Substituted 2,3-dihydroimidazo[1,2-c]quinazoline Derivatives Useful for Treating Hyper-Proliferative Disorders and Diseases Associated with Angiogenesis

Field of the Invention

This invention relates to novel 2,3-dihydroimidazo[1,2-c]quinazoline compounds, pharmaceutical compositions containing such compounds and the use of those compounds or compositions for phosphotidylinositol-3-kinase (PI3K) inhibition and treating diseases associated with phosphotidylinositol-3-kinase (PI3K) activity, in particular treating hyper-proliferative and/or angiogenesis disorders, as a sole agent or in combination with other active ingredients.

Background of the Invention

In the last decade the concept of developing anti-cancer medications which target abnormally active protein kinases has led to a number of successes. In addition to the actions of protein kinases, lipid kinases also play an important role in generating critical regulatory second messengers. The PI3K family of lipid kinases generates 3'-phosphoinositides that bind to and activate a variety of cellular targets, initiating a wide range of signal transduction cascades (Vanhaesebroeck *et al.*, 2001; Toker, 2002; Pendaries *et al.*, 2003; Downes *et al.*, 2005). These cascades ultimately induce changes in multiple cellular processes, including cell proliferation, cell survival, differentiation, vesicle trafficking, migration, and chemotaxis.

PI3Ks can be divided into three distinct classes based upon differences in both structure, and substrate preference. While members of the Class II family of PI3Ks have been implicated in the regulation of tumor growth (Brown and Shepard, 2001; Traer *et al.*, 2006), the bulk of research has focused on the Class I enzymes and their role in cancer (Vivanco And Sawyers, 2002; Workman, 2004, Chen *et al.*, 2005; Hennessey *et al.*, 2005; Stauffer *et al.*, 2005; Stephens *et al.*, 2005; Cully *et al.*, 2006).

Class I PI3Ks have traditionally been divided into two distinct sub-classes based upon differences in protein subunit composition. The Class I_A PI3Ks are comprised of a catalytic p110 catalytic subunit (p110α, β or δ) heterodimerized with a member of the p85 regulatory subunit family. In contrast, the Class I_B PI3K catalytic subunit (p110γ) heterodimerizes with a distinct p101 regulatory subunit (reviewed by Vanhaesebroeck and Waterfield, 1999; Funaki *et al.*, 2000; Katso *et al.*, 2001). The C-terminal region of

these proteins contains a catalytic domain that possesses distant homology to protein kinases. The PI3Kγ structure is similar to Class I_A p110s, but lacks the N-terminal p85 binding site (Domin and Waterfield, 1997). Though similar in overall structure, the homology between catalytic p110 subunits is low to moderate. The highest homology between the PI3K isoforms is in the kinase pocket of the kinase domain.

The Class I_A PI3K isoforms associate with activated receptor tyrosine kinases (RTKs) (including PDGFR, EGFR, VEGFR, IGF1-R, c-KIT, CSF-R and Met), or with tyrosine phosphorylated adapter proteins (such as Grb2, Cbl, IRS-1 or Gab1), via their p85 regulatory subunits resulting in stimulation of the lipid kinase activity. Activation of the lipid kinase activity of the p110β and p110γ isoforms has been shown to occur in response to binding to activated forms of the ras Oncogene (Kodaki *et al*, 1994). In fact, the oncogenic activity of these isoforms may require binding to ras (Kang *et al.*, 2006). In contrast, the p110α and p110δ isoforms exhibit oncogenic activity independent of ras binding, through constitutive activation of Akt.

Class I PI3Ks catalyze the conversion of $PI(4,5)P_2$ [PIP_2] to $PI(3,4,5)P_3$ [PIP_3]. The production of PIP_3 by PI3K affects multiple signaling processes that regulate and coordinate the biological end points of cell proliferation, cell survival, differentiation and cell migration. PIP_3 is bound by Pleckstrin-Homology (PH) domain-containing proteins, including the phosphoinositide-dependent kinase, PDK1 and the Akt proto-oncogene product, localizing these proteins in regions of active signal transduction and also contributing directly to their activation (Klippel *et al.*, 1997; Fleming *et al.*, 2000; Itoh and Takenawa, 2002; Lemmon, 2003). This co-localization of PDK1 with Akt facilitates the phosphorylation and activation of Akt. Carboxy-terminal phosphorylation of Akt on Ser^{473} promotes phosphorylation of Thr^{308} in the Akt activation loop (Chan and Tsichlis, 2001; Hodgekinson *et al.*, 2002; Scheid *et al.*, 2002; Hresko *et al.*, 2003). Once active, Akt phosphorylates and regulates multiple regulatory kinases of pathways that directly influence cell cycle progression and cell survival.

Many of the effects of Akt activation are mediated via its negative regulation of pathways which impact cell survival and which are commonly dysregulated in cancer. Akt promotes tumor cell survival by regulating components of the apoptotic and cell cycle machinery. Akt is one of several kinases that phosphorylate and inactivate pro-apoptotic BAD proteins (del Paso *et al.*, 1997; Pastorino *et al.*, 1999). Akt may also promote cell survival

through blocking cytochrome C-dependent caspase activation by phosphorylating Caspase 9 on Ser^{196} (Cardone *et al.*, 1998).

Akt impacts gene transcription on several levels. The Akt-mediated phosphorylation of the MDM2 E3 ubiquitin ligase on Ser^{166} and Ser^{186} facilitates the nuclear import of MDM2 and the formation and activation of the ubiquitin ligase complex. Nuclear MDM2 targets the p53 tumor suppressor for degradation, a process that can be blocked by LY294002 (Yap *et al.*, 2000; Ogarawa *et al.*, 2002). Downregulation of p53 by MDM2 negatively impacts the transcription of p53-regulated pro-apoptotic genes (e.g. Bax, Fas, PUMA and DR5), the cell cycle inhibitor, $p21^{Cip1}$, and the PTEN tumor suppressor (Momand *et al.*, 2000; Hupp *et al.*, 2000; Mayo *et al.*, 2002; Su *et al.*, 2003). Similarly, the Akt-mediated phosphorylation of the Forkhead transcription factors FKHR, FKHRL and AFX (Kops *et al.*, 1999; Tang *et al.*, 1999), facilitates their binding to 14-3-3 proteins and export from the cell nucleus to the cytosol (Brunet *et al.*, 1999). This functional inactivation of Forkhead activity also impacts pro-apoptotic and pro-angiogenic gene transcription including the transcription of Fas ligand (Ciechomska *et al.*, 2003) Bim, a pro-apoptotic Bcl-2 family member (Dijkers *et al.*, 2000), and the Angiopoietin-1 (Ang-1) antagonist, Ang-2 (Daly *et al.*, 2004). Forkhead transcription factors regulate the expression of the cyclin-dependent kinase (Cdk) inhibitor $p27^{Kip1}$. Indeed, PI3K inhibitors have been demonstrated to induce $p27^{Kip1}$ expression resulting in Cdk1 inhibition, cell cycle arrest and apoptosis (Dijkers *et al.*, 2000). Akt is also reported to phosphorylate $p21^{Cip1}$ on Thr^{145} and $p27^{Kip1}$ on Thr^{157} facilitating their association with 14-3-3 proteins, resulting in nuclear export and cytoplasmic retention, preventing their inhibition of nuclear Cdks (Zhou *et al.*, 2001; Motti *et al.*, 2004; Sekimoto *et al.*, 2004). In addition to these effects, Akt phosphorylates IKK (Romashkova and Makarov, 1999), leading to the phosphorylation and degradation of IκB and subsequent nuclear translocation of NFκB, resulting in the expression of survival genes such as IAP and Bcl-X_L.

The PI3K/Akt pathway is also linked to the suppression of apoptosis through the JNK and $p38^{MAPK}$ MAP Kinases that are associated with the induction of apoptosis. Akt is postulated to suppress JNK and $p38^{MAPK}$ signaling through the phosphorylation and inhibition of two JNK/p38 regulatory kinases, Apoptosis Signal-regulating Kinase 1 (ASK1) (Kim *et al.*, 2001: Liao and Hung, 2003; Yuan *et al.*, 2003), and Mixed Lineage Kinase 3 (MLK3) (Lopez-Ilasaca *et al.*, 1997; Barthwal *et al.*, 2003; Figueroa *et al.*, 2003;). The induction of $p38^{MAPK}$ activity is observed in tumors treated with cytotoxic agents and is required for those agents to induce cell death (reviewed by Olson and

Hallahan, 2004). Thus, inhibitors of the PI3K pathway may promote the activities of co-administered cytotoxic drugs.

An additional role for PI3K/Akt signaling involves the regulation of cell cycle progression through modulation of Glycogen Synthase Kinase 3 (GSK3) activity. GSK3 activity is elevated in quiescent cells, where it phosphorylates cyclin D_1 on Ser^{288}, targeting the protein for ubiquitination and degradation (Diehl *et al.*, 1998) and blocking entry into S-phase. Akt inhibits GSK3 activity through phosphorylation on Ser^{9} (Cross *et al.*, 1995). This results in the elevation of Cyclin D_1 levels which promotes cell cycle progression. Inhibition of GSK3 activity also impacts cell proliferation through activation of the wnt/beta-catenin signaling pathway (Abbosh and Nephew, 2005; Naito *et al.*, 2005; Wilker *et al.*, 2005; Kim *et al.*, 2006; Segrelles *et al.*, 2006). Akt mediated phosphorylation of GSK3 results in stabilization and nuclear localization of the beta-catenin protein, which in turn leads to increased expression of c-myc and cyclin D1, targets of the beta-catenin/Tcf pathway.

Although PI3K signaling is utilized by many of the signal transduction networks associated with both oncogenes and tumor suppressors, PI3K and its activity have been linked directly to cancer. Overexpression of both the p110α and p110β isoforms has been observed in bladder and colon tumors and cell lines, and overexpression generally correlates with increased PI3K activity (Bénistant *et al.*, 2000). Overexpression of p110α has also been reported in ovarian and cervical tumors and tumor cell lines, as well as in squamous cell lung carcinomas. The overexpression of p110α in cervical and ovarian tumor lines is associated with increased PI3K activity (Shayesteh *et al.*, 1999; Ma *et al.*, 2000). Elevated PI3K activity has been observed in colorectal carcinomas (Phillips *et al.*, 1998) and increased expression has been observed in breast carcinomas (Gershtein *et al.*, 1999).

Over the last few years, somatic mutations in the gene encoding p110α (PIK3CA) have been identified in numerous cancers. The data collected to date suggests that PIK3CA is mutated in approximately 32% of colorectal cancers (Samuels *et al.*, 2004; Ikenoue *et al.*, 2005), 18-40% of breast cancers (Bachman *et al.*, 2004; Campbell *et al.*, 2004; Levine *et al.*, 2005; Saal *et al.*, 2005; Wu *et al.*, 2005), 27% of glioblastomas (Samuels *et al.*, 2004; Hartmann *et al.*, 2005, Gallia *et al.*, 2006), 25% of gastric cancers (Byun *et al.*, 2003; Samuels *et al.*, 2004; Li *et al.*, 2005), 36% of hepatocellular carcinomas (Lee *et al.*, 2005), 4-12% of ovarian cancers (Levine *et al.*, 2005; Wang *et al.*, 2005), 4% of lung cancers

(Samuels *et al.*, 2004; Whyte and Holbeck, 2006), and up to 40% of endometrial cancers (Oda *et al.*, 2005). PIK3CA mutations have been reported in oligodendroma, astrocytoma, medulloblastoma, and thyroid tumors as well (Broderick *et al.*, 2004; Garcia-Rostan *et al.*, 2005). Based upon the observed high frequency of mutation, PIK3CA is one of the two most frequently mutated genes associated with cancer, the other being K-ras. More than 80% of the PIK3CA mutations cluster within two regions of the protein, the helical (E545K) and catalytic (H1047R) domains. Biochemical analysis and protein expression studies have demonstrated that both mutations lead to increased constitutive p110α catalytic activity and are in fact, oncogenic (Bader *et al.*, 2006; Kang *et al.*, 2005; Samuels *et al.*, 2005; Samuels and Ericson, 2006). Recently, it has been reported that PIK3CA knockout mouse embryo fibroblasts are deficient in signaling downstream from various growth factor receptors (IGF-1, Insulin, PDGF, EGF), and are resistant to transformation by a variety of oncogenic RTKs (IGFR, wild-type EGFR and somatic activating mutants of EGFR, Her2/Neu)(Zhao *et al.*, 2006).

Functional studies of PI3K *in vivo* have demonstrated that siRNA-mediated downregulation of p110β inhibits both Akt phosphorylation and HeLa cell tumor growth in nude mice (Czauderna *et al.*, 2003). In similar experiments, siRNA-mediated downregulation of p110β was also shown to inhibit the growth of malignant glioma cells *in vitro* and *in vivo* (Pu *et al.*, 2006). Inhibition of PI3K function by dominant-negative p85 regulatory subunits can block mitogenesis and cell transformation (Huang *et al.*, 1996; Rahimi *et al.*, 1996). Several somatic mutations in the genes encoding the p85α and p85β regulatory subunits of PI3K that result in elevated lipid kinase activity have been identified in a number of cancer cells as well (Janssen *et al.*, 1998; Jimenez *et al.*, 1998; Philp *et al.*, 2001; Jucker *et al.*, 2002; Shekar *et al.*, 2005). Neutralizing PI3K antibodies also block mitogenesis and can induce apoptosis *in vitro* (Roche *et al.*, 1994: Roche *et al.*, 1998; Bénistant *et al.*, 2000). *In vivo* proof-of-principle studies using the PI3K inhibitors LY294002 and wortmannin, demonstrate that inhibition of PI3K signaling slows tumor growth *in vivo* (Powis *et al.*, 1994; Shultz *et al.*, 1995; Semba *et al.*, 2002; Ihle *et al.*, 2004).

Overexpression of Class I PI3K activity, or stimulation of their lipid kinase activities, is associated with resistance to both targeted (such as imatinib and tratsuzumab) and cytotoxic chemotherapeutic approaches, as well as radiation therapy (West et al., *2002*; Gupta *et al.*, 2003; Osaki *et al.*, 2004; Nagata *et al.*, 2004; Gottschalk *et al.*, 2005; Kim *et al.*, 2005). Activation of PI3K has also been shown to lead to expression of multidrug

resistant protein-1 (MRP-1) in prostate cancer cells and the subsequent induction of resistance to chemotherapy (Lee *et al.*, 2004).

The importance of PI3K signaling in tumorigenesis is further underscored by the findings that the PTEN tumor suppressor, a PI(3)P phosphatase, is among the most commonly inactivated genes in human cancers (Li *et al.*, 1997, Steck *et al.*, 1997; Ali *et al.*, 1999; Ishii *et al.*, 1999). PTEN dephosphorylates $PI(3,4,5)P_3$ to $PI(4,5)P_2$ thereby antagonizing PI3K-dependent signaling. Cells containing functionally inactive PTEN have elevated levels of PIP_3, high levels of activity of PI3K signaling (Haas-Kogan *et al.*, 1998; Myers *et al.*, 1998; Taylor *et al.*, 2000), increased proliferative potential, and decreased sensitivity to pro-apoptotic stimuli (Stambolic *et al.*, 1998). Reconstitution of a functional PTEN suppresses PI3K signaling (Taylor *et al.*, 2000), inhibits cell growth and re-sensitizes cells to pro-apoptotic stimuli (Myers *et al.*, 1998; Zhao *et al.*, 2004). Similarly, restoration of PTEN function in tumors lacking functional PTEN inhibits tumor growth *in vivo* (Stahl *et al.*, 2003; Su *et al.*, 2003; Tanaka and Grossman, 2003) and sensitizes cells to cytotoxic agents (Tanaka and Grossman, 2003).

The class I family of PI3Ks clearly plays an important role in the regulation of multiple signal transduction pathways that promote cell survival and cell proliferation, and activation of their lipid kinase activity contributes significantly to the development of human malignancies. Furthermore, inhibition of PI3K may potentially circumvent the cellular mechanisms that underlie resistance to chemotherapeutic agents. A potent inhibitor of Class I PI3K activities would therefore have the potential not only to inhibit tumor growth but to also sensitize tumor cells to pro-apoptotic stimuli *in vivo*.

Signal transduction pathways originating from chemoattractant receptors are considered to be important targets in controlling leukocyte motility in inflammatory diseases. Leukocyte trafficking is controlled by chemoattractant factors that activate heterotrimeric GPCRs and thereby trigger a variety of downstream intracellular events. Signal transduction along one of these pathways that results in mobilization of free Ca^{2+}, cytoskelatal reorganization, and directional movement depends on lipid-dervied second messengers producted by PI3K activity (Wymann *et al.*, 2000; Stein and Waterfield, 2000).

PI3Kγ modulates baseline cAMP levels and controls contractility in cells. Recent research indicates that alterations in baseline cAMP levels contributes to the increased contractility

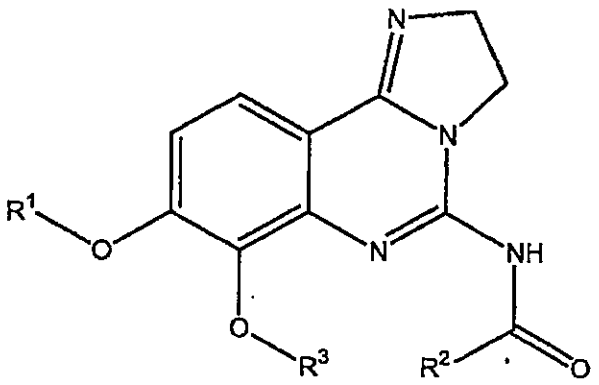
in mutant mice. This research, therefore, shows that PI3Kγ inhibitors would afford potential treatments for congestive heart failure, ischemia, pulmonary hypertension, renal failure, cardiac hypertrophy, atherosclerosis, thromboembolism, and diabetes.

PI3K inhibitors would be expected to block signal transduction from GPCRs and block the activation of various immune cells, leading to a broad anti-inflammatory profile with potential for the treatment of inflammatory and immunoregulatory diseases, including asthma, atopic dermatitis, rhinitis, allergic diseases, chronic obstructive pulmonary disease (COPD), septic shock, joint diseases, autoimmune pathologies such as rheumatoid arthritis and Graves' disease, diabetes, cancer, myocardial contractility disorders, thromboembolism, and atherosclerosis.

PI3K inhibitor compounds and compositions described herein, including salts, metabolites, solvates, solvates of salts, hydrates, and stereoisomeric forms thereof, exhibit anti-proliferative activity and are thus useful to prevent or treat the disorders associated with hyper-proliferation.

Description of the Invention

One embodiment of this invention encompasses a compound having the formula (I):



Formula I

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^1 is $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 is a heteroaryl optionally substituted with 1, 2 or 3 R^6 groups;

R^3 is alkyl or cycloalkyl;

R^4 is hydrogen, hydroxy or alkoxy and R^5 and $R^{5'}$ may be the same or different and are independently, hydrogen, alkyl, cycloalkylalklyl, or alkoxyalkyl or R^5 and $R^{5'}$ may be taken together with the nitrogen atom to which they are bound to form a 3-7 membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups, or R^4 and R^5 may be taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more $R^{6'}$ groups;

each occurrence of R^6 may be the same or different and is independently halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclylalkyl, alkyl-OR^7, alkyl-SR^7, alkyl-$N(R^7)(R^{7'})$, alkyl-COR^7,-CN, -$COOR^7$, -$CON(R^7)(R^{7'})$, -OR^7, -SR^7, -$N(R^7)(R^{7'})$, or $-NR^7COR^7$ each of which may be optionally substituted with 1 or more R^8 groups;

each occurrence of $R^{6'}$ may be the same or different and is independently alkyl, cycloalkylalklyl, or alkyl-OR^7;

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl;

each occurrence of R^8 is independently nitro, hydroxy, cyano, formyl, acetyl, halogen, amino, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl;

n is an integer from 1-4 and m is an integer from 0-4 with the proviso that when when R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing ring, $n + m \leq 4$.

In a preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^2 is a nitrogen containing heteroaryl optionally substituted with 1, 2 or 3 R^6 groups.

In another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^5 and $R^{5'}$ are independently alkyl;

In still another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^5 and $R^{5'}$ are taken together with the nitrogen atom to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups.

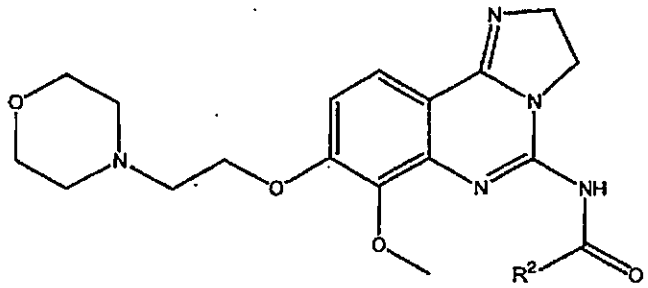
In yet another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^4 is hydroxy.

In another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more R^6 groups.

In yet another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^3 is methyl.

In still another preferred embodiment, the invention encompasses the compound of Formula (I), wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups; more preferably pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

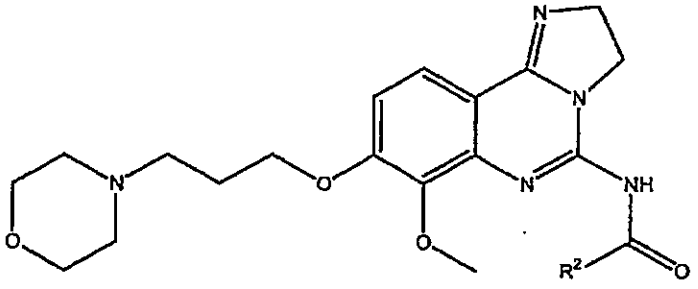
In a distinct embodiment, the invention encompasses a compound of formula (Ia)



Formula Ia

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above.

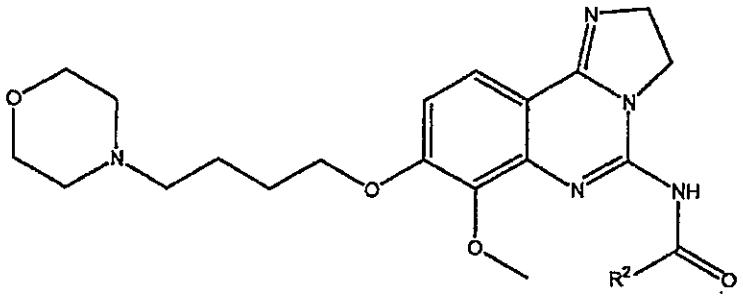
In another distinct embodiment, the invention encompasses a compound of formula (Ib)



Formula Ib

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above.

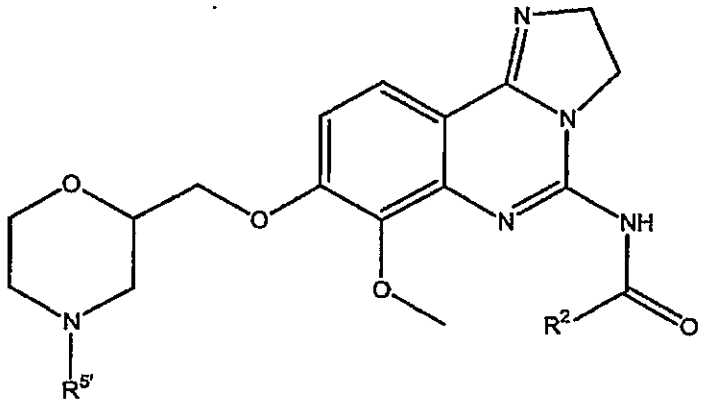
In still another distinct embodiment, the invention encompasses a compound of formula (Ic)



Formula Ic

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 is as defined above.

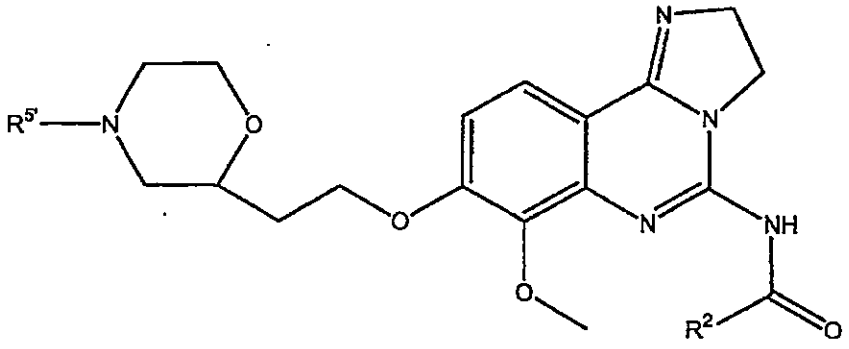
In yet another distinct embodiment, the invention encompasses a compound of the formula (Id):



Formula Id

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 and R^4 are as defined above.

In yet another distinct embodiment, the invention encompasses a compound of the formula (Ie):



Formula Ie

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein R^2 and R^4 are as defined above.

In a preferred embodiment, the invention encompasses a compound of formula (I) - (V), wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups; more preferrably wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

In still another preferred embodiment, the invention encompasses a compound having the formula:

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide ;

N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide;

N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide;

6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[8-(2-hydroxy-3-morpholin-4-ylpropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{7-methoxy-8-[3-(3-methylmorpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(8-{2-[4-(cyclobutylmethyl)morpholin-2-yl]ethoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-(7-methoxy-8-{2-[4-(2-methoxyethyl)morpholin-2-yl]ethoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-{8-[(4-ethylmorpholin-2-yl)methoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-(7-methoxy-8-{[4-(2-methoxyethyl)morpholin-2-yl]methoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-{7-methoxy-8-[(4-methylmorpholin-2-yl)methoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-4-carboxamide;

rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;

rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide;

rel-6-acetamido-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-5-carboxamide;

6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylnicotinamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methylpyrimidine-5-carboxamide;

6-amino-5-bromo-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-5-carboxamide;

N-[7-methoxy-8-(morpholin-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

2-{[2-(dimethylamino)ethyl]amino}-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-1,3-thiazole-5-carboxamide;

rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;

rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

2-[(2-hydroxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-methoxypropyl)amino]pyrimidine-5-carboxamide;

2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-morpholin-4-ylpropyl)amino]pyrimidine-5-carboxamide;

2-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

2-{[2-(dimethylamino)ethyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

6-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-pyrrolidin-1-ylpyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-piperazin-1-ylnicotinamide hydrochloride;

6-[(3S)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride hydrate;

6-[(3R)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride;

6-[(4-fluorobenzyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(2-furylmethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(1H-pyrrol-1-yl)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-morpholin-4-ylnicotinamide;

N-{7-methoxy-8-[3-(methylamino)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

6-[(2,2-dimethylpropanoyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(cyclopropylcarbonyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(trifluoromethyl)nicotinamide;

6-(isobutyrylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{7-methoxy-8-[3-(4-methylpiperazin-1-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-{[(methylamino)carbonyl]amino}-1,3-thiazole-4-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-{[(methylamino)carbonyl]amino}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)-1,3-thiazole-4-carboxamide;

N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-6-methylnicotinamide;

6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-pyrrolidin-1-ylnicotinamide;

6-(dimethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-piperidin-1-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(2-piperidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-{[(ethylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-fluoro-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-4-carboxamide;

2-(ethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-4-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrazine-2-carboxamide;

N-[8-(2-aminoethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;

N-{8-[3-(diethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[2-(diisopropylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[2-(diethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylthio)pyrimidine-5-carboxamide;

N-[8-(3-aminopropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-2-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;

2-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-3-furamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-3-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methyl-1,3-thiazole-4-carboxamide;

6-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;

6-(acetylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

In a preferred embodiment, the invention encompasses a compound having the formula:

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;

5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;

rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;

2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

Where there is a discrepancy between the chemical name and the chemical structure depicted, the chemical structure depicted takes precedence over the chemical name given.

Without being bound by theory or mechanism, the compounds of the present invention display surprising activity for the inhibition of phosphatidylinositol-3-kinase and chemical and structural stability over those compounds of the prior art. It is believed that this surprising activity is based on the chemical structure of the compounds, in particular the basicity of the compounds as a result of R^1 being amino optionally substituted with R^5 and $R^{5'}$. Further, the appropriate choice of R^3 and R^2 provide the necessary activity against the appropriate isoforms to allow for activity in vivo.

Definitions

The term `alkyl` refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, such as illustratively, methyl, ethyl, n-propyl 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

The term "alkenyl " refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-I-propenyl, 1-butenyl, 2-and butenyl.

The term "alkynyl" refers to a straight or branched chain hydrocarbonyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl.

The term "alkoxy" denotes an alkyl group as defined herein attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are methoxy and ethoxy.

The term "alkoxyakyl" denotes an alkoxy group as defined herein attached via oxygen linkage to an alkyl group which is then attached to the main structure at any carbon from

alkyl group that results in the creation of a stable structure the rest of the molecule. Representative examples of those groups are $-CH_2OCH_3$, $-CH_2OC_2H_5$.

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphththyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups e.g sprio (4,4) non-2-yl.

The term "cycloalkylalkyl" refers to cyclic ring-containing radicals containing in the range of about about 3 up to 8 carbon atoms directly attached to alkyl group which is then also attached to the main structure at any carbon from the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobuyylethyl, cyclopentylethyl.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl .

The term "arylalkyl" refers to an aryl group as defined herein directly bonded to an alkyl group as defined herein which is then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure the rest of the molecule. e.g., -$-CH_2C_6H_5$, $--C_2H_5C_6H_5$.

The term "heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl cinnolinyl dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazil, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-

piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl pyridazinyl, oxazolyl oxazolinyl oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, isochromanyl .

The term "heteroaryl" refers to heterocyclic ring radical as defined herein which are aromatic. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" refers to heteroaryl ring radical as defined herein directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term "heterocyclyl" refers to a heterocylic ring radical as defined herein. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" refers to a heterocylic ring radical as defined herein directly bonded to alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration, resulting in racemic mixtures in the case of a single asymmetric center, and diastereomeric mixtures in the case of multiple asymmetric centers. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention. Preferred compounds are those, which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chorine salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from

inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the

beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The compounds of the present invention can be administered with pharmaceutically-acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, nasally, ophthalmically, optically, sublingually, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting

agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent

such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting

agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct

techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*, "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology* 1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilized powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

Hard Shell Capsules: A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

Soft Gelatin Capsules: A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids

are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating,

alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder, such as a carcinoma.

Methods of treating kinase disorders

The present invention also provides methods for the treatment of disorders associated with aberrant kinase activity (such as tyrosine kinase activity), including, phosphotidylinositol-3-kinase.

Effective amounts of compounds of the present invention can be used to treat disorders, including angiogenic disorders, such as cancer; inflammatory disorders (including but not limited to Chronic obstructive pulmonary disorder (COPD)), autoimmune disorders, cardiovascular disorders (including but not limited to thrombosis, pulmonary hypertension, cardiac hypertophy, atherosclerosis or heart failure), neurodegenerative disorders, metabolic disorders, nociceptive disorders, ophthalmic disorders, pulmonary disorders, or renal disorders. Nonetheless, such cancers and other diseases can be treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the disorder.

The phrase "aberrant kinase activity" or "aberrant tyrosine kinase activity," includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or polypeptide; gene amplification; mutations which produce constitutively-active or hyperactive kinase activity; gene mutations, deletions, substitutions, additions, etc.

The present invention also provides for methods of inhibiting a kinase activity, especially of phosphotidylinositol-3-kinase, comprising administering an effective amount of a compound of the present invention, including salts, polymorphs, metabolites, hyrates, solvates, prodrugs (e.g.: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells (e.g., in vitro), or in the cells of a mammalian subject, especially a human patient in need of treatment.

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity (Aiello et al. *New Engl. J. Med.* 1994, *331*, 1480; Peer et al. *Lab. Invest.* 1995, *72*, 638), age-related macular degeneration (AMD; see, Lopez et al. *Invest. Opththalmol. Vis. Sci.* 1996, *37*, 855), neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about

0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Combination therapies

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhytmic, anti-hypercholsterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with admixtures and combinations thereof.

The additional pharmaceutical agent can be aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine, bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine,

virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

The additional pharmaceutical agent can also be gemcitabine, paclitaxel, cisplatin, carboplatin, sodium butyrate, 5-FU, doxirubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α-glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of*

Therapeutics (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Generally, the use of cytotoxic and/or cytostatic agents in combination with a compound or composition of the present invention will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

EXPERIMENTAL

Abbreviations and Acronyms

A comprehensive list of the abbreviations used by organic chemists of ordinary skill in the art appears in The ACS Style Guide (third edition) or the Guidelines for Authors for the *Journal of Organic Chemistry*. The abbreviations contained in said lists, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87.

More specifically, when the following abbreviations are used throughout this disclosure, they have the following meanings:

acac	acetylacetonate
Ac_2O	acetic anhydride
AcO (or OAc)	acetate
anhyd	anhydrous
aq	aqueous
Ar	aryl
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
br s	broad singlet
Bz	benzoyl
BOC	*tert*-butoxycarbonyl
n-BuOH	*n*-butanol
t-BuOH	*tert*-butanol
t-BuOK	potassium *tert*-butoxide
C	Celsius

calcd	calculated
CAN	ceric ammonium nitrate
Cbz	carbobenzyloxy
CDI	carbonyl diimidazole
CD_3OD	methanol-d_4
Celite®	diatomaceous earth filter agent, Celite ® Corp.
CI-MS	chemical ionization mass spectroscopy
^{13}C NMR	carbon-13 nuclear magnetic resonance
m-CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
dd	doublet of doublets
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
dec	decomposition
DIA	diisopropylamine
DIBAL	diisobutylaluminum hydride
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
E	entgegen (configuration)
EDCI or EDCI · HCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
ELSD	evaporative light scattering detector
equiv	equivalent
ES-MS	electrospray mass spectroscopy
EtOAc	ethyl acetate
EtOH	ethanol (100%)
EtSH	ethanethiol
Et_2O	diethyl ether
Et_3N	triethylamine

Fmoc	9-fluorenylmethoxycarbonyl
GC	gas chromatography
GC-MS	gas chromatography-mass spectroscopy
h	hour, hours
hex	hexanes, or hexane
^{1}H NMR	proton nuclear magnetic resonance
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphoric triamide
HOBT	hydroxybenzotriazole
HPLC	high performance liquid chromatography
insol	insoluble
IPA	isopropylamine
*i*PrOH	isopropylalcohol
IR	infrared
J	coupling constant (NMR spectroscopy)
L	liter
LAH	lithium aluminum hydride
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
M	mol L^{-1} (molar)
m	multiplet
m	meta
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minute, minutes
µL	microliter
mL	milliliter
µM	micromolar
mol	mole
mp	melting point
MS	mass spectrum, mass spectrometry
Ms	methanesulfonyl
m/z	mass-to-charge ratio
N	equiv L^{-1} (normal)

NBS	*N*-bromosuccinimide
nM	nanomolar
NMM	4-methylmorpholine
NMR	Nuclear Magnetic Resonance
o	ortho
obsd	observed
p	para
p	page
pp	pages
$PdCl_2dppf$	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd(OAc)_2$	palladium acetate
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
pK	negative logarithm of equilibrium constant
pK_a	negative logarithm of equilibrium constant for association
PPA	poly(phosphoric acid)
PS-DIEA	Polystyrene-bound diisopropylethylamine
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
rac	racemic
R	rectus (configurational)
R_f	retardation factor (TLC)
RT	retention time (HPLC)
rt	room temperature
s	singlet
S	sinister (configurational)
t	triplet
TBDMS, TBP	tert-butyldimethylsilyl
TBDPS, TPS	tert-butyldiphenylsilyl
TEA	triethylamine
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFFH	Fluoro-*N,N,N',N'*-tetramethylformamidinium

	hexafluorophosphate
TLC	thin layer chromatography
TMAD	*N,N,N',N'*-tetramethylethylenediamine
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
v/v	volume to volume ratio
w/v	weight to volume ratio
w/w	weight to weight ratio
Z	zusammen (configuration)

The percentage yields reported in the following examples are based on the starting component that was used in the lowest molar amount. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. The term "concentrated under reduced pressure" refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (°C). Thin layer chromatography (TLC) was performed on pre-coated glass-backed silica gel 60 A F-254 250 µm plates.

The structures of compounds of this invention were confirmed using one or more of the following procedures.

NMR

NMR spectra were acquired for each compound and were consistent with the structures shown.

Routine one-dimensional NMR spectroscopy was performed on either 300 or 400 MHz Varian® Mercury-plus spectrometers. The samples were dissolved in deuterated solvents. Chemical shifts were recorded on the ppm scale and were referenced to the appropriate solvent signals, such as 2.49 ppm for DMSO-d6, 1.93 ppm for CD3CN, 3.30 ppm for CD3OD, 5.32 ppm for CD2Cl2 and 7.26 ppm for CDCl3 for 1H spectra.

GC/MS

Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5973 mass spectrometer equipped Hewlett Packard 6890 Gas Chromatograph with a J & W HP-5 column (0.25 uM coating; 30 m x 0.32 mm). The ion source was maintained at 250 °C and spectra were scanned from 50-550 amu at 0.34 sec per scan.

LC/MS

Unless otherwise noted, all retention times are obtained from the LC/MS and correspond to the molecular ion. High pressure liquid chromatography-electrospray mass spectra (LC/MS) were obtained using one of the following:

Method A (LCQ)

Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a Waters Sunfire C18 column (2.1 x 30 mm, 3.5 □m), a Gilson autosampler and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonirile with 0.018% TFA. Gradient elution from 10% B to 95% B over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Method B (LCQ5)

Agilent 1100 HPLC system. The Agilent 1100 HPLC system was equipped with an Agilent 1100 autosampler, quaternary pump, a variable wavelength detector set at 254 nm. The HPLC column used was a Waters Sunfire C-18 column (2.1 x 30 mm, 3.5 µm). The HPLC eluent was directly coupled without splitting to a Finnigan LCQ DECA ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 140-1200 amu using a variable ion time according to the number of ions in the source using positive ion mode. The eluents were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonirile with 0.02% TFA. Gradient elution from 10% B to 90% B over 3.0 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 1.0 minutes and a final hold at 95% B of 1.0 minutes. Total run time was 7.0 minutes.

50

Method C (LTQ)

Agilent 1100 HPLC system. The Agilent 1100 HPLC system was equipped with an Agilent 1100 autosampler, quaternary pump, and a diode array. The HPLC column used was a Waters Sunfire C18 column (2.1 x 30 mm, 3.5 µm). The HPLC eluent was directly coupled with a 1:4 split to a Finnigan LTQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 50-800 amu using a variable ion time according to the number of ions in the source using positive or negative ion mode. The eluents were A: water with 0.1 formic acid, and B: acetonitrile with 0.1% formic acid. Gradient elution from 10% B to 90% B over 3.0 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 2.0 minutes and a final hold at 95% B of 1.0 minutes. Total run time was 8.0 minutes.

Method D

Gilson HPLC system equipped with a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluants were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes.

Method E

Agilent 1100 HPLC system. The Agilent 1100 HPLC system was equipped with an Agilent 1100 autosampler, quaternary pump, and a diode array. The HPLC column used was a Waters Sunfire (2.1 x 30 mm, 3.5 µm). The HPLC eluent was directly coupled with a 1:4 split to a Finnigan LTQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 50-1000 amu using a variable ion time according to the number of ions in the source in either positive or negative ion mode. The eluents were A: water with 0.1 formic acid, and B: acetonirile with 0.1% formic acid. Gradient elution from 10% B to 90% B over 3.0 minutes at a flow rate of 1.0 mL/min was used with an initial hold of 2.0 minutes and a final hold at 95% B of 1.0 minutes. Total run time was 8.0 minutes.

Preparative HPLC:

Preparative HPLC was carried out in reversed phase mode, typically using a Gilson HPLC system equipped with two Gilson 322 pumps, a Gilson 215 Autosampler, a Gilson diode array detector, and a C-18 column (e.g. YMC Pro 20 x 150 mm, 120 A). Gradient elution was used with solvent A as water with 0.1% TFA, and solvent B as acetonitrile with 0.1% TFA. Following injection onto the column as a solution, the compound was typically eluted with a mixed solvent gradient, such as 10-90% Solvent B in Solvent A over 15 minutes with flow rate of 25 mL/min. The fraction(s) containing the desired product were collected by UV monitoring at 254 or 220 nm.

Preparative MPLC:

Preparative medium pressure liquid chromatography (MPLC) was carried out by standard silica gel "flash chromatography" techniques (e.g., Still, W. C. et al. *J. Org. Chem.* **1978**, *43*, 2923-5), or by using silica gel cartridges and devices such as the Biotage Flash systems. A variety of eluting solvents were used, as described in the experimental protocols.

General Preparative Methods

The particular process to be utilized in the preparation of the compounds used in this embodiment of the invention depends upon the specific compound desired. Such factors as the selection of the specific substituents play a role in the path to be followed in the preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the compounds of the present invention, with more detailed particular examples being presented below in the experimental section describing the working examples.

The compounds of the invention can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either

commercially available or producible according to routine, conventional chemical methods. General methods for the preparation of the compounds are given below, and the preparation of representative compounds is specifically illustrated in examples.

Synthetic transformations that may be employed in the synthesis of compounds of this invention and in the synthesis of intermediates involved in the synthesis of compounds of this invention are known by or accessible to one skilled in the art. Collections of synthetic transformations may be found in compilations, such as:

J. March. *Advanced Organic Chemistry*, 4th ed.; John Wiley: New York (1992)
R.C. Larock. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York (1999)

F.A. Carey; R.J. Sundberg. *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York (1984)

T.W. Greene; P.G.M. Wuts. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York (1999)

L.S. Hegedus. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Mill Valley, CA (1994)

L.A. Paquette, Ed. *The Encyclopedia of Reagents for Organic Synthesis*; John Wiley: New York (1994)

A.R. Katritzky; O. Meth-Cohn; C.W. Rees, Eds. *Comprehensive Organic Functional Group Transformations*; Pergamon Press: Oxford, UK (1995)

G. Wilkinson; F.G A. Stone; E.W. Abel, Eds. *Comprehensive Organometallic Chemistry;* Pergamon Press: Oxford, UK (1982)

B.M. Trost; I. Fleming. *Comprehensive Organic Synthesis;* Pergamon Press: Oxford, UK (1991)

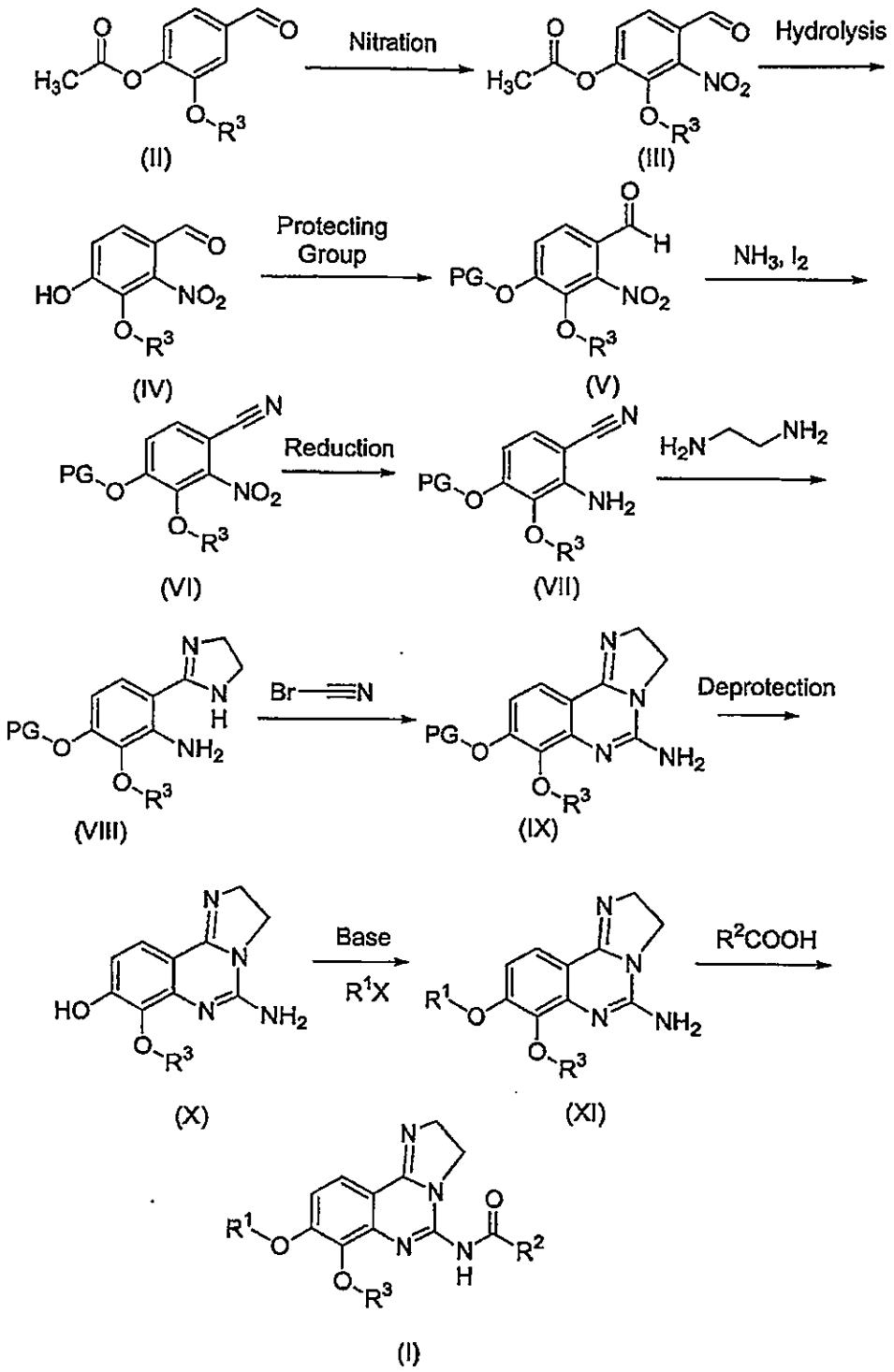
A.R. Katritzky; C.W. Rees Eds. *Comprehensive Heterocylic Chemistry*; Pergamon Press: Oxford, UK (1984)

A.R. Katritzky; C.W. Rees; E.F.V. Scriven, Eds. *Comprehensive Heterocylic Chemistry II*; Pergamon Press: Oxford, UK (1996)

C. Hansch; P.G. Sammes; J.B. Taylor, Eds. *Comprehensive Medicinal Chemistry*: Pergamon Press: Oxford, UK (1990).

In addition, recurring reviews of synthetic methodology and related topics include *Organic Reactions*; John Wiley: New York; *Organic Syntheses*; John Wiley: New York; *Reagents for Organic Synthesis*: John Wiley: New York; *The Total Synthesis of Natural Products*; John Wiley: New York; *The Organic Chemistry of Drug Synthesis*; John Wiley: New York; *Annual Reports in Organic Synthesis*; Academic Press: San Diego CA; and *Methoden der Organischen Chemie* (Houben-Weyl); Thieme: Stuttgart, Germany. Furthermore, databases of synthetic transformations include *Chemical Abstracts*, which may be searched using either CAS OnLine or SciFinder, *Handbuch der Organischen Chemie* (Beilstein), which may be searched using SpotFire, and REACCS.

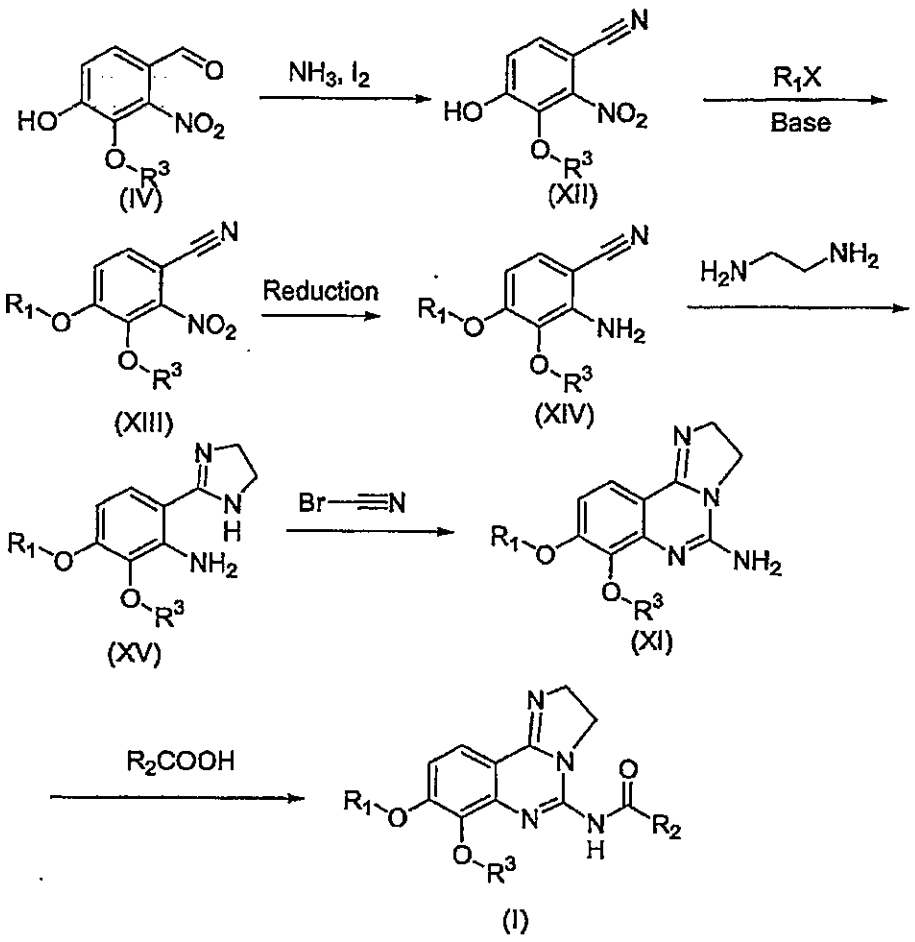
Reaction Scheme 1



In Reaction Scheme 1, vanillin acetate can be converted to intermediate (III) via nitration conditions such as neat fuming nitric acid or nitric acid in the presence of another strong

acid such as sulfuric acid. Hydrolysis of the acetate in intermediate (III) would be expected in the presence of bases such as sodium hydroxide, lithium hydroxide, or potassium hydroxide in a protic solvent such as methanol. Protection of intermediate (IV) to generate compounds of Formula (V) could be accomplished by standard methods (Greene, T.W.; Wuts, P.G.M.; *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1999). Conversion of compounds of formula (V) to those of formula (VI) can be achieved using ammonia in the presence of iodine in an aprotic solvent such as THF or dioxane. Reduction of the nitro group in formula (VI) could be accomplished using iron in acetic acid or hydrogen gas in the presence of a suitable palladium, platinum or nickel catalyst. Conversion of compounds of formula (VII) to the imidazoline of formula (VIII) is best accomplished using ethylenediamine in the presence of a catalyst such as elemental sulfur with heating. The cyclization of compounds of formula (VIII) to those of formula (IX) is accomplished using cyanogen bromide in the presence of an amine base such as triethylamine, diisopropylethylamine, or pyridine in a halogenated solvent such as DCM or dichloroethane. Removal of the protecting group in formula (IX) will be dependent on the group selected and can be accomplished by standard methods (Greene, T.W.; Wuts, P.G.M.; *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1999). Alkylation of the phenol in formula (X) can be achieved using a base such as cesium carbonate, sodium hydride, or potassium t-butoxide in a polar aprotic solvent such as DMF or DMSO with introduction of a side chain bearing an appropriate leaving group such as a halide, or a sulfonate group. Lastly, amides of formula (I) can be formed using activated esters such as acid chlorides and anhydrides or alternatively formed using carboxylic acids and appropriate coupling agents such as PYBOP, DCC, or EDCI in polar aprotic solvents.

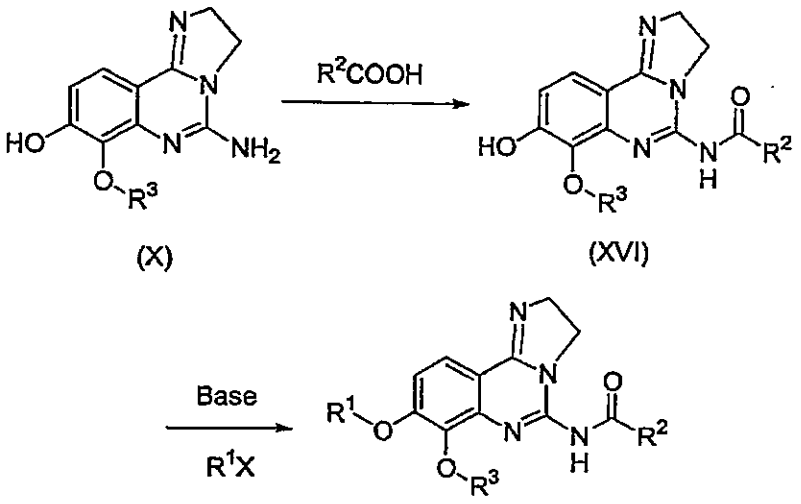
Reaction Scheme 2



In Reaction Scheme 2, a compound of formula (IV), prepared as described above, can be converted to a structure of formula (XII) using ammonia in the presence of iodine in an aprotic solvent such as THF or dioxane. Alkylation of the phenol in formula (XII) can be achieved using a base such as cesium carbonate, sodium hydride, or potassium t-butoxide in a polar aprotic solvent such as DMF or DMSO with introduction of a side chain bearing an appropriate leaving group such as a halide, or a sulfonate group. Reduction of the nitro group in formula (XIII) could be accomplished using iron in acetic acid or hydrogen gas in the presence of a suitable palladium, platinum or nickel catalyst. Conversion of compounds of formula (XIV) to the imidazoline of formula (XV) is best accomplished using ethylenediamine in the presence of a catalyst such as elemental sulfur with heating. The cyclization of compounds of formula (XV) to those of formula (XVI) is accomplished using cyanogen bromide in the presence of an amine base such as triethylamine, diisopropylethylamine, or pyridine in a halogenated solvent such as DCM or

dichloroethane. Lastly, amides of formula (I) can be formed using activated esters such as acid chlorides and anhydrides or alternatively formed using carboxylic acids and appropriate coupling agents such as PYBOP, DCC, or EDCI in polar aprotic solvents.

Reaction Scheme 3

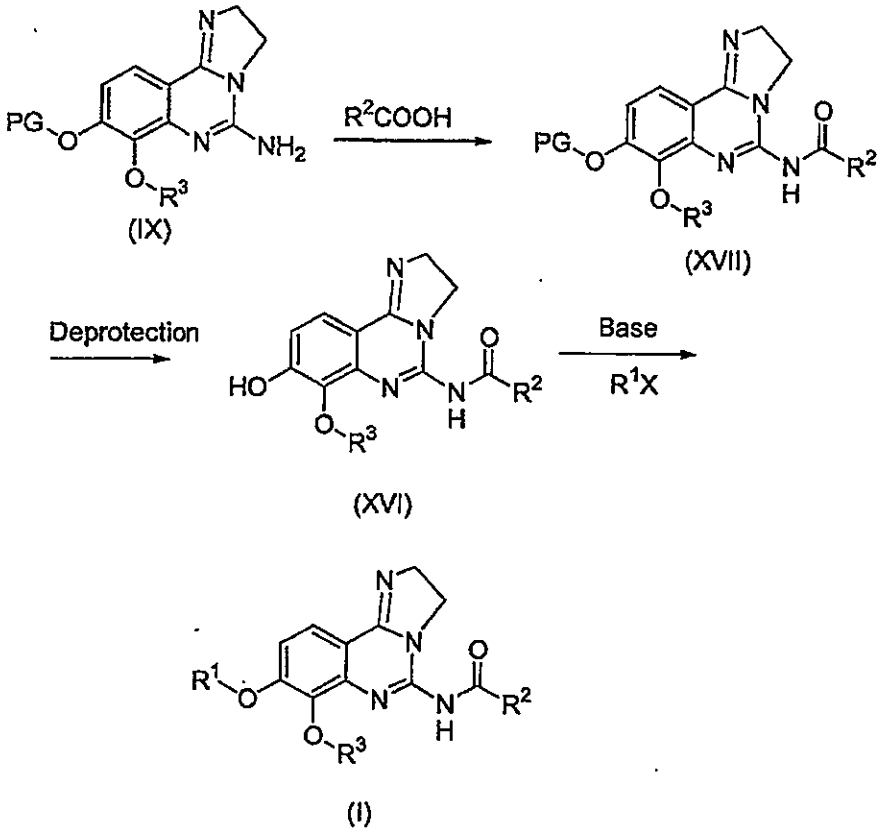


(X) (XVI)

(I)

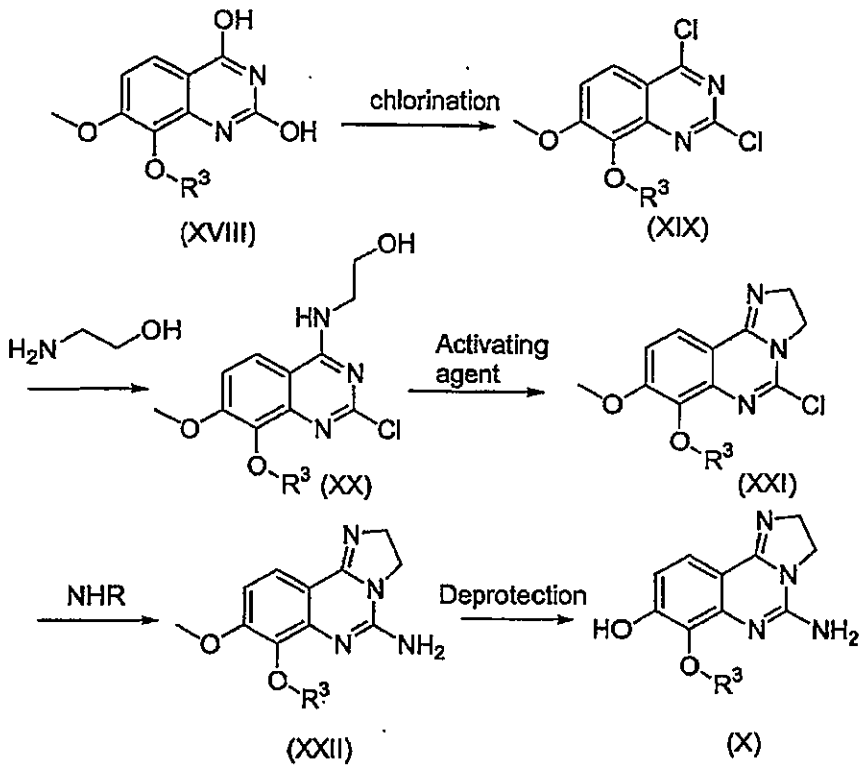
In Reaction Scheme 3, a compound of formula (X), prepared as described above, can be converted to amide (XVI) using activated esters such as acid chlorides and anhydrides or alternatively formed using carboxylic acids and appropriate coupling agents such as PYBOP, DCC, or EDCI in polar aprotic solvents. This could then be converted to compounds of formula (I) using a base such as cesium carbonate, sodium hydride, or potassium t-butoxide in a polar aprotic solvent such as DMF or DMSO with introduction of a side chain bearing an appropriate leaving group such as a halide, or a sulfonate group.

Reaction Scheme 4



In Reaction Scheme 4, a compound of formula (IX), prepared as described above, can be converted to amide (XVII) using activated esters such as acid chlorides and anhydrides or alternatively formed using carboxylic acids and appropriate coupling agents such as PYBOP, DCC, or EDCI in polar aprotic solvents. Removal of the protecting group in formula (XVII) will be dependent on the group selected and can be accomplished by standard methods (Greene, T.W.; Wuts, P.G.M.; *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1999). Alkylation of the phenol in formula (XVI) can be achieved using a base such as cesium carbonate, sodium hydride, or potassium t-butoxide in a polar aprotic solvent such as DMF or DMSO with introduction of a side chain bearing an appropriate leaving group such as a halide, or a sulfonate group.

Reaction Scheme 5



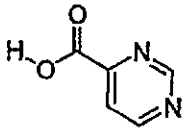
In Reaction Scheme 5, a compound of formula XVIII can be converted to the bis chloride compound of formula XIX using chlorinating agents such as $POCl_3$ or $COCl_2$ in aprotic solvents. The chloride thus obtained can be converted to imidazolines of formula XXI through reaction with appropriate quantities of ethanolamine or a suitably protected substitute, followed by activation with a suitable activating agent such as a sulfonyl chloride, PPh_3, or an halogenating agent such as $SOCl_2$. Chloride XXI can be converted to amine XXII through the use of any source of nucleophilic amine such as ammonia, phthalimide, or protected amines such as benzyl amine.in a polar solvent such as DMF or DMSO. Formation of the phenol depicted in formula X can be accomplished through deprotection of the methyl ether using any of the conditions outlined in the literature (Greene, T.W.; Wuts, P.G.M.; *Protective Groups in Organic Synthesis*; Wiley & Sons: New York, 1999).

In order that this invention may be better understood, the following examples are set forth. These examples are for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any manner. All publications mentioned herein are incorporated by reference in their entirety.

Intermediates

Intermediate A

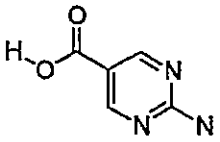
Preparation of pyrimidine 4-carboxylic acid



4-Methylpyrimidine (1.00 g, 10.6 mmol) was diluted in water (90 mL). Potassium permanganate (4.20 g, 26.5 mmol) and potassium hydroxide (4.20 g, 74.8 mmol) were added, and the mixture was heated at 75 °C for 1.5 h. Ethanol was added dropwise, and the precipitate was removed by filtration through Celite. The filtrate was concentrated under reduced pressure, diluted in water, and treated with a concentrated HCl solution until acidic. The title compound precipitated as a fine powder, which was collected by vacuum filtration and dried in a vacuum oven (770 mg, 58%): ^{1}H NMR (DMSO-d_6) δ: 13.92 (1H, br s), 9.35 (1H, d), 9.05 (1H, d), 7.99 (1H, dd).

Intermediate B

Preparation of 2-aminopyrimidine-5-carboxylic acid



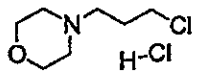
Sodium (1Z)-2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate was prepared as described by Zhichkin et al. (*Synthesis* 2002, *6*, p. 7720).

Sodium (1Z)-2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate (1.37 g, 7.8 mmol) was diluted in DMF (12 mL), and guanidine hydrochloride (640 mg, 6.7 mmol) was added. The mixture was stirred at 100 °C for 1 h, then was cooled to rt and diluted with water. Methyl 2-aminopyrimidine-5-carboxylate precipitated as a light yellow solid, which was isolated by vacuum filtration (510 mg, 50%): ^{1}H NMR (DMSO-d_6) δ: 8.67 (s, 2H), 7.56 (br s, 2H), 3.79 (s, 3H).

Methyl 2-aminopyrimidine-5-carboxylate (300 mg, 2.0 mmol) was diluted in methanol (5 mL) containing a few drops of water. Lithium hydroxide (122 mg, 5.1 mmol) was added, and the reaction mixture was stirred at 60 °C overnight. The mixture was concentrated under reduced pressure, then diluted in water and adjusted to pH 4 with 1 M HCl. 2-Aminopyrimidine-5-carboxylic acid precipitated as a white solid, which was isolated by vacuum filtration (244 mg, 90%): ^{1}H NMR (DMSO-d_6) δ: 12.73 (1H, br s), 8.63 (2H, s), 7.44 (2H, br s).

Intermediate C

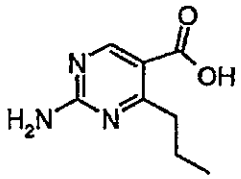
Preparation of 4-(3-chloropropyl)morpholine hydrochloride



To a solution of 1-bromo-3-chloropropane (45 g, 0.29 mol) in toluene (100 mL) was added morpholine (38 g, 0.44 mol). The solution was stirred at 84 °C for 3 h, during which time a precipitate formed. After cooling to rt, the precipitate was isolated by vacuum filtration, washed with ether, and the solid was discarded. The mother liquor was acidified with HCl (4 M in dioxane, 72 mL, 0.29 mol), which caused the desired product to precipitate as an HCl salt. Solvent was removed under reduced pressure, and the resultant solid was dried to afford the title compound (53 g, 90%): ^{1}H NMR (DMSO-d_6) δ: 11.45 (1H, br s), 3.94-3.77 (4H, m), 3.74 (2H, t), 3.39 (2H, m), 3.15 (2H, m), 3.03 (2H, m), 2.21 (2H, m).

Intermediate D

Preparation of 2-amino-4-propylpyrimidine-5-carboxylic acid

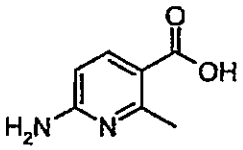


To a solution of ethyl 2-amino-4-propylpyrimidine-5-carboxylate (1.0 g, 4.8 mmol) in MeOH (20 mL) and THF (30 mL) was added a 2 N NaOH solution (10 mL). The solution was stirred at room temperature overnight and then neutralized with 1 N HCl (20 mL). It

was then concentrated under reduced pressure to 30 mL, filtered, and dried to give the desired product which was used without further purification (0.6 g, 69%).

Intermediate E

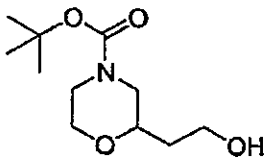
Preparation of 6-amino-2-methylnicotinic acid



A suspension of 6-amino-2-methylnicotinonitrile (1.0 g, 7.5 mmol) in an aqueous KOH solution (20%, 12 mL) was heated at the reflux temperature for 3 days. After this time, it was cooled to room temperature, neutralized with concentrated HCl, filtered and dried to give the desired product which was used without further purification (1.1 g, 96%).

Intermediate F

Preparation of *tert*-butyl 2-(2-hydroxyethyl)morpholine-4-carboxylate

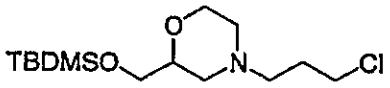


Methyl morpholin-2-yl acetate (5.0 g, 31.4 mmol) was diluted with THF (10 mL) and water (10 mL) and treated with potassium carbonate (4.34 g, 31.4 mmol). The thick suspension slowly went into solution. Di-*tert*-butyl dicarbonate (6.85 g, 31.4 mmol) was added and the reaction mixture was stirred at rt overnight. The reaction mixture was then extracted with THF and EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The sticky oil was triturated with ether and the resulting solid was collected by vacuum filtration (3.7 g, 45%). The mixture was diluted in THF (20 mL) and treated with a solution of sodium hydroxide (2 N, 5 mL) and stirred overnight. The reaction mixture was concentrated under reduced pressure and then diluted with water and EtOAc. The pH of the aqueous layer was adjusted to 5, and the organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The solid (2 g, 8.15

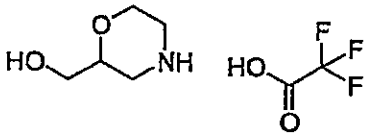
mmol) was then dissolved in THF (10 mL) and treated with a borane solution (1 M in THF, 16 mL, 16.4 mmol) and the mixture stirred at rt for 12h. The reaction mixture was then diluted with methanol (100 mL) and stirred at rt overnight. The solution was then concentrated under reduced pressure and then diluted with DCM. The solution was filtered through a layer of silica to remove the borane salts, and the filtrate was concentrated under reduced pressure to give an oil (1.8 g, 96%): HPLC MS RT = 2.22 min, MH^+ = 232.2; ^{1}H NMR (DMSO-d_6) δ: 4.46 (1H, t), 3.81-3.73 (2H, m), 3.72-3.64 (1H, br d), 3.45 (2H, t), 3.40-3.29 (3H, m), 2.93-2.73 (1H, br s), 1.55-1.48 (2H, m), 1.39 (9H, s).

Intermediate G

Preparation of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-(3-chloropropyl) morpholine

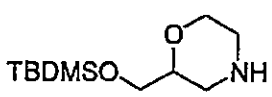


Step 1: Preparation of Morpholin-2-ylmethanol trifluoroacetate



A solution of *tert*-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (1.1 g, 5.06 mmol) in DCM (15 mL) was treated with trifluoroacetic acid (2.5 mL, 10.1 mmol) and stirred at rt overnight. The reaction mixture was concentrated under reduced pressure to yield a thick oil(1.1 g, 94%): NMR (DMSO-d_6) δ: 9.30 (1H, s), 4.95 (1H, s), 4.19-4.06 (1H, br s), 3.93 (1H, dd), 3.76-3.63 (2H, m), 3.47-3.32 (2H, m), 3.22-3.09 (3H, m), 3.92 (1H, td), 2.76 (1H, t).

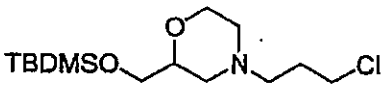
Step 2: Preparation of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)morpholine



Morpholin-2-ylmethanol trifluoroacetate (0.7 g, 3.03 mmol) in DCM was treated with triethylamine (1.67 mL, 12.1 mmol) and *tert*-butyldimethylsilyl chloride (0.91 g, 6.06

mmol). The mixture was stirred at rt for 2 h and then filtered. The filtrate was then concentrated under reduced pressure and the residue was suspended in a dilute solution of sodium hydroxide (10%, 5 mL), and the mixture was stirred for 30 min. The mixture was then extracted with DCM and concentrated under reduced pressure to a foam. The product was taken to the next step without further purification: ^{1}H NMR (DMSO-d_6) δ: 5.40-5.14 (1H, br s), 3.69 (1H, m), 3.56-3.50 (1H, m), 3.46-3.3 (3H, m), 3.27-2.97 (1H, br s), 2.78 (1H, dd), 2.68-2.55 (2H, m), 2.35 (1H, m), 0.87-0.82 (9H, m), 0.02 (6H, s).

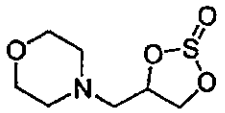
Step 3: Preparation of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-(3-chloropropyl)morpholine



A solution of 2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)morpholine (2.1 g, 9.07 mmol) in DCM (20 mL) was treated with triethylamine (3.8 mL, 27.2 mmol) and 1-chloro-3-iodopropane (1.95 mL, 18.1 mmol). The reaction mixture was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure then purified by MPLC (ISCO, 0% MeOH/100% DCM to 25% MeOH/75% DCM). The product was isolated as an oil (560mg, 20%): HPLC MS RT = 2.66 min, MH^+ = 308.4, 310.4; ^{1}H NMR (DMSO-d_6) δ: 3.79-3.69 (1H, m), 3.63 (2H, t) 3.59-3.52 (1H, m), 3.50-3.36 (3H, m), 2.73 (1H, d), 2.61 (1H, d), 2.35 (2H, t), 1.94 (1H, td), 1.83 (2H, qt), 1.73 (1H, t), 0.83 (9H, s), 0.00 (6H, s).

Intermediate H

Preparation of 4-[(2-oxido-1,3,2-dioxathiolan-4-yl)methyl]morpholine hydrochloride

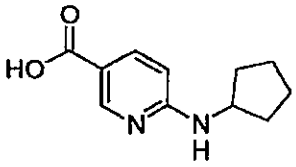


HCl

3-Morpholin-4-ylpropane-1,2-diol (2.1 g, 9.07 mmol) was dissolved in DCM (15 mL) and cooled to 0 °C. The cooled solution was treated with thionyl chloride (1.81 mL, 24.8 mmol) and then heated at the reflux temperature for 1 h. The reaction mixture was then concentrated under reduced pressure to give a solid (2.5 g, 97%): ^{1}H NMR (DMSO-d_6) δ: 11.4 (1H, br s), 5.64-5.55 (1H, m) 4.82 (1H, dd), 4.50 (1H, dd), 4.02-3.71(4H, m), 3.55-3.33(4H, m), 3.26-3.06 (2H, br s).

Intermediate I

Preparation of 6-(cyclopentylamino)nicotinic acid.

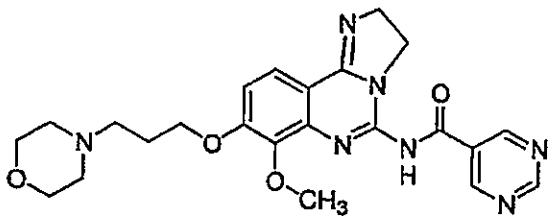


6-Fluoronicotinic acid (300 mg, 2.13 mmol) and cyclopentylamine (0.84 mL, 8.50 mmol) were combined in anhydrous THF (5 mL) and triethylamine (0.59 mL, 4.25 mmol). The mixture was heated at 60 °C for 3 days. The mixture was concentrated under reduced pressure, and the residue was suspended in water. The aqueous mixture was brought to pH 3 with phosphoric acid. The resulting precipitate was collected by vacuum filtration, washed with water, and dried in a vacuum oven for 1 h at 50 °C to give the title compound as a solid (63 mg, 14%): HPLC MS RT = 1.14 min, MH^+= 207.2; ^{1}H NMR (DMSO-d_6) δ: 12.29 (1H, broad s), 8.50 (1H, d), 7.73 (1H, dd), 7.29 (1H, d), 6.42 (1H, d), 4.16 (1H, broad s,), 1.90 (2H, m), 1.67 (2H, m), 1.53 (2H, m), 1.43 (2H, m).

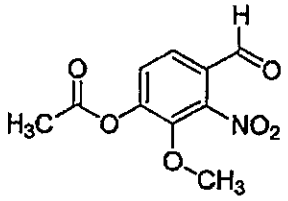
Examples

Example 1

Preparation of N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide .

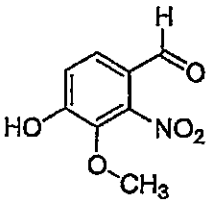


Step 1: Preparation of 4-formyl-2-methoxy-3-nitrophenyl acetate



Fuming nitric acid (2200 mL) under nitrogen was cooled to 0 °C at which time vanillin acetate (528 g, 2.7 mol) was added portionwise, keeping the internal temperature below 10 °C. After 2 h the resulting mixture was poured over ice with stirring. The slurry was filtered and the resulting solids were washed with water (3 x 100 mL) and air-dried. After 2 days the solids were heated in DCM (3000 mL) until complete dissolution. The solution was allowed to cool to room temperature while hexanes (3000 mL) was added dropwise. The solids were filtered, washed with hexanes (500 mL) and air dried to give the desired product (269 g, 41%): ^{1}H NMR, (DMSO-d_6) δ: 9.90 (s, 1H), 7.94 (d, 1H), 7.75 (d, 1H), 3.87 (s, 3H), 2.40 (s, 3H).

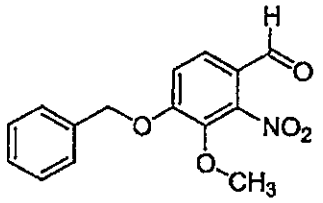
Step 2: Preparation of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde



A mixture of 4-formyl-2-methoxy-3-nitrophenyl acetate 438 g (1.8 mol) and potassium carbonate (506 g, 3.7 mol) in MeOH (4000 mL) was stirred at room temperature for 16 h.

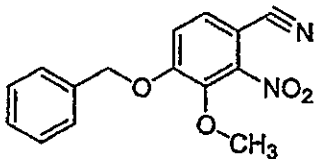
The reaction mixture was concentrated under reduced pressure to afford a viscous oil. This was dissolved in water, acidified using a solution of HCl (2 N) and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and filtered. The solvent was concentrated under reduced pressure to 1/3 volume and the resulting solids were filtered and air-dried to give the title compound (317 g, 88%): ^{1}H NMR (DMSO-d_6) δ: 9.69 (1H, s), 7.68 (1H, d), 7.19 (1H, d), 3.82 (3H, s).

Step 3: Preparation of 4-(benzyloxy)-3-methoxy-2-nitrobenzaldehyde



4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (155 g, 786 mmol) was dissolved in DMF (1500 mL) and the stirred solution was treated with potassium carbonate (217 g, 1.57 mol) followed by benzyl bromide (161 g, 0.94 mol). After stirring for 16 h the reaction mixture was concentrated under reduced pressure and separated between water (2 L) and EtOAc (2 L). The organic layer was washed with brine (3 x 2 L), dried (sodium sulfate) and concentrated under reduced pressure. The resulting solids were triturated with Et_2O (1 L) to give the title compound (220 g, 97%): ^{1}H NMR (DMSO-d_6) δ: 9.77 (1H, s), 7.87 (1H, d), 7.58 (1H, d), 7.51 (1H, m), 7.49 (1H, m), 7.39 (3H, m), 5.36 (2H, s), 3.05 (3H, s).

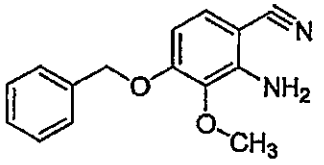
Step 4: Preparation of 4-(benzyloxy)-3-methoxy-2-nitrobenzonitrile



Iodine (272 g, 1.1 mmol) was added to a mixture of 4-(benzyloxy)-3-methoxy-2-nitrobenzaldehyde (220 g, 766 mmol) and ammonium hydroxide (28% solution, 3 L) dissolved in THF (5 L). After 16 h the reaction mixture was treated with sodium sulfite (49 g, 383 mmol) and concentrated under reduced pressure to afford a thick slurry. The

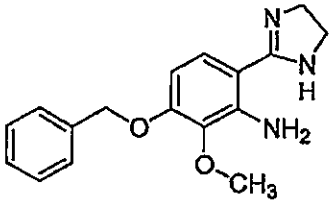
slurry was filtered, washed with water (250 mL) and dried to afford the title compound as a solid (206 g, 95%): ^{1}H NMR (DMSO-d_6) δ: 7.89 (1H, d), 7.59 (1H, d), 7.49 (2H, m), 7.40 (3H, m), 5.35 (2H, s), 3.91 (3H, s).

Step 5: Preparation of 2-amino-4-(benzyloxy)-3-methoxybenzonitrile



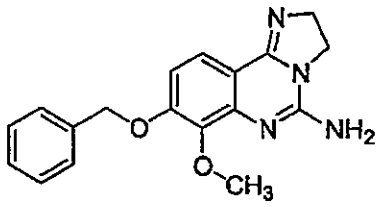
A degassed solution of 4-(benzyloxy)-3-methoxy-2-nitrobenzonitrile (185 g, 651 mmol) in glacial acetic acid (3500 mL) and water (10 mL) was cooled to 5 °C and treated with iron powder (182 g, 3.25 mol). After 3 days the reaction mixture was filtered through Celite, and the filtrate concentrated under reduced pressure. The oil, thus obtained, was treated with brine, neutralized with a sodium bicarbonate solution and extracted into DCM. The resulting emulsion was filtered through Celite after which the organic layer was separated, washed with brine, dried (sodium sulfate) and concentrated under reduced pressure to afford the title compound as a solid (145 g, 88%): ^{1}H NMR (DMSO-d_6) δ: 7.32-7.44 (5H, m), 7.15 (1H, d), 6.47 (1H, d), 5.69 (2H, s), 5.15 (2H, s), 3.68 (3H, s).

Step 6: Preparation of 3-(benzyloxy)-6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxyaniline



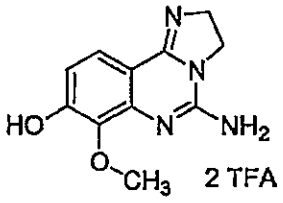
A mixture of 2-amino-4-(benzyloxy)-3-methoxybenzonitrile (144 g, 566 mmol) and sulfur (55 g, 1.7 mol) in ethylenediamine (800 mL) was degassed for 30 minutes then heated to 100 °C. After 16 h the reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated under reduced pressure, diluted with a saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried (sodium sulfate), filtered and concentrated under reduced pressure. The resulting solids were recrystallized from EtOAc and hexanes to afford the title compound (145 g, 86%): ^{1}H NMR (DMSO-d_6) δ: 7.27-7.48 (5H, m), 7.14 (1H, d), 6.92 (2H, m), 6.64 (1H, m), 6.32 (1H, d), 5.11 (2H, s), 3.67 (3H, s), 3.33 (2H, s).

Step 7: Preparation of 8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine



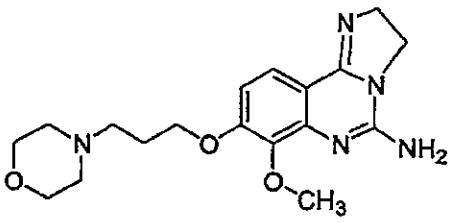
A mixture of 3-(benzyloxy)-6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxyaniline (100 g, 336 mmol) and triethylamine (188 mL) in DCM (3 L) was cooled to 0 °C and treated with cyanogen bromide (78.4 g, 740 mmol). The reaction mixture was stirred and allowed to warm to room temperature gradually. After 16 h the reaction mixture was diluted with a solution of saturated sodium bicarbonate and extracted with DCM. The organic layer was washed 3 times with saturated bicarbonate solution followed by multiple washes with brine. The organic layer was dried (sodium sulfate) and concentrated under reduced pressure to give a semi solid (130 g with triethylamine salt contamination): ^{1}H NMR (DMSO-d_6) δ: 7.30-7.48 (7H, m), 5.31 (2H, s), 4.32 (2H, m), 4.13 (2H, m), 3.81 (3H, s).

Step 8: Preparation of 5-amino-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol bis(trifluoroacetate)



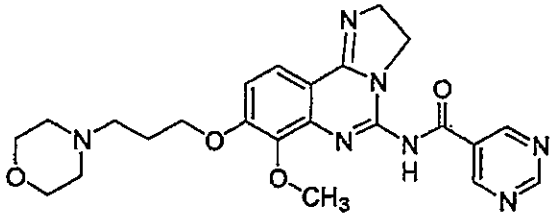
3-(Benzyloxy)-6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxyaniline (30 g, 93 mmol) was added portionwise over 1 h to a round bottom flask containing TFA (400 mL) precooled with an ice bath. The reaction mixture was heated to 60 °C and allowed to stir at this temperature for 17 h at which time it was cooled to rt and the reaction mixture concentrated under reduced pressure. The resulting residue was taken up in DCM and hexanes and concentrated under reduced pressure. The material thus obtained was dissolved in MeOH and DCM (250 mL, 1:1) and concentrated under reduced pressure. The resulting solid was dried overnight under vacuum with low heat to give the title compound (44.7 g, >100%): ^{1}H NMR (DMSO-d_6) δ: 7.61 (1H, m), 6.87 (1H, m), 4.15 (2H, br t), 4.00 (2H, m), 3.64 (3H, s).

Step 9: Preparation of 7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine.



5-Amino-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol bis(trifluoroacetate) (500 mg, 1.1 mmol) was diluted in DCM (10 mL), and triethylamine (0.75 mL, 5.4 mmol) was added. The suspension was stirred at rt for 1.5 h, after which time 5-amino-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-8-ol trifluoroacetate was isolated. The compound, thus prepared, (1.1 mmol) was dissolved in DMF (10 mL). Cesium carbonate (1.41 g, 4.3 mmol) and **Intermediate C** (218 mg, 1.1 mmol) were added, and the mixture was stirred at 70 °C for 30 min. Additional **Intermediate C** (109 mg, 0.55 mmol) and cesium carbonate (350 mg, 1.1 mmol) were added, and stirring was continued for 1 h. Another aliquot of **Intermediate C** (109 mg, 0.55 mmol) was added, and the temperature was increased to 75 °C. After 3 h, the reaction mixture was cooled to rt and filtered through a pad of Celite, washing with methanol and DCM. The filtrate was concentrated under reduced pressure, dry loaded onto silica gel, and purified by biotage eluting with 5-10% methanol in DCM followed by 5-15% methanolic ammonia (2.0 M, Aldrich) in DCM. The resultant oil was triturated with a 1:1 mixture of hexanes:EtOAc (15 mL) to afford the desired as a solid (171 mg, 44%): HPLC MS RT = 1.07 min, MH^+= 360.3; ^{1}H NMR (DMSO-d_6) δ: 7.43 (1H, d), 6.73 (3H, m), 4.03 (2H, t), 3.88 (4H, m), 3.69 (3H, s), 3.55 (4H, m), 2.42 (2H, t), 2.35 (4H, m), 1.87 (2H, m).

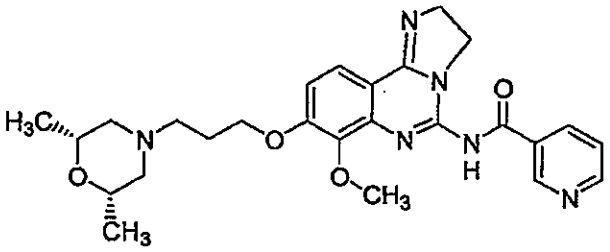
Step 10: Preparation of N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide .



7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (100 mg, 0.22 mol) was dissolved in DMF (5 mL), and pyrimidine-5-carboxylic acid (41 mg, 0.33 mmol) was added. PYBOP (173 mg, 0.33 mmol) and diisopropylethylamine (0.16 mL, 0.89 mmol) were subsequently added, and the mixture was stirred at rt overnight. EtOAc was added, and the precipitate was isolated by vacuum filtration to give the title compound (12 mg, 11%): HPLC MS RT = 1.07 min, MH^+= 466.2; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.48 (2H, s), 9.39 (1H, s), 8.05 (1H, d), 7.47 (1H, d), 4.59 (2H, m), 4.35 (2H, br t), 4.26 (2H, m), 4.02 (3H, s), 4.00 (2H, m), 3.67 (2H, br t), 3.52 (2H, m), 3.33 (2H, m), 3.16 (2H, m), 2.27 (2H, m).

Example 2

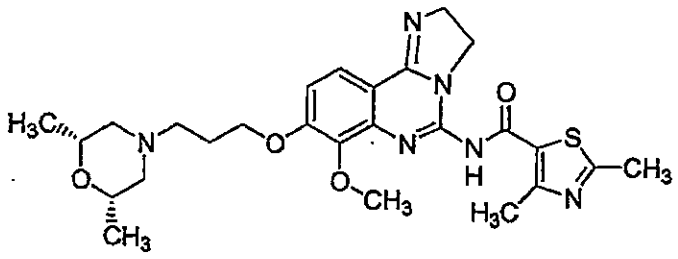
Preparation of N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



8-{3-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (200 mg, 0.52 mmol) was dissolved in DMF (2.0 mL), and nicotinic acid (76 mg, 0.62 mmol) was added. PYBOP (322 mg, 0.62 mmol) and diisopropylethylamine (0.33 mL, 1.55 mmol) were subsequently added, and the mixture was stirred at room temperature overnight. EtOAc was added, and the precipitate was isolated by vacuum filtration to give the title compound (156 mg, 61%): HPLC MS RT = 1.34 min, MH^+= 493.3; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.53 (1H, s), 9.03 (1H, d), 9.00 (1H, d), 8.07 (1H, d), 8.01 (1 H, dd), 7.49 (1H, d), 4.58 (2H, m), 4.34 (2H, t), 4.27 (2H, m), 4.03 (3H, s), 3.81 (2H, m), 3.53 (2H, d), 3.29 (2H, m), 2.69 (2H, m), 2.27 (2H, m), 1.15 (6H, d).

Example 3

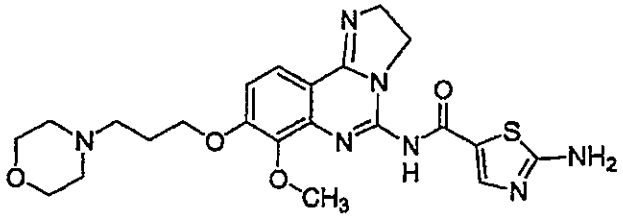
Preparation of N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide



8-{3-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (120 mg, 0.31 mmol) was dissolved in DMF (1.5 mL), and 2,4-dimethyl-1,3-thiazole-5-carboxylic acid (58 mg, 0.37 mmol) was added. PYBOP (193 mg, 0.37 mmol) and diisopropylethylamine (0.16 mL, 0.93 mmol) were subsequently added, and the mixture was stirred at room temperature overnight. EtOAc was added, and the precipitate was isolated by vacuum filtration to give the title compound (131 mg, 80%): HPLC MS RT = 2.05 min, MH^+= 527.1; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 8.02 (1H, d), 7.43 (1H, d), 4.38 (2H, m), 4.32 (2H, m), 4.22 (2H, m), 4.00 (3H, s), 3.81 (2H, m), 3.53 (2H, d), 3.28 (2H, m), 2.72- 2.63 (8H, m), 2.26 (2H, m), 1.13 (6H, d).

Example 4

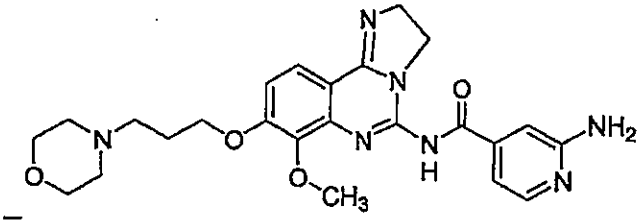
Preparation of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide.



7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (250 mg, 0.70 mol) was dissolved in DMF (4 mL), and 2-amino-1,3-thiazole-5-carboxylic acid (110 mg, 0.76 mmol) was added. PYBOP (543 mg, 1.04 mmol) and diisopropylethylamine (0.61 mL, 3.50 mmol) were subsequently added, and the mixture was stirred at room temperature overnight. The desired product was isolated *via* HPLC to give the title compound (80.0 mg, 24%): HPLC MS RT = 1.03 min, MH^+= 486.3; ^1H NMR (MeOH-d_4 + 2 drops TFA-*d*) δ: 7.90 (1H, d), 7.79 (1H, d), 7.50-7.60 (2H, m), 3.70 (2H, m), 3.30 (2H, d), 3.20 (2H, q), 2.10 (2H, s), 1.35 (10H, m).

Example 5

Preparation of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide

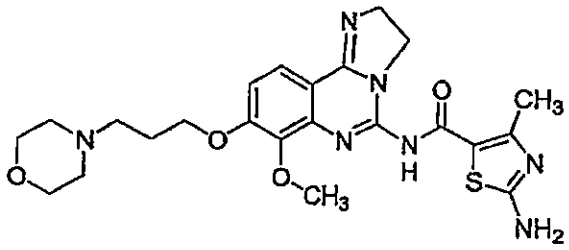


7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (100 mg, 0.28 mol) was dissolved in DMF (3 mL), and 2-aminopyridine-4-carboxylic acid (38 mg, 0.28 mmol) was added. PYBOP (217 mg, 0.42 mmol) and diisopropylethylamine (0.15 mL, 0.83 mmol) were subsequently added, and the mixture was stirred at rt

overnight. The mixture was purified by HPLC to give the title compound (50 mg, 37%). LC MS RT = 1.02 min, MH^+= 480.3. ^{1}H NMR (DMSO-d_6) δ: 13.25 (1H, br s), 10.15 (1H, br s), 8.42 (1H, br s), 8.08 (1H, s), 8.06 (1H, d), 7.43 (1H, d), 7.75 (1H, s), 7.50 (1H,d), 7.38 (1H, dd), 4.50 (2H, dd), 4.35 (2H, br t), 4.27 (2H, dd), 4.01 (3H, s), 3.99 (2H, br s), 3.66 (2H, t), 3.50 (2H, d), 3.31 (2H, br t), 3.13 (2H, m), 2.25 (2H, m).

Example 6

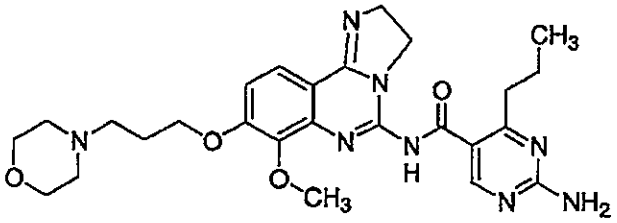
Preparation of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide



7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (100 mg, 0.28 mol) was dissolved in DMF (3 mL), and 2-amino-4-methylthiazole-5-carboxylic acid (44 mg, 0.28 mmol) was added. PYBOP (217 mg, 0.42 mmol) and diisopropylethylamine (0.15 mL, 0.83 mmol) were subsequently added, and the mixture was stirred at rt overnight. The mixture was purified by HPLC to give the title compound (6 mg, 4%): LC MS RT = 1.06 min, MH^+= 500.1; ^{1}H NMR (DMSO-d_6) δ: 12.59 (1H, s), 7.55 (1H, d), 7.47 (1H,s), 6.98 (1H, d), 4.13 (2H, t), 3.93 (4H, m), 3.86 (3H, s), 3.55 (4H, t), 2.47 (3H, s), 2.45 (2H, t), 2.33 (4H, m), 1.93 (2H, m).

Example 7

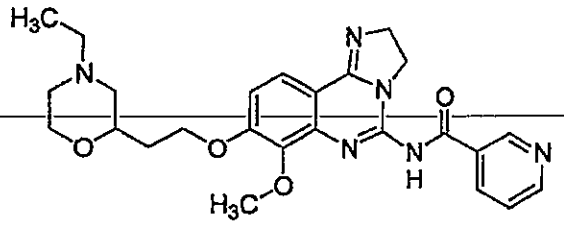
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide



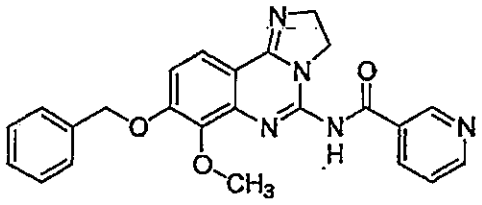
7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (100 mg, 0.28 mol) was dissolved in DMF (3 mL), and **Intermediate D** (50 mg, 0.28 mmol) was added. PYBOP (217 mg, 0.42 mmol) and diisopropylethylamine (0.15 mL, 0.83 mmol) were subsequently added, and the mixture was stirred at rt overnight. The resulting precipitate was filtered and washed with MeOH to give the title compound (76 mg, 52%): LC MS RT = 1.64 min, MH^+= 523.3; ^1H NMR (DMSO-d_6 with 2 drops TFA-d) δ: 10.04 (1H, br s), 9.14 (1H, s), 8.02 (1H, d), 7.43 (1H, d), 4.48 (2H, dd), 4.33 (2H, t), 4.21 (2H, dd), 4.01 (2H, m) 3.98 (3H, s), 3.65 (2H, t), 3.52 (2H, d), 3.30 (2H, br t), 3.13 (4H, m), 2.24 (2H, m), 1.68 (2H, m), 0.95 (3H, t).

Example 8

Preparation of N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide.

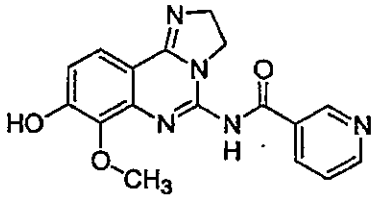


Step 1: Preparation of N-[8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide



8-(Benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (21 g, 65 mmol) and nicotinic acid (12 g, 97.7 mmol) were suspended in DMF (240 mL). Diisopropylethylamine (33.7 g, 260.4 mmol) and then PYBOP (51 g, 97.7 mmol) were added and the resulting mixture stirred with overhead stirring for 3 days at ambient temperature. At this time, the resultant precipitate was isolated by vacuum filtration. After repeated washing with EtOAc, the material was dried under vacuum with slight heating to yield the title compound (27.3 g, 98%): HPLC MS RT = 1.09 min, MH^+= 481.2; ^{1}H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.32 (1H, s), 8.89 (1H, br m), 8.84 (1H, d), 7.89 (1H, br m), 7.82 (1H, d), 7.37 (1H, d), 7.27 (1H, d), 7.16 (6H, m), 5.18 (2H, s), 4.36 (2H, t), 4.04 (2H, t), 3.78 (3H, s).

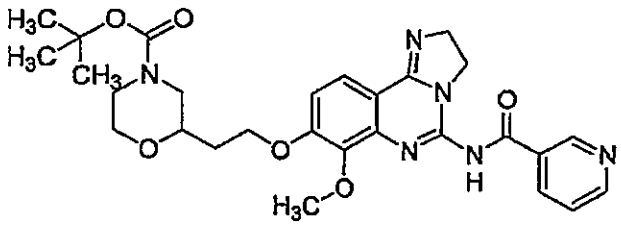
Step 2: Preparation of N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



N-[8-(Benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide (20 g, 45.1 mmol) was added portionwise over 1 h to a round bottom flask containing TFA (400 mL) precooled with an ice bath. The reaction mixture was heated to 60 °C and allowed to stir at this temperature for 17 h at which time it was cooled to ambient. The reaction mixture was then concentrated under reduced pressure. The resulting residue was taken up in DCM and hexane and concentrated under reduced pressure. The material thus obtained was dissolved in MeOH and DCM (250 mL, 1:1) and concentrated under reduced pressure. The resulting solids were dried overnight under vacuum with low heat to give the title compound (17.3 g, 66%): HPLC MS RT = 1.09 min, MH^+= 481.2; ^{1}H NMR

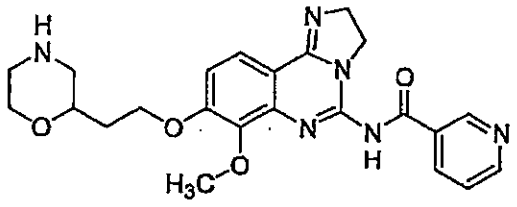
(DMSO-d_6 + 2 drops TFA-d) δ: 13.41 (1H, s), 12.21 (1H, br s), 9.38 (1H, s), 8.78 (1H, d), 8.53 (1H, d), 7.85 (1H, d), 7.59 (1H, m), 7.17 (1H, d), 4.54 (2H, m), 4.21 (2H, m), 3.98 (3H, s).

Step 3: Preparation of *tert*-Butyl 2-[2-({7-methoxy-5-[(pyridin-3-ylcarbonyl)amino]-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)ethyl]morpholine-4-carboxylate.



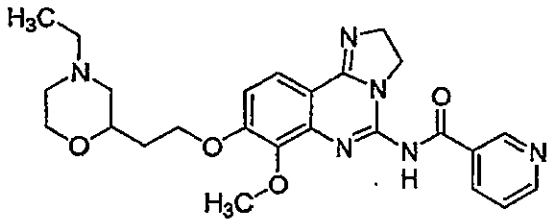
A solution of **Intermediate F** (420 mg, 1.83 mmol) in DMF (5 mL) was treated with triethylamine (340 µL, 2.44 mmol) and methanesulfonyl chloride (141 µL, 1.83 mmol) and the mixture was stirred at rt for 1.5 h. A suspension of the compound prepared in example 8 step 2 (650 mg, 1.22 mmol) in DMF (20 mL) was treated with cesium carbonate (2.0 g, 6.10 mmol) and stirred for 1.5 h before adding the preformed and filtered mesylate. The reaction mixture was stirred at 60 °C overnight and then concentrated under reduced pressure and the residue was extracted with a solution of 20% isopropanol / 80% chloroform and washed with a saturated solution of sodium hydrogen carbonate. The organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with EtOAc and filtered to give the title compound as a solid (850 mg, 84%): HPLC MS RT = 2.48 min, MH^+= 551.2; ^{1}H NMR (DMSO-d_6) δ: 12.7 (1H, s), 9.32 (1H, dd), 8.72 (1H, dd), 8.46 (1H, dt), 7.60 (1H, d), 7.51 (1H, dd), 7.07 (1H, d), 4.23-4.19 (2H, m), 4.15-4.10 (2H, m), 4.04-4.02 (2H, m), 3.93 (3H, s), 3.91-3.78 (2H, m), 3.75-3.66 (1H, m) 3.56-3.48 (1H, m), 3.41-3.35 (1H, td), 2.97.2.76 (1H, br s), 2.74-2.55 (1H, br s), 2.04-1.94 (1H, br m) 1.94-1.84 (1H, br m), 1.39 (9H, s).

Step 4: Preparation of N-[7-methoxy-8-(2-morpholin-2-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide.



tert-Butyl 2-[2-({7-methoxy-5-[(pyridin-3-ylcarbonyl)amino]-2,3-dihydroimidazo[1,2-c]quinazolin-8-yl}oxy)ethyl]morpholine-4-carboxylate (650 mg, 1.44 mmol) was dissolved in trifluoroacetic acid (10 mL) and stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure, and the resulting oil was diluted with methanol (1 mL) and pulled through a silica bound-NH_2 cartridge. The solution was concentrated under reduced pressure to give the title compound as a solid (45 mg, 69%): HPLC MS RT = 0.21 min, MH^+= 451.1; ^1H NMR (DMSO-d_6) δ: 12.8-12.7 (1H, br s), 9.32 (1H, s), 8.73 (1H, d), 8.46 (1H, d), 7.60 (1H, d), 7.54-7.49 (1H, m), 7.06 (1H, d) 4.22-3.99 (6H, m), 3.94 (3H, s), 3.78 (1H, d), 3.66-3.58 (1H, m), 3.47 (1H, t), 2.95 (1H, d), 2.82-2.65 (2H, m), 1.98-1.78 (2H, m).

Step 5: Preparation of N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide

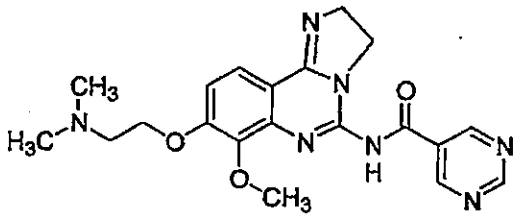


N-[7-Methoxy-8-(2-morpholin-2-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate (100 mg, 0.18 mol) in THF was treated with acetaldehyde (30 µL, 0.53 mmol) and stirred for 30 min. before adding sodium triacetoxyborohydride (113 mg, 0.53 mmol) and acetic acid (13 µL, 0.23 mmol). The reaction mixture was stirred at 60 C overnight after which it was diluted with methanol and a drop of 2 N hydrochloric acid to dissolve all solids. The crude solution was purified by HPLC (Gilson, 5% MeCN / 95% H_2O to 50% MeCN / 50%H_2O gradient, 0.1% TFA). The fractions were

concentrated under reduced pressure then diluted with a minimum of methanol and pulled through a silica bound NH_2 cartridge to give the title compound as a solid (17 mg, 20%): HPLC MS RT = 0.21 min, MH^+= 479.1; ^1H NMR (DMSO-d_6) δ: 12.75 (1H, s), 9.32 (1H, s), 8.71 (1H, d), 8.45 (1H, d), 7.59 (1H, d), 7.54-7.47 (1H, m), 7.06 (2H, d), 4.23-4.08 (3H, m), 4.06-3.98 (2H, m) 3.92 (3H, s), 3.77 (1H, d), 3.67-3.57 (1H, m), 3.46 (1H, t), 2.84 (1H, d), 2.68 (1H, d), 2.30 (2H, q), 1.99-1.79 (3H, m), 1.74 (1H, t), 0.99 (3H, t).

Example 9

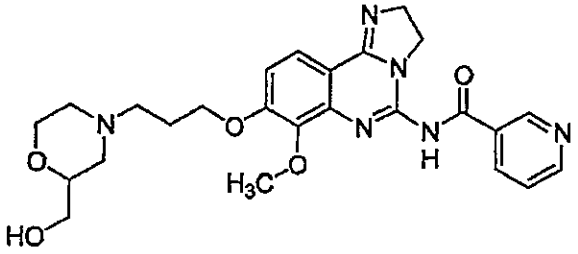
Preparation of N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide



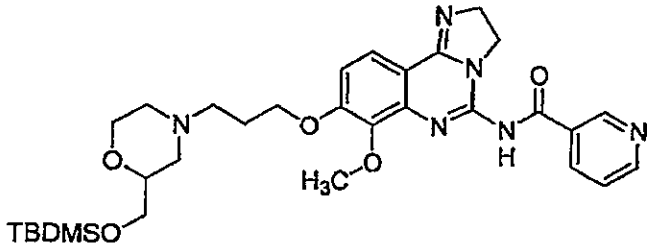
Sodium hydride (865 mg, 22 mmol, 60% dispersion in mineral oil) was diluted in DMF (35 mL). N-(8-Hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide bis(trifluoroacetate) (1.75 g, 3.1 mmol) was added, followed by 2-chloro-N,N-dimethylethanamine hydrochloride (890 mg, 6.2 mmol). The reaction mixture was stirred at rt until gas evolution ceased and then was heated to 50 °C for 2 h. At this time, the mixture was cooled to rt, and an additional equivalent of 2-chloro-N,N-dimethylethanamine hydrochloride (445 mg, 3.1 mmol) was added. The resulting reaction mixture was stirred at 50 °C overnight. After cooling to rt, the excess sodium hydride was carefully quenched by the addition of water and the mixture was extracted several times with DCM. The combined organic layers were dried (sodium sulfate) and concentrated under reduced pressure. The resultant solid was triturated with EtOAc and hexanes to afford the title compound as a solid (710 mg, 56%): HPLC MS RT = 1.09 min, MH^+= 410.1; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.47 (2H, s), 9.39 (1H, s), 8.12 (1H, d), 7.52 (1H, d), 4.61 (4H, m), 4.26 (2H, m), 4.03 (3H, s), 3.67 (2H, br t), 2.93 (6H, s).

Example 10

Preparation of N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide.

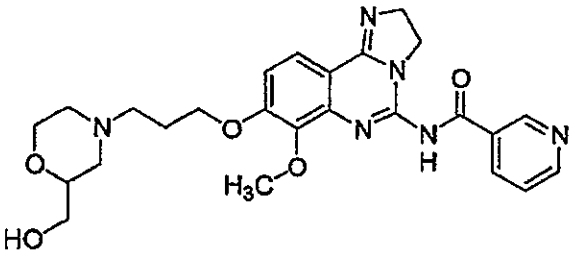


Step 1: Preparation of N-{8-{3-[2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide



A suspension of N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide bis-trifluoroacetate (650 mg, 1.22 mmol) in DMF (20 mL) was treated with cesium carbonate (2.0 g, 6.10 mmol) and stirred for 1.5 h before adding **Intermediate G** (0.56 g, 1.83 mmol) and triethylamine (0.34 mL, 2.44 mmol). The reaction mixture was stirred at 60 °C overnight, after which time it was concentrated under reduced pressure and the residue was extracted with a solution of 20% isopropanol/ 80% chloroform and washed with a saturated solution of sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated with EtOAc and filtered to give the title compound as a solid (260 mg, 35%): HPLC MS RT = 2.36 min, MH^+= 609.2; ^1H NMR (CD_3OD-d_4) δ: 9.24 (1H, d), 8.60 (1H, dd), 8.48 (1H, dt), 7.53 (1H, d), 7.46 (1H, dd), 6.94(1H, d), 4.21-4.05 (6H, m), 3.88 (1H, br d), 3.74-3.55 (4H, m), 2.95 (1H, d), 2.82 (1H, d), 2.60 (2H, t) 2.22-2.13 (1H, m), 2.05 (2H, qt), 1.94 (1H, t), 0.91 (9H, s), 0.08 (6H, s).

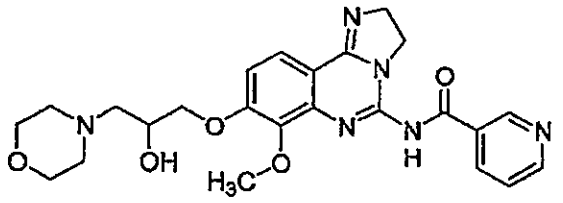
Step 2: Preparation of N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide.



N-{8-{3-[2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide (260 mg, 0.43 mmol) was suspended in THF (2 mL) and treated with a solution of tetra-n-butylammonium fluoride (1N, 0.64 mL, 0.64 mmol) in THF. The resulting mixture was stirred at rt for 4 h and was then diluted with water and extracted with 20% isopropanol/80% chloroform, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then triturated with methanol and filtered to give the product as a solid (100 mg, 47%): HPLC MS RT = 0.19 min, MH^+= 495.2; ^1H NMR (DMSO-d_6) δ: 12.7 (1H, s), 9.33 (1H, dd), 8.73 (1H, dd), 8.46 (1H, dt), 7.60 (1H, d), 7.54-7.49(1H, m), 7.06 (1H, d) 4.66 (1H, t), 4.20-4.09 (4H, m), 4.07-3.98 (2H, m) 3.93 (3H, s), 3.76 (1H, br d), 3.48 (1H, td), 3.42-3.26 (4H, m), 2.83 (1H, d), 2.70 (1H, d), 2.47 (2H, t), 2.03-1.91 (3H, m).

Example 11

Preparation of N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide.

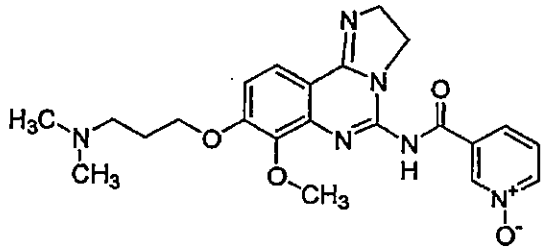


Cesium carbonate (3 g, 9.37 mmol) was added to a suspension of N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide bis-trifluoroacetate (1.0 g, 1.88 mmol) in DMF (40 mL) and stirred for 1.5 h before adding **Intermediate H** (0.39 g, 1.88 mmol). After 3 h, the reaction mixture was treated with another equivalent of **Intermediate H** and stirred at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the product was extracted with a solution of 20% isopropanol/ 80% chloroform and washed with a saturated solution of sodium hydrogen carbonate. The organics were dried ($MgSO_4$) and concentrated under reduced pressure,

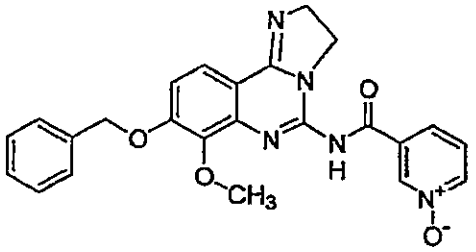
and the resulting residue was triturated with EtOAc and filtered. The solid was then purified by HPLC (Gilson, 5% MeOH/ 95% H_2O to 50% MeOH/ 50% H_2O gradient, 0.1% NH_4OH) to give the title compound (160 mg, 18%): HPLC MS RT = 0.19 min, MH^+= 495.2; ^1H NMR (DMSO-d_6 + 1 drop TFA-d) δ: 13.40-13.38 (1H, br s), 9.45 (1H, d), 8.90 (1H, dd), 8.72 (1H, d), 8.06 (1H, d), 7.77 (1H, dd), 7.51 (1H, d) 4.59 (2H, t), 4.49-4.41 (1H, br s), 4.33-4.22 (4H, m), 4.06 (3H, s) 4.05-3.92 (2H, m), 3.86-3.67 (2H, m), 3.51 (2H, d), 3.43-3.13 (4H, m).

Example 12

Preparation of N-[8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide 1-oxide.

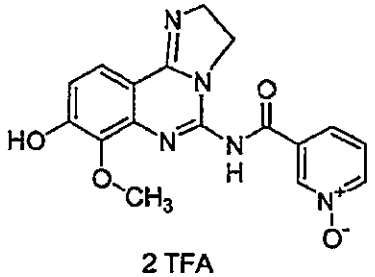


Step 1: Preparation of N-[8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide 1-oxide.



The title compound was synthesized from 8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine as described in **Example 8, step 1** (1.31 g, 95%): HPLC MS RT = 2.38 min, MH^+= 444.1; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 4.00 (3H, s), 4.22-4.28 (2H, m), 4.53-4.60 (2H, m), 5.42 (2H, s), 7.36-7.46 (3H, m), 7.51-7.54 (2H, m), 7.58-7.69 (2H, m), 8.04 (1H, d), 8.17 (1H, d), 8.56 (1H, d), 8.93-8.94 (1H, m).

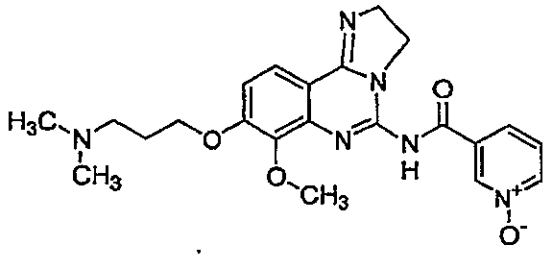
Step 2: Preparation of N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide 1-oxide bistrifluoroacetate salt.



2 TFA

The title compound was synthesized from N-[8-(benzyloxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide 1-oxide as described in **Example 8, step 2** (1.41 g, 94%): HPLC MS RT = 0.35 min, MH^+= 354.2; ^1H NMR (DMSO-d_6 + 2 drops TFA-*d*) δ: 3.97 (3H, s), 4.17-4.24 (2H, m), 4.51-4.57 (2H, m), 7.17 (1H, d), 7.66 (1H, dd), 7.88 (1H, d), 8.17 (1H, d), 8.53-8.56 (1H, m), 8.93-8.94 (1H, m).

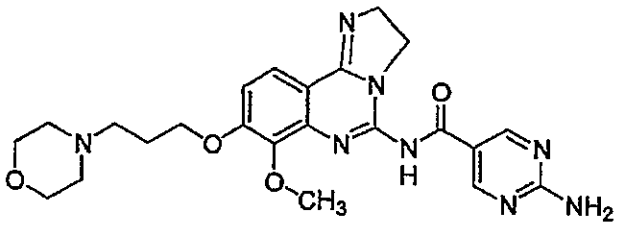
Step 3: Preparation of N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide.



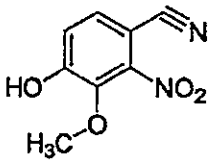
The title compound was synthesized from N-(8-hydroxy-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide 1-oxide bistrifluoroacetate salt as described in **Example 9** (42 mg, 37%): HPLC MS RT = 1.08 min, MH^+= 439.2; ^1H NMR (DMSO-d_6 + 2 drops TFA-*d*) δ: 2.19-2.25 (2H, m), 2.84 (3H, s), 3.23-3.28 (2H, m), 4.02 (3H, s), 4.22-4.35 (4H, m), 4.54-4.61 (2H, m), 7.48 (1H, d), 7.66-7.71 (1H, m), 8.06 (1H, d), 8.19 (1H, d), 8.57 (1H, d), 8.95 (1H, bs).

Example 13

Preparation of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.

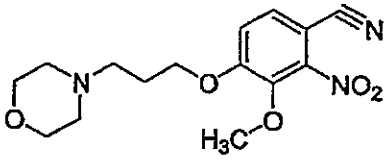


Step 1: Preparation of 4-hydroxy-3-methoxy-2-nitrobenzonitrile



4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (200 g, 1.01 mol) was dissolved in THF (2.5 L) and then ammonium hydroxide (2.5 L) was added followed by iodine (464 g, 1.8 mol). The resulting mixture was allowed to stir for 2 days at which time it was concentrated under reduced pressure. The residue was acidified with HCl (2 N) and extracted into diethyl ether. The organic layer was washed with brine and dried (sodium sulfate) and concentrated under reduced pressure. The residue was washed with diethyl ether and dried under vacuum to provide the title compound (166 g, 84%): ^{1}H NMR (DMSO-d_6) δ: 11.91 (1H, s), 7.67 (1H, d), 7.20 (1H, d), 3.88 (3H, s)

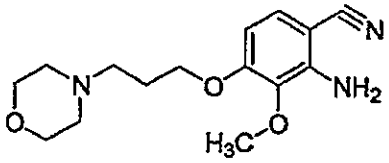
Step 2: Preparation of 3-methoxy-4-(3-morpholin-4-ylpropoxy)-2-nitrobenzonitrile



To a solution of 4-hydroxy-3-methoxy-2-nitrobenzonitrile (3.9 g, 20.1 mmol) in DMF (150 mL) was added cesium carbonate (19.6 g, 60.3 mmol) and **Intermediate C** (5.0 g, 24.8 mmol). The reaction mixture was heated at 75 °C overnight then cooled to room temperature and filtered through a pad of silica gel and concentrated under reduced pressure. The material thus obtained was used without further purification

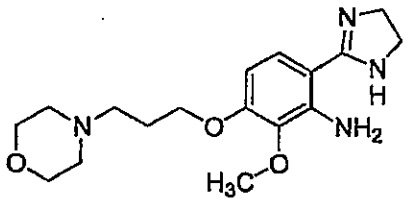
Step 3: Preparation of 2-amino-3-methoxy-4-(3-morpholin-4-ylpropoxy)benzonitrile

150



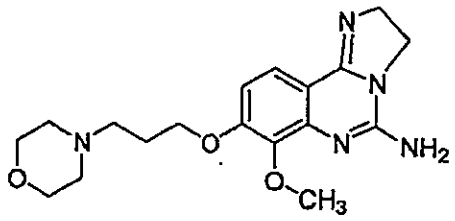
3-Methoxy-4-(3-morpholin-4-ylpropoxy)-2-nitrobenzonitrile (7.7 g, 24.1 mmol) was suspended in acetic acid (170 mL) and cooled to 0 °C. Water (0.4 mL) was added, followed by iron powder (6.7 g, 120 mmol) and the resulting mixture was stirred at room temperature for 4 h at which time the reaction mixture was filtered through a pad of Celite and washed with acetic acid (400 mL). The filtrate was concentrated under reduced pressure to 100 mL and diluted with EtOAc (200 mL) at which time potassium carbonate was added slowly. The resulting slurry was filtered through a pad of Celite washing with EtOAc and water. The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution. The organic layer was separated and passed through a pad of silica gel. The resultant solution was concentrated under reduced pressure to provide the title compound (6.5 g, 92%): ^{1}H NMR (DMSO-d_6) δ: 7.13 (1H, d), 6.38 (1H, d), 5.63 (2H, br s), 4.04 (2H, t), 3.65 (3H, s), 3.55 (4H, br t), 2.41 (2H, t), 2.38 (4H, m), 1.88 (2H, quint.).

Step 4: Preparation of 6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-3-(3-morpholin-4-ylpropoxy)aniline



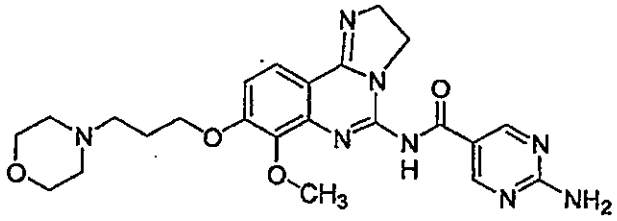
To a degassed mixture of 2-amino-3-methoxy-4-(3-morpholin-4-ylpropoxy)benzonitrile (6.5 g, 22.2 mmol) and ethylene diamine (40 mL) was added sulfur (1.8 g, 55.4 mmol). The mixture was stirred at 100 °C for 3 h at which time water was added to the reaction mixture. The precipitate that was formed was collected and washed with water and then dried overnight under vacuum to provide the title compound (3.2 g, 43%): HPLC MS RT = 1.25 min, MH^+= 335.2; ^{1}H NMR (DMSO-d_6) δ: 7.15 (1H, d), 6.86 (2H, br s), 6.25 (1H, d), 4.02 (2H, t), 3.66 (3H, s), 3.57 (8H, m), 2.46 (2H, t), 2.44 (4H, m), 1.89 (2H, quint.).

Step 5: Preparation of 7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine



Cyanogen bromide (10.9 g, 102.9 mmol) was added to a mixture of 6-(4,5-dihydro-1H-imidazol-2-yl)-2-methoxy-3-(3-morpholin-4-ylpropoxy)aniline (17.2 g, 51.4 mmol) and TEA (15.6 g, 154.3 mmol) in DCM (200 mL) precooled to 0 °C. After 1 h the reaction mixture was concentrated under reduced pressure and the resulting residue stirred with EtOAc (300 mL) overnight at rt. The resulting slurry was filtered to generate the title compound contaminated with triethylamine hydrobromide (26.2 g, 71%): HPLC MS RT = 0.17 min, MH^+= 360.2.

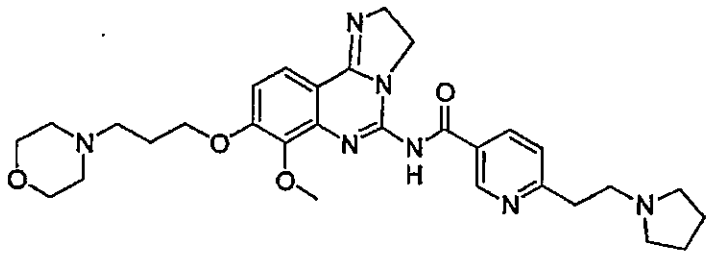
Step 6: Preparation of 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide.



7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (100 mg, 0.22 mol) was dissolved in DMF (5 mL), and **Intermediate B** (46 mg, 0.33 mmol) was added. PYBOP (173 mg, 0.33 mmol) and diisopropylethylamine (0.16 mL, 0.89 mmol) were subsequently added, and the mixture was stirred at rt overnight. EtOAc was added, and the solids were isolated by vacuum filtration to give the title compound (42.7 mg, 40%): HPLC MS RT = 1.09 min, MH^+= 481.2; ^{1}H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.01 (2H, s), 8.04 (1H, d), 7.43 (1H, d), 4.54 (2H, m), 4:34 (2H, br t), 4.23 (2H, m), 4.04 (2H, m), 4.00 (3H, s), 3.65 (2H, br t), 3.52 (2H, m), 3.31 (2H, m), 3.18 (2H, m), 2.25 (2H, m).

Example 14

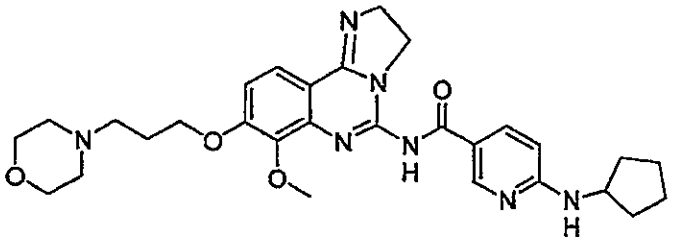
Preparation of N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide.



7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (150 mg, 0.21 mmol) was dissolved in DMF (2 mL), and 6-(2-pyrrolidin-1-ylethyl)nicotinic acid (92 mg, 0.42 mmol) was added. PYBOP (217 mg, 0.42 mmol) and diisopropylethylamine (73 µL, 0.42 mmol) were subsequently added, and the mixture was stirred at rt overnight. The solids that formed were isolated by vacuum filtration and washed copiously with ethyl acetate to give the title compound (81 mg, 69%): HPLC MS RT = 1.05 min, MH^+= 562.2; ^1H NMR (DMSO-d_6 + 2 drops TFA-d) δ: 9.30 (1H, s), 8.99 (0.5H, m), 8.50 (1H, d), 8.24 (0.5H, m), 8.06 (1H, d), 7.53 (1H, d), 7.46 (1H, d), 4.55 (2H, t), 4.35 (2H, t), 4.24 (2H, t), 4.01 (3H, s), 4.00 (2H, m), 3.68 (2H, m), 3.60 (4H, m), 3.51 (2H, m), 3.29 (4H, m), 3.11 (2H, m), 2.26 (2H, m), 2.02 (3H, m), 1.87 (3H, m).

Example 15

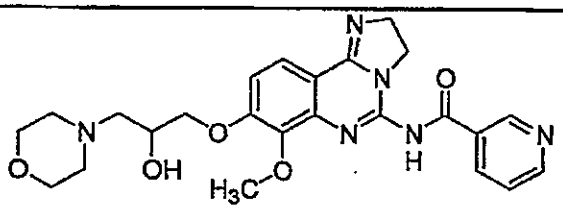
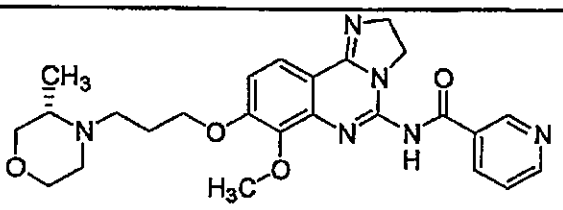
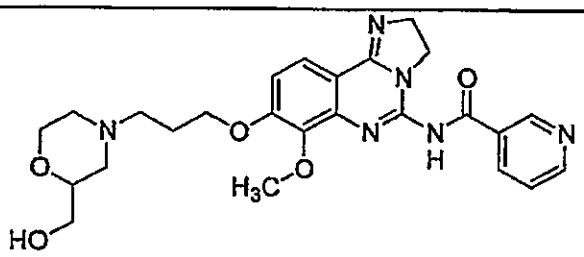
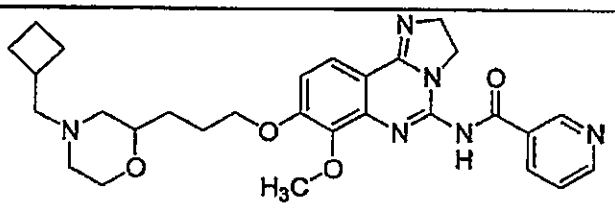
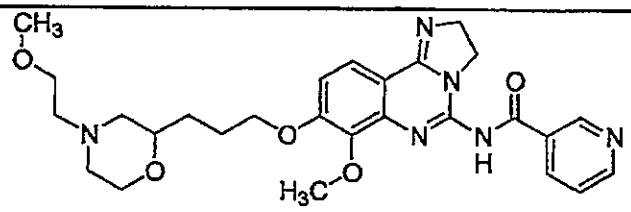
Preparation of 6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide.

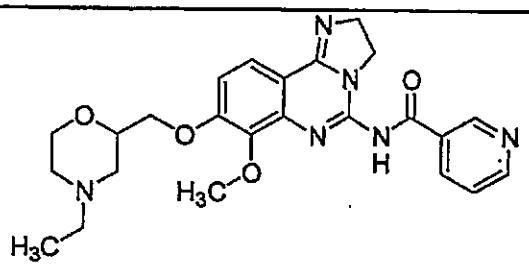
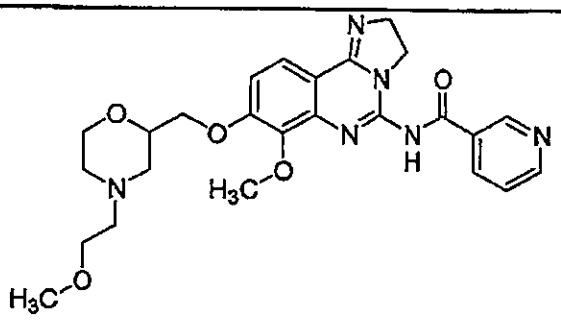
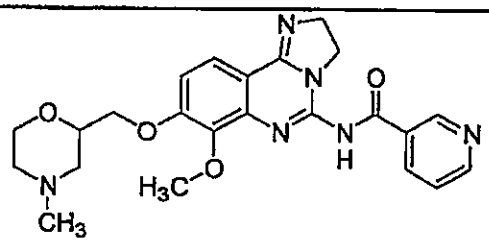
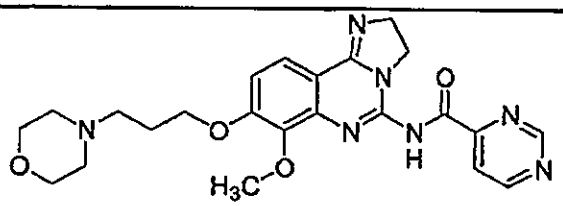
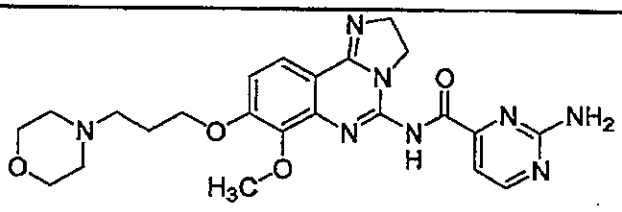
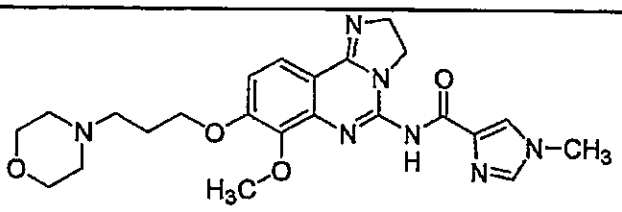


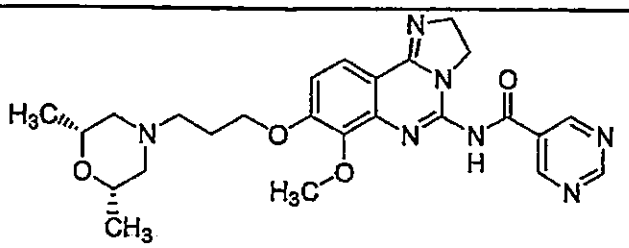
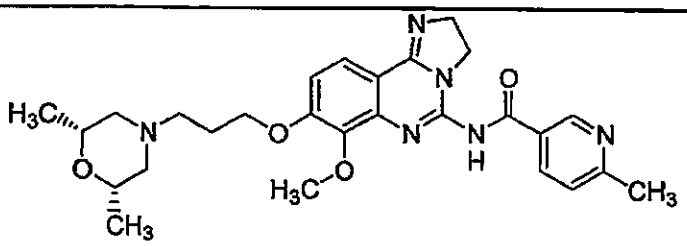
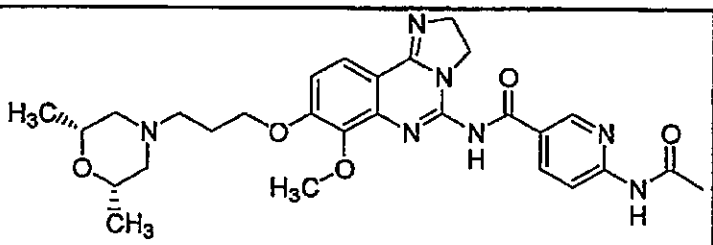
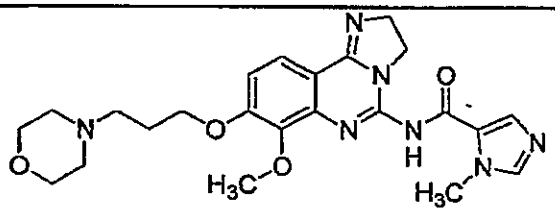
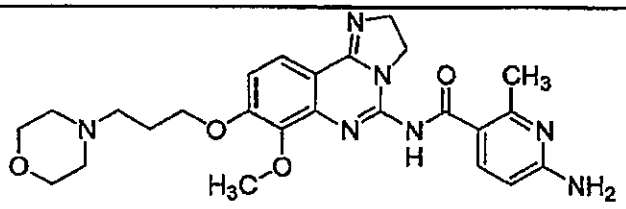
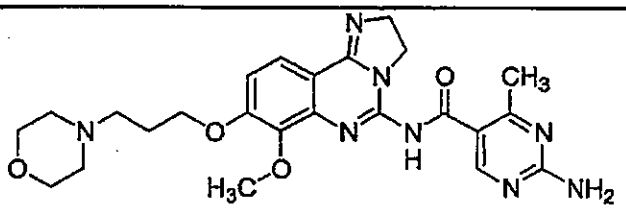
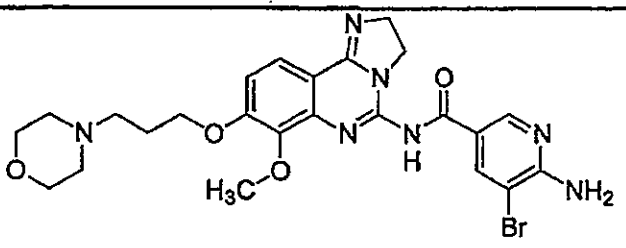
7-Methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-amine (150 mg, 0.21 mmol) was dissolved in DMF (2 mL), and **Intermediate I** (60 mg, 0.29 mmol) was added. PYBOP (217 mg, 0.42 mmol) and diisopropylethylamine (73 µL, 0.42 mmol) were subsequently added, and the mixture was stirred at rt overnight. The solids that formed were isolated by vacuum filtration and washed copiously with ethyl acetate to give the title compound (80 mg, 69%): HPLC MS RT = 1.74 min, MH^+= 548.2; ^1H NMR (DMSO-d_6 + 2 drops TFA-*d*) δ: 8.71 (1H, broad s), 8.39 (1H, broad s), 8.03 (1H, d), 7.44 (1H, d), 7.04 (1H, broad s), 4.51 (2H, t), 4.34 (2H, t), 4.25 (2H, t), 4.13 (1H, m), 4.03 (2H, m), 4.00 (3H, s), 3.67 (2H, t), 3.52 (2H, d), 3.32 (2H, t), 3.15 (2H, t), 2.26 (2H, m), 2.03 (2H, m), 1.72 (2H, m), 1.61 (4H, m).

By using the methods described above for Examples 1-15, and by substituting the appropriate starting materials, Examples 16-104 found in the table below were similarly prepared.

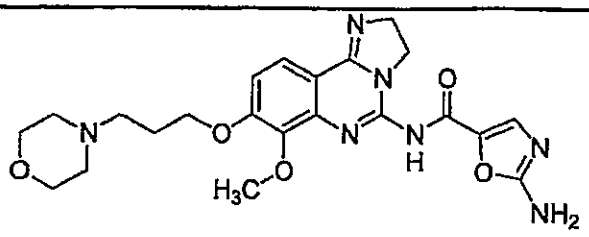
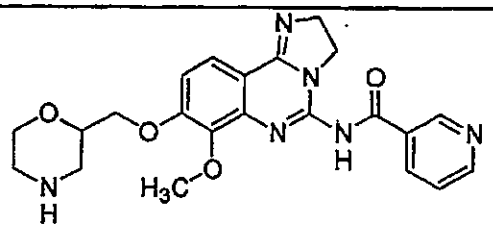
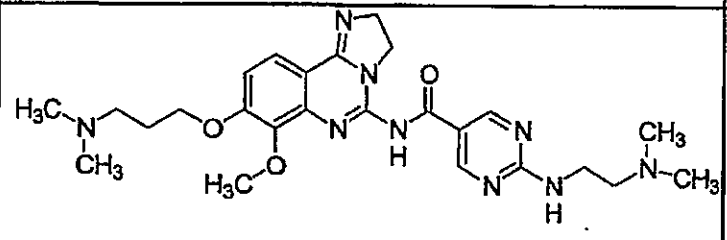
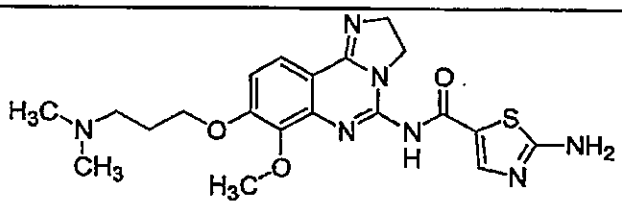
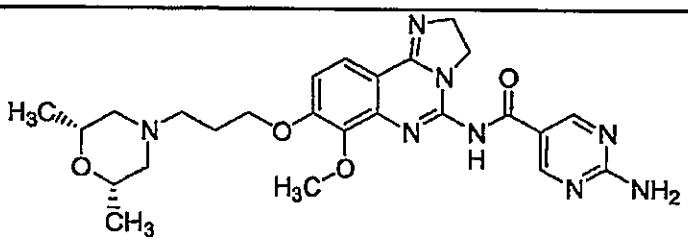
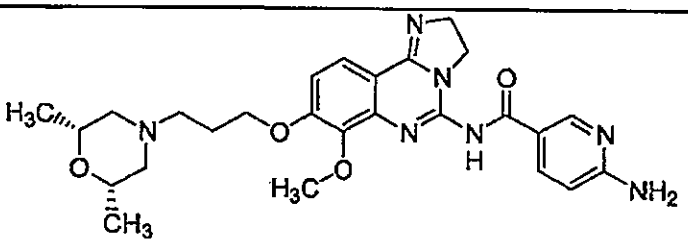
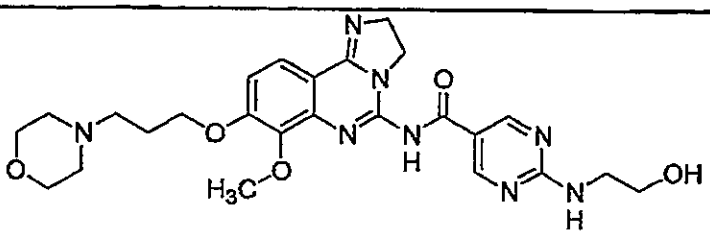
Table 1

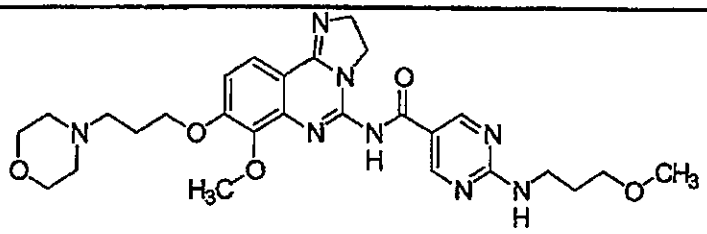
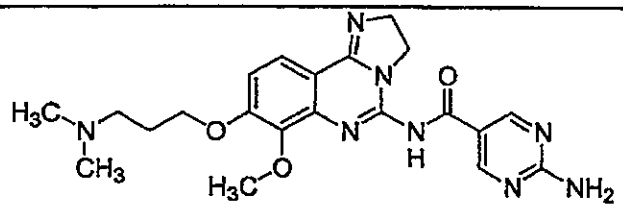
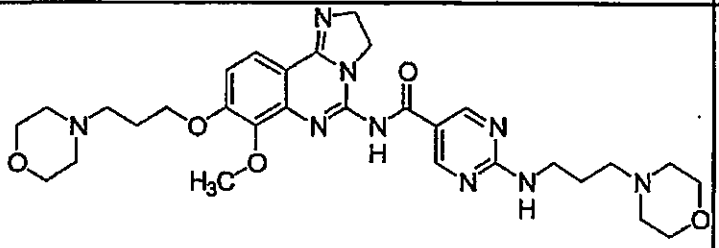
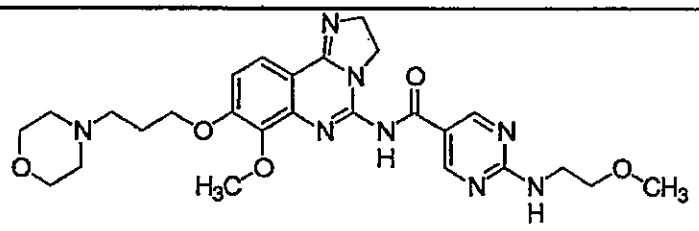
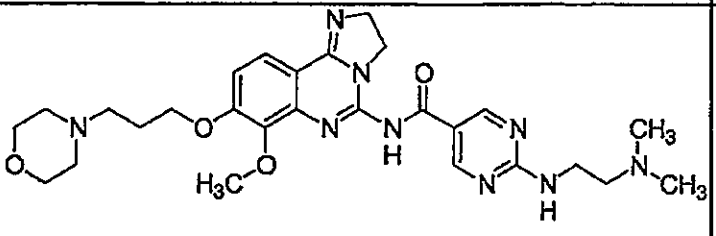
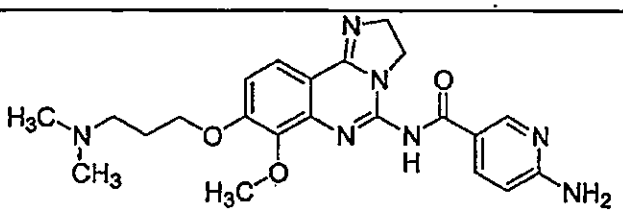
Ex	Structure	LC-MS *m/z* Method
16		RT=1.13 Min MH^+ = 481.4 Route 4
17		RT=1.12 Min MH^+ = 479.1 Route 4
18		RT=0.19 Min MH^+ = 495.1 Route 4
19		RT=0.21 Min MH^+ = 519.1 Route 4
20		RT=0.20 Min MH^+ = 509.1 Route 4

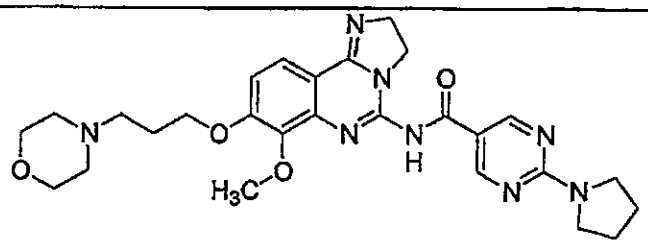
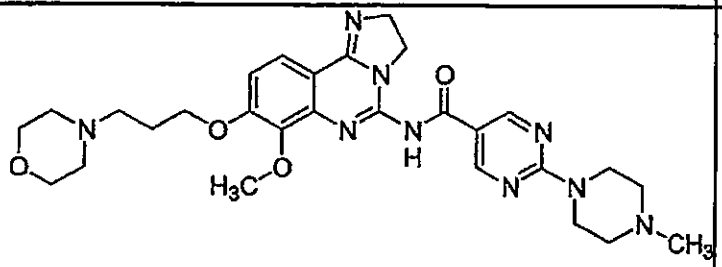
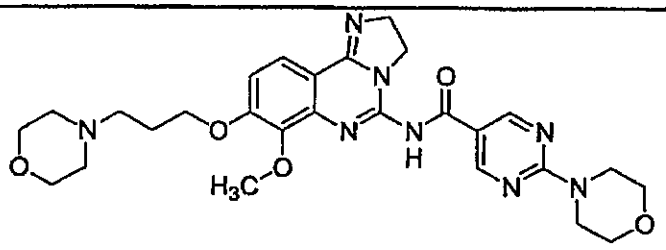
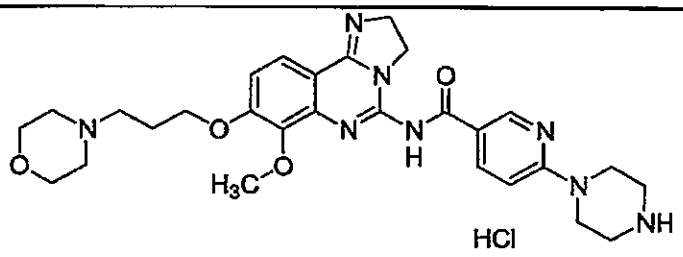
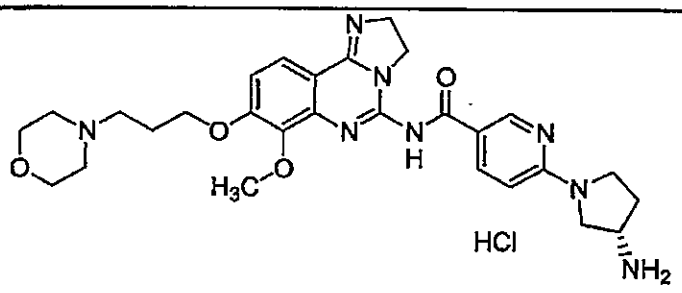
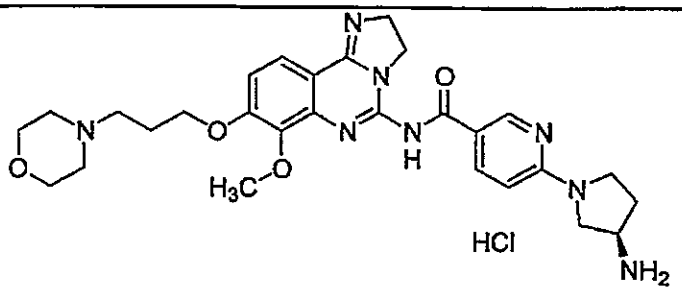
21		RT=0.23 Min MH^+ = 465.2 Route 4
22		RT=1.12 Min MH^+ = 495.3 Route 4
23		RT=1.03 Min MH^+ = 451.4 Route 4
24		RT=0.32 Min MH^+ = 466.3 Route 1
25		RT=0.34 Min MH^+ = 481.3 Route 1
26		RT=1.11 Min MH^+ = 468.4 Route 1

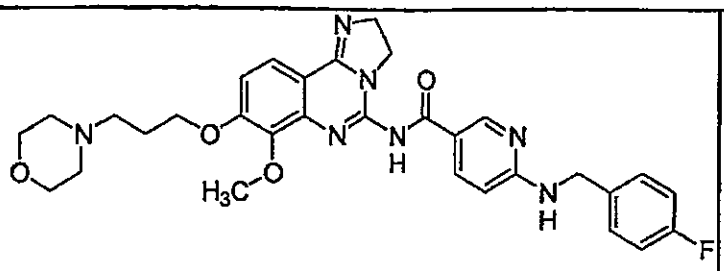
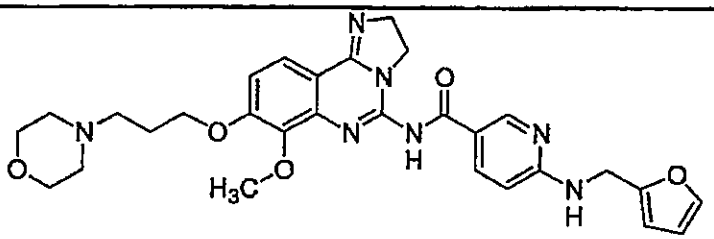
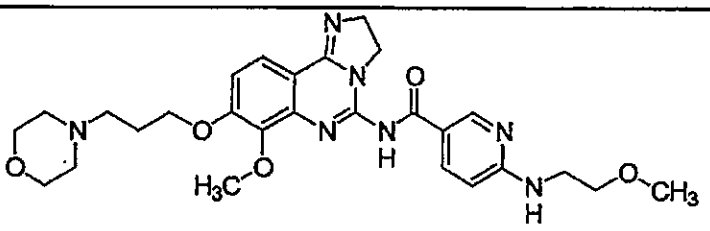
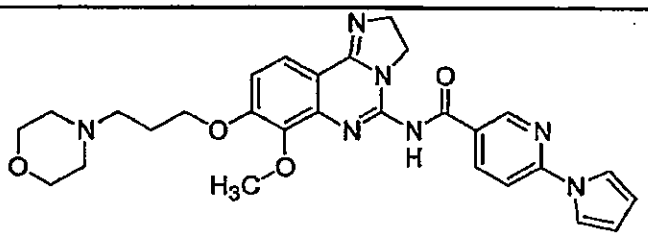
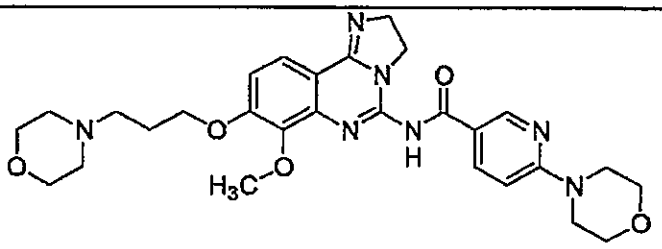
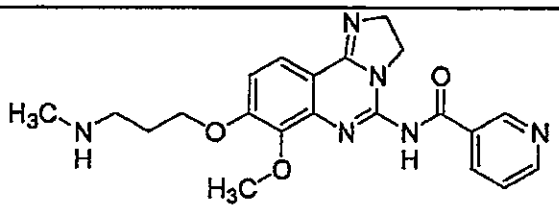
27		RT=1.54 Min MH^+ = 494.3 Route 1
28		RT=1.23 Min MH^+ = 507.2 Route 1
29		RT=1.95 Min MH^+ = 550.2 Route 1
30		RT=1.09 Min MH^+ = 468.4 Route 1
31		RT=1.13 Min MH^+ = 494.4 Route 1
32		RT=1.20 Min MH^+ = 495.3 Route 1
33		RT=1.69 Min MH^+ = 558.2 Route 1

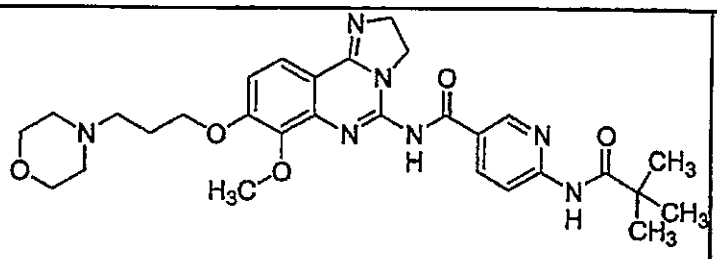
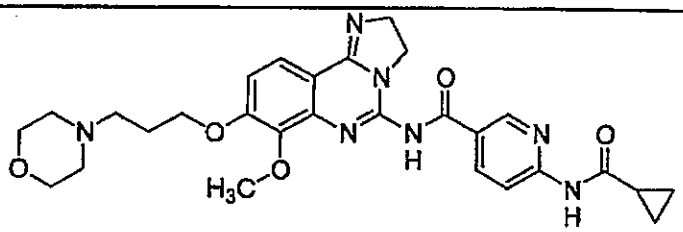
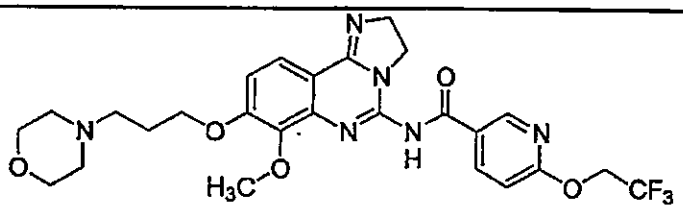
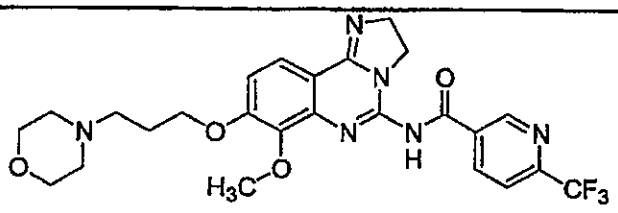
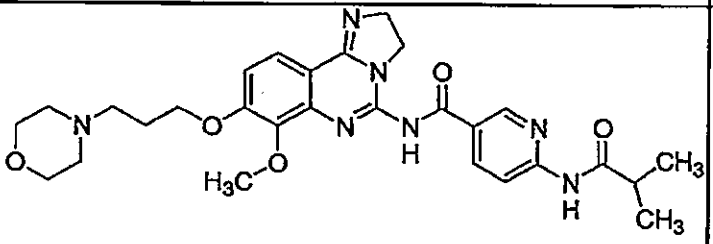
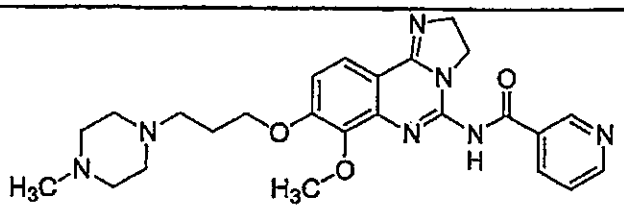
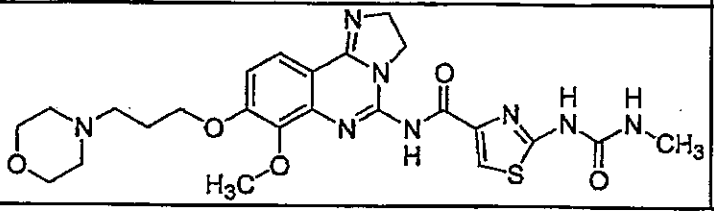
50

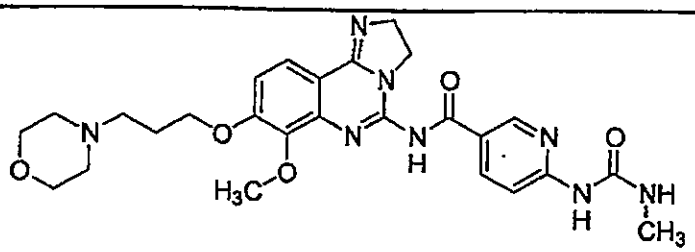
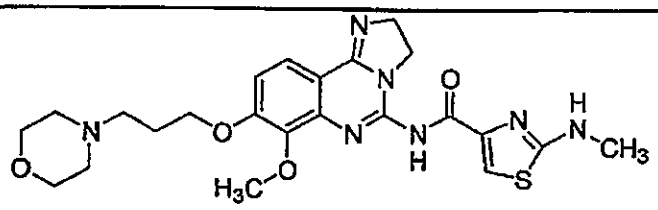
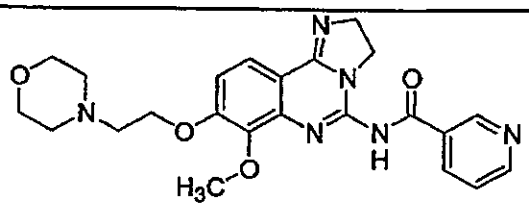
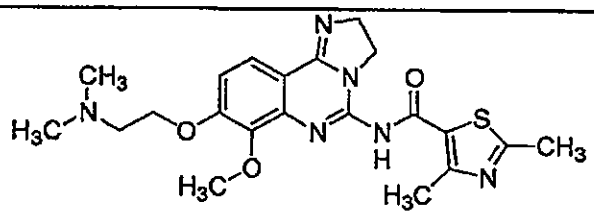
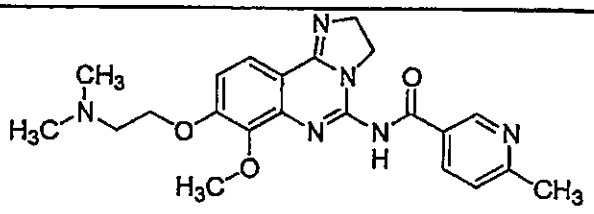
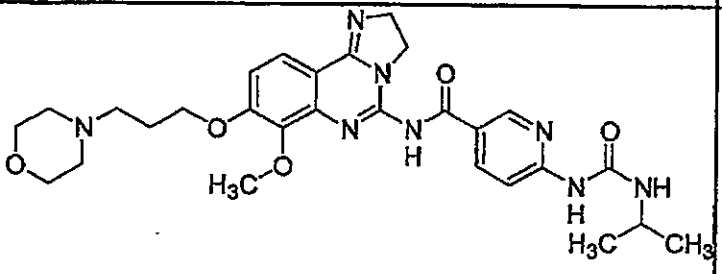
34		RT=1.05 Min MH^+ = 470.3 Route 1
35		RT=1.00 Min MH^+ = 437.2 Route 4
36		RT=0.27 Min MH^+ = 510.3 Route 2
37		RT=0.24 Min MH^+ = 444.1 Route 1
38		RT=1.36 Min MH^+ = 508.8 Route 1
39		RT=1.07 Min MH^+ 508.2 Route 1
40		RT=1.34 Min MH^+ = 525.2 Route 2

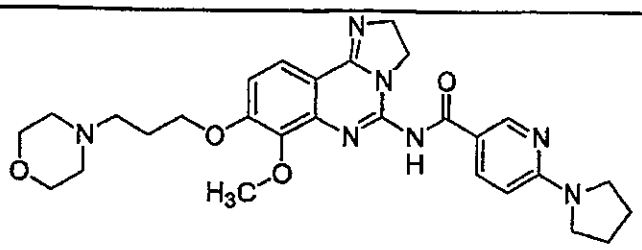
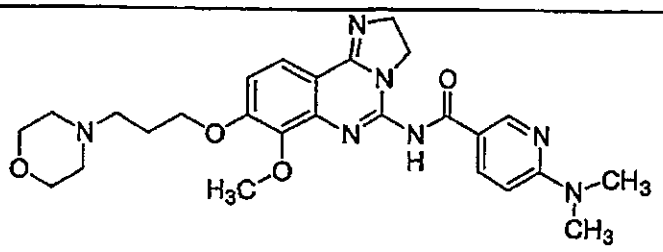
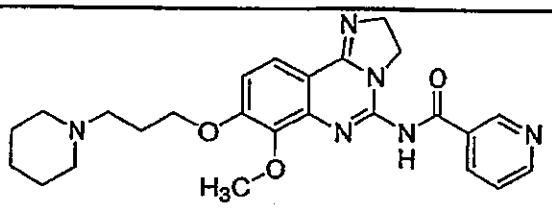
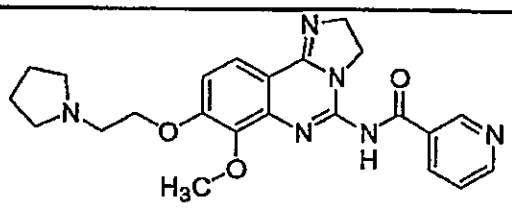
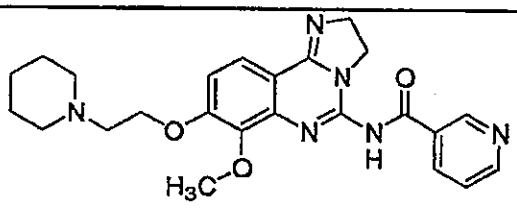
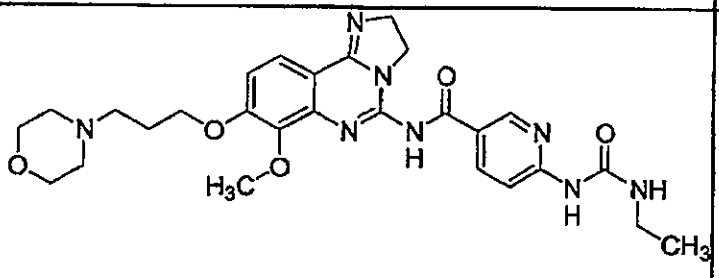
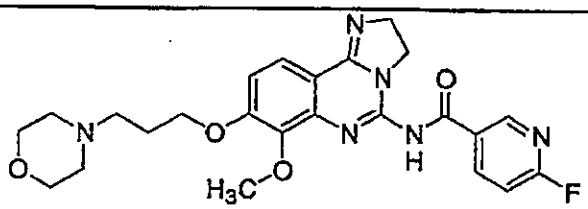
41		RT=1.90 Min MH^+ = 553.2 Route 2
42		RT=1.17 Min MH^+ = 439.1 Route 1
43		RT=1.14 Min MH^+ = 608.3 Route 2
44		RT=1.66 Min MH^+ = 539.2 Route 2
45		RT=1.14 Min MH^+ = 552.3 Route 2
46		RT=1.04 Min MH^+ = 438.1 Route 1

47		RT=0.48 Min MH^+ = 535.3 Route 2
48		RT=0.33 Min MH^+ = 564.3 Route 2
49		RT=1.93 Min MH^+ = 551.2 Route 2
50		RT=1.03 Min MH^+ = 549.1 Route 2
51		RT=0.99 Min MH^+ = 549.2 Route 2
52		RT=0.98 Min MH^+ = 549.2 Route 2

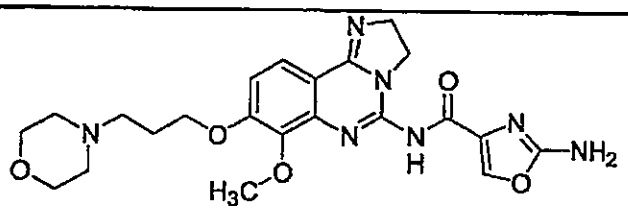
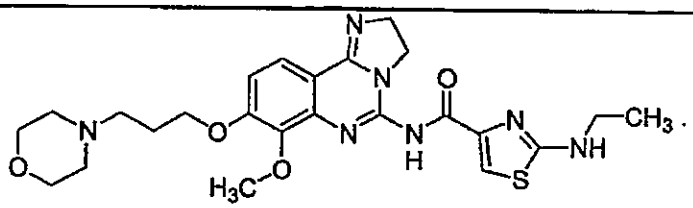
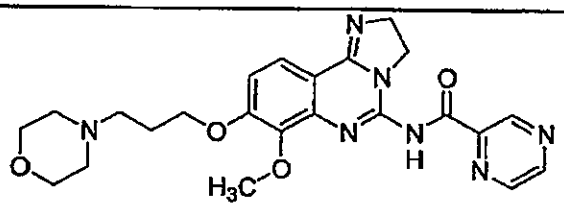
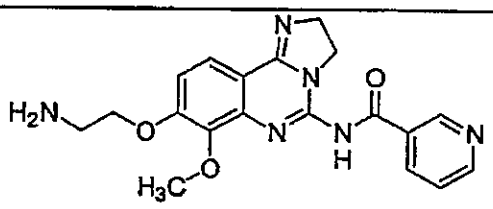
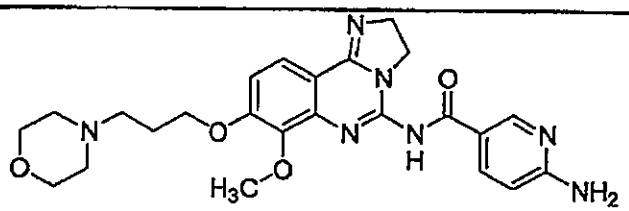
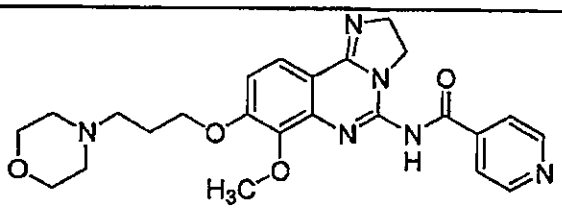
53		RT=1.84 Min MH^+ = 588.2 Route 2
54		RT=1.48 Min MH^+ = 560.2 Route 2
55		RT=1.07 Min MH^+ = 538.2 Route 2
56		RT=2.10 Min MH^+ = 530.1 Route 2
57		RT=1.43 Min MH^+ = 550.2 Route 2
58		RT=0.31 Min MH^+ = 409.2 Route 4

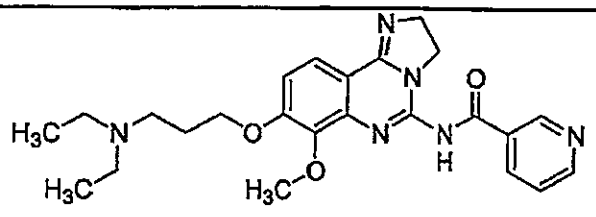
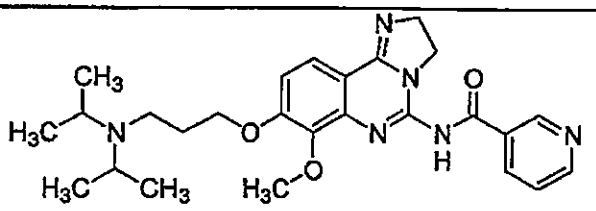
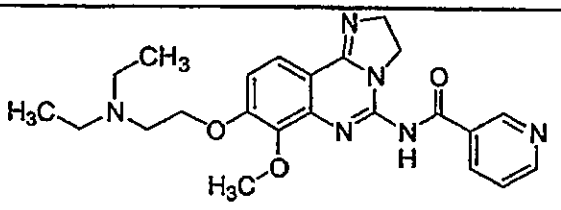
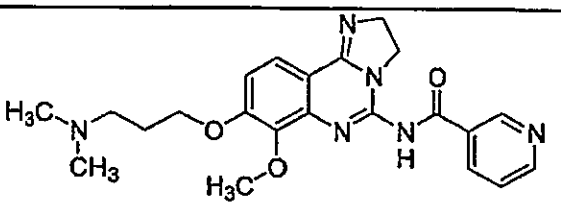
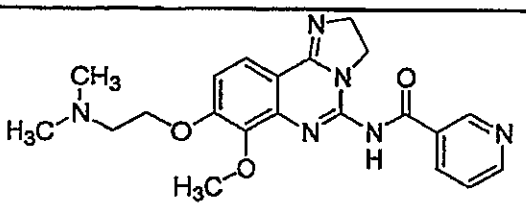
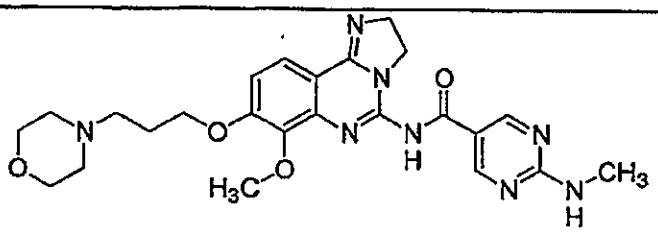
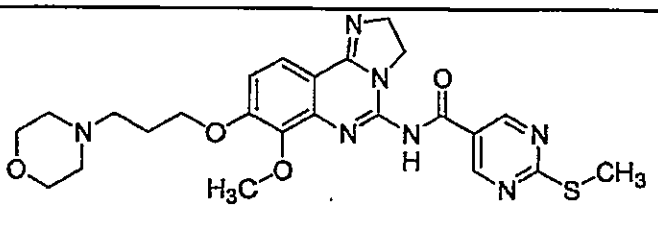
59		RT=2.06 Min MH^+ = 564.2 Route 2
60		RT=1.90 Min MH^+ = 548.2 Route 2
61		RT=2.15 Min MH^+ = 563.1 Route 2
62		RT=1.94 Min MH^+ = 533.1 Route 2
63		RT=1.93 Min MH^+ = 550.2 Route 2
64		RT=1.04 Min MH^+ = 478.1 Route 4
65		RT=1.25 Min+ MH^+ = 543.1

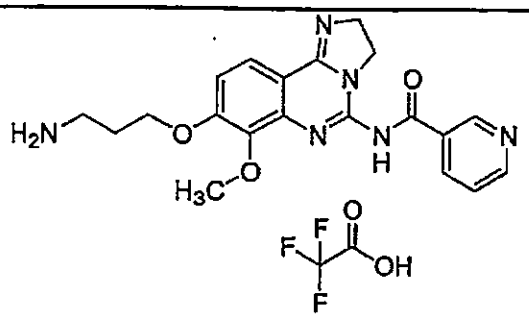
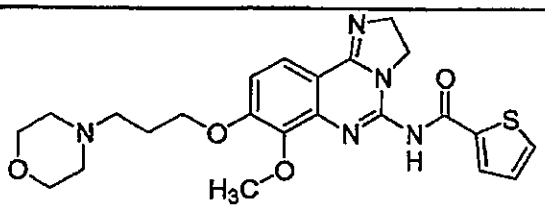
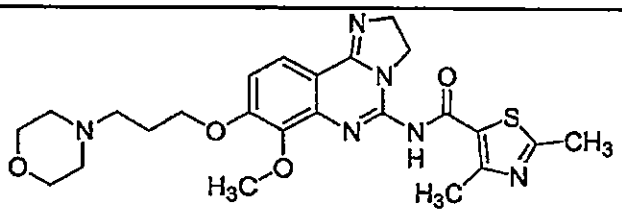
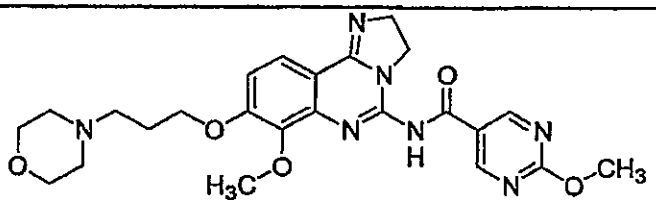
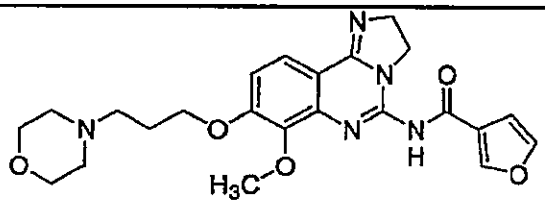
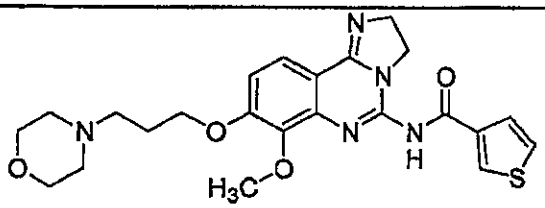
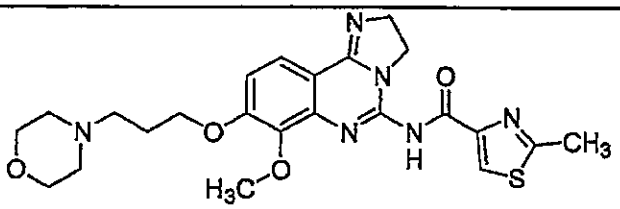
		Route 2
66		RT=1.53 Min MH^+ = 537.0 Route 2
67		RT=1.07 Min MH^+ = 500.1 Route 2
68		RT=1.02 Min MH^+ = 451 Route 4
69		RT=1.38 Min MH^+ = 443.0 Route 4
70		RT= 1.03 Min MH^+ = 423 Route 4
71		RT=1.91 Min MH^+ = 565.2 Route 2

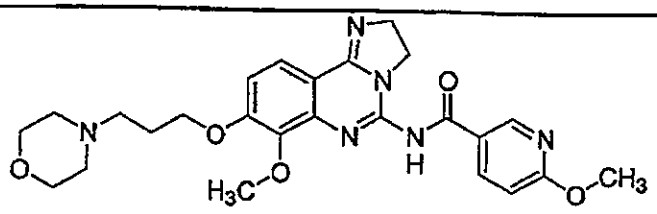
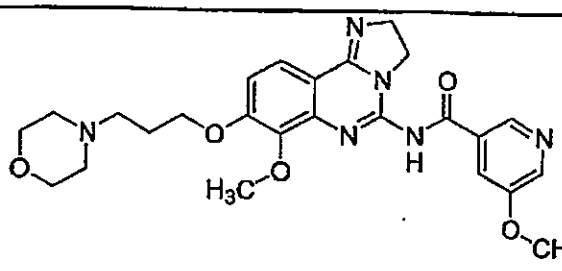
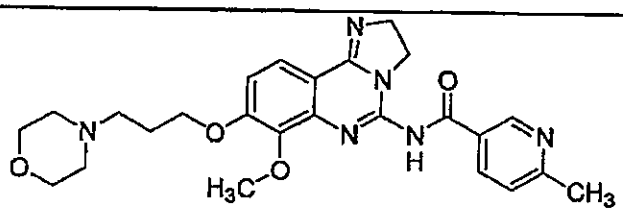
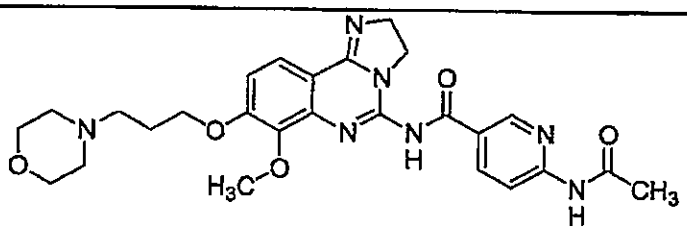
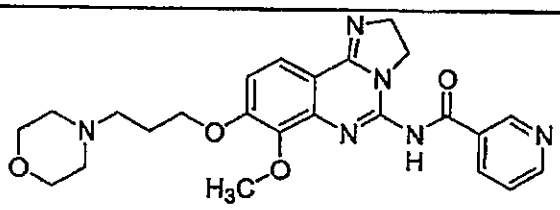
72		RT=1.11 Min MH^+= 534.2 Route 2
73		RT=1.05 Min MH^+ = 508.2 Route 2
74		RT=1.15 Min MH^+ = 463.1 Route 4
75		RT=1.05 Min MH^+ = 435.0 Route 4
76		RT=1.09 Min MH^+ = 449.0 Route 4
77		RT=1.81 Min MH^+ = 555.1 Route 2
78		RT=1.76 Min MH^+ = 483.0

50

		Route 2
79		RT=1.07 Min MH^+ = 470.2 Route 2
80		RT=1.28 Min MH^+ = 514.3 Route 2
81		RT=1.07 Min MH^+ = 466.0 Route 2
82		RT=1.89 Min MH^+ = 381.4 Route 4
83		RT= 0.23 Min MH^+ = 480.2 Route 1
84		RT=0.21 Min MH^+ = 465 Route 2

85		RT=0.25 Min MH^+ = 451.3 Route 4
86		RT=1.19 Min MH^+ = 465.2 Route 4
87		RT=1.07 Min MH^+ = 437.1 Route 4
88		RT=1.04 Min MH^+ = 423.2 Route 4
89		RT=1.03 Min MH^+ = 409.3 Route 4
90		RT=1.28 Min MH^+ = 495.2 Route 2
91		RT=1.27 Min MH^+ = 512.3 Route 2

92		RT=0.95 Min MH^+ = 395.1 Route 4
93		RT=1.86 Min MH^+ = 470.2 Route 2
94		RT=1.74 Min MH^+ = 499.1 Route 2
95		RT=1.55 Min MH^+ = 496.1 Route 2
96		RT=0.61 Min MH^+ = 454.2 Route 2
97		RT=1.09 Min MH^+ = 470.1 Route 2
98		RT=0.35 Min MH^+ = 485.3

		Route 2
99		RT=1.91 Min MH^+ = 495.1 Route 2
100		RT=1.38 Min MH^+ = 495.1 Route 2
101		RT=1.03 Min MH^+ = 479.2 Route 4
102		RT=1.60 Min MH^+ = 522.1 Route 4
103		RT=1.04 Min MH^+ = 465.2 Route 2

BIOLOGICAL EVALUATION

The utility of the compounds of the present invention can be illustrated, for example, by their activity *in vitro* in the *in vitro* tumor cell proliferation assay described below. The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the

clinical setting has been very well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* 1993, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* 1995, 6(3), 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother. Pharmacol.* 1996, 37(5), 385-93) were demonstrated with the use of *in vitro* tumor proliferation assays.

Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo,* and *in vivo* assays that are well known in the art. For example, to demonstrate the activity of the compounds of the present invention, the following assays may be used.

Biological Assays

The effects of the compounds of the present invention were examined by the following assays.

[Determination of IC_{50} values of compounds in kinase assay of PI3Kα]

Chemicals and assay materials

Phosphatidylinositol (PtdIns) and phosphatidylserine (PtdSer) were purchased from DOOSAN SERDARY RESEARCH LABORATORIES (Toronto, Canada). Recombinant truncated forms (ΔN 1-108) of the human p110α and p110α subunits of PI3K with N-terminal His_6-Tags were expressed in *S. frugiperda* 9 insect cells. Recombinant human PI3Kγ (full length human PI3K p110γ fused with a His_6-tag at the C-terminus expressed in *S. frugiperda* 9 insect cells) was obtained from ALEXIS BIOCHEMICALS (#201-055-C010; San Diego, CA). [γ^{33}P]ATP and unlabeled ATP were purchased from AMERSHAM PHARMACIA BIOTECH (Buckinghamshire, UK) and ROCHE DIAGNOSTICS (Mannheim, Germany), respectively. Scintillation cocktails and MicroScint PS™ were purchased from PACKARD (Meriden, CT). Maxisorp™ plates were purchased from NALGE NUNC INTERNATIONAL K.K. (Tokyo, Japan). All other chemicals not further specified were from WAKO PURE CHEMICALS (Osaka, Japan).

Solid-Phase Lipid Kinase Assay

To assess inhibition of PI3Kα by compounds, the Maxisorp™ plates were coated with 50 µL/well of a solution containing 50 µg/ml PtdIns and 50 µg/ml PtdSer dissolved in chloroform:ethanol (3:7). The plates were subsequently air-dried by incubation for at least

2 hours in a fume hood. The reaction was set up by mixing 25 µL/well of assay buffer 2x (100 mM MOPSO/NaOH, 0.2 M NaCl, pH 7.0, 8 mM $MgCl_2$, 2 mg/mL BSA (fatty acid-free)), and 7.5 ng/well PI3Kα in the lipid pre-coated plate.10x test compounds were added in 2% DMSO. The reaction was started by adding 20 µL/well of ATP mix (final 10 µM ATP; 0.05 µCi/well [γ^{33}P]ATP). After incubation at RT for 2 hours, the reaction was terminated by adding 50 µl/well stop solution (50 mM EDTA, pH 8.0). The plate was then washed twice with Tris–buffered saline (TBS, pH 7.4). MicroScint PS™ (PACKARD) scintillation mix was added at 100 µL/well, and radioactivity was counted using a TopCount™ (PACKARD) scintillation counter.

The inhibition percent at each concentration of compound was calculated, and IC_{50} values were determined from the inhibition of curve.

The following compounds displayed an average IC_{50} of less than 10 nanomolar in the p110α assay: Entries: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16, 18, 19, 20, 22, 23, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 44, 45, 46, 51, 52, 54, 55, 58, 60, 63, 66, 68, 69, 71, 73, 74, 75, 76, 78, 83, 85, 87, 88, 89, 92, 94, 100, 101 and 103. The following compounds displayed an average IC_{50} of between 10 nanomolar and 100 nanomolar in this assay: Entries: 14, 15, 17, 21, 25, 26, 41, 43, 47, 49, 50, 53, 56, 57, 61, 62, 93 and 98. The following compounds displayed an average IC_{50} of greater than 100 nanomolar in this assay: Entries: 12, 24, 48 and 59.

[Isozyme selectivity test in PI3K]

Chemicals and assay materials

A recombinant truncated form (ΔN 1-108) of the human p110β subunit of PI3K with an N-terminal His_6-Tag was expressed in *S. frugiperda* 9 insect cells. Recombinant human PI3Kγ (full length human PI3K p110γ fused with a His_6-tag at the C-terminus expressed in *S. frugiperda* 9 insect cells) was obtained from ALEXIS BIOCHEMICALS (#201-055-C010; San Diego, CA).

Determination of IC_{50} values of compounds in kinase assays of PI3Kβ and PI3Kγ

Kinase assays using recombinant truncated p110β or the full length p110γ were performed in a similar manner as described in the part of [Determination of IC_{50} values of

compounds in kinase assay of PI3Kα] except that these isoforms were assayed using 7.5 ng and 25.0 ng of protein/well, respectively.

The following compounds displayed an average IC_{50} of less than 10 nanomolar in the p110β assay: Entries: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16, 18, 19, 20, 22, 23, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 42, 44, 45, 46, 51, 52, 54, 55, 58, 60, 63, 66, 68, 69, 71, 73, 74, 75, 76, 78, 83, 85, 87, 88, 89, 92, 94, 100, 101 and 103. The following compounds displayed an average IC_{50} of between 10 nanomolar and 100 nanomolar in this assay: Entries: 14, 15, 17, 21, 25, 26, 41, 43, 47, 49, 50, 53, 56, 57, 61, 62, 93 and 98. The following compounds displayed an average IC_{50} of greater than 100 nanomolar in this assay: Entries: 12, 24, 48 and 59.

[Determination of IC_{50} values of compounds in cell based assays of PI3K activity]

Chemicals and assay materials

96-well collagen treated clear bottom/black sided Costar plates were purchased from CORNING LIFE SCIENCES (Corning, NY; at.#3904). Gibco RPMI medium (Cat.# 11875), Biosource anti-phospho-AKT(Ser 473) antibody (Cat.# 44-621G) and recombinant IGF-1 (Cat.# PHG0074) were purchased from INVITROGEN (Carlsbad, CA). The secondary donkey anti-rabbit IgG horse radish peroxidase conjugate (Cat. # NA934V) and ECL chemiluminesence reagent (Cat.# RPN2209) were purchased from AMERSHAM (Buckinghamshire, UK). Cell culture tested bovine serum albumin solution (35% in DPBS; Cat.# A7979) and all other chemicals were purchased from SIGMA (St. Louis, MO). The Wallac Victor2 1420 Multilabel HTS Counter was purchased from PERKINELMER (Wellesley, MA)

IGF-1 induced AKT phosphorylation assay

To test inhibition of IGF-1 induced AKT phosphorylation by compounds, A549 cells (5 x 10^4 cells/well) were seeded in 100 µL of 0.1% bovine serum albumin (BSA) in RPMI medium in 96-well collagen treated clear bottom/black sided plates and incubated overnight at 37 °C in a 5% CO_2 incubator. 10x compound solution (in 0.1% BSA in RPMI) was added to the plates and incubation at 37 °C was continued for 1 hour. All wells (except no IGF-1 controls) were then treated with 25 ng/ml IGF-1 for 10 minutes at 37 °C in a 5% CO_2 incubator. Following removal of the supernatants and washing with the wells

with TBS (50 mM Tris pH 8.0 containing138 mM NaCL and 27 mM KCl), 200 µL of 3.7% formaldehyde in TBS was added to each well, and the plate was incubated at 4 °C for 10 minutes. Supernatants were once again removed and replaced with 50 µL Methanol (-20 °C) and the plate incubated at 4 °C for 5 minutes. 200 µL of 0.1% BSA in TBS was then added to each well and the plate incubated at room temperature for ½ hour. Supernatants were removed and 50 µL of a solution comprising the primary anti-phospho-AKT(Ser 473) antibody diluted 1:250 in TBS containing 0.1% BSA was added to each well (except control/background wells). The plate was then incubated for 1½ hour at room temperature. Supernatants were removed, each well was washed 3 times with 200 µL TBS, and 100 µL of a solution containing the secondary donkey anti-rabbit IgG antibody HRP-conjugate diluted 1:100 in TBS-T (TBS containing 0.1% triton). Plates were then incubated for 1 hour at room temperature. After removing the secondary antibody, each well was washed 6 times with cold TBS-T, 100 µL of ECL was added to each well, and the plate was placed on an orbital shaker for 1 minute. The plates were then read on a Wallac Victor2 1420 Multilabel HTS Counter using the luminometry window (maximum light detection is measured at 428 nM). IC_{50} values were determined from the inhibition curve.

The following compounds displayed an average IC_{50} of less than 100 nanomolar in the A549 cell assay: Entries: 2, 3, 6, 7, 8, 10, 11, 13, 16, 18, 19, 20, 21, 22, 23, 27, 28, 29, 31, 32, 33, 35, 37, 38, 39, 42, 46, 47, 52, 60, 63, 66, 68, 69, 70, 71, 74, 75, 76, 77, 83, 85, 90, 91, 94, 95, 99, 101 and 103. The following compounds displayed an average IC_{50} of between 100 nanomolar and 1000 nanomolar in this assay: Entries: 1, 4, 5, 9, 30, 34, 36, 40, 41, 45, 51, 54, 55, 57, 58, 61, 62, 64, 67, 72, 73, 78, 80, 82, 84, 86, 87, 88, 89, 93, 96, 97 and 100. The following compounds displayed an average IC_{50} of greater than 1000 nanomolar in this assay: Entries: 12, 14, 15, 24, 25, 26, 43, 44, 48, 50, 53, 56, 59, 65, 79, 81, 92 and 98.

Mouse

To evaluate the in vivo anti-tumor effect of PI3K inhibitors, efficacy studies were conducted in the NCr athymic female mice (Taconic, NY). Human carcinoma cells of various histological types were harvested from mid-log phase cultures using Trypsin-EDTA (Gibco). Cells were pelleted, rinsed twice, and resuspended in sterile HBSS (Hank's Balanced Salt Solution) to final concentration of 2.5 x 106 cells/ml. Cells were implanted subcutaneously (s.c.) in a 0.2ml volume (5 x 106 cells) into the right flank.

When tumors reached an average size of ~100-125 mg, the mice were randomized, and treatment initiated. Each experimental group consisted of 10 mice and the dosing volume was 10ml/kg body weight. Compounds were dissolved in a compatible vehicle for both intravenous and oral administration. For intravenous administration, mice are placed under a heat lamp to warm for 5 minutes, then placed in a restraining device and the tail vein injected with a sterile 27 gauge ½ inch needle. Oral dosing utilizes sterile disposable feeding needles (20 gauge/1 ½ inches) from Popper and Sons, New Hyde Park, NY. Tumor growth was measured with electronic calipers 2-3 times a week and tumor weight (mg) calculated according to the following formula: [length (mm) x width (mm)2]/2. Percent inhibition or tumor growth inhibition (TGI) is calculated on days of measurement using the following formula: (100 - mean tumor value of treated (T)/mean tumor of control value (C) x 100) = % T/C. Of note: the control used in the calculations is either the "untreated control" or "vehicle", whichever provides the most conservative representation of the data.

Rat

To evaluate the in vivo anti-tumor effect of PI3K inhibitors, efficacy studies were conducted in the HSD athymic female rats (Harlan, ID). Human carcinoma cells of various histological types were harvested from mid-log phase cultures using Trypsin-EDTA (Gibco). Cells were pelleted, rinsed twice, and resuspended in sterile HBSS (Hank's Balanced Salt Solution) to final concentration of 2.5 x 106 cells/ml. Cells were implanted subcutaneously (s.c.) in a 0.2ml volume (5 x 106 cells) into the right flank. When tumors reached an average size of ~200-400 mg, the rats were randomized, and treatment initiated. Each experimental group consisted of 10 nude rats. Compounds were dissolved in a compatible vehicle for both intravenous and oral administration. For intravenous administration of compound, rats were warmed under a heating lamp for 5 minutes, then placed in a restraining device, and injected intravenously via the tail vein using a dosing volume ranging from 2 mL/kg to 5 mL/kg with a sterile 25 gauge needle. Oral dosing utilizes sterile disposable feeding needles (18 gauge/2 inch) from Popper and Sons, New Hyde Park, NY. Tumor growth was measured with electronic calipers 2-3 times a week and tumor weight (mg) calculated according to the following formula: [length (mm) x width (mm)2]/2. Percent inhibition or tumor growth inhibition (TGI) is calculated on days of measurement using the following formula: (100 - mean tumor value of treated (T)/mean tumor of control value (C) x 100) = % T/C. Of note: the control used in the calculations is either the "untreated control" or "vehicle", whichever provides the most conservative representation of the data.

It is believed that one skilled in the art, using the preceeding information and information available in the art, can utilize the present invention to its fullest extent. Those skilled in the art will recognize that the invention may be practiced with variations on the disclosed structures, materials, compositions and methods without departing from the spirit or scope of the invention as it is set forth herein and such variations are regarded as within the ambit of the invention. The compounds described in the examples are intended to be representative of the invention, and it will be understood that the scope of the invention is not limited by the scope of the examples. The topic headings set forth above are meant as guidance where certain information can be found in the application, but are not intended to be the only source in the application where information on such topics can be found. All publications and patents cited above are incorporated herein by reference.

References:

1. Abbosh, P. H.; Nephew, K. P. Multiple signaling pathways converge on b-catenin in thyroid cancer. Thyroid 2005, 15, 551-561.

2. Ali, I. U.; Schriml, L. M.; Dean, M. Mutational spectra of PTEN/MMAC1 gene: a tumor suppressor with lipid phosphatase activity. J. Natl. Cancer Inst. 1999, 91, 1922-1932.

3. Bachman, K. E.; Argani, P.; Samuels, Y.; Silliman, N.; Ptak, J.; Szabo, S.; Konishi, H.; Karakas, B.; Blair, B. G.; Lin, C.; Peters, B. A.; Velculescu, V. E.; Park, B. H. The PIK3CA gene is mutated with high frequency in human breast cancers. Cancer Biol. Therap. 2004, 3, 772-775.

4. Bader, A. G.; Kang, S.; Vogt, P. K. Cancer-specific mutations in PIK3CA are oncogenic in vivo. Proc. Natl. Acad. Sci. U. S. A. 2006, 103, 1475-1479.

5. Barthwal, M. K.; Sathyanarayana, P.; Kundu, C. N.; Rana, B.; Pradeep, A.; Sharma, C.; Woodgett, J. R.; Rana, A. Negative Regulation of Mixed Lineage Kinase 3 by Protein Kinase B/AKT Leads to Cell Survival. J. Biol. Chem. 2003, 278, 3897-3902.

6. Bénistant, C.; Chapuis, H.; Roche, S. A specific function for phosphatidylinositol 3-kinase a (p85a-p110a) in cell survival and for phosphatidylinositol 3-kinase b (p85a-p110b) in de novo DNA synthesis of human colon carcinoma cells. Oncogene 2000, 19, 5083-5090.

7. Broderick, D. K.; Di, C.; Parrett, T. J.; Samuels, Y. R.; Cummins, J. M.; McLendon, R. E.; Fults, D. W.; Velculescu, V. E.; Bigner, D. D.; Yan, H. Mutations of PIK3CA in anaplastic oligodendrogliomas, high-grade astrocytomas, and medulloblastomas. Cancer Res. 2004, 64, 5048-5050.

8. Brown, R. A.; Shepherd, P. R. Growth factor regulation of the novel class II phosphoinositide 3-kinases. Biochem. Soc. Trans. 2001, 29, 535-537.

9. Brunet, A.; Bonni, A.; Zigmond, M. J.; Lin, M. Z.; Juo, P.; Hu, L. S.; Anderson, M. J.; Arden, K. C.; Blenis, J.; Greenberg, M. E. Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell 1999, 96, 857-868.

10. Byun, D.-S.; Cho, K.; Ryu, B.-K.; Lee, M.-G.; Park, J.-I.; Chae, K.-S.; Kim, H.-J.; Chi, S.-G. Frequent monoallelic deletion of PTEN and its reciprocal association with PIK3CA amplification in gastric carcinoma. Int. J. Cancer 2003, 104, 318-327.

11. Campbell, I. G.; Russell, S. E.; Choong, D. Y. H.; Montgomery, K. G.; Ciavarella, M. L.; Hooi, C. S. F.; Cristiano, B. E.; Pearson, R. B.; Phillips, W. A. Mutation of the PIK3CA gene in ovarian and breast cancer. Cancer Res. 2004, 64, 7678-7681.

12. Cardone, M. H.; Roy, N.; Stennicke, H. R.; Salvesen, G. S.; Franke, T. F.; Stanbridge, E.; Frisch, S.; Reed, J. C. Regulation of cell death protease caspase-9 by phosphorylation. Science 1998, 282, 1318-1321.

13. Chen, Y. L.; Law, P.-Y.; Loh, H. H. Inhibition of PI3K/Akt signaling: An emerging paradigm for targeted cancer therapy. Curr. Med. Chem. Anticancer Agents 2005, 5, 575-589.

14. Ciechomska, I.; Pyrzynska, B.; Kazmierczak, P.; Kaminska, B. Inhibition of Akt kinase signalling and activation of Forkhead are indispensable for up-regulation of FasL expression in apoptosis of glioma cells. Oncogene 2003, 22, 7617-7627.

15. Cross, D. A. E.; Alessi, D. R.; Cohen, P.; Andjelkovich, M.; Hemmings, B. A. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature 1995, 378, 785-9.

16. Cully, M.; You, H.; Levine, A. J.; Mak, T. W. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. Nat. Rev. Cancer 2006, 6, 184-192.

17. Czauderna, F.; Fechtner, M.; Aygun, H.; Arnold, W.; Klippel, A.; Giese, K.; Kaufmann, J. Functional studies of the PI(3)-kinase signalling pathway employing synthetic and expressed siRNA. Nucleic Acids Res. 2003, 31, 670-682.

18. del Peso, L.; González-Garcia, M.; Page, C.; Herrera, R.; Nunez, G. Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. Science 1997, 278, 687-689.

19. Diehl, J. A.; Cheng, M.; Roussel, M. F.; Sherr, C. J. Glycogen synthase kinase-3b regulates cyclin D1 proteolysis and subcellular localization. Genes Dev. 1998, 12, 3499-3511.

20. Dijkers, P. F.; Medema, R. H.; Lammers, J.-W. J.; Koenderman, L.; Coffer, P. J. Expression of the pro-apoptotic Bcl-2 family member Bim is regulated by the Forkhead transcription factor FKHR-L1. Curr. Biol. 2000, 10, 1201-1204.

21. Domin, J.; Waterfield, M. D. Using structure to define the function of phosphoinositide 3-kinase family members. FEBS Lett. 1997, 410, 91-95.

22. Downes, C. P.; Gray, A.; Lucocq, J. M. Probing phosphoinositide functions in signaling and membrane trafficking. Trends Cell Biol. 2005, 15, 259-268.

23. Figueroa, C.; Tarras, S.; Taylor, J.; Vojtek, A. B. Akt2 negatively regulates assembly of the POSH-MLK-JNK signaling complex. J. Biol. Chem. 2003, 278, 47922-47927.

24. Fleming, I. N.; Gray, A.; Downes, C. P. Regulation of the Rac1-specific exchange factor tiam1 involves both phosphoinositide 3-kinase-dependent and -independent components. Biochem. J. 2000, 351, 173-182.

25. Funaki, M.; Katagiri, H.; Inukai, K.; Kikuchi, M.; Asano, T. Structure and function of phosphatidylinositol-3,4 kinase. Cell. Signal. 2000, 12, 135-142.

26. Gallia, G. L.; Rand, V.; Siu, I. M.; Eberhart, C. G.; James, C. D.; Marie, S. K. N.; Oba-Shinjo, S. M.; Carlotti, C. G.; Caballero, O. L.; Simpson, A. J. G.; Brock, M. V.; Massion, P. P.; Carson, B. S., Sr.; Riggins, G. J. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. Mol. Cancer Res. 2006, 4, 709-714.

27. Gershtein, E. S.; Shatskaya, V. A.; Ermilova, V. D.; Kushlinsky, N. E.; Krasil'nikov, M. A. Phosphatidylinositol 3-kinase expression in human breast cancer. Clin. Chim. Acta 1999, 287, 59-67.

28. Gottschalk, A. R.; Doan, A.; Nakamura, J. L.; Stokoe, D.; Haas-Kogan, D. A. Inhibition of phosphatidylinositol-3-kinase causes increased sensitivity to radiation through a PKB-dependent mechanism. Int. J. Radiat. Oncol. Biol. Phys. 2005, 63, 1221-1227.

29. Gupta, A. K.; Cerniglia, G. J.; Mick, R.; Ahmed, M. S.; Bakanauskas, V. J.; Muschel, R. J.; McKenna, W. G. Radiation sensitization of human cancer cells in vivo by inhibiting the activity of PI3K using LY294002. Int. J. Radiat. Oncol. Biol. Phys. 2003, 56, 846-853.

30. Haas-Kogan, D.; Shalev, N.; Wong, M.; Mills, G.; Yount, G.; Stokoe, D. Protein kinase B (PKB/Akt) activity is elevated in glioblastoma cells due to mutation of the tumor suppressor PTEN/MMAC. Curr. Biol. 1998, 8, 1195-1198.

31. Hartmann, C.; Bartels, G.; Gehlhaar, C.; Holtkamp, N.; von Deimling, A. PIK3CA mutations in glioblastoma multiforme. Acta Neuropathol. 2005, 109, 639-642.

32. Hennessy, B. T.; Smith, D. L.; Ram, P. T.; Lu, Y.; Mills, G. B. Exploiting the PI3K/AKT Pathway for Cancer Drug Discovery. Nat. Rev. Drug Disc. 2005, 4, 988-1004.

33. Hodgkinson, C. P.; Sale, E. M.; Sale, G. J. Characterization of PDK2 activity against Protein Kinase B gamma. Biochemistry 2002, 41, 10351-10359.

34. Hresko, R. C.; Murata, H.; Mueckler, M. Phosphoinositide-dependent Kinase-2 is a distinct protein kinase enriched in a novel cytoskeletal fraction associated with adipocyte plasma membranes. J. Biol. Chem. 2003, 278, 21615-21622.

35. Huang, C.; Ma, W.-Y.; Dong, Z. Requirement for phosphatidylinositol 3-kinase in epidermal growth factor-induced AP-1 transactivation and transformation in JB6 P+ cells. Mol. Cell. Biol. 1996, 16, 6427-6435.

36. Hupp, T. R.; Lane, D. P.; Ball, K. L. Strategies for manipulating the p53 pathway in the treatment of human cancer. Biochem. J. 2000, 352, 1-17.

37. Ihle, N. T.; Williams, R.; Chow, S.; Chew, W.; Berggren, M. I.; Paine-Murrieta, G.; Minion, D. J.; Halter, R. J.; Wipf, P.; Abraham, R.; Kirkpatrick, L.; Powis, G. Molecular pharmacology and antitumor activity of PX-866, a novel inhibitor of phosphoinositide-3-kinase signaling. Mol. Cancer Therap. 2004, 3, 763-772.

38. Ikenoue, T.; Kanai, F.; Hikiba, Y.; Obata, T.; Tanaka, Y.; Imamura, J.; Ohta, M.; Jazag, A.; Guleng, B.; Tateishi, K.; Asaoka, Y.; Matsumura, M.; Kawabe, T.; Omata, M. Functional analysis of PIK3CA gene mutations in human colorectal cancer. Cancer Res. 2005, 65, 4562-4567.

39. Ishii, N.; Maier, D.; Merlo, A.; Tada, M.; Sawamura, Y.; Diserens, A.-C.; Van Meir, E. G. Frequent co-alterations of TP53, p16/CDKN2A, p14ARF, PTEN tumor suppressor genes in human glioma cell lines. Brain Pathol. 1999, 9, 469-479.

40. Itoh, T.; Takenawa, T. Phosphoinositide-binding domains. Functional units for temporal and spatial regulation of intracellular signalling. Cell. Signal. 2002, 14, 733-743.

41. Janssen, J. W. G.; Schleithoff, L.; Bartram, C. R.; Schulz, A. S. An oncogenic fusion product of the phosphatidylinositol 3-kinase p85b subunit and HUMORF8, a putative deubiquitinating enzyme. Oncogene 1998, 16, 1767-1772.

42. Jimenez, C.; Jones, D. R.; Rodriguez-Viciana, P.; Gonzalez-Garcia, A.; Leonardo, E.; Wennstrom, S.; Von Kobbe, C.; Toran, J. L.; R.-Borlado, L.; Calvo, V.; Copin, S. G.; Albar, J. P.; Gaspar, M. L.; Diez, E.; Marcos, M. A. R.; Downward, J.; Martinez-A, C.; Merida, I.; Carrera, A. C. Identification and characterization of a new oncogene derived from the regulatory subunit of phosphoinositide 3-kinase. EMBO J. 1998, 17, 743-753.

43. Jucker, M.; Sudel, K.; Horn, S.; Sickel, M.; Wegner, W.; Fiedler, W.; Feldman, R. A. Expression of a mutated form of the p85a regulatory subunit of phosphatidylinositol 3-kinase in a Hodgkin's lymphoma-derived cell line (CO). Leukemia 2002, 16, 894-901.

44. Kang, S.; Bader, A. G.; Vogt, P. K. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proc. Natl. Acad. Sci. U. S. A. 2005, 102, 802-807.

45. Kang, S.; Denley, A.; Vanhaesebroeck, B.; Vogt, P. K. Oncogenic transformation induced by the p110b, -g, and -d isoforms of class I phosphoinositide 3-kinase. Proc. Natl. Acad. Sci. U. S. A. 2006, 103, 1289-1294.

46. Katso, R.; Okkenhaug, K.; Ahmadi, K.; White, S.; Timms, J.; Waterfield, M. D. Cellular function of phosphoinositide 3-kinases: implications for development, immunity, homeostasis, and cancer. Annu. Rev. Cell Dev. Biol. 2001, 17, 615-675.

47. Kim, A. H.; Khursigara, G.; Sun, X.; Franke, T. F.; Chao, M. V. Akt phosphorylates and negatively regulates apoptosis signal-regulating kinase 1. Mol. Cell. Biol. 2001, 21, 893-901.

48. Kim, D.; Dan, H. C.; Park, S.; Yang, L.; Liu, Q.; Kaneko, S.; Ning, J.; He, L.; Yang, H.; Sun, M.; Nicosia, S. V.; Cheng, J. Q. AKT/PKB signaling mechanisms in cancer and chemoresistance. Front. Biosci. 2005, 10, 975-987.

49. Klippel, A.; Kavanaugh, W. M.; Pot, D.; Williams, L. T. A specific product of phosphatidylinositol 3-kinase directly activates the protein kinase Akt through its pleckstrin homology domain. Mol. Cell. Biol. 1997, 17, 338-44.

50. Kodaki, T.; Woscholski, R.; Hallberg, B.; Rodriguez-Viciana, P.; Downward, J.; Parker, P. J. The activation of phosphatidylinositol 3-kinase by Ras. Curr. Biol. 1994, 4, 798-806.

51. Kops, G. J. P. L.; De Ruiter, N. D.; De Vries-Smits, A. M. M.; Powell, D. R.; Bos, J. L.; Burgering, B. M. T. Direct control of the Forkhead transcription factor AFX by protein kinase B. Nature 1999, 398, 630-634.

52. Lee, J. T., Jr.; Steelman, L. S.; McCubrey, J. A. Phosphatidylinositol 3'-Kinase Activation Leads to Multidrug Resistance Protein-1 Expression and Subsequent Chemoresistance in Advanced Prostate Cancer Cells. Cancer Res. 2004, 64, 8397-8404.

53. Lee, J. W.; Soung, Y. H.; Kim, S. Y.; Lee, H. W.; Park, W. S.; Nam, S. W.; Kim, S. H.; Lee, J. Y.; Yoo, N. J.; Lee, S. H. PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas. Oncogene 2005, 24, 1477-1480.

54. Lemmon, M. A. Phosphoinositide recognition domains. Traffic 2003, 4, 201-213.

55. Levine, D. A.; Bogomolniy, F.; Yee, C. J.; Lash, A.; Barakat, R. R.; Borgen, P. I.; Boyd, J. Frequent Mutation of the PIK3CA Gene in Ovarian and Breast Cancers. Clin. Cancer Res. 2005, 11, 2875-2878.

56. Li, J.; Yen, C.; Liaw, D.; Podsypanina, K.; Bose, S.; Wang, S. I.; Puc, J.; Miliaresis, C.; Rodgers, L.; McCombie, R.; Bigner, S. H.; Giovanella, B. C.; Ittmann, M.; Tycko, B.; Hibshoosh, H.; Wigler, M. H.; Parsons, R. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997, 275, 1943-1947.

57. Li, V. S. W.; Wong, C. W.; Chan, T. L.; Chan, A. S. W.; Zhao, W.; Chu, K.-M.; So, S.; Chen, X.; Yuen, S. T.; Leung, S. Y. Mutations of PIK3CA in gastric adenocarcinoma. BMC Cancer 2005, 5, 29.

58. Liao, Y.; Hung, M.-C. Regulation of the activity of p38 mitogen-activated protein kinase by Akt in cancer and adenoviral protein E1A-mediated sensitization to apoptosis. Mol. Cell. Biol. 2003, 23, 6836-6848.

59. Lopez-Ilasaca, M.; Li, W.; Uren, A.; Yu, J.-c.; Kazlauskas, A.; Gutkind, J. S.; Heidaran, M. A. Requirement of phosphatidylinositol-3 kinase for activation of JNK/SAPKs by PDGF. Biochem. Biophys. Res. Commun. 1997, 232, 273-277.

60. Ma, Y.-Y.; Wei, S.-J.; Lin, Y.-C.; Lung, J.-C.; Chang, T.-C.; Whang-Peng, J.; Liu, J. M.; Yang, D.-M.; Yang, W. K.; Shen, C.-Y. PIK3CA as an oncogene in cervical cancer. Oncogene 2000, 19, 2739-2744.

61. Mayo, L. D.; Dixon, J. E.; Durden, D. L.; Tonks, N. K.; Donner, D. B. PTEN protects p53 from Mdm2 and sensitizes cancer cells to chemotherapy. J. Biol. Chem. 2002, 277, 5484-5489.

62. Momand, J.; Wu, H.-H.; Dasgupta, G. MDM2 - master regulator of the p53 tumor suppressor protein. Gene 2000, 242, 15-29.

63. Motti, M. L.; De Marco, C.; Califano, D.; Fusco, A.; Viglietto, G. Akt-dependent T198 phosphorylation of cyclin-dependent kinase inhibitor p27kip1 in breast cancer. Cell Cycle 2004, 3, 1074-1080.

64. Myers, M. P.; Pass, I.; Batty, I. H.; Van Der Kaay, J.; Stolarov, J. P.; Hemmings, B. A.; Wigler, M. H.; Downes, C. P.; Tonks, N. K. The lipid phosphatase activity of PTEN is critical for its tumor suppressor function. Proc. Natl. Acad. Sci. U. S. A. 1998, 95, 13513-13518.

65. Nagata, Y.; Lan, K.-H.; Zhou, X.; Tan, M.; Esteva, F. J.; Sahin, A. A.; Klos, K. S.; Li, P.; Monia, B. P.; Nguyen, N. T.; Hortobagyi, G. N.; Hung, M.-C.; Yu, D. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. Cancer Cell 2004, 6, 117-127.

66. Naito, A. T.; Akazawa, H.; Takano, H.; Minamino, T.; Nagai, T.; Aburatani, H.; Komuro, I. Phosphatidylinositol 3-Kinase-Akt Pathway Plays a Critical Role in Early Cardiomyogenesis by Regulating Canonical Wnt Signaling. Circ. Res. 2005, 97, 144-151.

67. Oda, K.; Stokoe, D.; Taketani, Y.; McCormick, F. High Frequency of Coexistent Mutations of PIK3CA and PTEN Genes in Endometrial Carcinoma. Cancer Res. 2005, 65, 10669-10673.

68. Ogawara, Y.; Kishishita, S.; Obata, T.; Isazawa, Y.; Suzuki, T.; Tanaka, K.; Masuyama, N.; Gotoh, Y. Akt enhances Mdm2-mediated ubiquitination and degradation of p53. J. Biol. Chem. 2002, 277, 21843-21850.

69. Olson, J. M.; Hallahan, A. R. p38 MAP kinase: a convergence point in cancer therapy. Trends Mol. Med. 2004, 10, 125-129.

70. Osaki, M.; Oshimura, M.; Ito, H. PI3K-Akt pathway: Its functions and alterations in human cancer. Apoptosis 2004, 9, 667-676.

71. Pastorino, J. G.; Tafani, M.; Farber, J. L. Tumor necrosis factor induces phosphorylation and translocation of BAD through a phosphatidylinositide-3-OH kinase-dependent pathway. J. Biol. Chem. 1999, 274, 19411-19416.

72. Pendaries, C.; Tronchere, H.; Plantavid, M.; Payrastre, B. Phosphoinositide signaling disorders in human diseases. FEBS Lett. 2003, 546, 25-31.

73. Phillips, W. A.; St. Clair, F.; Munday, A. D.; Thomas, R. J. S.; Mitchell, C. A. Increased levels of phosphatidylinositol 3-kinase activity in colorectal tumors. Cancer 1998, 83, 41-47.

74. Philp, A. J.; Campbell, I. G.; Leet, C.; Vincan, E.; Rockman, S. P.; Whitehead, R. H.; Thomas, R. J. S.; Phillips, W. A. The phosphatidylinositol 3'-kinase p85a gene is an oncogene in human ovarian and colon tumors. Cancer Res. 2001, 61, 7426-7429.

75. Powis, G.; Bonjouklian, R.; Berggren, M. M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W. F.; Dodge, J. Wortmannin, a potent and selective inhibitor of phosphatidylinositol-3-kinase. Cancer Res. 1994, 54, 2419-23.

76. Pu, P.; Kang, C.; Zhang, Z.; Liu, X.; Jiang, H. Downregulation of PIK3CB by siRNA suppresses malignant glioma cell growth in vitro and in vivo. Technol. Cancer Res. Treat. 2006, 5, 271-280.

77. Rahimi, N.; Tremblay, E.; Elliott, B. Phosphatidylinositol 3-kinase activity is required for hepatocyte growth factor-induced mitogenic signals in epithelial cells. J. Biol. Chem. 1996, 271, 24850-24855.

78. Roche, S.; Downward, J.; Raynal, P.; Courtneidge, S. A. A function for phosphatidylinositol 3-kinase b (p85a-p110b) in fibroblasts during mitogenesis: requirement for insulin- and lysophosphatidic acid-mediated signal transduction. Mol. Cell. Biol. 1998, 18, 7119-7129.

79. Roche, S.; Koegl, M.; Courtneidge, S. A. The phosphatidylinositol 3-kinase a is required for DNA synthesis induced by some, but not all, growth factors. Proc. Natl. Acad. Sci. U. S. A. 1994, 91, 9185-9.

80. Romashkova, J. A.; Makarov, S. S. Nf-kB is a target of Akt in anti-apoptotic PDGF signalling. Nature 1999, 401, 86-90.

81. Saal, L. H.; Holm, K.; Maurer, M.; Memeo, L.; Su, T.; Wang, X.; Yu, J. S.; Malmstroem, P.-O.; Mansukhani, M.; Enoksson, J.; Hibshoosh, H.; Borg, A.; Parsons, R. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res. 2005, 65, 2554-2559.

82. Samuels, Y.; Diaz, L. A., Jr.; Schmidt-Kittler, O.; Cummins, J. M.; DeLong, L.; Cheong, I.; Rago, C.; Huso, D. L.; Lengauer, C.; Kinzler, K. W.; Vogelstein, B.; Velculescu, V. E. Mutant PIK3CA promotes cell growth and invasion of human cancer cells. Cancer Cell 2005, 7, 561-573.

83. Samuels, Y.; Ericson, K. Oncogenic PI3K and its role in cancer. Curr. Opin. Oncol. 2006, 18, 77-82.

84. Samuels, Y.; Wang, Z.; Bardelli, A.; Silliman, N.; Ptak, J.; Szabo, S.; Yan, H.; Gazdar, A.; Powell, S. M.; Riggins, G. J.; Willson, J. K. V.; Markowitz, S.; Kinzler, K. W.; Vogelstein, B.; Velculescu, V. E. Brevia: High frequency of mutations of the PIK3Ca gene in human cancers. Science 2004, 304, 554.

85. Scheid, M. P.; Marignani, P. A.; Woodgett, J. R. Multiple phosphoinositide 3-kinase-dependent steps in activation of protein kinase B. Mol. Cell. Biol. 2002, 22, 6247-6260.

86. Schultz, R. M.; Merriman, R. L.; Andis, S. L.; Bonjouklian, R.; Grindey, G. B.; Rutherford, P. G.; Gallegos, A.; Massey, K.; Powis, G. In vitro and in vivo antitumor activity of the phosphatidylinositol-3-kinase inhibitor, wortmannin. Anticancer Res. 1995, 15, 1135-9.

87. Segrelles, C.; Moral, M.; Lara, M. F.; Ruiz, S.; Santos, M.; Leis, H.; Garcia-Escudero, R.; Martinez-Cruz, A. B.; Martinez-Palacio, J.; Hernandez, P.; Ballestin, C.; Paramio, J. M. Molecular determinants of Akt-induced keratinocyte transformation. Oncogene 2006, 25, 1174-1185.

88. Sekimoto, T.; Fukumoto, M.; Yoneda, Y. 14-3-3 suppresses the nuclear localization of threonine 157-phosphorylated p27Kip1. EMBO J. 2004, 23, 1934-1942.

89. Semba, S.; Itoh, N.; Ito, M.; Youssef, E. M.; Harada, M.; Moriya, T.; Kimura, W.; Yamakawa, M. Down-regulation of PIK3CG catalytic subunit of phosphatidylinositol 3-OH kinase by CpG hypermethylation in human colorectal carcinoma. Clin. Cancer Res. 2002, 8, 3824-3831.

90. Shayesteh, L.; Lu, Y.; Kuo, W.-L.; Baldocchi, R.; Godfrey, T.; Collins, C.; Pinkel, D.; Powell, B.; Mills, G. B.; Gray, J. W. PIK3CA is implicated as an oncogene in ovarian cancer. Nat. Genet. 1999, 21, 99-102.

91. Shekar, S. C.; Wu, H.; Fu, Z.; Yip, S.-C.; Nagajyothi; Cahill, S. M.; Girvin, M. E.; Backer, J. M. Mechanism of Constitutive Phosphoinositide 3-Kinase Activation by Oncogenic Mutants of the p85 Regulatory Subunit. J. Biol. Chem. 2005, 280, 27850-27855.

92. Stahl, J. M.; Cheung, M.; Sharma, A.; Trivedi, N. R.; Shanmugam, S.; Robertson, G. P. Loss of PTEN Promotes Tumor Development in Malignant Melanoma. Cancer Res. 2003, 63, 2881-2890.

93. Stambolic, V.; Suzuki, A.; De La Pompa, J. L.; Brothers, G. M.; Mirtsos, C.; Sasaki, T.; Ruland, J.; Penninger, J. M.; Siderovski, D. P.; Mak, T. W. Negative regulation of PKB/Akt-Dependent cell survival by the tumor suppressor PTEN. Cell 1998, 95, 29-39.

94. Stauffer, F.; Holzer, P.; Garcia-Echeverria, C. Blocking the PI3K/PKB pathway in tumor cells. Curr. Med. Chem. Anticancer Agents 2005, 5, 449-462.

95. Steck, P. A.; Pershouse, M. A.; Jasser, S. A.; Yung, W. K. A.; Lin, H.; Ligon, A. H.; Langford, L. A.; Baumgard, M. L.; Hattier, T.; Davis, T.; Frye, C.; Hu, R.; Swedlund, B.; Teng, D. H. F.; Tavtigian, S. V. Identification of a candidate tumor suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat. Genet. 1997, 15, 356-362.

96. Stein, R. C.; Waterfield, M. D. PI3-kinase inhibition: a target for drug development? Mol. Med. Today 2000, 6, 347-358.

97. Stephens, L.; Williams, R.; Hawkins, P. Phosphoinositide 3-kinases as drug targets in cancer. Curr. Opin. Pharmacol. 2005, 5, 357-365.

98. Su, J. D.; Mayo, L. D.; Donner, D. B.; Durden, D. L. PTEN and Phosphatidylinositol 3'-Kinase Inhibitors Up-Regulate p53 and Block Tumor-induced Angiogenesis: Evidence for an Effect on the Tumor and Endothelial Compartment. Cancer Res. 2003, 63, 3585-3592.

99. Tanaka, M.; Grossman, H. B. In vivo gene therapy of human bladder cancer with PTEN suppresses tumor growth, downregulates phosphorylated Akt, and increases sensitivity to doxorubicin. Gene Ther. 2003, 10, 1636-1642.

100. Tang, E. D.; Nunez, G.; Barr, F. G.; Guan, K.-L. Negative regulation of the forkhead transcription factor FKHR by Akt. J. Biol. Chem. 1999, 274, 16741-16746.

101. Taylor, V.; Wong, M.; Brandts, C.; Reilly, L.; Dean, N. M.; Cowsert, L. M.; Moodie, S.; Stokoe, D. 5' Phospholipid phosphatase SHIP-2 causes protein kinase B inactivation and cell cycle arrest in glioblastoma cells. Mol. Cell. Biol. 2000, 20, 6860-6871.

102. Toker, A. Phosphoinositides and signal transduction. Cell. Mol. Life Sci. 2002, 59, 761-779.

103. Traer, C. J.; Foster, F. M.; Abraham, S. M.; Fry, M. J. Are class II phosphoinositide 3-kinases potential targets for anticancer therapies? Bull. Cancer (Paris). 2006, 93, E53-8.

104. Vanhaesebroeck, B.; Leevers, S. J.; Ahmadi, K.; Timms, J.; Katso, R.; Driscoll, P. C.; Woscholski, R.; Parker, P. J.; Waterfield, M. D. Synthesis and function of 3-phosphorylated inositol lipids. Annu. Rev. Biochem. 2001, 70, 535-602.

105. Vanhaesebroeck, B.; Waterfield, M. D. Signaling by Distinct Classes of Phosphoinositide 3-Kinases. Exp. Cell Res. 1999, 253, 239-254.

106. Vivanco, I.; Sawyers, C. L. The phosphatidylinositol 3-Kinase-AKT pathway in human cancer. Nat. Rev. Cancer 2002, 2, 489-501.

107. Wang, Y.; Helland, A.; Holm, R.; Kristensen Gunnar, B.; Borresen-Dale, A.-L. PIK3CA mutations in advanced ovarian carcinomas. Hum. Mutat. 2005, 25, 322.

108. West, K. A.; Castillo, S. S.; Dennis, P. A. Activation of the PI3K/Akt pathway and chemotherapeutic resistance. Drug Resist. Update. 2002, 5, 234-48.

109. Whyte, D. B.; Holbeck, S. L. Correlation of PIK3Ca mutations with gene expression and drug sensitivity in NCI-60 cell lines. Biochem. Biophys. Res. Commun. 2006, 340, 469-475.

110. Wilker, E.; Lu, J.; Rho, O.; Carbajal, S.; Beltran, L.; DiGiovanni, J. Role of PI3K/Akt signaling in insulin-like growth factor-1 (IGF-1) skin tumor promotion. Mol. Carcinog. 2005, 44, 137-145.

111. Workman, P. Inhibiting the phosphoinositide 3-kinase pathway for cancer treatment. Biochem. Soc. Trans. 2004, 32, 393-396.

112. Wu, G.; Xing, M.; Mambo, E.; Huang, X.; Liu, J.; Guo, Z.; Chatterjee, A.; Goldenberg, D.; Gollin, S. M.; Sukumar, S.; Trink, B.; Sidransky, D. Somatic mutation and gain of copy number of PIK3CA in human breast cancer. Breast Cancer Res. 2005, 7, R609-R616.

113. Wymann, M. P.; Sozzani, S.; Altruda, F.; Mantovani, A.; Hirsch, E. Lipids on the move: phosphoinositide 3-kinases in leukocyte function. Immunol. Today 2000, 21, 260-264.

114. Yap, D. B.; Hsieh, J. K.; Lu, X. Mdm2 inhibits the apoptotic function of p53 mainly by targeting it for degradation. J. Biol. Chem. 2000, 275, 37296-302.

115. Yuan, Z.-q.; Feldman, R. I.; Sussman, G. E.; Coppola, D.; Nicosia, S. V.; Cheng, J. Q. AKT2 Inhibition of Cisplatin-induced JNK/p38 and Bax Activation by Phosphorylation of ASK1: Implication of AKT2 in Chemoresistance. J. Biol. Chem. 2003, 278, 23432-23440.

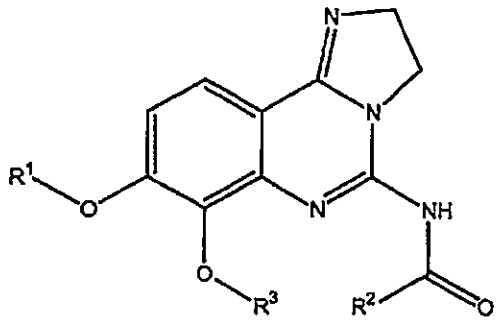
116. Zhao, H.; Dupont, J.; Yakar, S.; Karas, M.; LeRoith, D. PTEN inhibits cell proliferation and induces apoptosis by downregulating cell surface IGF-IR expression in prostate cancer cells. Oncogene 2004, 23, 786-794.

117. Zhao, J. J.; Cheng, H.; Jia, S.; Wang, L.; Gjoerup, O. V.; Mikami, A.; Roberts, T. M. The p110a isoform of PI3K is essential for proper growth factor signaling and oncogenic transformation. Proc. Natl. Acad. Sci. U. S. A. 2006, 103, 16296-300.

118. Zhou, B. P.; Liao, Y.; Xia, W.; Spohn, B.; Lee, M.-H.; Hung, M.-C. Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells. Nat. Cell Biol. 2001, 3, 245-252.

What is claimed is:

1. A compound having the formula:



or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^1 is $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 is a heteroaryl optionally substituted with 1, 2 or 3 R^6 groups;

R^3 is alkyl or cycloalkyl;

R^4 is hydrogen, hydroxy or alkoxy and R^5 and $R^{5'}$ may be the same or different and are independently, hydrogen, alkyl, cycloalkylalklyl, or alkoxyalkyl or R^5 and $R^{5'}$ may be taken together with the nitrogen atom to which they are bound to form a 3-7 membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups, or R^4 and R^5 may be taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more $R^{6'}$ groups;

each occurrence of R^6 may be the same or different and is independently halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclic ring, heterocyclylalkyl, alkyl-OR^7, alkyl-SR^7, alkyl-$N(R^7)(R^{7'})$, alkyl-COR^7,-CN, -$COOR^7$, -$CON(R^7)(R^{7'})$, -OR^7, -SR^7, -$N(R^7)(R^{7'})$, or –NR^7COR^7 each of which may be optionally substituted with 1 or more R^8 groups;

each occurrence of $R^{6'}$ may be the same or different and is independently alkyl, cycloalkylalklyl, or alkyl-OR^7;

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl;

each occurrence of R^8 is independently nitro, hydroxy, cyano, formyl, acetyl, halogen, amino, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalklyl, cycloalkenyl, aryl, arylalkyl, heteroaryl, heterocyclic ring, heterocyclylalkyl, or heteroarylalkyl;

n is an integer from 1-4 and m is an integer from 0-4 with the proviso that when when R^4 and R^5 are taken together with the atoms to which they are bound to form a 3-7 membered nitrogen containing ring, $n + m \leq 4$.

2. The compound of claim 1, wherein R^2 is a nitrogen containing heteroaryl optionally substituted with 1, 2 or 3 R^6 groups.

3. The compound of claim 1, wherein R^5 and $R^{5'}$ are independently alkyl.

4. The compound of claim 1, wherein R^5 and $R^{5'}$ are taken together with the nitrogen atom to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups.

5. The compound of claim 1, wherein R^4 is hydroxy.

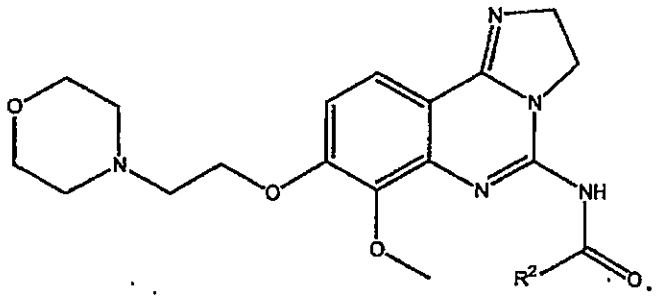
6. The compound of claim 1, wherein R^4 and R^5 are taken together with the atoms to which they are bound to form a 5-6 membered nitrogen containing heterocyclic ring optionally containing 1 or more nitrogen, oxygen or sulfur atoms and which may be optionally substituted with 1 or more $R^{6'}$ groups.

7. The compound of claim 1, wherein R^3 is methyl.

8. The compound of claim 1, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

9. The compound of claim 2, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

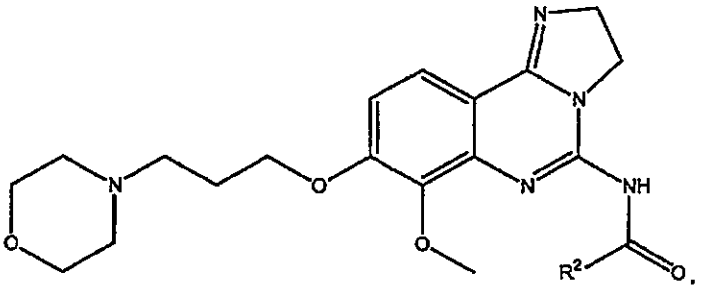
10. The compound of claim 1, having the formula:



11. The compound of claim 10, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

12. The compound of claim 11, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

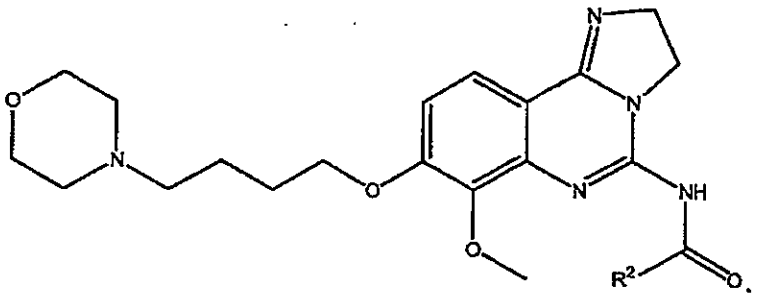
13. The compound of claim 1 having the formula:



14. The compound of claim 13, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

15. The compound of claim 14, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

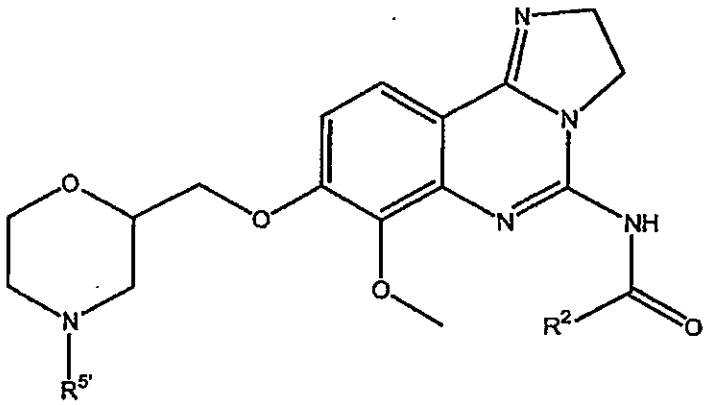
16. The compound of claim 1 having the formula:



17. The compound of claim 16, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

18. The compound of claim 17, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

19. The compound of claim 1 having the formula:

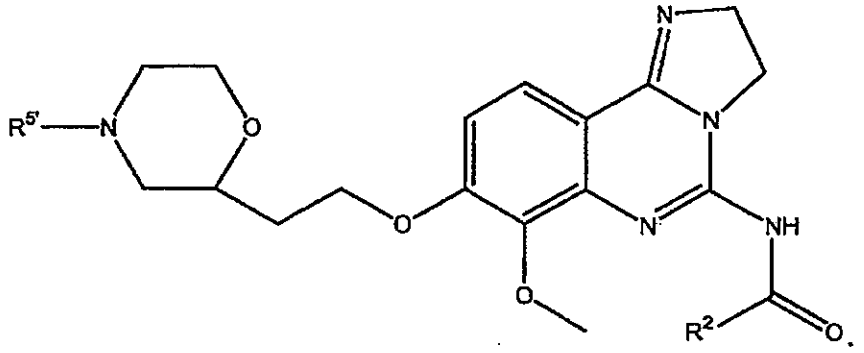


20. The compound of claim 19, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

21. The compound of claim 20, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

22. The compound of claim 19 wherein $R^{5'}$ is alkyl.

23. The compound of claim 1 having the formula:



24. The compound of claim 23, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole, thiazole, furan or thiophene, optionally substituted with 1, 2 or 3 R^6 groups.

25. The compound of claim 24, wherein R^2 is pyridine, pyridazine, pyrimidine, pyrazine, pyrole, oxazole or thiazole, optionally substituted with 1, 2 or 3 R^6 groups.

26. The compound of claim 23 wherein $R^{5'}$ is alkyl.

27. Compounds according to any one of the preceding claims, namely:
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide ;
N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2,4-dimethyl-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methyl-1,3-thiazole-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-propylpyrimidine-5-carboxamide;
N-{8-[2-(4-ethylmorpholin-2-yl)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide 1-oxide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2-pyrrolidin-1-ylethyl)nicotinamide;
6-(cyclopentylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[8-(2-hydroxy-3-morpholin-4-ylpropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{7-methoxy-8-[3-(3-methylmorpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(8-{3-[2-(hydroxymethyl)morpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(8-{2-[4-(cyclobutylmethyl)morpholin-2-yl]ethoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-(7-methoxy-8-{2-[4-(2-methoxyethyl)morpholin-2-yl]ethoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{8-[(4-ethylmorpholin-2-yl)methoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-(7-methoxy-8-{[4-(2-methoxyethyl)morpholin-2-yl]methoxy}-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-{7-methoxy-8-[(4-methylmorpholin-2-yl)methoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-4-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-4-carboxamide;
rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
rel-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-6-methylnicotinamide;
rel-6-acetamido-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1-methyl-1H-imidazole-5-carboxamide;
6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylnicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-4-methylpyrimidine-5-carboxamide;
6-amino-5-bromo-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-5-carboxamide;
N-[7-methoxy-8-(morpholin-2-ylmethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-{[2-(dimethylamino)ethyl]amino}-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-1,3-thiazole-5-carboxamide;
rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
2-[(2-hydroxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-methoxypropyl)amino]pyrimidine-5-carboxamide;
2-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-[(3-morpholin-4-ylpropyl)amino]pyrimidine-5-carboxamide;
2-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
2-{[2-(dimethylamino)ethyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
6-amino-N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-pyrrolidin-1-ylpyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(4-methylpiperazin-1-yl)pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-morpholin-4-ylpyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-piperazin-1-ylnicotinamide hydrochloride;
6-[(3S)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride hydrate;
6-[(3R)-3-aminopyrrolidin-1-yl]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide hydrochloride;
6-[(4-fluorobenzyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-[(2-furylmethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-[(2-methoxyethyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(1H-pyrrol-1-yl)nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-morpholin-4-ylnicotinamide;
N-{7-methoxy-8-[3-(methylamino)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
6-[(2,2-dimethylpropanoyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-[(cyclopropylcarbonyl)amino]-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-(trifluoromethyl)nicotinamide;

6-(isobutyrylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{7-methoxy-8-[3-(4-methylpiperazin-1-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-{[(methylamino)carbonyl]amino}-1,3-thiazole-4-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-{[(methylamino)carbonyl]amino}nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)-1,3-thiazole-4-carboxamide;

N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;

N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-6-methylnicotinamide;

6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-pyrrolidin-1-ylnicotinamide;

6-(dimethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(3-piperidin-1-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

N-[7-methoxy-8-(2-piperidin-1-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;

6-{[(ethylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-fluoro-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-oxazole-4-carboxamide;
2-(ethylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-4-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrazine-2-carboxamide;
N-[8-(2-aminoethoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
6-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]isonicotinamide;
N-{8-[3-(diethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(diisopropylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(diethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylamino)pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-(methylthio)pyrimidine-5-carboxamide;
N-[8-(3-aminopropoxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide trifluoroacetate;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-2-carboxamide;

N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
2-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-3-furamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]thiophene-3-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methyl-1,3-thiazole-4-carboxamide;
6-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
6-(acetylamino)-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

28. Compounds according to any one of the claims 1–26, namely:
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-6-methylnicotinamide;
5-methoxy-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;
N-{8-[3-(dimethylamino)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}nicotinamide;

6-{[(isopropylamino)carbonyl]amino}-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}-2,4-dimethyl-1,3-thiazole-5-carboxamide;
N-[7-methoxy-8-(2-morpholin-4-ylethoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]nicotinamide;
rel-6-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)nicotinamide;
rel-2-amino-N-(8-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide;
2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
N-{8-[2-(dimethylamino)ethoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide;
N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide;
or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

29. A pharmaceutical composition comprising a compound according to claim 1 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof and a pharmaceutically acceptable diluent or carrier.

30. The pharmaceutical composition of claim 29 wherein the compound is present in a therapeutically effective amount.

31. The pharmaceutical composition of claim 29 further comprising at least one further active compound.

32. The pharmaceutical composition of claim 29, wherein the further active compound is an anti-hyper-proliferative, anti-inflammatory, analgesic, immunoregulatory, diuretic, anti-arrhythmic, anti-hypercholesterolemic, anti-diabetic, anti-dyslipidemia, anti-diabetic or antiviral agent.

33. The pharmaceutical composition of claim 32, wherein the further active compound is gemcitabine, paclitaxel, cisplatin, carboplatin, sodium butyrate, 5-FU,

doxirubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α-glucosidase inhibitor, a biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin, secretin derivative, aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine , bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol,

sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582, lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof

34. A packaged pharmaceutical composition comprising a container, the pharmaceutical composition of claim 29 and instructions for using the pharmaceutical composition to treat a disease or condition in a mammal.

35. A method of inhibiting phosphotidylinositol-3-kinase in cells comprising contacting a cell with one or more compounds of claim 1.

36. A method of treating a disorder mediated by phosphotidylinositol-3-kinase inhibition in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of claim 1.

37. The method of claim 36, wherein the disorder mediated by phosphotidylinosito-3-kinase is an angiogenic disorder, an inflammatory disorder, an autoimmune disorder, a

cardiovascular disorder, a neurodegenerative disorder, a metabolic disorder, a nociceptive disorder, an ophthalmic disorder, a pulmonary disorder, or a renal disorder.

38. The method of claim 37, wherein the cardiovascular disorder is thrombosis, pulmonary hypertension, cardiac hypertophy, atherosclerosis or heart failure.

39. The method of claim 37, wherein the inflammatory disorder is COPD.

40. The method of claim 37, wherein the angiogenic disorder diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, macular degeneration, neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis, restenosis, in-stent restenosis, or vascular graft restenosis.

41. A method of treating a hyperproliferative disorder in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of claim 1.

42. The method of claim 41, wherein the hyperproliferative disorder is cancer.

43. The method of claim 42, wherein the cancer is a cancer of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid or a distant metastasis of a solid tumor.

44. The method of claim 42 wherein the cancer is a lymphoma, sarcoma, or leukemia.