey et al., *Nature*, 376, 313-320 (1995)).

CDK4/Cyclin D Construct for Assay: A complex of human CDK4 and cyclin D3, or a complex of cyclin D1 and a fusion protein of human CDK4 and glutathione-S-transferase (GST-CDK4), was purified using traditional biochemical chromatographic techniques from insect cells that had been co-infected with the corresponding baculovirus expression vectors.

FAK Construct for Assay. The catalytic domain of human FAK (FAKcd409) was expressed using the baculovirus vector expression system. The 280 amino acid domain expressed comprises residues methionine 409 to glutamate 689. One amino acid substitution exists (P410T) relative to the sequence assession number L13616 published by Whithey, G.S. et al., *DNA Cell Biol*, 9, 823-30 (1993). The protein was purified using classical chromatography techniques.

TIE-2 (TEK) Construct for Assay

The TIE-2 tyrosine kinase domain was expressed in insect cells as an N-terminal deletion starting from amino acid residue 774 to the end of the protein at residue 1124. This construct also carries a R774M mutation, which serves as the initiating methionine residue in translation.

VEGF-R2 Assay

Coupled Spectrophotometric (FLVK-P) Assay

The production of ADP from ATP that accompanies phosphoryl transfer was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) and a system having pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by following the decrease of absorbance at 340 nm ($e_{340}$ = 6.22 $cm^{-1}$ $mM^{-1}$) using a Beckman DU 650 spectrophotometer. Assay conditions for phosphorylated VEGF-R2Δ50 (indicated as FLVK-P in the tables below) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 5.1 mM poly($E_4Y_1$); 1 mM ATP; and 25 mM $MgCl_2$ in 200 mM HEPES, pH 7.5. Assay conditions for unphosphorylated VEGF-R2Δ50 (indicated as FLVK in the tables) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 20 mM poly($E_4Y_1$); 3 mM ATP; and 60 mM $MgCl_2$ and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. Assays were initiated with 5 to 40 nM of enzyme. $K_i$ values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

ELISA Assay

Formation of phosphogastrin was monitored using biotinylated gastrin peptide (1-17) as substrate. Biotinylated phosphogastrin was immobilized using streptavidin coated 96-well microtiter plates followed by detection using anti-phosphotyrosine-antibody conjugated to horseradish peroxidase. The activity of horseradish peroxidase was monitored using 2,2'-azino-di-[3-ethylbenzathiazoline sulfonate(6)] diammonium salt (ABTS). Typical assay solutions contained: 2 μM biotinylated gastrin peptide; 5 mM DTT; 20 μM ATP; 26 mM $MgCl_2$;

and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. The assay was initiated with 0.8 nM of phosphorylated VEGF-R2Δ50. Horseradish peroxidase activity was assayed using ABTS, 10 mM. The horseradish peroxidase reaction was quenched by addition of acid ($H_2SO_4$), followed by absorbance reading at 405 nm. $K_i$ values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

FGF-R Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: FGF-R = 50 nM, ATP = 2 mM, and poly(E4Y1) = 15 mM.

LCK Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: LCK = 60 nM, $MgCl_2$ = 0 mM, poly(E4Y1) = 20 mM.

CHK1 Assay

The production of ADP from ATP that accompanies phosphoryl transfer to the synthetic substrate peptide Syntide-2 (PLARTLSVAGLPGKK) was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) through the actions of pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by following the decrease of absorbance at 340 nm ($\epsilon$340 = 6.22 $cm^{-1}$ $mM^{-1}$) using a HP8452 spectrophotometer. Typical reaction solutions contained: 4 mN PEP; 0.15 mM NADH; 28 units of LDH/mL; 16 units of PK/mL; 3 mM DTT; 0.125 mM Syntide-2; 0.15 mM ATP; 25 mM $MgCl_2$ in 50 mM TRIS, pH 7.5; and 400 mM NaCl. Assays were initiated with 10 nM of FL-CHK1. $K_i$ values were determined by measuring initial enzyme activity in the presence of varying concentrations of test compounds. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

CDK2/Cyclin A and CDK4/Cyclin D Assays

Cyclin-dependent kinase activity was measured by quantifying the enzyme-catalyzed, time-dependent incorporation of radioactive phosphate from [$^{32}$P]ATP into a recombinant fragment of the retinoblastoma protein. Unless noted otherwise, assays were performed in 96-well plates in a total volume of 50 µL, in the presence of 10 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]) (pH 7.4), 10 mM $MgCl_2$, 25 µM adenosine triphosphate (ATP), 1 mg/mL ovalbumin, 5 µg/mL leupeptin, 1 mM dithiothreitol, 10 mM β-glycerophosphate, 0.1 mM sodium vanadate, 1 mM sodium fluoride, 2.5 mM ethylene glycol-bis(β-aminoethyl ether)-N,N,N'N'-tetraacetic acid (EGTA), 2% (v/v) dimethylsulfoxide, and 0.03 - 0.2 µCi [$^{32}$P]ATP. The substrate (0.3-0.5 µg) was purified recombinant retinoblastoma

protein fragment (Rb) (residues 386-928 of the native retinoblastoma protein; 62.3 kDa, containing the majority of the phosphorylation sites found in the native 106-kDa protein, as well as a tag of six histidine residues for ease of purification). Reactions were initiated with CDK2 (150 nM CDK2/Cyclin A complex) or CDK4 (50 nM CDK4/Cyclin D3 complex), incubated at 30 °C, and terminated after 20 minutes (min.) by the addition of ethylenediaminetetraacetic acid (EDTA) to 250 mM. The phosphorylated substrate was then captured on a nitrocellulose membrane using a 96-well filtration manifold, and unincorporated radioactivity was removed by repeated washing with 0.85% phosphoric acid. Radioactivity was quantified by exposing the dried nitrocellulose membranes to a phosphorimager. Apparent $K_i$ values were measured by assaying enzyme activity in the presence of different compound concentrations and subtracting the background radioactivity measured in the absence of enzyme. The kinetic parameters (kcat, Km for ATP) were measured for each enzyme under the usual assay conditions by determining the dependence of initial rates on ATP concentration. The data were fit to an equation for competitive inhibition using Kaleidagraph (Synergy Software), or were fit to an equation for competitive tight-binding inhibition using the software KineTic (BioKin, Ltd.). Measured $K_i$ values for known inhibitors against CDK4 and CDK2 agreed with published $IC_{50}$ values. The specific activity of CDK4 was the same whether complexed to full-length cyclin D3 or the truncated Cyclin D3 construct; both complexes also yielded very similar $K_i$ values for selected inhibitors.

FAK Assay

FAK HTS utilized the fluorescence polarization assay provided by LJL Biosystems. The kinase reaction contained: 100mM Hepes pH 7.5, 10mM $MgCl_2$, 1mM DTT, 1mM ATP, and 1mg/ml poly Glu-Tyr (4:1). The reaction is initiated by the addition of 5nM FAKcd409. The reaction is terminated by the addition of EDTA followed by addition of fluor-labelled peptide and anti-phosphotyrosine antibody, both provided by LJL Biosystems. Inhibition results are read on a Analyst (LJL) detector.

TIE-2 Spectrophotometric Assay

The kinase-catalyzed production of ADP from ATP that accompanies phosphoryl transfer to the random copolymer poly($Glu_4Tyr$) was coupled to the oxidation of NADH through the activities of pyruvate kinase (PK) and lactate dehydrogenase (LDH). NADH conversion to $NAD^+$ was monitored by the decrease in absorbance at 340 nm ($\varepsilon$ = 6.22 $cm^{-1}mM^{-1}$) using a Beckman DU650 spectrophotometer. Typical reaction solutions contained 1 mM phosphoenolpyruvate, 0.24 mM NADH, 40 mM $MgCl_2$, 5 mM DTT, 2.9 mg/mL poly($Glu_4Tyr$), 0.5 mM ATP, 15 units/mL PK, 15 units/mL LDH in 100 mM HEPES, pH 7.5. Assays were initiated with the addition of 4 to 12 nM phosphorylated Tie-2 (aa 775-1122). Percent inhibition was determined in triplicate at a 1 µM level of inhibitor.

TIE-2 DELFIA Assay

Formation of phosphotyrosine was monitored using biotinylated p34cdc2 (aa6-20 = KVEKIGEGTYGVVYK) peptide as substrate. Biotinylated peptide was immobilized using NeutrAvidin™ coated 96-well microtiter plates followed by detection using anti-phosphotyrosine-antibody (PY20) conjugated to europium N1 chelate. Typical assay solutions contained: 1 µM biotinylated p34cdc2 peptide, 150 µM ATP, 5 mM $MgCl_2$, 1 mM DTT, 0.01% BSA, 5% glycerol, 2% DMSO, 25 mM HEPES pH 7.5. The assay was initiated in the NeutrAvidin plate with 50 nM of TIE2 intracellular domain. The kinase reaction was terminated with 50 mM EDTA. Plates were then washed, and europium antibody added. After incubation, they were again washed, and DELFIA™ Enhancement Solution added. Plates were read at standard Europium time-resolved settings (ex 340 nm, em 615 nm, delay 400 µsec, window 400 µsec). Percent inhibition was calculated with reference to intraplate wells which had added DMSO rather than compound in DMSO, with background subtracted from both experimental and control with reference to an intraplate well which had EDTA added prior to addition of enzyme.

HUVEC Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells ("HUVEC"). HUVEC cells (passage 3-4, Clonetics, Corp.) were thawed into EGM2 culture medium (Clonetics Corp) in T75 flasks. Fresh EGM2 medium was added to the flasks 24 hours later. Four or five days later, cells were exposed to another culture medium (F12K medium supplemented with 10% fetal bovine serum (FBS), 60 µg/mL endothelial cell growth supplement (ECGS), and 0.1 mg/mL heparin). Exponentially-growing HUVEC cells were used in experiments thereafter. Ten to twelve thousand HUVEC cells were plated in 96-well dishes in 100 µl of rich, culture medium (described above). The cells were allowed to attach for 24 hours in this medium. The medium was then removed by aspiration and 105 µl of starvation media (F12K+1% FBS) was added to each well. After 24 hours, 15 µl of test agent dissolved in 1% DMSO in starvation medium or this vehicle alone was added into each treatment well; the final DMSO concentration was 0.1%. One hour later, 30 µl of VEGF (30 ng/mL) in starvation media was added to all wells except those containing untreated controls; the final VEGF concentration was 6 ng/mL. Cellular proliferation was quantified 72 hours later by MTT dye reduction, at which time cells were exposed for 4 hours MTT (Promega Corp.). Dye reduction was stopped by addition of a stop solution (Promega Corp.) and absorbance at 595 λ was determined on a 96-well spectrophotometer plate reader.

$IC_{50}$ values were calculated by curve-fitting the response of $A^{595}$ to various concentrations of the test agent; typically, seven concentrations separated by 0.5 log were

employed, with triplicate wells at each concentration. For screening compound library plates, one or two concentrations (one well per concentration) were employed, and the % inhibition was calculated by the following formula:

% inhibition = (control – test) ÷ (control – starvation)

where

control = $A^{595}$ when VEGF is present without test agent

test = $A^{595}$ when VEGF is present with test agent

starvation = $A^{595}$ when VEGF and test agent are both absent.

Mouse PK Assay

The pharmacokinetics (e.g., absorption and elimination) of drugs in mice were analyzed using the following experiment. Test compounds were formulated as a solution or suspension in a 30:70 (PEG 400: acidified $H_20$) vehicle or as a suspension in 0.5% CMC. This was administered orally (p.o.) and intraperitoneally (i.p.) at variable doses to two distinct groups (n=4) of B6 female mice. Blood samples were collected via an orbital bleed at time points: 0 hour (pre-dose), 0.5 h, 1.0 h, 2.0 h, and 4.0 h, and 7.0 h post dose. Plasma was obtained from each sample by centrifugation at 2500 rpm for 5 min. Test compound was extracted from the plasma by an organic protein precipitation method. For each time bleed 50 µL of plasma was combined with 1.0 mL of acetonitrile, vortexed for 2 min. and then spun at 4000 rpm for 15 min. to precipitate the protein and extract out the test compound. Next, the acetonitrile supernatant (the extract containing test compound) was poured into new test tubes and evaporated on a hot plate (25°C) under a steam of $N_2$ gas. To each tube containing the dried test compound extract 125 µL of mobile phase (60:40, 0.025 M $NH_4H_2PO_4$ +2.5 mL/L TEA:acetonitrile) was added. The test compound was resuspended in the mobile phase by vortexing and more protein was removed by centrifugation at 4000 rpm for 5 min. Each sample was poured into an HPLC vial for test compound analysis on an Hewlett Packard 1100 series HPLC with UV detection. From each sample, 95 □L was injected onto a Phenomenex-Prodigy reverse phase C-18, 150 x 3.2 mm column and eluted with a 45-50% acetonitrile gradient run over 10 min. Test-compound plasma concentrations (µg/mL) were determined by a comparison to standard curve (peak area vs. conc. µg/mL) using known concentrations of test compound extracted from plasma samples in the manner described above. Along with the standards and unknowns, three groups (n=4) of quality controls (0.25 µg/mL, 1.5 µg/mL, and 7.5 µg/mL) were run to insure the consistency of the analysis. The standard curve had an R2> 0.99 and the quality controls were all within 10 % of their expected values. The quantitated test samples were plotted for visual display using Kalidagraph software and their pharmacokinetic parameters were determined using WIN NONLIN software. Example 1(a)

provided the following results: 0.69 (Mouse pK, AUC, ip, µg-h/ml); 0.33 (Mouse pK, AUC, po, µg-h/ml).

KDR (VEGFR2) phosphorylation in PAE-KDR cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of KDR in porcine aorta endothelial (PAE)-KDR cells. PAE cells that overexpress human KDR were used in this assay. The cells were cultured in Ham's F12 media supplemented with 10% fetal bovine serum (FBS) and 400ug/mL G418. Thirty thousands cells were seeded into each well of a 96-well plate in 75 µL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 µL of test agent in 5% DMSO in starvation media were added to the test wells and 10 µL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37µC for 1 hour and the cells were then stimulated with 500 ng/ml VEGF (commercially available from R & D System) in the presence of 2mM $Na_3VO_4$ for 8 minutes. The cells were washed once with 1 mm $Na_3VO_4$ in HBSS and lysed by adding 50 µL per well of lysis buffer. One hundred µL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat ant-rabbit coated plate (commercially available from Pierce) which was pre-coated with Rabbit anti Human Anti-flk-1 C-20 antibody (commercially available from Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (commercially available from Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (commercially available from Kirkegaard & Perry) was added for a 10-minute incubation. One hundred µL of 0.09 N $H_2SO_4$ was added to each well of the 96-well plates to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. $IC_{50}$ values were calculated by curve fitting using a four-parameter analysis.

PAE-PDGFRβ phosphorylation in PAE-PDGFRB cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of PDGFRβ in porcine aorta endothelial (PAE)- PDGFRβ cells. PAE cells that overexpress human PDGFRβ were used in this assay. The cells were cultured in Ham's F12 media supplemented with 10% fetal bovine serum (FBS) and 400ug/ml G418. Twenty thousands cells were seeded in each well of a 96-well plate in 50 µL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 µL of test agent in 5% DMSO in starvation media were added to the test wells

and 10 µL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37°C for 1 hour and the cells were then stimulated with 1µg/mL PDGF-BB (R & D System) in the presence of 2mM $Na_3VO_4$ for 8 minutes. The cells were washed once with 1 mm $Na_3VO_4$ in HBSS and lysed by adding 50 µL per well of lysis buffer. One hundred µL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat ant-rabbit coated plate (Pierce), which was pre-coated with Rabbit anti Human PDGFRβ antibody (Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (Kirkegaard & Perry) was added for a 10-minute incubation. One hundred µL of 0.09 N $H_2SO_4$ was added into each well of the 96-well plate to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. $IC_{50}$ values were calculated by curve fitting using a four-parameter analysis.

Human Liver Microsome (HLM) Assay

Compound metabolism in human liver microsomes was measured by LC-MS analytical assay procedures as follows. First, human liver microsomes (HLM) were thawed and diluted to 5 mg/mL with cold 100 mM potassium phosphate (KPO4) buffer. Appropriate amounts of KPO4 buffer, NADPH-regenerating solution (containing B-NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, and $MgCl_2$), and HLM were preincubated in 13 x 100 mm glass tubes at 37 C for 10 min. (3 tubes per test compound--triplicate). Test compound (5 DM final) was added to each tube to initiate reaction and was mixed by gentle vortexing, followed by incubation at 37 °C. At t=0, 2 h, a 250-µL sample was removed from each incubation tube to separate 12 x 75 mm glass tubes containing 1 mL ice-cold acetonitrile with 0.05 µM reserpine. Samples were centrifuged at 4000 rpm for 20 min. to precipitate proteins and salt (Beckman Allegra 6KR, S/N ALK98D06, #634). Supernatant was transferred to new 12 x 75 mm glass tubes and evaporated by Speed-Vac centrifugal vacuum evaporator. Samples were reconstituted in 200 µL 0.1% formic acid/acetonitrile (90/10) and vortexed vigorously to dissolve. The samples were then transferred to separate polypropylene microcentrifuge tubes and centrifuged at 14000 x g for 10 min. (Fisher Micro 14, S/N M0017580). For each replicate (#1-3) at each timepoint (0 and 2 h), an aliquot sample of each test compound was combined into a single HPLC vial insert (6 total samples) for LC-MS analysis, which is described below.

The combined compound samples were injected into the LC-MS system, composed of a Hewlett-Packard HP1100 diode array HPLC and a Micromass Quattro II triple quadruple mass spectrometer operating in positive electrospray SIR mode (programmed to scan

specifically for the molecular ion of each test compound. Each test compound peak was integrated at each timepoint. For each compound, peak area at each timepoint (n=3) was averaged, and this mean peak area at 2 h was divided by the average peak area at time 0 hour to obtain the percent test compound remaining at 2 h.

The results of the testing of the compounds using various assays are summarized in the table below, where a notation of "% @" indicates the percent inhibition at the stated concentration, "*" values represent Ki (nM) or % inhibition at a compound concentration of 1 μM for * or 50 nM for **, unless otherwise indicated. "NT" indicates no significant inhibition or not tested.

TABLE 1

| Example # | FLVK Ki % inh @ 50 nM | FLVK-P** | LckP* %inhibit @1μM | FGF-P %inhibit @1μM | HUVEC IC50 (nM) | HUVEC + albumin IC50 (nM) | %remaining (HLM) | PAE PDGFR autophos IC50 (nM) | PAE KDR IC50 nM AVG | bFGF Huvec IC50 (nM) AVG |
|---|---|---|---|---|---|---|---|---|---|---|
| 3(a) | 98 | NT | 30 | 99 | 12.7 | NT | NT | NT | NT | NT |
| 3(b) | 98 | NT | 27 | 96 | 5.7 | NT | 84@2h | NT | NT | NT |
| 3(c) | 91 | NT | 9 | 83 | 0.43 | 9.2 | 46@0.5h | NT | NT | NT |
| 3(d) | 89 | NT | 11 | 80 | 0.4 | 7.5 | 68@2h | 3.5 | NT | 147 |
| 3(f) | 95 | NT | 41 | 60 | NT | > 100 | NT | NT | NT | NT |
| 3(g) | 95 | NT | 28 | 72 | 1.1 | NT | 72@0.5h | NT | NT | NT |
| 3(h) | 96 | NT | 37 | 85 | 1.6 | NT | 75@0.5h | 0.63 | NT | NT |
| 3(i) | 88 | NT | 22 | 45 | 0.2 | NT | NT | 1.9 | NT | 1000 |
| 3(j) | 80 | NT | 17 | 43 | 1.7 | NT | 65@0.5h | 4.7 | NT | NT |
| 3(k) | 74 | NT | 19 | 36 | 0.8 | NT | 75@0.5h | 5 | NT | 1000 |
| 3(q) | 47 | NT | 7 | 31 | 5 | NT | 82@0.5h | 5.2 | NT | NT |
| 2(h) | 84 | NT | NT | 75 | 1.6 | NT | 74@0.5h | 2.8 | NT | 70 |
| 1(k) | 27 | NT | NT | 12 | >10 | NT | NT | NT | NT | NT |
| 2(g) | 83 | NT | NT | 79 | 0.71 | NT | 85@0.5h | 10.5 | NT | 173 |
| 64 | 94 | NT | NT | 39 | 0.15 | NT | 66@0.5h | 5.5 | NT | 1250 |
| 65 | 3.11nM | NT | NT | NT | 3.4 | NT | 86@0.5h | 5.8 | NT | NT |
| 61 | 65 | NT | NT | 14 | 6.5 | NT | NT | NT | NT | 662 |
| 41 | 45 | NT | NT | 11 | 6.4 | NT | NT | NT | NT | 3775 |
| 51 | 82 | NT | NT | 52 | NT | NT | NT | NT | NT | NT |
| 15 | 64 | NT | NT | 29 | 1.5 | NT | NT | 12.3 | NT | 1613 |
| 36 | 95 | 0.3nM | NT | 69 | 1.67 | NT | NT | NT | 1.62 | 935 |

TABLE 1 CONTINUED

| Example # | FLVK Ki % inh @ 50 nM | FLVK-P** | LckP* %inhibit @1□M | FGF-P %inhibit @1□M | HUVEC IC50 (nM) | HUVEC + albumin IC50 (nM) | %remaining (HLM) | PAE PDGFR autophos IC50 (nM) | PAE KDR IC50 nM AVG | bFGF Huvec IC50 (nM) AVG |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 80 | NT | NT | 63 | NT | NT | NT | 6 | NT | NT |
| 18 | 94 | NT | NT | 59% | NT | NT | NT | NT | NT | 1882 |
| 20 | 91 | NT | NT | 35% | 0.084 | NT | NT | NT | NT | NT |
| 37 | 90 | NT | NT | 45 | NT | NT | NT | NT | 0.76 | NT |
| 38 | 75 | NT | NT | NT | NT | 0.68 | NT | 2 | NT | NT |
| 39 | 96 | NT | NT | 76% | NT | NT | NT | 4.7 | NT | NT |
| 32 | 78 | NT | NT | 70% | 0.61 | NT | 97@0.5h | 0.5 | NT | NT |
| 55 | 97 | NT | NT | 67% | 0.2 | NT | NT | 3.7 | NT | NT |
| 57 | 91 | NT | NT | 52% | <1.8 | NT | NT | 1.3 | NT | NT |
| 63 | 85 | NT | NT | 63% | 0.1 | NT | NT | 2.4 | NT | NT |
| 34 | 72 | NT | NT | NT | NT | NT | NT | 4.5 | NT | NT |
| 10 | 76 | 6.07 | NT | 38, 197nM | 0.67 | NT | 80@0.5h | 21 | NT | NT |
| 45 | 28 | NT | NT | 24 | NT | NT | NT | NT | NT | NT |
| 49 | 11 | NT | NT | 36 | NT | NT | NT | NT | NT | NT |
| 23 | 23 | NT | NT | 56 | NT | NT | NT | 40 | NT | NT |
| 25 | 64 | NT | NT | 13 | 3 | NT | NT | NT | NT | NT |

*In Vivo* Assay of Retinal Vascular Development in Neonatal Rats

The development of the retinal vascular in rats occurs from postnatal day 1 to postnatal day 14 (P1-P14). This process is dependent on the activity of VEGF (J. Stone, et al, *J. Neurosci.*, 15, 4738 (1995)). Previous work has demonstrated that VEGF also acts as a survival factor for the vessels of the retina during early vascular development (Alon, et. al, *Nat. Med.*, 1, 1024 (1995)). To assess the ability of specific compounds to inhibit the activity of VEGF *in vivo*, compounds were formulated in an appropriate vehicle, usually 50% polyethylene glycol, average molecular weight 400 daltons, and 50% solution of 300 mM sucrose in deionized water. Typically, two microliters (2 □l) of the drug solution was injected into the midvitreous of the eye of rat pups on postnatal day 8 or 9. Six days after the intravitreal injection, the animals were sacrificed and the retinas dissected free from the remaining ocular tissue. The isolated retinas were then subjected to a

histochemical staining protocol that stains endothelial cells specifically (Lutty and McLeod, *Arch. Ophthalmol.*, 110, 267 (1992 )), revealing the extent of vascularization within the tissue sample. The individual retinas are then flat-mount onto glass slides and examined to determine the extent of vascularization. Effective compounds inhibit the further development of the retinal vasculature and induce a regression of all but the largest vessels within the retina. The amount of vessel regression was used to assess the relative potency of the compounds after in vivo administration. Vessel regression is graded on subjective scale of one to three pluses, with one plus being detectable regression judged to be approximately 25 percent or less, two pluses being judged to be approximately 25-75% regression and three pluses give to retinas with near total regression (approximately 75% or greater).

For more quantitative analysis of regression, images of ADPase-stained, flat-mounted retinas were captured with a digital camera attached to a dissecting microscope. Retinal images were then imported into an image analysis software (Image Pro Plus 4.0, Media Cybernetics, Silver Spring, MD). The software was employed to determine the percentage of the area of the retina that contained stained vessels. This value for the experimental eye was compared to that measured for the vehicle injected, contralateral eye from the same animal. The reduction in the vascular area seen in the eye that received compound as compared to the vehicle-injected eye was then expressed as the "percent regression" for that sample. Percent regression values were averaged for groups of 5-8 animals.

In samples in which observation through the microscope indicated near total regression, a percent regression value of 65-70% was routinely measured. This was due to stain deposits within folds of retina, folds that were induced by the vehicle used for drug injection. The image analysis software interpreted these stain-containing folds as vessels. No attempt was made to correct for these folds since they varied from eye to eye. Thus, it should be noted that the percent regression values reported result from a conservative measurement that accurately rank orders compounds, but underestimates their absolute potency.

<u>In Vivo Assay of Retinal Vascular Development in Neonatal Rat Model of Retinopathy of Prematurity</u>

A second model of VEGF dependent retinal neovascularization was employed to evaluate the activities of this series of compounds. In this model (Penn et. al, *Invest. Ophthalmol. Vis. Sci.*, 36, 2063, (1995)), rats pups (n=16) with their mother are placed in a computer controlled chamber that regulates the concentration of oxygen. The animals are exposed for 24 hours to a concentration of 50% oxygen followed by 24 hours at a concentration of 10% oxygen. This alternating cycle of hyperoxia followed by hypoxia is

repeated 7 times after which the animals are removed to room air (P14). Compounds are administered via intravitreal injection upon removal to room air and the animals are sacrificed 6 days later (P20). The isolated retinas are then isolated, stained mounted and analyzed as detail above in the development model. The effectiveness was also graded as is described for the development model.

The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Example 1: Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula I is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 2: Oral Composition

To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

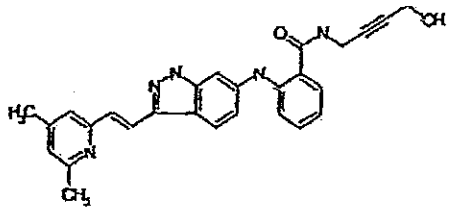
Example 3: Intraocular Composition

To prepare a sustained-release pharmaceutical composition for intraocular delivery, a compound of Formula I is suspended in a neutral, isotonic solution of hyaluronic acid (1.5% conc.) in phosphate buffer (pH 7.4) to form a 1% suspension.

It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, the artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

CLAIMS:

1. A compound represented by the formula



or a pharmaceutically acceptable salt thereof.

2. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating age related macular degeneration in a mammal.

3. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating choroidal neovascularization in a mammal.

4. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating retinopathy in a mammal.

5. The compound or pharmaceutically acceptable salt of claim 4 wherein the retinopathy comprises diabetic retinopathy, vitreoretinopathy, or retinopathy of prematurity.

6. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating retinitis in a mammal.

7. The compound or pharmaceutically acceptable salt of claim 6 wherein the retinitis comprises cytomegalovirus retinitis.

8. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating macular edema in a mammal.

9. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating an ophthalmic disease in a mammal.

10. A pharmaceutical composition comprising:

a) a therapeutically effective amount of a compound or pharmaceutically acceptable salt of claim 1;and

b) a pharmaceutically acceptable carrier, diluent, or vehicle therefor.

11. The compound or pharmaceutically acceptable salt of claim 1 for use as a medicament for treating a mammalian disease condition mediated by protein kinase activity.

12. The compound or pharmaceutically acceptable salt of claim 11, wherein the mammalian disease condition is associated with tumor growth, cell proliferation, or angiogenesis.

13. A method of modulating the activity of a protein kinase receptor, comprising contacting the kinase receptor with an effective amount of a compound or pharmaceutically acceptable salt as defined in claim 1.

14. A method according to claim 13, wherein the protein kinase receptor is a VEGF receptor.