

(51) International Patent Classification:
A61K 31/517 (2006.01)(21) International Application Number:
PCT/US2011/052816(22) International Filing Date:
22 September 2011 (22.09.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/385,471 22 September 2010 (22.09.2010) US(71) Applicant (for all designated States except US): **SURFACE LOGIX, INC.** [US/US]; 50 Soldiers Field Place, Brighton, MA 02135 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **KIM, Enoch** [US/US]; 50 Soldiers Field Place, Boston, MA (US). **COLE, Bridget** [US/US]; 50 Soldiers Field Place, Quincy, MA (US). **SWEETNAM, Paul** [US/US]; 50 Soldiers Field Place, Marblehead, MA (US). **WONG, Eric** [US/US]; 50 Soldiers Field Place, Quincy, MA (US).(74) Agent: **CASSON, Lawrence, P.**; Kenyon & Kenyon LLP, One Broadway, New York, NY 10004 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: METABOLIC INHIBITORS

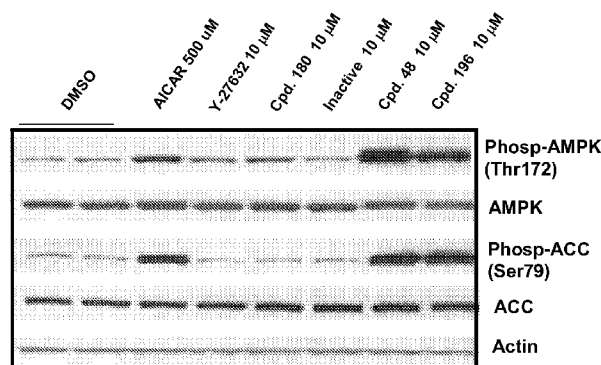


Fig. 1

(57) Abstract: The invention provides compounds useful for treating diseases, including neoplasias and metabolic disorders. Compounds of the invention modulate GLUT1 function and/or AMPK activity.

METABOLIC INHIBITORS

FIELD OF THE INVENTION

[0001] The invention provides compounds useful for treating diseases, including neoplasias and metabolic disorders. Compounds of the invention modulate AMPK activity.

SUMMARY OF THE INVENTION

[0002] The invention is based, at least in part, on the discovery of compounds that modulate AMPK activity. In one embodiment, the compounds of the invention are useful for treating neoplastic diseases. In another embodiment, the compounds are useful for modulating metabolic diseases. In certain embodiments, the compounds modulate AMPK activity by modulating other cellular components, including, but not limited to, GLUT1.

BACKGROUND OF THE INVENTION

[0003] AMPK is a master energy regulator, affecting fundamental mechanisms of cellular metabolism. AMPK is activated in response to increases in the cellular AMP/ATP ratio, for example in response to inhibition of ATP production or increased consumption. AMPK is activated by exercise and diet, and has been shown to mediate many of their benefits. It is a key component necessary for efficacy of metformin, thiazolidinediones, and resveratrol. AMPK has also been linked to growth and survival of cancer cells, and is thought to facilitate the activity of certain tumor suppressors.

[0004] GLUT1 is the primary glucose transporter found in muscle and adipose tissue. GLUT1 also provides a mechanism for increased metabolism necessary for sustained tumor growth.

DESCRIPTION OF THE DRAWING

[0005] Figure 1 shows activation of AMPK by compounds of the invention, compared to AICAR, a known activator of AMPK. AMPK activation is observed by detecting phosphorylation of threonine 172 using a specific antibody.

[0006] Figure 2 shows selectivity of an AMPK activator of the invention. Compound 48 demonstrated activity with respect to AMPK and three other targets ROCK2, CK2, and GLUT1.

[0007] Figure 3 shows that activation of AMPK by Compound 48 is specific for phosphorylation of Thr172 and dose dependent.

[0008] Figure 4 shows that the ACC phosphorylation induced by Compound 48, which depends on AMPK activation, is also dose dependent.

[0009] Figure 5 shows dose dependent AMPK activation by Compound 48 in skeletal muscle cells.

[0010] Figure 6 shows dose dependent AMPK activation by Compound 48 in adipocytes

[0011] Figure 7 show that AMPK activation by Compound 48 in HT-1080 cells is rapid and reversible.

[0012] Figure 8 show that AMPK activation and ACC phosphorylation by Compound 48 in HT-1080 cells is rapid and reversible..

[0013] Figure 9 shows that tumor cells treated with Compound 48 demonstrated a significant increase in the [AMP]/[ATP] ratio, along with increased levels of AMP.

[0014] Figure 10 shows AMPK activation in a fibrosarcoma tumor line HT-1080 when treated with inhibitors of glucose uptake (Compound 48, AICAR), or a control (DMSO).

[0015] Figure 11 shows that in the presence of an AMPK phosphorylation inhibitor (an inhibitor of CAM kinase), inhibition of glucose transport increases phosphorylation of AMPK and ACC.

[0016] Figure 12 shows an increase in fatty acid oxidation in mice fed a high fat diet and supplemented with an activator of AMPK activity.

[0017] Figure 13 shows improvements in serum insulin, blood glucose, serum cholesterol, visceral fat, liver weight, and serum ALT resulting from administration of Compound 48 in a mouse model of diabetes.

[0018] Figure 14 shows improved levels of urinary protein excretion in a mouse model maintained on a high fat diet supplemented with Compound 48.

DETAILED DESCRIPTION OF THE INVENTION

[0019] AMP kinase (AMPK) plays an important role in energy homeostasis. For example, AMPK phosphorylation is observed in physiological conditions of increased ATP consumption and/or where AMP concentrations are high. The AMPK pathway involves several components, which for example, act to phosphorylate AMPK, or downstream from AMPK. One such component is ACC, which is specifically phosphorylated in connection with AMPK activation. The invention provides new compounds and methods for control of AMPK activation, either directly, or indirectly.

[0020] AMPK has also been implicated in growth and survival of cancer cells. For example, AMPK is phosphorylated and activated by the tumor suppressor LKB1, and functions in the phosphorylation and activation of tuberous sclerosis complex 2, another tumor suppressor. The AMPK pathway is a target for treatment of metabolic disease, including, but not limited to insulin resistance and diabetes. Diabetes is characterized by abnormal glucose and lipid metabolism. Diabetes is generally classified into two categories. In insulin-dependent diabetes mellitus (“IDDM” or “type 1”), β -cells of the pancreas produce little or no insulin. Non-insulin-dependent diabetes mellitus (“NIDDM” or “type 2”), which is much more prevalent, is caused by a defect in insulin secretion and insulin resistance in cells that normally respond to diabetes. For example, type 2 diabetes is characterized by resistance to insulin action in skeletal muscle, liver, and fat. Insulin resistance occurs when insulin is unable to stimulate normal metabolic responses in those targets. AMPK activation improves glucose and lipid levels in the blood. The effects of AMPK activation, for example using compounds of the invention, can be demonstrated in tissue culture, normal and insulin-resistant rodent models of diabetes, and in humans.

[0021] According to the invention, in certain embodiments, the compounds disclosed herein are used to treat or prevent neoplastic diseases. The neoplasm may be cancer. Examples of neoplasms and cancers to be treated or prevented include, without limitation, colon cancer, pancreatic cancer, lung cancer, breast cancer, cervical cancer, gastric cancer, kidney cancer, leukemia, liver cancer, lymphoma, ovarian cancer, prostate cancer, rectal cancer, sarcoma, skin cancer, testicular cancer, and uterine cancer. In other embodiments, the compounds disclosed herein are used to treat or prevent metabolic diseases and associated conditions. These include, but are not limited to, diabetes, insulin resistance, metabolic syndrome, atherosclerosis,

hypertension, and Alzheimer's. The compounds can be administered alone or in combination with other drugs normally used to treat such conditions. For example, a compound of Formula I is used in combination with metformin to treat type 2 diabetes. The compounds can be observed to improve one or more of the following: β -cell mass, function, β -cell function, insulin sensitivity, muscle glucose uptake and utilization, and glycemic control. The compounds can be used to improve lipid profile, decrease body weight, decrease percentage body fat, reduce blood pressure, cardiovascular disease (CVD). Further, the compounds reduce diabetes risk and CVD risk.

[0022] The AMPK pathway is well conserved, and is a target of major antidiabetic drugs, such as metformin and thiazolidinediones (TZDs). Metformin is a biguanide drug and is thought to reduce gluconeogenesis in the liver. TZDs are compounds that activate peroxisome proliferator-activated receptors (PPARs), which are involved in control of metabolism of carbohydrate, lipid, and protein. Sulfonylureas are another class of drugs for diabetes management which act by increasing insulin release from the β -cells of the pancreas. Also, α -glucosidase inhibitors are oral drugs that prevent digestion of carbohydrates into simple sugars, and thus reduce the impact of carbohydrates on blood sugar. Accordingly, the invention provides methods of treatment of metabolic disease using compounds of the invention in combination with the aforementioned antidiabetic drugs.

[0023] Certain compounds of the invention are also inhibitors of Rho-kinase, which is found in two forms, ROCK 1 (ROCK β ; p160- ROCK) and ROCK 2 (ROCK α) inhibitors. Rho kinase (ROCK), a serine/threonine kinase, serves as a target protein for small GTP-binding protein Rho. It serves as an important mediator of numerous cellular functions, including focal adhesions, motility, smooth muscle contraction, and cytokinesis. In smooth muscle, ROCK plays an important role in Ca^{2+} sensitization and the control of vascular tone. It modulates the level of phosphorylation of the myosin II light chain of myosin II, mainly through inhibition of myosin phosphatase, and contributes to agonist-induced Ca^{2+} sensitization in smooth muscle contraction.

[0024] Preferred compounds are more efficient inhibitors of ROCK2 than of ROCK1. ROCK-mediated pathway plays an important role in vascular smooth muscle contraction, cell adhesion, cell motility, and pathogenesis of atherosclerosis. ROCK also suppress coronary

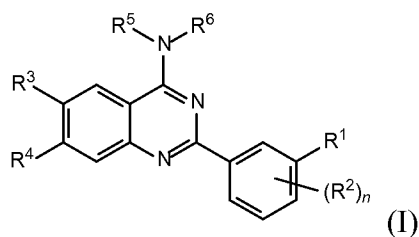
artery spasms. Long-term inhibition of ROCK is reported to block the development of coronary arteriosclerotic lesions. ROCK mediated pathways mediate numerous different cellular functions and ROCK inhibitors can be useful in treatments of patients in need thereof suffering from cardiovascular diseases such as hypertension, atherosclerosis, restenosis, cardiac hypertrophy, ocular hypertension, cerebral ischemia, cerebral vasospasm, penile erectile dysfunction, central nervous system disorders such as neuronal degeneration and spinal cord injury, and in neoplasias where inhibition of Rho-kinase has been shown to inhibit tumor cell growth and metastasis, angiogenesis, arterial thrombotic disorders such as platelet aggregation and leukocyte aggregation, asthma, regulation of intraocular pressure, and bone resorption. Such treatment often relies on administering a therapeutic agent to a patient, wherein the therapeutic agent has a high specificity for a particular pathway or enzyme which is in need of regulation in the patient, by the therapeutic agent such as an enzyme inhibitor. Accordingly, the invention provides compounds that inhibit a Rho kinase (ROCK). Preferably the compound is an inhibitor of ROCK2.

[0025] Certain compounds of the invention are inhibitors of GLUT1. GLUT1 is one of several transporters that facilitate transport of glucose and/or other molecules, and is the primary glucose transporter found in muscle and adipose tissue. Glucose transporters facilitate glucose uptake by tumors, in which they are frequently overexpressed. In particular, increased GLUT1 expression has also been found to provide a mechanism for increased metabolism necessary for sustained tumor growth. Accordingly, compounds of the invention that inhibit GLUT1 activity are used to treat cancer. Further, GLUT1 expression is often observed in advanced tumors, which may be anoxic. Anoxia and GLUT1 expression is associated with resistance to radiation and/or chemotherapy. Accordingly, compounds of the invention are used to treat anoxic tumors.

[0026] It has been found that in cancer lines that express GLUT1, incubation with GLUT1 inhibitors of the invention inhibits proliferation by as much as 50% or more. GLUT1 inhibitors of the invention are compounds of Formulas I-V. The GLUT1 inhibitors also increase the anti-proliferative effects of non-targeted and targeted chemotherapeutic agents, including, but not limited to, paclitaxel, cisplatin, and gefitinib. The compounds of the invention also restore chemosensitivity and radiation sensitivity to GLUT1-expressing tumors. Accordingly, compounds of the invention are used to treat neoplastic disease, particularly cancer, in combination with antineoplastic agents such as chemotherapeutics and/or radiation therapy.

[0027] In certain embodiments, compounds of the invention are used to reduce or block weight loss associated with disease. For example, weight loss is a complaint of half of cancer patients and indicates a poor prognosis. Excessive glucose uptake and lactate production by tumor cells exacerbates weight loss. Not only is anaerobic glycolysis without respiration an inefficient route to ATP production, the lactate produced by glycolysis induces the Cori cycle in liver and other tissues. The Cori cycle is a metabolic pathway in which lactate produced by anaerobic glycolysis in muscles moves to the liver and is converted to glucose, which then returns to the muscles and is converted back to lactate. Similarly, the Cori cycle converts lactate produced by anaerobic glycolysis in tumors back to glucose. For every 2 ATP produced by glycolysis, 6 ATP molecules are consumed by gluconeogenesis.

[0028] Compounds useful according to the present invention include those having the formula I:



wherein:

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$, $-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$, $-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl, $-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, aryl, $-(C_1-C_6 \text{ alkyl})-O-(\text{aryl})$, aralkyl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹³ and R¹⁴ are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, -SO₂-alkyl, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R¹³ and R¹⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, -SO₂-alkyl, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R^{18} is selected from the group consisting of aryl, aralkyl, heteroaryl, C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

each R^2 is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

n is selected from 0 to 4;

R^3 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, $-(CH_2)_a-NR^{33}R^{34}$, $-Y-R^{32}$, $-O-(CH_2)_a-CO_2R^{32}$, $-O-(CH_2)_a-C(=O)NR^{33}R^{34}$, $-O-(CH_2)_a$ -heteroaryl, $-O-(CH_2)_a$ -cycloalkyl, $-O-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-O-(CH_2)_e-NR^{33}R^{34}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-NH-C(=O)-Y-R^{35}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$;

R^{32} is selected from the group consisting of C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{33} and R^{34} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{33} and R^{34} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

Y is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R³⁵ is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR³⁶R³⁷, -CO₂R³⁸, -O-(CH₂)_b-CO₂R³⁸, and -C(=O)NR³⁶R³⁷,

R³⁶ and R³⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R³⁶ and R³⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R³⁸ is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR³⁶R³⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

R⁴ is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, -(CH₂)_a-NR⁴³R⁴⁴, -Z-R⁴², -O-(CH₂)_a-CO₂R⁴², -O-(CH₂)_a-C(=O)NR⁴³R⁴⁴, -O-(CH₂)_a-heteroaryl, -O-(CH₂)_a-cycloalkyl, -O-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -O-(CH₂)_c-NR⁴³R⁴⁴, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -NH-C(=O)-Z-R⁴⁵, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴;

R⁴² is selected from the group consisting of C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{43} and R^{44} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{43} and R^{44} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

Z is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R^{45} is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -CO₂R⁴⁸, -O-(CH₂)_b-CO₂R⁴⁸, and -C(=O)NR⁴⁶R⁴⁷;

R^{46} and R^{47} independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R^{46} and R^{47} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R^{48} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

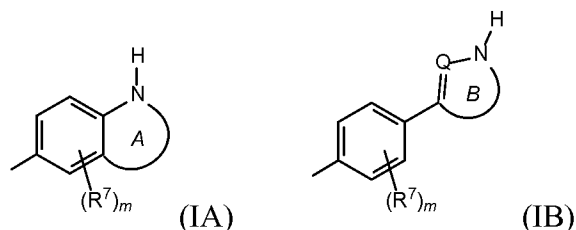
each *a* is independently selected from 0 to 6;

each *b* is independently selected from 0 to 6;

each c is independently selected from 2 to 6;

R^5 is selected from the group consisting of H and C_1 - C_6 alkyl;

R^6 is selected from the group of formula (IA) and (IB):



wherein

Ring A is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

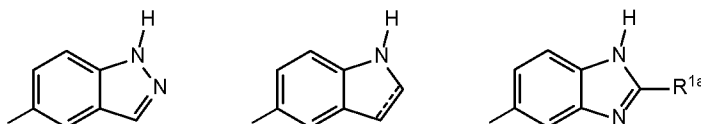
Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

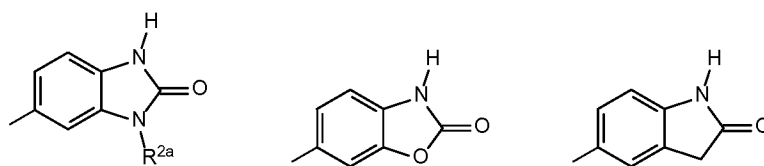
R^7 is selected from the group consisting of halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

m is 0 to 2.

[0029] In preferred embodiments of the invention in which GLUT1 activity is sought, R^1 does not contain a charged group. In these embodiments, R^1 preferably does not contain an amine, a carboxyl, or other readily ionizable group.

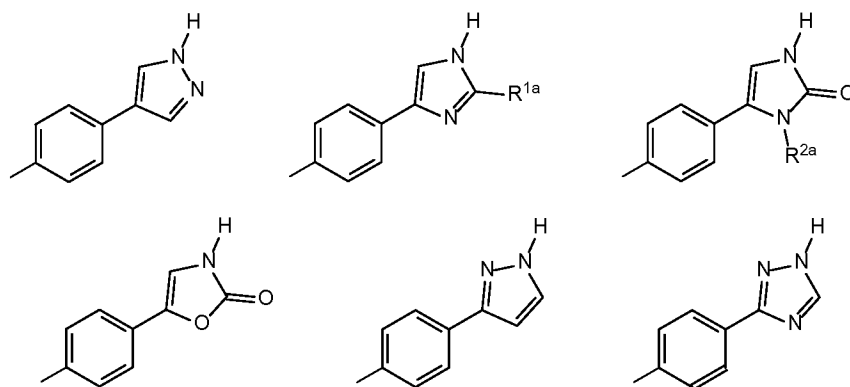
[0030] In certain embodiments of the invention, the group of formula IA is selected from:





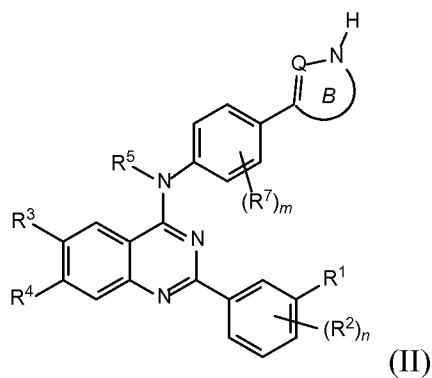
wherein the dotted line represents an optional double bond; R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

[0031] In certain embodiments of the invention, the group of formula IB is selected from:



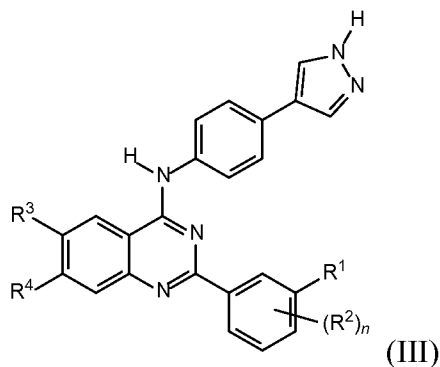
wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

[0032] In a certain embodiments of the present invention, there is provided a compound of the formula II:



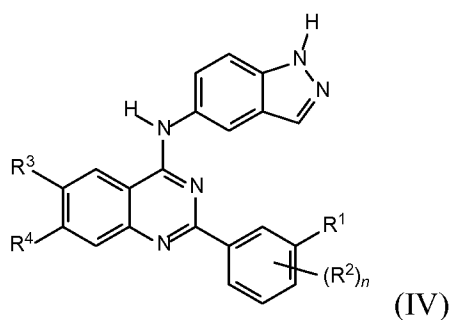
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , *Ring B*, n and m are as stated above for formula I.

[0033] In a certain embodiments of the present invention, there is provided a compound of the formula III:



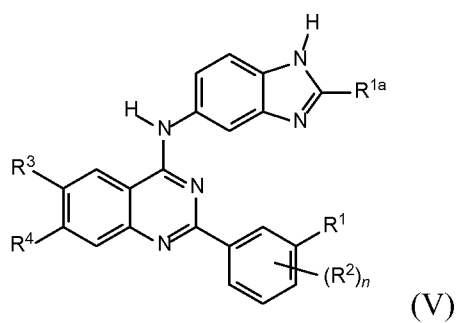
wherein R^1 , R^2 , R^3 , R^4 , n and m are as stated above for formula I.

[0034] In a certain embodiments of the present invention, there is provided a compound of the formula IV:



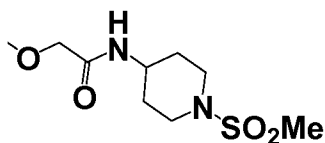
wherein R^1 , R^2 , R^3 , R^4 , n and m are as stated above for formula I.

[0035] In a certain embodiments of the present invention, there is provided a compound of the formula V:

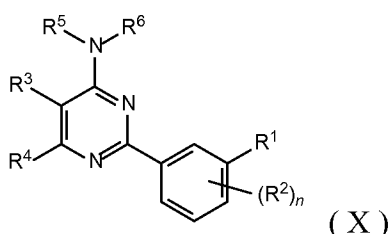


wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^1 , R^2 , R^3 , R^4 , n and m are as stated above for formula I.

[0036] In certain embodiments, substituent at R^1 may preferably have the structure:



[0037] Compounds useful according to the present invention include those having the formula X:



wherein:

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$,

$-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$,

$-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$,

$-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$,

$-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl,

$-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$,

$-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$,

$-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, aryl, $-(C_1-C_6 \text{ alkyl})-O-(\text{aryl})$, aralkyl, C_3 - C_7 cycloalkyl, a three to

twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents

independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8

alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$,

aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to

3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;
 or R¹³ and R¹⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, -SO₂-alkyl, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

each R^2 is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

n is selected from 0 to 4;

R^3 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, $-(CH_2)_a-NR^{33}R^{34}$, $-Y-R^{32}$, $-O-(CH_2)_a-CO_2R^{32}$, $-O-(CH_2)_a-C(=O)NR^{33}R^{34}$, $-O-(CH_2)_a$ -heteroaryl, $-O-(CH_2)_a$ -cycloalkyl, $-O-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-O-(CH_2)_c-NR^{33}R^{34}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-NH-C(=O)-Y-R^{35}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$;

R^{32} is selected from the group consisting of C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{33} and R^{34} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{33} and R^{34} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

Y is selected from a covalent bond, O, NH, and C_1 - C_6 alkyl;

R^{35} is selected from the group consisting of H, aryl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-CO_2R^{38}$, $-O-(CH_2)_b-CO_2R^{38}$, and $-C(=O)NR^{36}R^{37}$;

R^{36} and R^{37} independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3

heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R³⁶ and R³⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R³⁸ is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR³⁶R³⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

R⁴ is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, -(CH₂)_a-NR⁴³R⁴⁴, -Z-R⁴², -O-(CH₂)_a-CO₂R⁴², -O-(CH₂)_a-C(=O)NR⁴³R⁴⁴, -O-(CH₂)_a-heteroaryl, -O-(CH₂)_a-cycloalkyl, -O-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -O-(CH₂)_c-NR⁴³R⁴⁴, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -NH-C(=O)-Z-R⁴⁵, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴;

R⁴² is selected from the group consisting of C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R⁴³ and R⁴⁴ are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R⁴³ and R⁴⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

alternatively, R³ and R⁴ may be taken together to form a 5- or 6-membered ring;

Z is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R⁴⁵ is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -CO₂R⁴⁸, -O-(CH₂)_b-CO₂R⁴⁸, and -C(=O)NR⁴⁶R⁴⁷;

R⁴⁶ and R⁴⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R⁴⁶ and R⁴⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R⁴⁸ is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

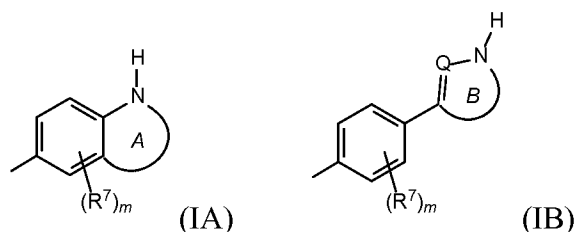
each *a* is independently selected from 0 to 6;

each *b* is independently selected from 0 to 6;

each *c* is independently selected from 2 to 6;

R⁵ is selected from the group consisting of H and C₁-C₆ alkyl;

R⁶ is selected from the group of formula (IA) and (IB):



wherein

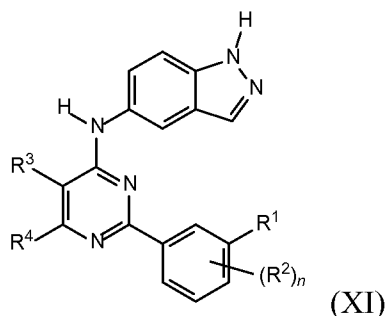
Ring A is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

R^7 is selected from the group consisting of halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

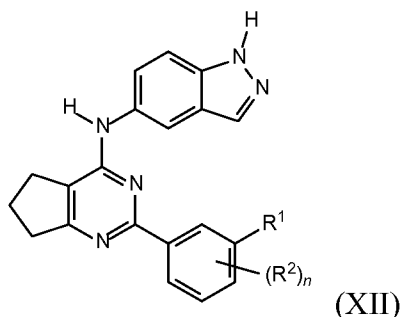
m is 0 to 2.

[0038] In a certain embodiments of the present invention, there is provided a compound of the formula XI:



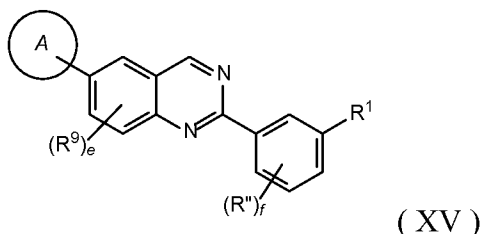
wherein R^1 , R^2 , R^3 , R^4 , and n are as stated above for formula X.

[0039] In a certain embodiments of the present invention, there is provided a compound of the formula XII:



wherein R^1 , R^2 , and n are as stated above for formula X.

[0040] Compounds useful according to the present invention include those having the formula XV:



wherein

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$,

$-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$,

$-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$,

$-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$,

$-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl,

$-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$,

$-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$,

$-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, aryl, $-(C_1-C_6 \text{ alkyl})-O$ -(aryl), aralkyl, C_3 - C_7 cycloalkyl, a three to

twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may

be optionally substituted at one or more carbon atoms by from 1 to 3 substituents

independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3

perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8

alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$,

aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring

containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to

3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7

cycloalkyl, C_1 - C_6 alkoxy, $-SO_2$ -alkyl, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

or R^{13} and R^{14} may be taken together form a three to twelve membered heterocyclic ring

having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₂-C₆, alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

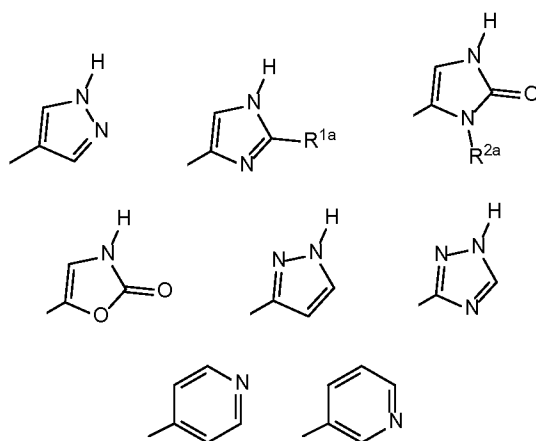
z is selected from 2 to 6;

each R⁹ is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

e is selected from 0 to 3;

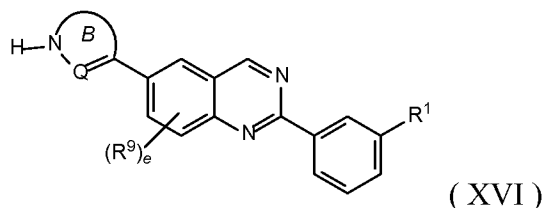
Ring A is a 5- or 6-membered ring which may comprise 0-3 ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;
 R" is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl; and
f is selected from 0 to 2.

[0041] In certain embodiments of the invention, the *Ring A* of compound XV is a 5- or 6-membered aromatic ring which comprises 1-3 ring heteroatoms selected from N, O and S. In certain embodiments *Ring A* of compound XV may have the formula selected from:



wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

[0042] Compounds useful according to the present invention include those having the formula XVI:



wherein

R¹ is selected from the group consisting of aryl, -(CH₂)_y-NR¹³R¹⁴, -X-R¹²,
 -(CH₂)_y-C(=O)NR¹³R¹⁴, -O-(CH₂)_y-CO₂R¹², -O-(CH₂)_y-C(=O)NR¹³R¹⁴,

-O-(CH₂)_y-cycloalkyl, -(CH₂)_y-O-C(=O)-NR¹³R¹⁴, -NH-C(=O)-(CH₂)_y-NR¹³R¹⁴,
 -NH-C(=O)-X-R¹⁵, -(CH₂)_y-S(=O)₂NR¹³R¹⁴, -O-(CH₂)_y-S(=O)₂NR¹³R¹⁴,
 -NH-S(=O)₂-X-R¹⁵, -NH-(CH₂)_y-NR¹³R¹⁴, -O-(CH₂)_y-heteroaryl,
 -O-C(=O)-(CH₂)_y-NR¹³R¹⁴, and -O-(CH₂)_z-NR¹³R¹⁴;

R¹² is selected from the group consisting of C₁-C₁₀ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl),
 -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl),
 -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, aryl, -(C₁-C₆ alkyl)-O-(aryl), aralkyl, C₃-C₇ cycloalkyl, a three to
 twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may
 be optionally substituted at one or more carbon atoms by from 1 to 3 substituents
 independently selected from halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃
 perfluoro alkyl;

R¹³ and R¹⁴ are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈
 alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷,
 aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring
 containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to
 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇
 cycloalkyl, C₁-C₆ alkoxy, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹³ and R¹⁴ may be taken together form a three to twelve membered heterocyclic ring
 having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents
 independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇
 cycloalkyl, -SO₂-alkyl, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl,
 -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl),
 -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷,
 -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up
 to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents
 independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy,
 cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈
 alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇

cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

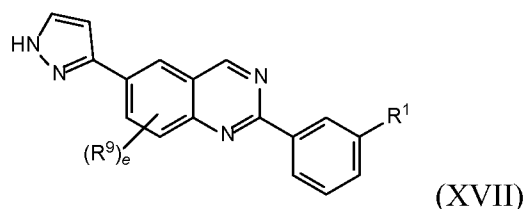
each R⁹ is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

e is selected from 0 to 3;

Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

Q is selected from CH or N.

[0043] Compounds useful according to the present invention include those having the formula XVII:



wherein R^1 , R^9 and e are as stated above for formula XV.

[0044] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium. Most preferred are nitrogen or oxygen.

[0045] The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1 - C_{30} for straight chain, C_3 - C_{30} for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

[0046] Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to six carbons, and more preferably from one to four carbon atoms. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

[0047] The term "cycloalkyl" refers to saturated, carbocyclic groups having from 3 to 7 carbons in the ring. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0048] The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[0049] The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[0050] The term "aryl" as used herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may

also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxy, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF₃, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, aryls and/or heterocyclic groups.

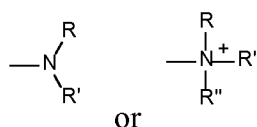
[0051] The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 5- or 6-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclic groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, or the like.

[0052] The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycyclic group can be substituted with such substituents as described above, for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate,

phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, or the like.

[0053] As used herein, the term "nitro" means -NO₂; the term "halogen" or "halo" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means -SO₂-.

[0054] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



wherein R, R' and R" each independently represent a group permitted by the rules of valence, preferably H, alkyl, alkenyl, alkynyl, aralkyl, aryl, and heterocyclic groups.

[0055] The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. The term lower alkoxy refers to an alkoxy group having from 1 to 6 carbon atoms.

[0056] The term "oxo" as used herein refers to an oxygen atom that has a double bond to a carbon.

[0057] The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

[0058] As used herein, the definition of each expression, e.g. alkyl, m, n, R, R', R², R⁷, R⁹, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0059] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0060] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

[0061] The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

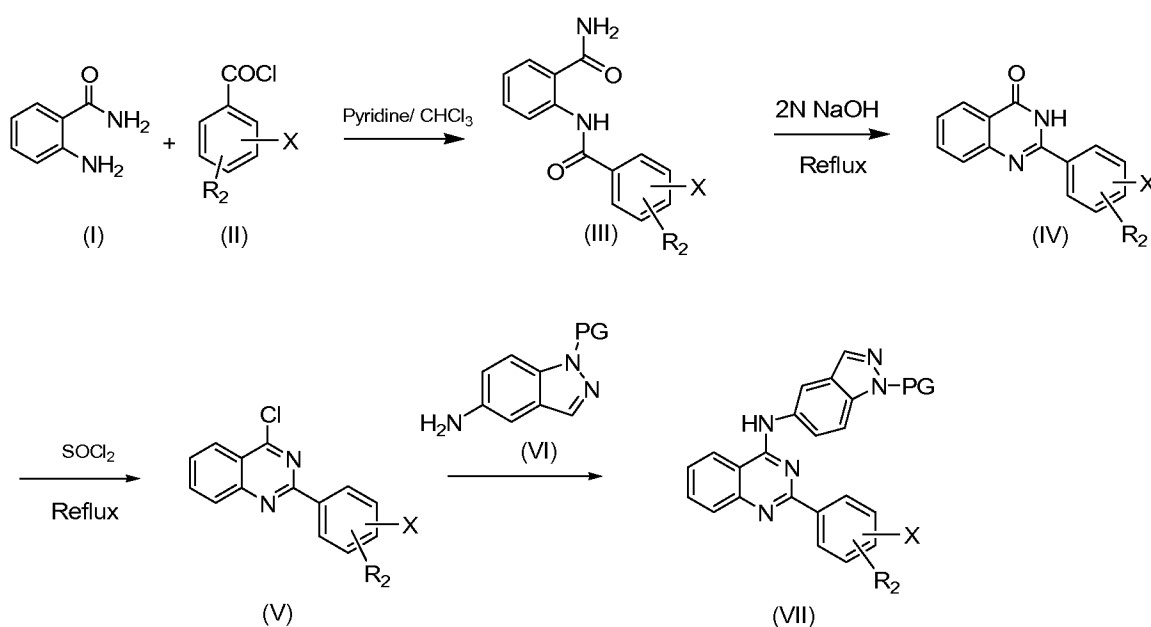
[0062] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[0063] In addition, if, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved, or otherwise removed, to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group,

such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0064] 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, inside cover.

[0065] The compounds of the invention may be prepared according to the following synthetic schemes:



Scheme A

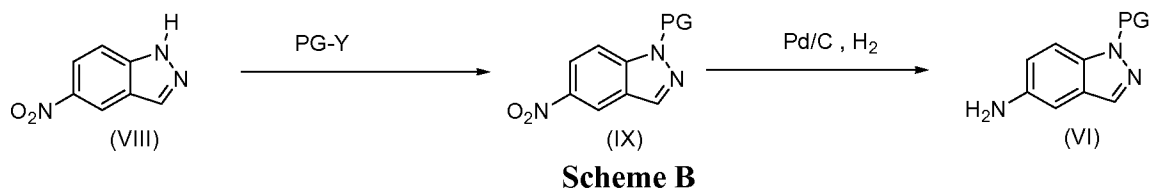
[0066] The general intermediate of formula (VII) may be prepared as illustrated in Scheme A. As illustrated in Scheme A, anthralamide (2-aminobenzamide (I)) is coupled with an appropriately substituted acid chloride of formula (II) in the presence of a base such as pyridine to give the benzamide (III). The reaction is run in an aprotic solvent such as chloroform (CHCl₃) at a temperature of -20 to 50°C, preferably at room temperature for 1-24 hours, preferably for 6 hours. Alternatively the benzamide (III) may be formed by treatment of the anthralamide (2-aminobenzamide (I)) with the benzoic acid in the presence of a coupling agent. Suitable coupling agents include N-cyclohexyl-N'-(4-diethylaminocyclohexyl)-carbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and bromotripyrrolidino phosphonium

hexafluorophosphate (PyBroP[®]), benzotriazole-1-yl-oxy-tris-pyrrolidino phosphonium hexafluorophosphate (PyBOP[®]) with suitable additives if necessary which include 1-hydroxybenzotriazole (HOBt) and 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine.

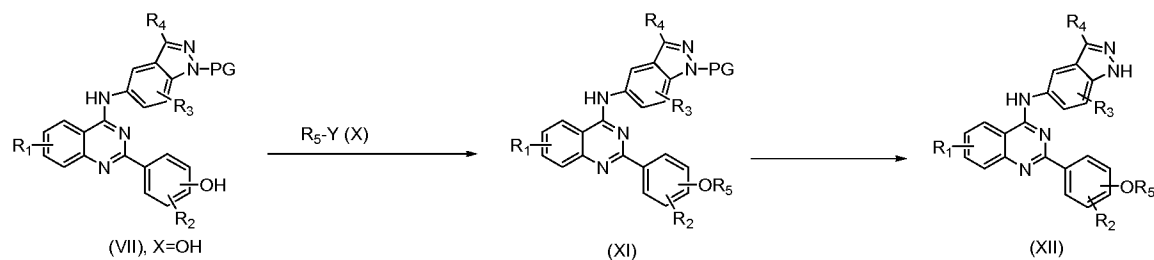
[0067] Cyclodehydration of compound (III) is carried out under refluxing basic aqueous conditions using sodium hydroxide (NaOH) as base, though other bases such as potassium hydroxide (KOH) may also be used. The reaction of compound (III) is carried out at the reflux temperature of the mixture for about 1-24 hours, preferably about 4 hours. When X=OMe (compound VII) it may be necessary to exchange phenol protecting groups. This can be achieved *via* methods known to those skilled in the art.

[0068] The compound (IV) is aromatized to the chloroquinazoline (V) by treatment with thionyl chloride (SOCl₂) with catalytic dimethylformamide (DMF). The reaction mixture is heated to reflux for 1-6 hours preferably 4 hours. Alternatively phosphorous oxy trichloride (POCl₃) or oxalyl chloride can be used instead of SOCl₂ to effect this transformation.

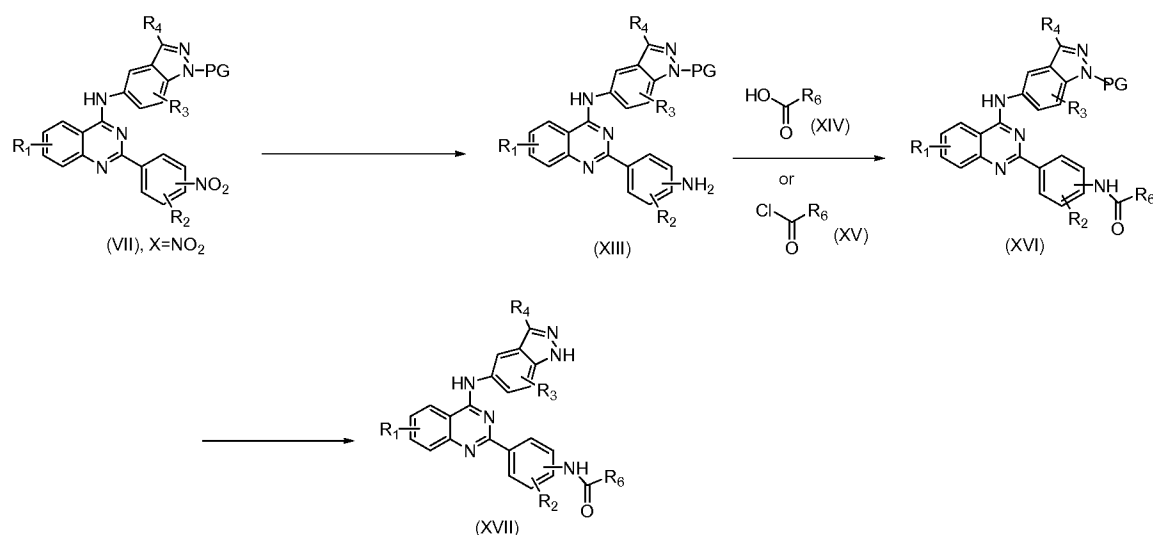
[0069] The chloroquinazoline is reacted with an appropriately protected 5-amino indazole (VI) to give the amino quinazoline (VII). The reaction is carried out in *iso*-propanol at 95°C for a reaction time of 30 minutes to 2 hours.



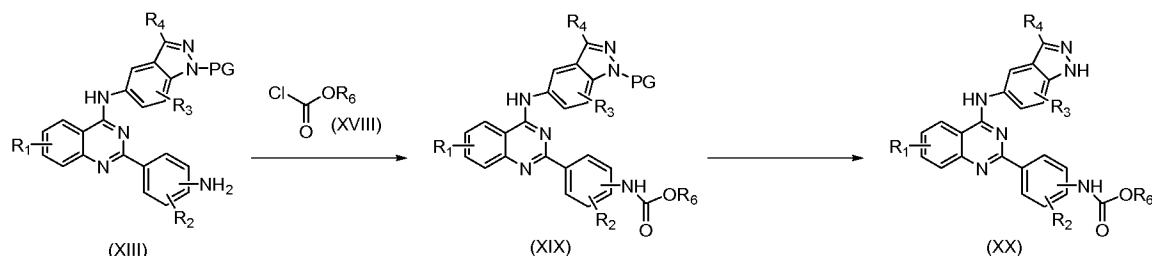
[0070] The protected indazole (VI) can be prepared as depicted in Scheme B. 5-Nitro-indazole is appropriately protected *via* methods known to those skilled in the art, preferably with a *tert*-butoxy carbonyl group. The nitro group is reduced to the amino group *via* hydrogenation using a metal catalyst such as Pd/C in an inert solvent such as methanol (MeOH), 1,2 dimethoxyethane (DME), ethanol (EtOH) or acetic acid (AcOH) or a combination of solvents preferably in a combination of MeOH and DME. The reaction can be carried out under balloon pressure or under a pressure of 20-50 pounds per square inch (p.s.i.).

X=OH**Scheme C**

[0071] Compounds of formula (XII) can be synthesized as depicted in scheme C. Compound (VII) can undergo selective deprotection of the O-protecting group functionality to give compound (VII) where X=OH. This can be done by a variety of methods, which are well known to those skilled in the art. The phenol (VII) is then alkylated with an electrophile of formula (X) in the presence of a base such as potassium carbonate (K_2CO_3), potassium *tert*-butoxide (KO^tBu), sodium hydride (NaH), sodium hexamethylsilazide (NaHMDS) or potassium hexamethylsilazide (KHMDS) preferably K_2CO_3 to give the ether (XI). The reaction is run in an inert solvent such as DMF at a temperature of 20-100 °C, preferably at 30-40°C. The electrophile (X) can be either a chloride ($Y=Cl$), bromide, ($Y=Br$), iodide ($Y=I$) or other suitable leaving group though it is preferred to use a bromide. Additives such as sodium iodide (NaI) or potassium iodide (KI) may be optionally added to the reaction.

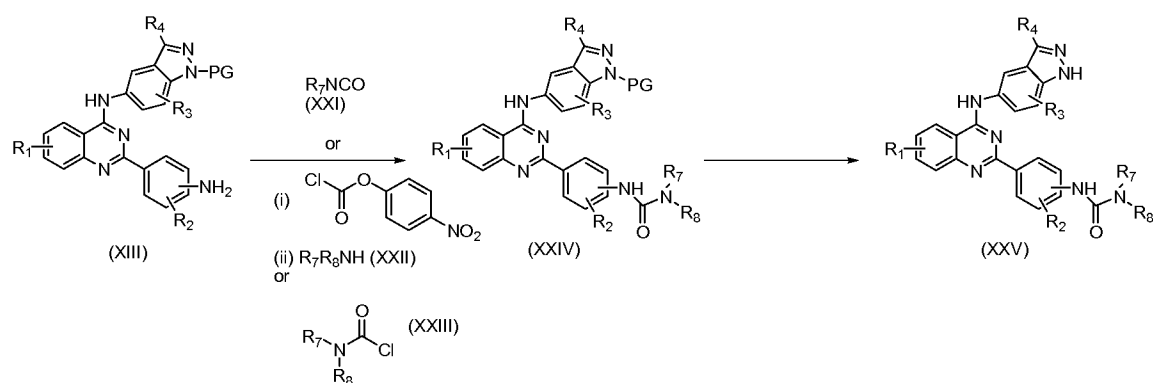
**Scheme D**

[0072] Compounds of formula (XVII) may be synthesized as depicted in Scheme D. A compound of formula (VII) where $X=NO_2$, may be reduced to the anilino compound (XIII) *via* catalytic hydrogenation in an inert solvent or mixture of solvents such as EtOH, MeOH, THF or DME preferably a mixture of MeOH and DME. The transformation is effected by use of a metal catalyst such as palladium on carbon (Pd/C). The compound of formula (XIII) can be treated with, preferably at room temperature, with a carboxylic acid of formula (XIV) in the presence of a coupling agent (e.g., PyBOP, PyBrOP, dicyclohexylcarbodiimide (DCC), 1-(3'-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), or 1-propanephosphonic acid cyclic anhydride (PPAA)) and a suitable base (e.g., triethylamine, DMAP, or N-methylmorpholine (NMO)) in a solvent such as dichloromethane, chloroform, or dimethylformamide. Optionally, agents such as HOBt may be added to the reaction. Alternatively the compound of formula (XVI) may be synthesized via treatment with an acid chloride of formula (XV) in the presence a tertiary amine base such as triethylamine or DMAP to give an amide of formula (XVI). The acid chlorides of formula (XV) are commercially available or can be prepared from carboxylic acids by procedures known to those skilled in the art. If necessary the indazole protecting group can be removed at this point to reveal the final compounds (XVII) *via* methods known to those skilled in the art.



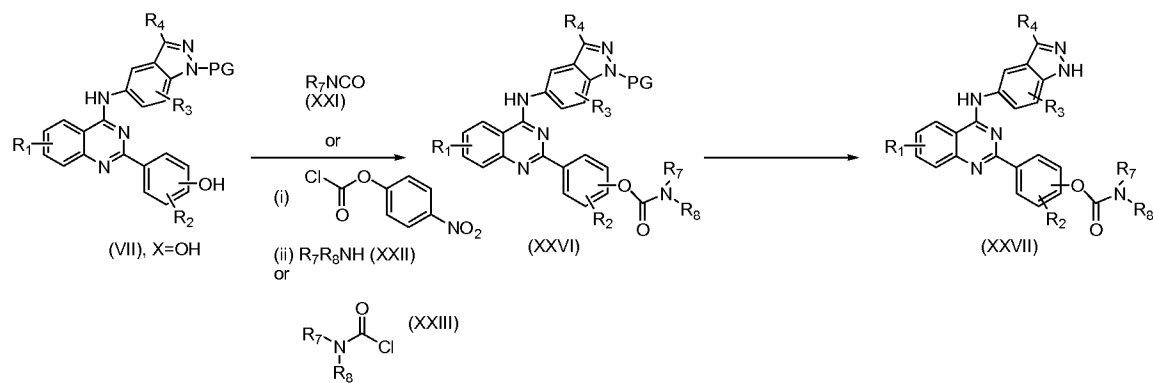
Scheme E

[0073] Compounds of formula (XX) can be prepared by reacting the amines of formula (XIII) with a chloroformate of formula (XVI) in the presence of a base such as triethylamine, DMAP, NMO, or sodium hydrogen carbonate in a suitable solvent such as dichloromethane, chloroform, aqueous or anhydrous tetrahydrofuran, or dimethylformamide or in a combination of such solvents. The reaction can be run at 0 to 60°C, though room temperature is preferred. If required the indazole protecting group may be removed to give compound of formula (XX) by methods known to those skilled in the art.



Scheme F

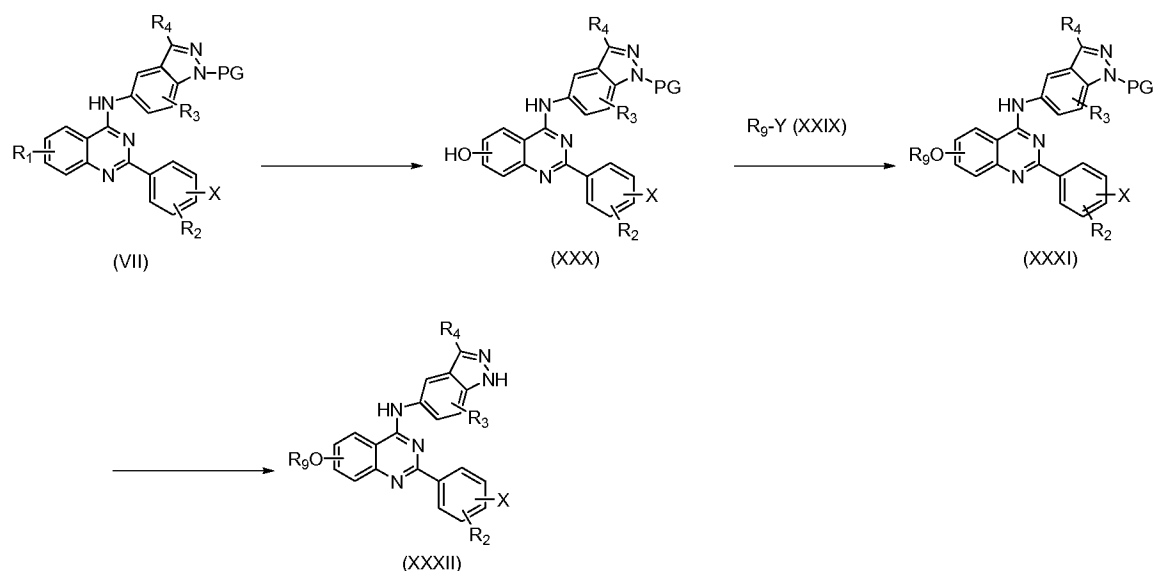
[0074] Ureas of formula (XXV) may be synthesized as depicted in Scheme F. Treatment of an aniline of formula (XIII) with an isocyanate of formula (XXI) in an inert solvent such as CH_2Cl_2 in the presence of an amine base such as Et_3N , DIEA or NMO to give the urea of formula (XXIV) where R_8 is a hydrogen. Alternatively, anilines of formula (XIII) may be treated with 4-nitrophenyl carbonochloridate followed by the sequential addition of an amine of formula (XXII). The reaction is run in an inert solvent such as THF, DMF or CH_2Cl_2 in the presence of an amine base such as Et_3N , DIEA or NMO. Another option of the synthesis of the ureas of formula (XXIV) is to treat the anilines of formula (XIII) with a carbamoyl chloride of formula (XXIII) in the presence of a base such as Et_3N , DIEA or NMO. If appropriate protecting groups (e.g. indazole) may be removed by methods known to those skilled in the art.



Scheme G

[0075] Carbamates of formula (XXVII) may be synthesized as depicted in Scheme G. Treatment of a phenol of formula (VII) where $X=OH$ with an isocyanate of formula (XXII) in an inert solvent such as CH_2Cl_2 in the presence of an amine base such as Et_3N , DIEA or NMO.

Alternatively, phenols of formula (VII) where $X=OH$) may be treated with 4-nitrophenyl carbonochloridate followed by the sequential addition of an amine of formula (XXII). The reaction is run in an inert solvent such as THF, DMF or CH_2Cl_2 in the presence of an amine base such as Et_3N , DIEA or NMO. Another option of the synthesis of the carbamates of formula (XXVI) is to treat the phenols of formula (VII) where $X=OH$) with a carbamoyl chloride of formula (XXIII) in the presence of a base such as Et_3N , DIEA or NMO. If appropriate protecting groups (e.g. indazole) may be removed by methods known to those skilled in the art to give the final compounds (XXVII).



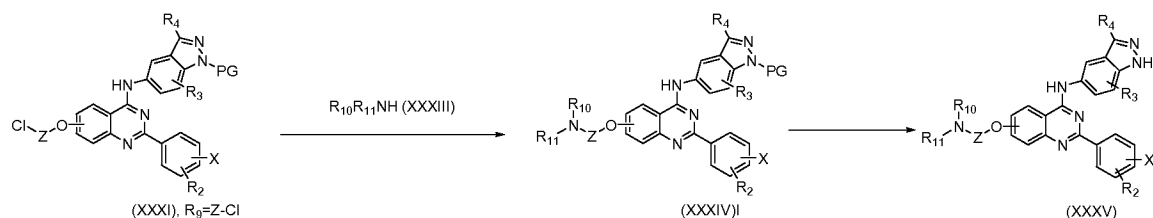
Scheme H

[0076] Compounds of general formula (XXXIII) can be synthesized as depicted in Scheme H. Compound (VII) can undergo selective deprotection of the O-protecting group (R_1) functionality to give compound (XXX). This can be done by a variety of methods, which are well known to those skilled in the art. The phenol (XXX) is then alkylated with an electrophile of formula (XXIX) in the presence of a base such as potassium carbonate (K_2CO_3), potassium *tert*-butoxide (KO^tBu), sodium hydride (NaH), sodium hexamethylsilazide ($NaHMDS$) or potassium hexamethylsilazide ($KHMDS$) preferably K_2CO_3 to give the ether (XXXI). The reaction is run in an inert solvent such as DMF at a temperature of 20-100 °C, preferably at 85°C. The electrophile (XXIX) can be either a chloride ($Y=Cl$), bromide, ($Y=Br$), iodide ($Y=I$) or other suitable leaving

group though it is preferred to use a bromide. Additives such as sodium iodide (NaI) or potassium iodide (KI) may be optionally added to the reaction.

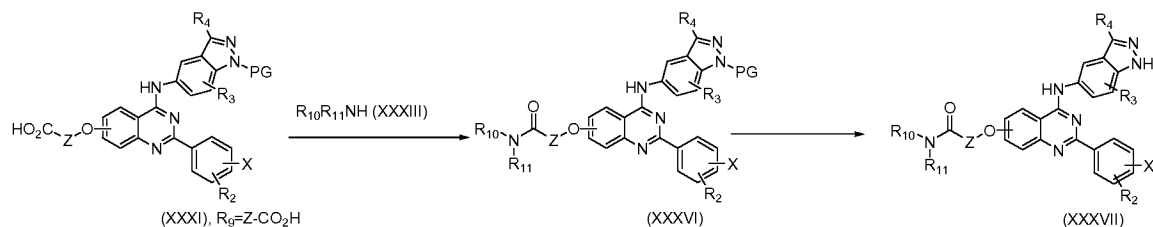
[0077] Deprotection of the indazole protecting group, which is well known by those skilled in the art, gives the desired compounds (XXXII).

[0078] Practitioners of the art will recognize that subsequent modification of R₉ may be necessary and can be performed as depicted in scheme I-J.



Scheme I

[0079] In Scheme I the chloro compounds of formula (XXXI) where R₉ is Z-Cl and Z is an appropriate linker is heated in the presence of an amine of formula (XXXIII) in a suitable solvent such as DMSO or DMF to give the amine containing compounds (XXXIV). Additives such as NaI or KI may be optionally added to the reaction. If appropriate protecting groups may be removed at this point by methods known to those skilled in the art.

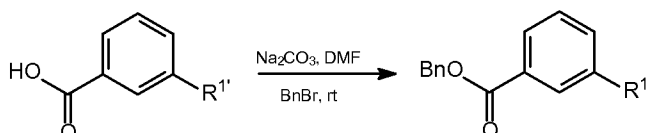


Scheme J

[0080] In scheme J the acid compounds of formula (XXXI) where R₉ is Z-CO₂H and Z is an appropriate linker is treated with an amine of formula (XXXIII) preferably at room temperature, in the presence of a coupling agent (e.g., PyBOP, PyBrOP[®], dicyclohexylcarbodiimide (DCC), 1-(3'-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), or 1-propanephosphonic acid cyclic anhydride (PPAA)) and a suitable base (e.g., triethylamine, DMAP, or N-methylmorpholine (NMO)) in a solvent such as dichloromethane, chloroform, or

dimethylformamide to give the amides of formula (XXXVI). Optionally, agents such as HOBt maybe added to the reaction. If appropriate protecting groups may be removed at this point by methods known to those skilled in the art to give the product compounds of formula (XXXVII).

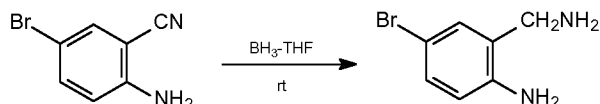
[0081] The compounds of the invention of formula XV, XVI and XVII may be prepared according to the following synthetic schemes:



Scheme K

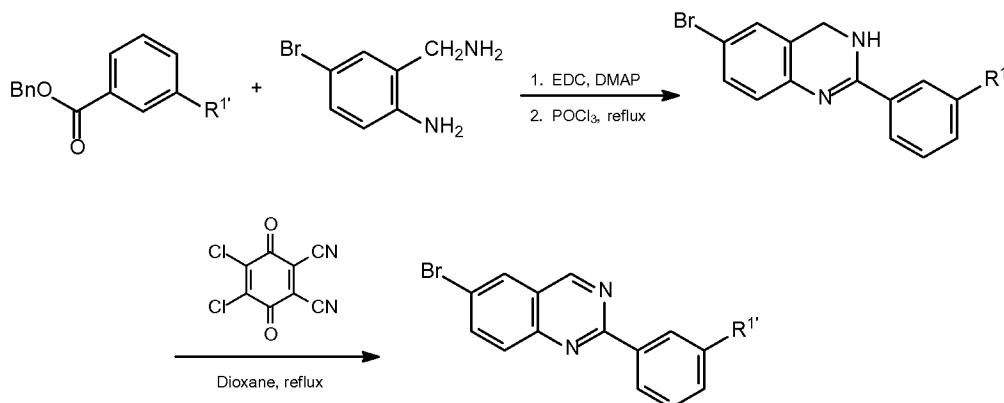
[0082] The acid coupling partner may be esterified following the literature protocol utilizing benzyl bromide and sodium carbonate in DMF at room temperature. *See* Tetrahedron, 58, 2231, 2002. R^{1'} is a substituent selected from R¹, or a precursor or protected group which may be converted to R¹.

[0083]



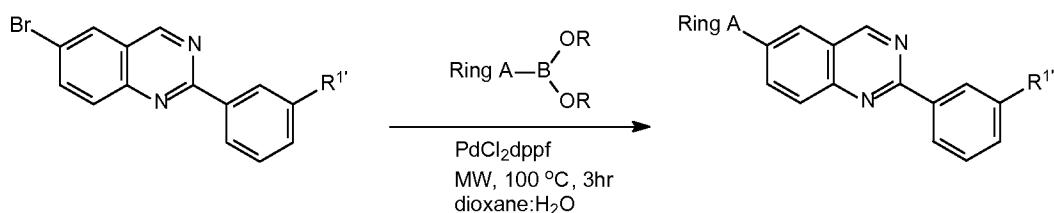
Scheme L

[0084] 2-Amino-5-bromobenzonitrile may be reduced using 1M-borane-THF solution according the literature procedure to provide 2-(aminomethyl)-4-bromobenzenamine. *See* WO 2008/014822.



Scheme M

[0085] The bis-amine product of Scheme L may then be coupled with the product of Scheme K using EDC as a peptide coupling agent and DMAP as the base. The resultant crude product may be treated with DDQ to provide the quinazoline ring structure.



Scheme N

[0086] Ring A may be coupled to the product of Scheme M using a microwave promoted Suzuki conditions at 100 °C using PdCl₂dppf as the catalyst and the Ring A-boronic acid or the corresponding boronate ester as the boronate coupling partner and cesium carbonate as the base. The final compound may be obtained upon aqueous workup.

[0087] Practitioners of the art will also recognize that the order of certain steps in the above schemes may be altered. Further, certain conditions such as solvent, temperature, etc. may be adjusted as would be recognized by the ordinarily skilled practitioner.

[0088] Reactive groups not involved in the above process steps can be protected with standard protecting groups during the reactions and removed by standard procedures (T. W. Greene & P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley-Interscience) known to those of ordinary skill in the art. Presently preferred protecting groups include methyl, benzyl, acetate and tetrahydropyranyl for the hydroxyl moiety, and BOC, CBz, trifluoroacetamide and benzyl for the amino moiety, methyl, ethyl, *tert*-butyl and benzyl esters for the carboxylic acid moiety. The preferred protecting groups for the indazole moiety are BOC, CBz, trifluoroacetamide and benzyl.

[0089] Compounds of Formula I-V are used to reduce or inhibit glucose uptake in cells or tissues via the GLUT1 transporter. The compounds are particularly useful for limiting glucose availability and metabolism in cells that consume glucose at a high rate. More particularly, expression of hypoxia-regulated genes such as GLUT1 allows tumor cells to survive under hypoxic conditions of the tumor microenvironment, which leads to increased malignancy and likelihood of metastasis. Upregulation of GLUT1 in cancer cells allows increased glucose

uptake, which promotes glycolysis, as opposed to aerobic respiration, as an energy source. Even though less efficient per glucose molecule consumed, cells become dependent on glycolysis for ATP production. However, such cells are highly sensitive to inhibition of glycolysis.

[0090] GLUT1 inhibitors of the invention are cytotoxic in cancer cells, including cancer cells with mitochondrial defects and cancer cells in hypoxic environments. Accordingly, in one embodiment of the invention, neoplasias that express GLUT1 are treated by administering a therapeutically effective amount of a compound of Formula I-V or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof. In another embodiment of the invention, hypoxic tumors are treated by administering a therapeutically effective amount of a compound of Formula I-V or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof. Tumors to be treated include, but are not limited to, solid tumors, such as mammary tumors, brain tumors, squamous cell carcinoma, hypopharyngeal carcinoma, breast cancer, cervical carcinoma, ovarian carcinoma, pancreatic cancer, and the like. In a further embodiment of the invention, the suitability of a neoplasm or tumor for treatment with a compound of the invention may be assessed by determining the level of expression of GLUT1 in the tumor. In yet another embodiment of the invention, the suitability of a neoplasm or tumor for treatment with a compound of the invention may be assessed by determining whether the neoplasm or tumor is hypoxic.

[0091] Hypoxia can be determined by testing a tumor directly or testing biopsy tissue. For example, hypoxia can be determined using polarographic needle electrode to measure dissolved oxygen. Hypoxia-inducible factor 1 (HIF-1) is known to induce the expression of several proteins linked to the maintenance of oxygen homeostasis, cellular energy metabolism, and tumor progression. Its α subunit (HIF-1 α) is stabilized under hypoxic conditions and is a suitable marker for hypoxia. Other endogenous markers include HIF-regulated proteins, such as GLUT1 and carbonic anhydrase IX (CAIX). Such markers can be detected in biopsies using immunological methods. Also, nitroimidazoles such as pimonidazole can be injected prior to biopsy and detected by immunohistochemical methods.

[0092] Notably, certain normal tissues, particularly brain, use glucose as a main energy source, though the glucose requirements of such normal tissues may be small compared to tumor tissue, and alternative energy sources or transporters may be available. For example, 2-DG at

certain doses is considered safe. Thus, in certain embodiments, compounds of the invention are used in an amount effective to limit glucose uptake by neoplastic cells, but non-toxic to normal cells that express GLUT1. For example, compound 48 has been administered to test animals without apparent adverse effects.

[0093] GLUT1 inhibitors of the invention may be coadministered with other antineoplastic agents, including chemotherapeutic agents and radiation. Anti-neoplastic agents can be grouped into a variety of classes including, for example, mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, anti survival agents, biological response modifiers, anti-hormones, and anti-angiogenesis agents. Examples of alkylating agents include, but are not limited to, cisplatin, cyclophosphamide, melphalan, and dacarbazine. Examples of anti-metabolites include, but are not limited to, doxorubicin, daunorubicin, and paclitaxel, gemcitabine. Non-limiting examples of topoisomerase inhibitors are irinotecan (CPT-11), aminocamptothecin, camptothecin, DX-8951f, and topotecan (topoisomerase I) and etoposide (VP-16) and teniposide (VM-26) (topoisomerase II). When the anti-neoplastic agent is radiation, the source of the radiation can be either external (*e.g.*, external beam radiation therapy – EBRT) or internal (*i.e.*, brachytherapy – BT) to the patient being treated. The dose of anti-neoplastic agent administered depends on numerous factors, including, for example, the type of agent, the type and severity tumor being treated and the route of administration of the agent. It should be emphasized, however, that the present invention is not limited to any particular dose.

[0094] In an embodiment of the invention, a compound of Formula I-V is coadministered with a drug that targets a cellular component or pathway. For example, a compound of Formula I-V is coadministered with an anti-angiogenic agent, for example a small molecule or biological molecule that targets a vascular endothelial growth factor (*e.g.*, VEGF) or its receptor (*e.g.*, VEGFR1, VEGFR2). In another embodiment, the compound is coadministered with an antagonist of the human EGFR related family of receptor tyrosine kinases (HER1/EGFR (epidermal growth factor receptor)/c-erbB1, HER2/c-erbB2, HER3/c-erbB3 and HER4/c-erbB4).

[0095] In an embodiment of the invention, a compound of formula I-V is coadministered with a second agent that depletes cellular ATP. In certain instances, it can be beneficial to restrict energy generation further, for example by coadministering a compound of the invention

with an ATP-depleting levels even further. Accordingly, a GLUT1 inhibitor of the invention may be coadministered with

[0096] The present invention also provides compounds and methods for preventing, treating, or ameliorating a neoplastic disease or condition in a patient in need thereof. The present invention also provides compounds and methods for preventing, treating, or ameliorating a metabolic disease or condition in a patient in need thereof. According to the invention, compounds are provided that are activators of AMPK. The compounds include GLUT1 inhibitors as described above. AMPK activators further include, but are not limited to, ROCK2 inhibitors and CK2 inhibitors. The metabolic diseases are treated by administering a therapeutically effective amount of a compound of Formula I-V, X, XI, XV and XVI or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof. Metabolic diseases or conditions include, without limitation, diabetes (type 1 and type 2), insulin resistance, metabolic syndrome, hyperinsulinemia, dyslipidemia, and hypercholesterolemia, obesity, hypertension, retinal degeneration, retinal detachment, Parkinson's disease, cardiovascular diseases including vascular disease, atherosclerosis, coronary heart disease, cerebrovascular disease, heart failure and peripheral vascular disease in a subject.

[0097] For treatment of metabolic disease, the invention also provides for coadministration of a compound of Formula I-V, X, XI, XV and XVI (or a pharmaceutically acceptable salt, ester, amide, prodrug, or solvate) to a subject in combination with a second therapeutic agent or other treatment.

[0098] For example, second therapeutic agents for treatment of metabolic diseases such as diabetes and related conditions include biguanides (including, but not limited to metformin), which reduce hepatic glucose output and increase uptake of glucose by the periphery, insulin secretagogues (including but not limited to sulfonylureas and meglitinides) which trigger or enhance insulin release by pancreatic β -cells, and PPAR γ , PPAR α , and PPAR α/γ modulators (*e.g.*, thiazolidinediones such as pioglitazone and rosiglitazone).

[0099] Additional second therapeutic agents include GLP1 receptor agonists, including but not limited to GLP1 analogs such as exendin-4 and liraglutide and agents that inhibit degradation of GLP1 by dipeptidyl peptidase-4 (DPP-4). Vildagliptin and sitagliptin are non-limiting examples of DPP-4 inhibitors.

[00100] In certain embodiments of the invention, compounds of Formula I-V, X, XI, XV and XVI are coadministered with insulin replacement therapy.

[00101] According to the invention, compounds of I-V, X, XI, XV and XVI can be coadministered with statins and/or other lipid lowering drugs such as MTP inhibitors and LDLR upregulators, antihypertensive agents such as angiotensin antagonists, e.g., losartan, irbesartan, olmesartan, candesartan, and telmisartan, calcium channel antagonists, e.g. lacidipine, ACE inhibitors, e.g., enalapril, and β -adrenergic blockers (β -blockers), e.g., atenolol, labetalol, and nebivolol.

[0100] In another embodiment, a subject is prescribed a compound of the invention in combination with instructions to consume foods with a low glycemic index.

[0101] In a combination therapy, the compound of Formula I-V, X, XI, XV and XVI is administered before, during, or after another therapy as well as any combination thereof, *i.e.*, before and during, before and after, during and after, or before, during and after administering the second therapeutic agent. For example, a compound of the invention can be administered daily while extended release metformin is administered daily. In another example, a compound of the invention is administered once daily and while exenatide is administered once weekly. Also, therapy with a compound of the invention can be commenced before, during, or after commencing therapy with another agent. For example, therapy with a compound of the invention can be introduced into a patient already receiving therapy with an insulin secretagogue.

[0102] Compounds that inhibit GLUT1 can be tested *in vivo* in animal models. Animal models of diabetes and obesity include leptin deficient ob/ob mice (Jackson Laboratories; B6.V-Lep(ob)/J), leptin receptor deficient db/db mice, fatty Zucker rats, and the like. See, e.g., Sima A F, Shafir E. *Animal Models in Diabetes: A Primer*. Taylor and Francis, Publ Amsterdam, Netherlands, 2000). Such models may be used to test safety and efficacy of compounds of the invention, and to formulate appropriate dosages for use in humans.

[0103] In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds of the present invention, including but not limited to the compounds described above and those shown in the Figures, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical

compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[0104] The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment, e.g. reasonable side effects applicable to any medical treatment.

[0105] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals with toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

[0106] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils,

such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

[0107] As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

[0108] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0109] In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with

pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*).

[0110] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0111] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0112] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.1 per cent to about ninety-nine percent of active

ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

[0113] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[0114] Throughout this application, various publications, reference texts, textbooks, technical manuals, patents, and patent applications have been referred to. The teachings and disclosures of these publications, patents, patent applications and other documents in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which the present invention pertains.

[0115] It is to be understood and expected that variations in the principles of invention herein disclosed may be made by one skilled in the art and it is intended that such modifications are to be included within the scope of the present invention. The following examples are illustrative of the invention, and should not be construed to limit the invention.

EXAMPLES

[0116] The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

[0117] Abbreviations used in the following examples and preparations include:

Ac ₂ O	Acetic anhydride
AcOH	Acetic acid
Bn	Benzyl
Celite®	Diatomaceous earth
1,2 DCE	1,2-Dichloroethane
d	Doublet

dd	Double Doublet
DIEA	Di-isopropylethyl amine
DMAP	4-Dimethylamino Pyridine
DME	1,2 Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride
EtOAc	Ethyl Acetate
EtOH	Ethyl Alcohol or Ethanol
Et ₂ O	Ethyl Ether
Et ₃ N	Triethylamine
g	grams
HOBt	1-Hydroxybenzotriazole
HPLC	High Pressure Liquid Chromatography
h	Hour(s)
hr	Hour(s)
m	Multiplet
mins.	Minutes
MeOH	Methyl Alcohol or Methanol
min	Minute(s)
mmol	millimoles
mmole	millimoles
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
o/n	overnight
ⁱ PrOH	Iso-propanol
PPAA	1-Propanephosphonic Acid Cyclic Anhydride
PyBOP [®]	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q	Quartet
RT (or rt)	room temperature (about 20-25 °C)
s	Singlet

sat.	Saturated
t	Triplet
TBAF	<i>Tetra</i> -Butyl Ammonium Fluoride
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
v/v	volume/volume
wt/v	weight/volume

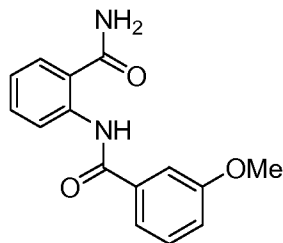
[0118] Mass spectrometry was conducted by: SynPep Co., 6905 Sierra Ct. Dublin, CA 94568, or it was recorded on an LC-MS: Waters 2695 Separations Module with a Waters ZQ 2000 single quadrapole MS detector. Unless stated all mass spectrometry was run in ESI mode.

[0119] ¹H NMR spectra were recorded on a Varian 400 MHz machine using Mercury software.

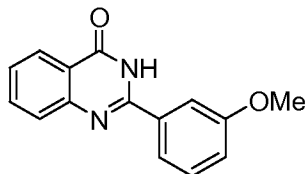
[0120] Analytical HPLC was run on an Agilent 1100 Series machine using an YMC ProC18 column (4.6x50 mm, 5µm particle size). Unless stated the method used was 5-95-10 which refers to a gradient of 5% of buffer A increased to 95% over 10 minutes with Buffer B. Buffer A is 0.1% TFA/H₂O and Buffer B is 0.0085% TFA/MeCN.

[0121] Preparative HPLC was performed on Waters Delta machine (600 and 515 Pumps) using an YMC- Pack ProC18 (150 x 20 mm I.D.) column using a combination of Buffer A (0.1% TFA/H₂O) and Buffer B (0.0085% TFA/MeCN) as the mobile phase.

[0122] Insofar as the synthesis of the following examples of compounds of the present invention is not explicitly described in such example, the synthesis is as described herein in general terms and the appropriate starting material can be easily selected for synthesizing the compound of the example.

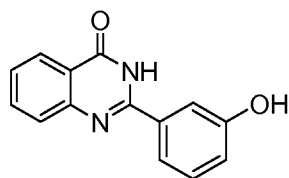
[0123] Example 1.

[0124] To a solution of anthranilamide (7.0 g, 51.41 mmole) in CHCl_3 (260 mL) was added pyridine (8.13 g, 102.8 mmole, 8.28 mL) followed by slow addition of *m*-anisoyl chloride (9.20 g, 53.94 mmole, 7.35 mL). The reaction mixture was stirred at ambient temperature for 6 h and then concentrated *in vacuo* and subsequently dried under high vacuum for 4 h to give the product. (13.89g, mmol, 100%)

[0125] Example 2.**[0126] 2-(3-Methoxyphenyl)quinazolin-4(3H)-one**

[0127] A solution of 2 N NaOH (250 mL) was added to the amide from example 1 (13.89 g, 51.41 mmole) and the reaction mixture was refluxed for 4 h. The reaction was cooled to ambient temperature and then adjusted to pH = 7 with 1 N HCl. The resulting solid was stirred at ambient temperature for 2 h and then filtered. The filtered solid was washed with water, ether and dried under high vacuum overnight. The crude product was also azeotroped from MeOH (1X) and toluene (2 X) and dried under high vacuum for several hours to give 2-(3-methoxyphenyl)quinazolin-4(3H)-one. (15.5 g, mmol, %)

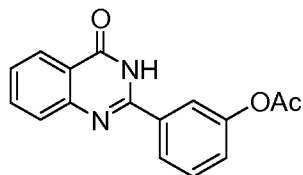
[0128] Example 3.**[0129] 2-(3-Hydroxyphenyl)quinazolin-4(3H)-one**



[0130] To 2-(3-methoxyphenyl)quinazolin-4(3H)-one (11.6 g, 45.98 mmole) was added of CH_2Cl_2 (120 mL) and the mixture was cooled to -78°C . Then, a 1 M solution of BBr_3 in CH_2Cl_2 (60 mL, 60.0 mmol) was added drop wise and the reaction was stirred at -78°C for 1 h and then ambient temperature for 3 h. The reaction was re-cooled to -78°C and cautiously quenched with MeOH (20 mL). The ice bath was removed and the system allowed to stir at ambient temperature for 0.5 h. The pH was adjusted to 7 with 10 % w/w NaHCO_3 solution. The solid was filtered, washed with ether, dried and then azeotroped from toluene (3 X) and dried under high vacuum overnight to give 2-(3-hydroxyphenyl)quinazolin-4(3H)-one. (11.0g, mmol, 100%).

[0131] **Example 4.**

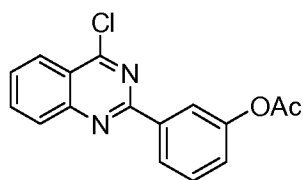
[0132] **3-(4-Oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate**



[0133] To 2-(3-hydroxyphenyl)quinazolin-4(3H)-one (11.0g, 45.98 mmole) was added pyridine (16.06 mL, 15.71 g, 0.199 mmole) followed by addition of acetic anhydride (145 mL) and the reaction mixture was heated to 105°C and stirred for 3.5 h. The reaction mixture was cooled to ambient temperature and then poured onto ice-water (800 mL) and stirred for 2 h. The solid was then filtered and washed with water, ethanol, ether and finally hexane and dried for several hours under high vacuum to give 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate. (8.4 g, mmol, 65 %).

[0134] **Example 5.**

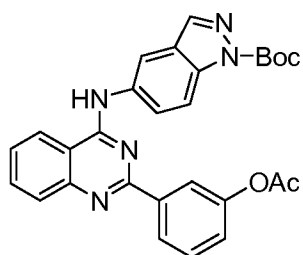
[0135] **3-(4-Chloroquinazolin-2-yl)phenyl acetate**



[0136] To 3-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate was added thionyl chloride (100 mL) and DMF (2 mL) and the reaction was heated to reflux for 4 h. The flask was allowed to cool to RT and then concentrated *in vacuo*. The crude product was azeotroped with toluene (2 X 50 mL), taken up in CH₂Cl₂ (300 mL) and washed with saturated NaHCO₃ (3 X 50 mL), water (1 X 50 mL) and brine (1 X 50 mL), dried with MgSO₄ and concentrated *in vacuo* to give 3-(4-chloroquinazolin-2-yl)phenyl acetate. (9.77 g, mmol, 100%).

[0137] **Example 6.**

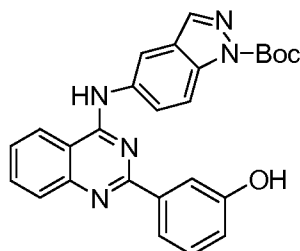
[0138] ***tert*-Butyl 5-(2-(3-acetoxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0139] 3-(4-Chloroquinazolin-2-yl)phenyl acetate (9.77 g, 29.97mmole) was dissolved in isopropanol (290 mL) and *tert*-butyl 5-amino-1H-indazole-1-carboxylate (6.99 g, 29.97 mmole) was added. The solution was heated to 95 °C and stirred for 0.25 h. A gelatinous formation developed which was manually broken up and dissolution gradually occurred followed by formation of a yellow precipitate. The reaction was stirred for an additional 0.25 h, cooled to ambient temperature and filtered. The filtered solid was washed with ether and then dried under high vacuum overnight to give *tert*-butyl 5-(2-(3-acetoxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (14.58 g, mmol, 98 %)

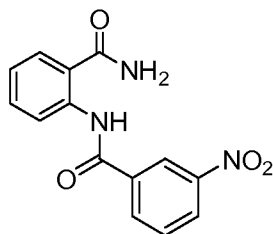
[0140] Example 7.

[0141] *tert*-Butyl 5-(2-(3-hydroxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0142] To a solution of give *tert*-butyl 5-(2-(3-acetoxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (5.85 g, 11.8 mmole) in anhydrous MeOH (400 mL) was added 28 % (wt/v) NH₄OH solution (6.50 mL). The reaction mixture was stirred at ambient temperature for 48 h. The crude product was filtered and washed with ether followed by hexane and dried under high vacuum overnight to give *tert*-butyl 5-(2-(3-hydroxyphenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (4.85g, mmol, 91 %).

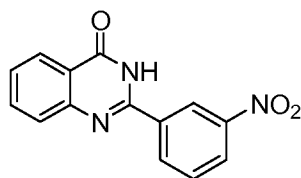
[0143] Example 8.



[0144] To a suspension of anthranilamide (24.0 g, 176.28 mmole) and 3-nitro benzoyl chloride (34.5 g, 186.3 mmole) CHCl₃ (700 ml) was added pyridine (30 ml) drop wise at RT. The reaction mixture was stirred at ambient temperature for 8 h. The solvent was removed *in vacuo* and residue dried under high vacuum to give the product. (73 g, mmol, %)

[0145] Example 9.

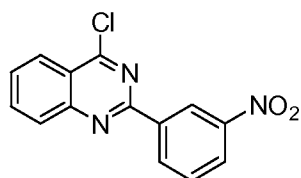
[0146] 2-(3-Nitrophenyl)quinazolin-4(3H)-one



[0147] A suspension of amide from example 8 (estimated 176.3 mmole) was taken up in 2 N NaOH (800 mL) and was refluxed for 7h. The reaction mixture was cooled to ambient temperature and then pH adjusted to 7 with 3 N HCl. The suspension was stirred at RT for 2 h, filtered, and the filtered solid washed with water and dried under high vacuum to give 2-(3-nitrophenyl)quinazolin-4(3H)-one. (45 g, mmol, 96 % from anthranilamide).

[0148] **Example 10.**

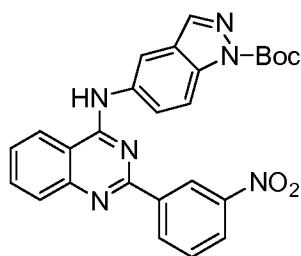
[0149] **4-Chloro-2-(3-nitrophenyl)quinazoline**



[0150] To a suspension of 2-(3-nitrophenyl)quinazolin-4(3H)-one (5.7 g, 21.32 mmole) in thionyl chloride (70 mL) was added of DMF (2 mL). The reaction mixture was refluxed for 4.5 h. The reaction was then concentrated *in vacuo* and residue suspended in a mixture of CH₂Cl₂ (400 mL) and CHCl₃ (500 mL). The organic layer was washed with water, saturated NaHCO₃, water, brine, dried with Na₂SO₄ and concentrated *in vacuo*. The residue was dried under high vacuum to afford 4-chloro-2-(3-nitrophenyl)quinazoline as an off-white solid. (6.0 g, mmol, 97%).

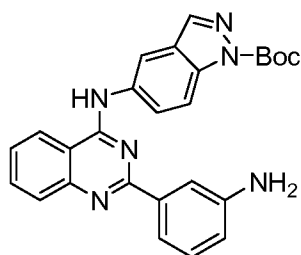
[0151] **Example 11.**

[0152] ***tert*-Butyl 5-(2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0153] A suspension of 4-chloro-2-(3-nitrophenyl)quinazoline (6.3 g, 21.9 mmole), *tert*-butyl 5-amino-1H-indazole-1-carboxylate (5.10 g, 21.9 mmole) in isopropanol (300 mL) was heated at 95 °C for 1.5 h. The suspension was filtered and the filtered solid was washed with isopropanol. The product was dried under high vacuum for several hours to give the desired product *tert*-butyl 5-(2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (8.3 g, mmol, 79%).

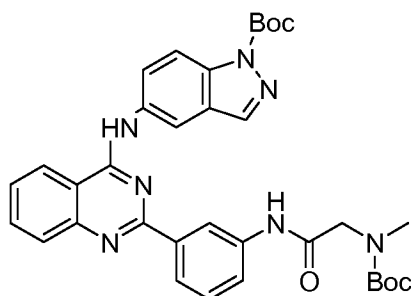
[0154] **Example 12.**



[0155] A suspension of product *tert*-butyl 5-(2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (9.0 g, 18.65 mmole) in a mixture of DME / MeOH (300 mL / 100 mL) was hydrogenated in the presence of 10 % Pd / C (1.25 g) at RT using a balloon filled with hydrogen gas. The reaction was stirred for 16 h and the reaction mixture filtered through Celite™. The pad of Celite™ was washed with a 1 : 1 mixture of MeOH / CH₂Cl₂ (200 mL). The filtrate was then concentrated *in vacuo* and dried under high vacuum overnight to give *tert*-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (8.8 g, mmol, %).

[0156] **Example 13.**

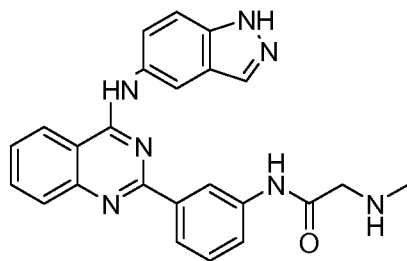
[0157] ***tert*-butyl 5-(2-(3-(2-(*tert*-butoxycarbonyl)acetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0158] A suspension of 2-(tert-butoxycarbonyl)acetic acid (21 mg, 0.11 mmol), PyBOP[®] (57 mg, 0.11 mmol), DIEA (38 μ L, 0.22 mmol) in anhydrous CH₂Cl₂ (0.5 mL) was stirred at RT for 10 minutes. This solution of activated acid was added to a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (100 mg, 0.22 mmol) and anhydrous CH₂Cl₂ (1 mL). The reaction mixture was stirred at RT for 1 h. Activated and added another 0.5 equivalent of the acid as described above and stirred for 1 h. Activated and added another 0.3 equivalents of the acid as described above. Stirred for and additional hour and diluted with CH₂Cl₂. Extracted with H₂O (3x) and the organic layer was dried under Na₂SO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica (1:1 EtOAc:Hexanes) to give the desired product tert-butyl 5-(2-(3-(2-(tert-butoxycarbonyl)acetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (123 mg, 0.20 mmol, 90%).

[0159] **Example 14.**

[0160] **N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-(methylamino)acetamide**

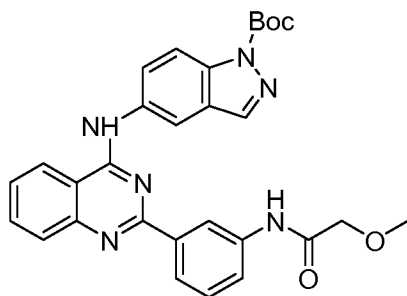


[0161] To tert-butyl 5-(2-(3-(2-(tert-butoxycarbonyl)acetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (123 mg, 0.20 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (4 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo*

and the residue was triturated with ethyl ether to afford 2-methoxyacetyl chloride N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-(dimethylamino)acetamide. (95 mg, 0.22 mmol, 100%)

[0162] **Example 15.**

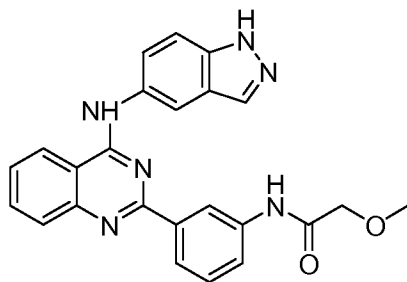
[0163] **tert-butyl 5-(2-(3-(2-methoxyacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0164] A suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (100 mg, 22.0 mmol), 4-methoxyacetyl chloride (40 μ L, 0.44 mmol), Et_3N (61 μ L, 0.44 mmol), in CH_2Cl_2 (1 mL) was stirred at RT temperature for 30 minutes. The reaction was then concentrated *in vacuo* and residue was triturated with MeOH and drops of CH_2Cl_2 . The solid was filtered under high vacuum to afford tert-butyl 5-(2-(3-(2-methoxyacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (98mg, 85%)

[0165] **Example 16.**

[0166] **N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-methoxyacetamide**

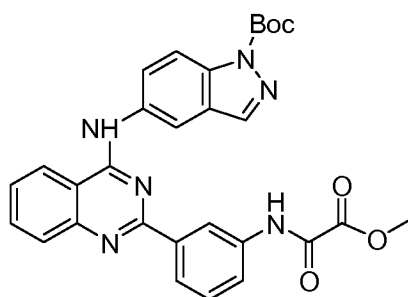


[0167] To tert-butyl 5-(2-(3-(2-methoxyacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (95 mg, 0.18 mmol) was added a solution of 1:1 TFA: CH_2Cl_2 (2 mL)

and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with ethyl ether to get a yellow solid. Product was purified using prep HPLC (method 25-50_70mins) to afford 2-methoxyacetyl chloride N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-methoxyacetamide. (45 mg, 59%)

[0168] **Example 17.**

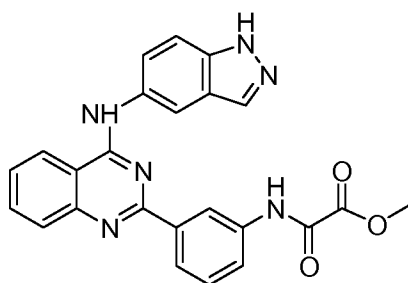
[0169] **tert-butyl 5-(2-(3-(2-methoxy-2-oxoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0170] To a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (85 mg, 0.19 mmol) and methyl 2-chloro-2-oxoacetate (35 μ L, 0.38 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (53 μ L, 0.38 mmol), and catalytic amount of DMAP. The reaction mixture was stirred at RT for 3 h. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography on silica (10:1 CH_2Cl_2 :MeOH). The product tert-butyl 5-(2-(3-(2-methoxy-2-oxoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate was isolate. (18 mg, 18%)

[0171] **Example 18.**

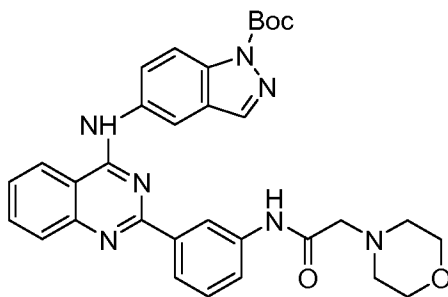
[0172] **methyl 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenylamino)-2-oxoacetate**



[0173] To tert-butyl 5-(2-(3-(2-methoxy-2-oxoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (18 mg, 0.033 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (2 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with ethyl ether to get a yellow solid to afford methyl 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenylamino)-2-oxoacetate. (15mg, 100%).

[0174] **Example 19.**

[0175] **tert-butyl 5-(2-(3-(2-morpholinoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

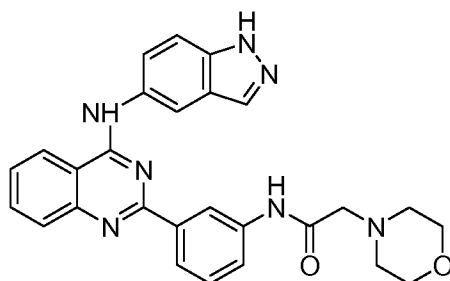


[0176] A suspension of 2-morpholinoacetic acid (16 mg, 0.11 mmol), PyBOP® (57 mg, 0.11 mmol), DIEA (96 µL, 0.55 mmol) in CH₂Cl₂ (0.5 mL) was stirred at RT for 10-15 minutes. This solution of activated acid was added to a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate **9** (100 mg, 0.22 mmol) and CH₂Cl₂ (1 mL). The reaction mixture was stirred at RT for 1.5 h. Activated another 0.5 equivalent of the acid as described above and it was once again added to the reaction mixture and stirred for 1.5 h. Added two more 0.5 equivalents of activated acid while stirring 1.5 hr between each addition. Diluted with more CH₂Cl₂ and extracted with H₂O (3x). Organic layer was dried

under Na₂SO₄ and concentrated *in vacuo* to give the desired oil product tert-butyl 5-(2-(3-(2-morpholinoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate.

[0177] **Example 20.**

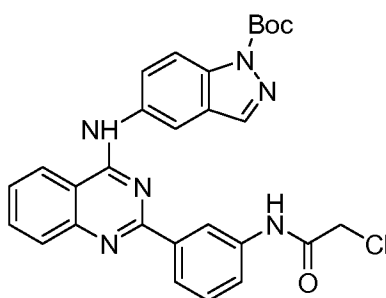
[0178] **N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-morpholinoacetamide**



[0179] To tert-butyl 5-(2-(3-((R)-2-(tert-butoxycarbonyl)propanamido)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (100 mg, 0.16 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (2 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by prep HPLC (method 10-35_90 mins) to afford N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-morpholinoacetamide. (24mg, 38%)

[0180] **Example 21.**

[0181] **tert-butyl 5-(2-(3-(2-chloroacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

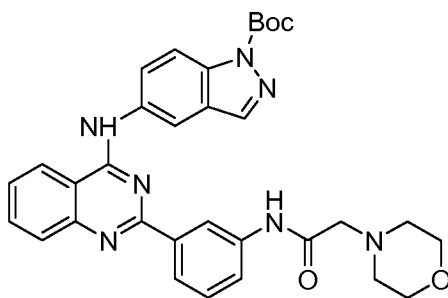


[0182] To a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.0 g, 2.21 mmol) in EtOAc:THF:sat'd NaHCO₃ (110 mL: 30 mL: 50 mL) was added 2-chloroacetyl chloride (1 mL, 12.6 mmol) and stirred at RT for 2.5 hr. The

reaction mixture was stirred at RT for 1.5 h. Another addition of 2-chloroacetyl chloride (0.5 mL) was added and continued to stir for 2 h. Concentrated *in vacuo* to remove volatiles and residue was washed with 5% citric acid (2 x 50 mL), water (2 x 100 mL), and sat'd NaCl (1 x 50 mL). The organic layer was dried under Na₂SO₄ and concentrated *in vacuo* to give the desired product tert-butyl 5-(2-(3-(2-chloroacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (1.02 g, 87%)

[0183] **Example 22.**

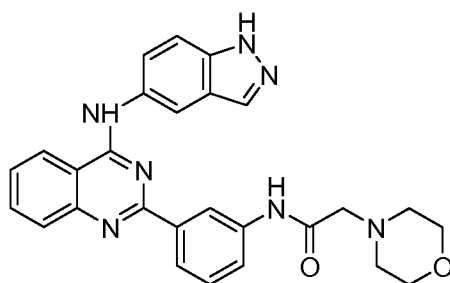
[0184] **tert-butyl 5-(2-(3-(2-morpholinoacetamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0185] To a suspension of tert-butyl 5-(2-(3-(2-chloroacetamido)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.0 g, 1.89 mmol) in DMF:THF (3 mL:4 mL) was added morpholine (1.8 mL, 20.6 mmol). The reaction mixture was stirred at RT for 2.5 h. The reaction mixture was concentrated *in vacuo* to remove volatiles. The residue was poured into ice-water and the resulting white solid was filtered and dried for several hours under high vacuum. The crude product re-crystallized using absolute EtOH to afford tert-butyl 5-(2-(3-(2-morpholinoacetamido)-phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (830 mg, 75%)

[0186] **Example 23.**

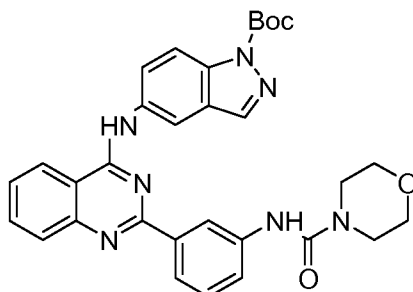
[0187] **N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-morpholinoacetamide**



[0188] To tert-butyl 5-(2-(3-((R)-2-(tert-butoxycarbonyl)propanamido)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (805 mg, 1.39 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (10 mL) and stirred at RT for 3 h. Added an additional portion of TFA (1.5 mL) and stirred for another 2 h. The reaction mixture was diluted with ethyl ether (200 mL) and solid was filtered and dried for several hours under high vacuum to afford N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-2-morpholinoacetamide. (917 mg, 100 %)

[0189] **Example 24.**

[0190] **tert-butyl 5-(2-(3-(morpholine-4-carboxamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

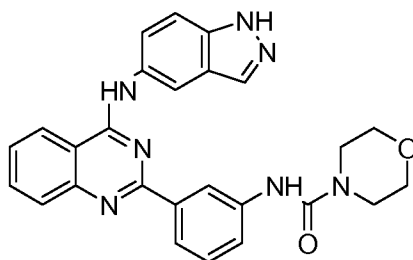


[0191] To a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (100 mg, 0.22 mmol) and morpholine-4-carbonyl chloride (51 μ L, 0.44 mmol,) in CH₂Cl₂ (2 mL) was added Et₃N (61 μ L, 0.44 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at RT for 2 h after which 2 equivalents each of morpholine-4-carbonyl chloride and Et₃N were added. After 2 h of stirring another 2 equivalents of both the chloride and Et₃N were added and continued to stir at ambient temperature for 16 hours. The reaction was concentrated *in vacuo* and the residue was purified by flash chromatography on silica (12:1 CH₂Cl₂:MeOH). The product tert-butyl 5-(2-(3-(morpholine-4-

carboxamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate was isolated. (80 mg, 65%)

[0192] **Example 25.**

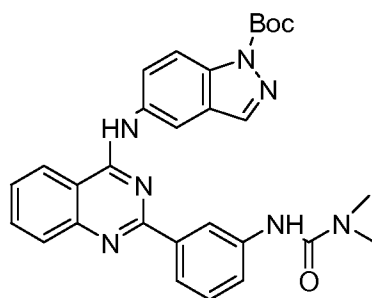
[0193] **N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)morpholine-4-carboxamide**



[0194] To tert-butyl 5-(2-(3-(morpholine-4-carboxamido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (25 mg, 0.044 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (2 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the product triturated with ethyl ether to afford N-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)morpholine-4-carboxamide. (24 mg, 100%)

[0195] **Example 26.**

[0196] **tert-butyl 5-(2-(3-(3,3-dimethylureido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

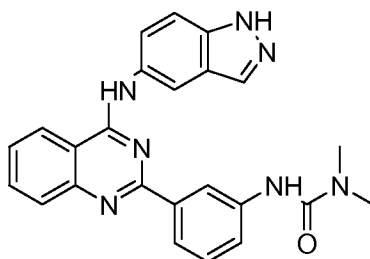


[0197] To a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (75 mg, 0.17 mmol) and dimethylcarbamic chloride (30 μ L, 0.33 mmol,) in CH₂Cl₂ (2 mL) was added Et₃N (46 μ L, 0.33 mmol) and catalytic amount of DMAP. The

reaction mixture was stirred at RT for 2 h after which 2 equivalents each of dimethylcarbamic chloride and Et₃N were added. After 2 h of stirring another 2 equivalents of both the chloride and Et₃N were added. Upon the addition of the third addition of the chloride and the Et₃N the temperature was raised to 45⁰ C. The reaction mixture was stirred for 48 h. Concentrated *in vacuo* and the residue was purified by flash chromatography on silica (10:1 CH₂Cl₂:MeOH). The product tert-butyl 5-(2-(3-(3,3-dimethylureido)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate was isolated. (62 mg, 70%)

[0198] **Example 27.**

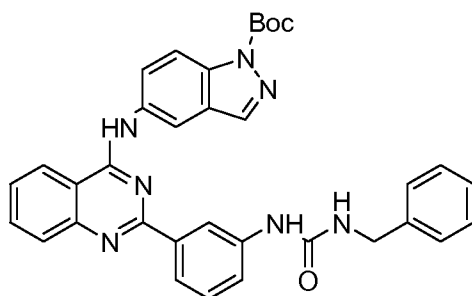
[0199] **3-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-1,1-dimethylurea**



[0200] To tert-butyl 5-(2-(3-(3,3-dimethylureido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (50 mg, 0.10 mmol) was added a solution of 1:1 TFA:CH₂Cl₂ (3 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and left under high vacuum for several hours. The crude product was triturated with ethyl ether and the yellow solid was purified by prep HPLC (method 25-50_70 mins) to afford 3-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-1,1-dimethylurea. (36 mg, 86%)

[0201] **Example 28.**

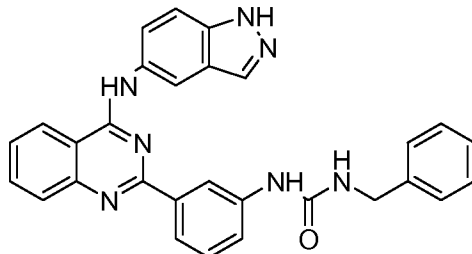
[0202] **tert-butyl 5-(2-(3-(3-benzylureido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0203] To a suspension of tert-butyl 5-(2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (150 mg, 0.33 mmol) and 1-(isocyanatomethyl)benzene (162 μ L, 1.32 mmol,) in CH_2Cl_2 (2 mL) was added Et_3N (1.38 mL, 9.9 mmol). The reaction mixture was stirred at RT for 4 h and concentrated *in vacuo*. The residue was triturated using MeOH and drops of CH_2Cl_2 to afford tert-butyl 5-(2-(3-(3-benzylureido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (100 mg, 52%)

[0204] **Example 29.**

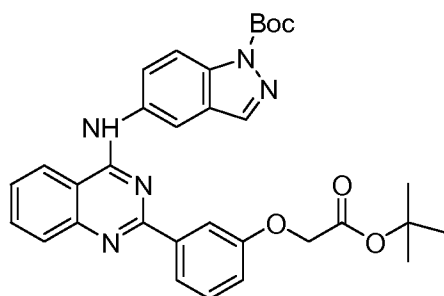
[0205] **1-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-3-benzylurea**



[0206] To tert-butyl 5-(2-(3-(3-benzylureido)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (30 mg, 0.051 mmol) was added a solution of 1:1 TFA: CH_2Cl_2 (2 mL) and stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and left under high vacuum for several hours. The crude product was triturated with ethyl ether to afford 1-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenyl)-3-benzylurea. (25 mg, 100 %)

[0207] **Example 30.**

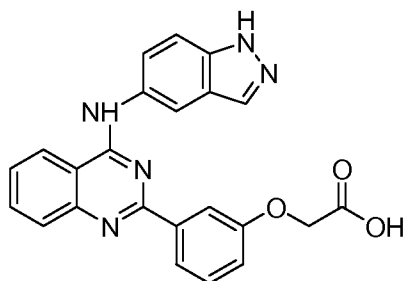
[0208] ***tert*-Butyl 5-(2-(3-(2-*tert*-butoxy-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



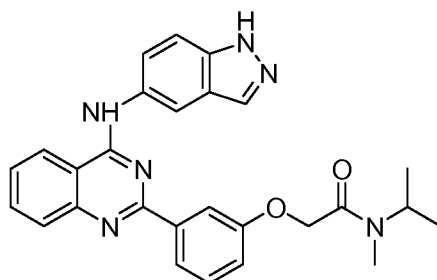
[0209] A mixture of *tert*-butyl 5-(2-(3-hydroxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.800g, 1.76 mmol), *tert*-butyl 2-bromoacetate (130 μ L, 0.88 mmol) and K_2CO_3 (0.972 g, 7.04 mmol) in DMF (35 mL) was heated at 80 $^{\circ}C$ for 2 h. Upon which additional *tert*-butyl 2-bromoacetate (130 μ L, 0.88 mmol) was added, heating at 80 $^{\circ}C$ was continued for a further 1.5 h. The mixture was allowed to cool to RT and concentrated in vacuo. Diluted with CH_2Cl_2 and extracted with water (3x). Dried under Na_2SO_4 and concentrated in vacuo to give *tert*-Butyl 5-(2-(3-(2-*tert*-butoxy-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.950g, 1.68 mmol, 95%).

[0210] **Example 31.**

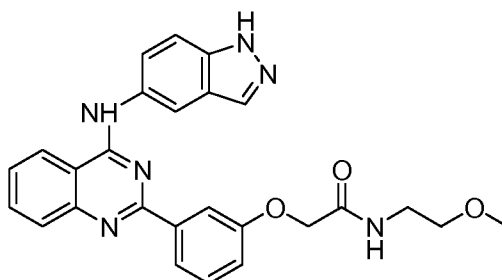
[0211] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid**



[0212] A solution of *tert*-butyl 5-(2-(3-(2-*tert*-butoxy-2-oxoethoxy)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate was stirred in CH_2Cl_2 (2 mL) and TFA (2 mL) for 1h. The volatiles were removed *in vacuo* and the residue was triturated with ethyl ether. The crude product was purified using prep HPLC (method 10-35_90mins) to afford to give 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid. (0.43 mg, 0.10 mmol).

[0213] Example 32.**[0214] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-
-N-isopropyl-N-methylacetamide**

[0215] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (120 mg, 0.29 mmol), PyBOP[®] (150 mg, 0.29 mmol), DIEA (152 μ L, 0.87 mmol) in CH₂Cl₂ (5 mL) was stirred at RT for 10-15 minutes. To this solution of activated acid was added N-methylpropan-2-amine (30 μ L, 0.29 mmol). The reaction mixture was stirred at RT for 3 h and concentrated *in vacuo*. The crude product was purified using prep HPLC (method 5-25-50_80mins) and was further washed with ethyl ether and drops of CH₂Cl₂ to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropyl-N-methylacetamide. (12mg, 0.025 mmol, 9 %).

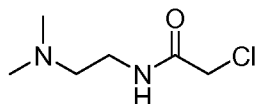
[0216] Example 33.**[0217] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2-methoxyethyl)acetamide**

[0218] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (100 mg, 0.24 mmol), PyBOP[®] (125 mg, 0.24 mmol), DIEA (125 μ L, 0.72 mmol) in CH₂Cl₂:DMF (4 mL : 0.5 mL) stirred at RT for 10-15 minutes. To this solution of activated acid was added 2-methoxyethanamine (21 μ L, 0.24 mmol) and the reaction mixture was stirred at RT

for 3 h. Concentrated *in vacuo* and the crude product was purified using prep HPLC (method 10-35_90mins) and was further washed with ethyl ether and drops of CH₂Cl₂ to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2-methoxyethyl)acetamide. (25mg, 0.053 mmol, 22 %).

[0219] **Example 34.**

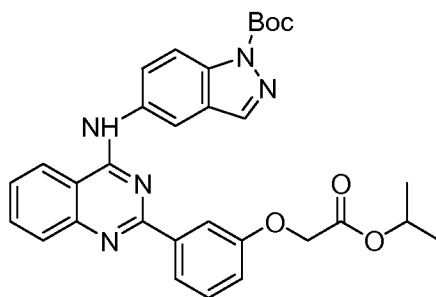
[0220] **2-chloro-N-(2-(dimethylamino)ethyl)acetamide**



[0221] A suspension of 2-chloroacetic acid (214 mg, 2.27 mmol), PyBOP® (1.18, 2.27 mmol), DIEA (1.18 mL, 6.81 mmol) in CH₂Cl₂ (1 mL) was stirred at RT for 10-15 minutes. This solution of activated acid was added to a suspension of N1,N1-dimethylethane-1,2-diamine (249 µL, 2.27 mmol) and CH₂Cl₂ (4 mL). The reaction mixture was stirred at RT for 1.5 h. Diluted with more CH₂Cl₂ and extracted with H₂O (3x). Organic layer was dried under Na₂SO₄ and concentrated *in vacuo* to give the desired product 2-chloro-N-(2-(dimethylamino)ethyl)acetamide.

[0222] **Example 35.**

[0223] **tert-butyl 5-(2-(3-(2-isopropoxy-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

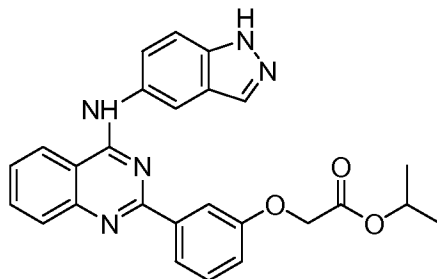


[0224] A suspension of tert-butyl 5-(2-(3-hydroxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (120 mg, 0.26 mmol), isopropyl 2-chloroacetate (45 mL, 0.36 mmol), K₂CO₃ (125 µL, 0.24 mmol), in DMF (5 mL) stirred at RT for 2 h. Concentrated *in vacuo* to

afford the crude tert-butyl 5-(2-(3-(2-isopropoxy-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.26 mmol).

[0225] **Example 36.**

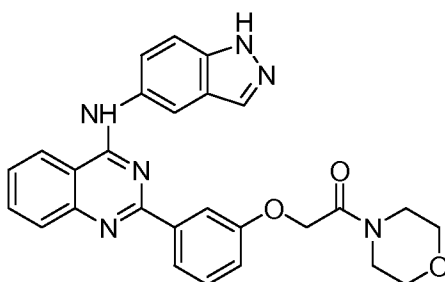
[0226] **isopropyl 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetate**



[0227] To a suspension of tert-butyl 5-(2-(3-(2-isopropoxy-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.26mmol) in 1,4-dioxane (0.5 mL) was added a 4M solution of hydrogen chloride in 1,4-dioxane (3 mL) and stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* residue was purified using prep HPLC (method 10-35_90mins) to afford isopropyl 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetate. (28 mg, 0.062 mmol, 24%).

[0228] **Example 37.**

[0229] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-1-morpholinoethanone**

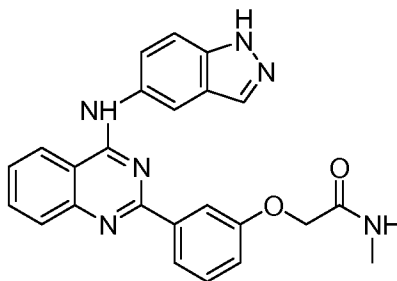


[0230] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (80 mg, 0.16 mmol), PyBOP[®] (46 mg, 0.088 mmol), DIEA (28 μ L, 0.16 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid

was added morpholine (8.7 mg, 0.10 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalent of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of morpholine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (20-45_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-1-morpholinoethanone. (13 mg, 0.027 mmol, 17 %).

[0231] **Example 38.**

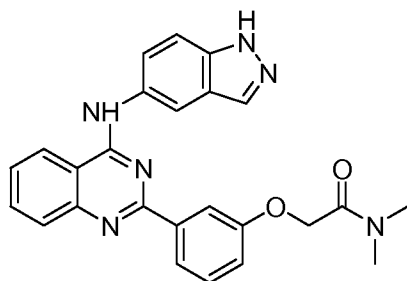
[0232] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-methylacetamide**



[0233] To a solution of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (80 mg, 0.16 mmol) in dry CH₂Cl₂: DMF (2.0:0.1 mL), added DIEA (29 μ L, 0.16 mmol) and PyBOP[®] (46 mg, 0.088 mmol). After stirring the mixture at RT for 15 minutes, methanamine was bubbled through the solution for 15minutes. Added another 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] after stirring the solution for 15 minutes, followed by methanamine bubbling for an additional 15 minutes. The solvent was removed *in vacuo* and the crude material was purified by prep HPLC (method 20-45_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-methylacetamide. (46 mg, 0.11 mmol, 68%).

[0234] **Example 39.**

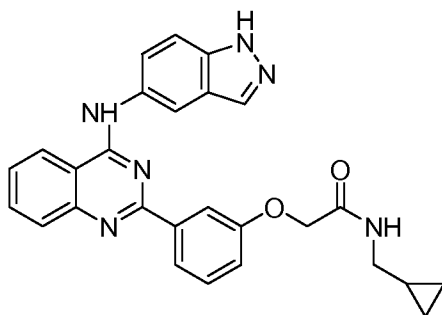
[0235] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N,N-dimethylacetamide**



[0236] To a solution of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (80 mg, 0.16 mmol) in dry CH₂Cl₂: DMF (2.0:0.1 mL), added DIEA (29 μ L, 0.16 mmol) and PyBOP[®] (46 mg, 0.088 mmol). After stirring the mixture at RT for 15 minutes, dimethylamine was bubbled through the solution for 15 minutes. Added another 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] after stirring the solution for 15 minutes, followed by dimethylamine bubbling for an additional 15 minutes. The solvent was removed *in vacuo* and the crude material was purified by prep HPLC (method 20-45_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N,N-dimethylacetamide (26 mg, 0.059 mmol, 37 %).

[0237] **Example 40.**

[0238] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(cyclopropylmethyl)acetamide**

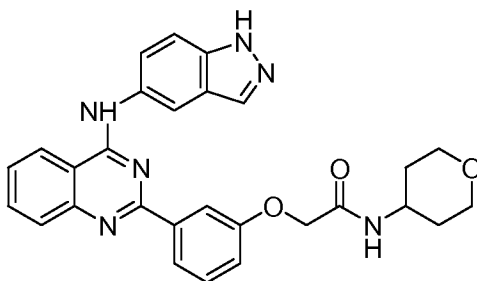


[0239] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (80 mg, 0.16 mmol), PyBOP[®] (46 mg, 0.088 mmol), DIEA (28 μ L, 0.16 mmol) in dry CH₂Cl₂: DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added cyclopropylmethanamine (7.1 mg, 0.10 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes,

0.65 equivalents of cyclopropylmethanamine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (20-45_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(cyclopropylmethyl)-acetamide. (60 mg, 0.13 mmol, 81 %).

[0240] **Example 41.**

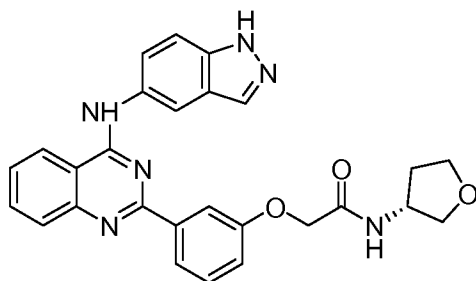
[0241] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-
N-(tetrahydro-2H-pyran-4-yl)acetamide**



[0242] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added tetrahydro-2H-pyran-4-amine hydrochloride (13 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of tetrahydro-2H-pyran-4-amine hydrochloride were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-40_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(tetrahydro-2H-pyran-4-yl)acetamide. (32 mg, 0.065 mmol, 46 %).

[0243] **Example 42.**

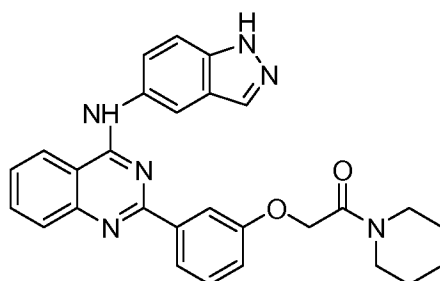
[0244] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-
N-((R)-tetrahydrofuran-3-yl)acetamide**



[0245] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added (R)-tetrahydrofuran-3-aminium 4-methylbenzenesulfonate (24 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of (R)-tetrahydrofuran-3-aminium 4-methylbenzenesulfonate were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-40_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-((R)-tetrahydrofuran-3-yl)acetamide. (41 mg, 0.085 mmol, 61 %).

[0246] **Example 43.**

[0247] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-1-(piperidin-1-yl)ethanone**

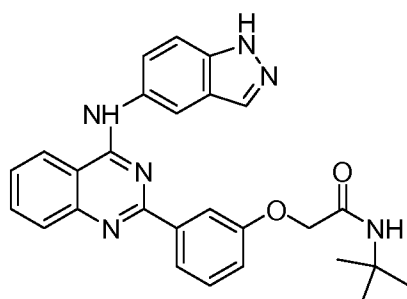


[0248] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added piperidine (7.7 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents

of piperidine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-55_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-1-(piperidin-1-yl)ethanone. (29 mg, 0.061 mmol, 43 %).

[0249] **Example 44.**

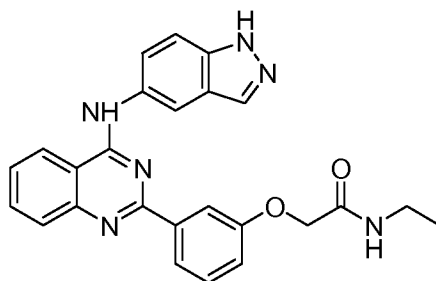
[0250] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-tert-butylacetamide**



[0251] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added 2-methylpropan-2-amine (6.7 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of 2-methylpropan-2-amine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-55_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-tert-butylacetamide. (36 mg, 0.061 mmol, 55 %).

[0252] **Example 45.**

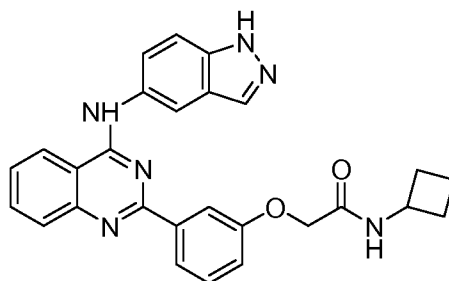
[0253] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-ethylacetamide**



[0254] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added ethanamine hydrochloride (7.4 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of ethanamine hydrochloride were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-40_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-ethylacetamide. (19 mg, 0.043 mmol, 31 %).

[0255] **Example 46.**

[0256] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-cyclobutylacetamide**

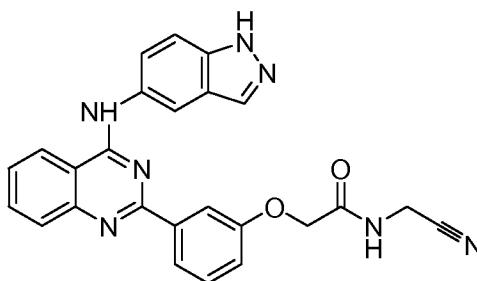


[0257] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added cyclobutanamine (6.5 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of cyclobutanamine were added and the mixture was stirred for an additional 30

minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-50_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-cyclobutylacetamide. (36 mg, 0.077 mmol, 55%).

[0258] Example 47.

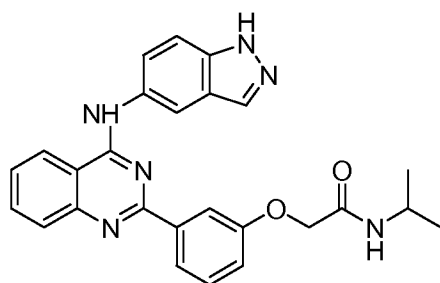
[0259] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(cyanomethyl)acetamide



[0260] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added aminoacetonitrile monosulfate (14 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of aminoacetonitrile monosulfate were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-40_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(cyanomethyl)acetamide. (12 mg, 0.027 mmol, 19 %).

[0261] Example 48.

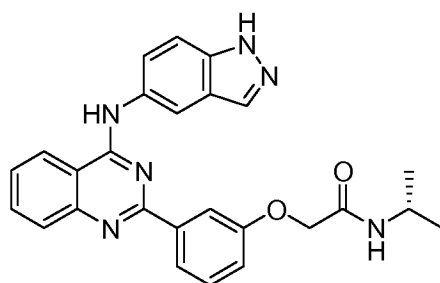
[0262] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide



[0263] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added propan-2-amine (5.4 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of propan-2-amine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-50_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide. (40 mg, 0.086 mmol, 61 %).

[0264] **Example 49.**

[0265] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(R)-sec-butylacetamide**

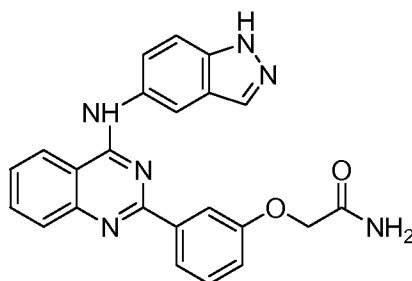


[0266] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added (R)-butan-2-amine (6.6 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of (R)-butan-2-amine were added and the mixture was stirred for an additional 30

minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-40_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(R)-sec-butylacetamide. (34 mg, 0.073 mmol, 52 %).

[0267] **Example 50.**

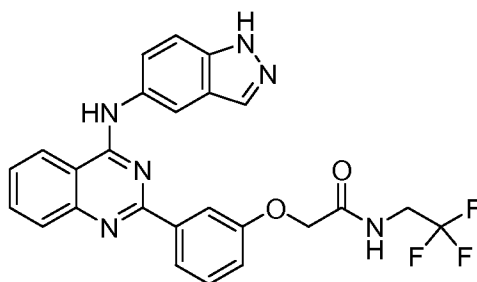
[0268] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetamide**



[0269] To a solution of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol) in dry CH₂Cl₂: DMF (2.0:0.1 mL), added DIEA (24 μ L, 0.14 mmol) and PyBOP[®] (40 mg, 0.077 mmol). After stirring the mixture at RT for 15 minutes, ammonia was bubbled through the solution for 15 minutes. Added another 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] after stirring the solution for 15 minutes, followed by ammonia bubbling for an additional 15 minutes. The solvent was removed *in vacuo* and the crude material was purified by prep HPLC (method 10-35_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetamide. (27 mg, 0.066 mol, 47 %).

[0270] **Example 51.**

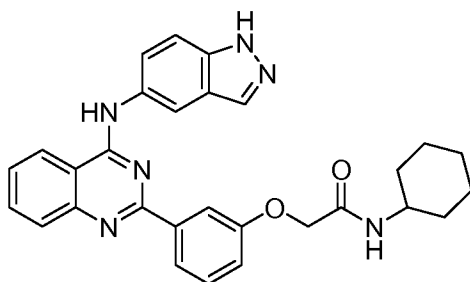
[0271] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2,2,2-trifluoroethyl)acetamide**



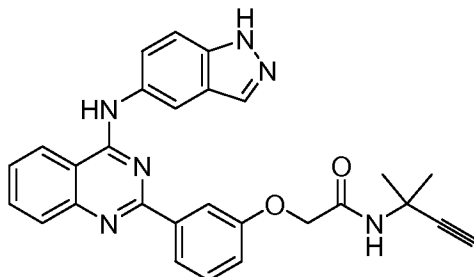
[0272] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added 2,2,2-trifluoroethanamine (9.0 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of 2,2,2-trifluoroethanamine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-50_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2,2,2-trifluoroethyl)acetamide. (16 mg, 0.032 mmol, 23 %).

[0273] **Example 52.**

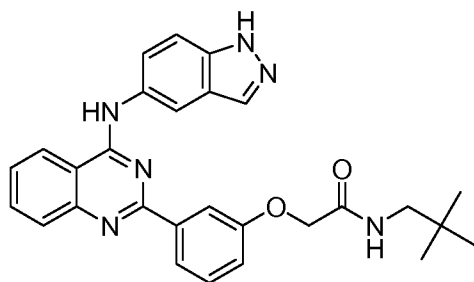
[0274] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-cyclohexylacetamide**



[0275] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added cyclohexanamine (9.0 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of cyclohexanamine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (20-50_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-cyclohexylacetamide. (27 mg, 0.055 mmol, 39 %).

[0276] Example 53.**[0277] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2-methylbut-3-yn-2-yl)acetamide**

[0278] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added 2-methylbut-3-yn-2-amine (7.6 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of 2-methylbut-3-yn-2-amine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (20-45_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(2-methylbut-3-yn-2-yl)acetamide. (22 mg, 0.046 mmol, 33 %).

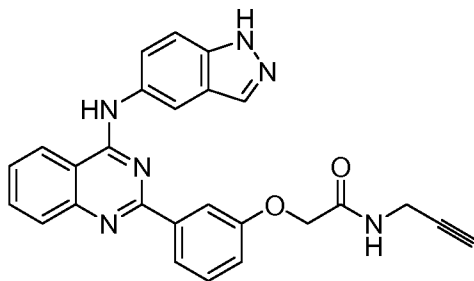
[0279] Example 54.**[0280] 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-neopentylacetamide**

[0281] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH₂Cl₂ : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid

was added 2,2-dimethylpropan-1-amine (7.9 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of 2,2-dimethylpropan-1-amine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (25-50_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-neopentylacetamide. (40 mg, 0.083 mmol, 59 %).

[0282] **Example 55.**

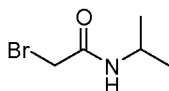
[0283] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(prop-2-ynyl)acetamide**



[0284] A suspension of 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)acetic acid (70 mg, 0.14 mmol), PyBOP[®] (40 mg, 0.077 mmol), DIEA (24 μ L, 0.14 mmol) in dry CH_2Cl_2 : DMF (2 : 0.1 mL) was stirred at RT for 15 minutes. To this solution of activated acid was added prop-2-yn-1-amine (5.0 mg, 0.091 mmol). After 30 minutes, 1.0 equivalent of DIEA and 0.55 equivalents of PyBOP[®] were added. After stirring the solution for 15 minutes, 0.65 equivalents of prop-2-yn-1-amine were added and the mixture was stirred for an additional 30 minutes. The solvent was removed *in vacuo* and the crude product was purified using prep HPLC (15-28_90 mins and 0-15_90 mins) to afford 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-(prop-2-ynyl)acetamide. (14 mg, 0.031 mmol, 22 %).

[0285] **Example 56.**

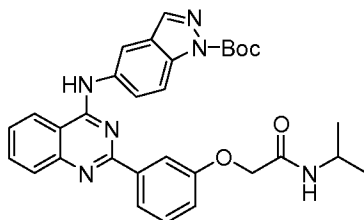
[0286] **2-Bromo-N-isopropylacetamide**



[0287] A solution of *iso*-propyl amine (5.0 g, 7.20 mL, 84.6 mmole) in 63 mL of ethylene dichloride was cooled to -10 °C. To this was added a solution of α -bromoacetyl bromide (8.53 g, 3.68 mL, 42.3 mmole) in 10.5 mL of ethylene dichloride. The reaction mixture was stirred for 10 mins. The *iso*-propylammonium hydrobromide was filtered from the mixture and the filtrate then concentrated in *vacuo* to give 2-bromo-N-isopropylacetamide as a white solid. (5.30 g, 29.4 mmol 70 %).

[0288] **Example 57.**

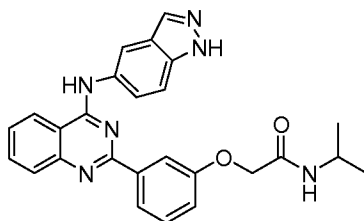
[0289] ***tert*-Butyl 5-(2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0290] A solution of *tert*-butyl 5-(2-(3-hydroxyphenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.3 g, 0.66 mmol), N-isopropylbromoacetamide (0.132 g, 0.726 mmole), and K₂CO₃ (0.183 g, 1.32 mmole) in DMF (3.6 mL) was heated overnight at 30 °C. The crude product was poured onto ice-water (ca. 50 mL) and the suspension was stirred for approximately 0.5 h, filtered and dried (Na₂SO₄). The crude product was recrystallized from absolute EtOH (10 mL) to afford *tert*-butyl 5-(2-(3-(2-(isopropylamino)-2-oxoethoxy)-phenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.160 g, mmol, 45%).

[0291] **Example 58.**

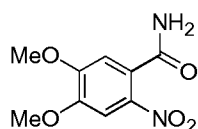
[0292] **2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide**



[0293] A solution of *tert*-butyl 5-(2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (4.30 g, 7.79 mmole) in TFA (20 mL) and CH₂Cl₂ (20 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo*, and to the crude residue was added ca. 50 mL Et₂O. The resulting bright yellow suspension was stirred for 15 minutes and filtered and dried giving 2-(3-(4-(1H-indazol-5-ylamino)quinazolin-2-yl)phenoxy)-N-isopropylacetamide trifluoroacetate salt. (4.1 g, mmol, %).

[0294] **Example 59.**

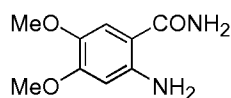
[0295] **4,5-Dimethoxy-2-nitrobenzamide**



[0296] To a suspension of 4,5-dimethoxy-2-nitrobenzoic acid (4.95g, 21.8 mmol) in anhydrous benzene (30 mL) was added SOCl₂ (1.75 mL). The resulting mixture was heated at 75 °C for 3.5 h. The solvent was evaporated under reduced pressure and the residue was dried under high vacuum. The residue was dissolved in anhydrous THF (30mL) and cooled to 0°C. To the cooled solution was added a saturated solution of ammonia in THF (ca. 50mL). A precipitate began to form and stirring was continued for 12 hours at RT. The solvent was removed under reduced pressure and the residue was dried under high vacuum to give 4,5-dimethoxy-2-nitrobenzamide which was used without further purification (6.0g). HPLC retention time 4.438 mins.

[0297] **Example 60.**

[0298] **2-Amino-4,5-dimethoxybenzamide**

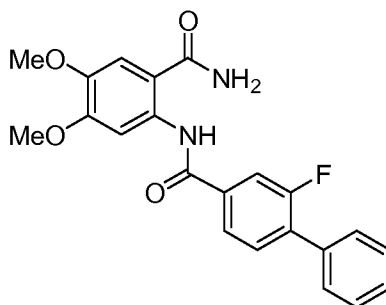


[0299] A suspension of 4,5-dimethoxy-2-nitrobenzamide (5.8g, 25.6mmol) in a 1:1 mixture of DME/MeOH (total volume 200 ml) and 10 % Pd / C (0.7 g) was hydrogenated at RT using a balloon filled with hydrogen gas. The reaction was stirred for 16 h and the reaction

mixture filtered through Celite®. The pad of Celite® was washed with a 1 : 1 mixture of MeOH / CH₂Cl₂ (200 mL). The filtrate was then concentrated *in vacuo* and dried under high vacuum overnight to give 2-amino-4,5-dimethoxybenzamide. (5.0g, 25.5mmol, 99%). HPLC retention time 2.303 mins.

[0300] **Example 61.**

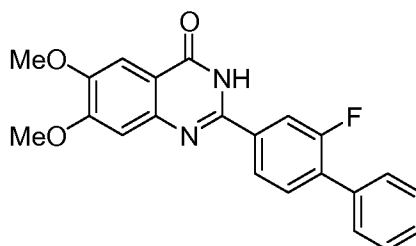
[0301] **4,5-Di-methoxy-2-(3-fluoro-4-(phenyl)phenyl)benzamide**



[0302] To a solution of 2-amino-4,5-dimethoxybenzamide (3.1 g, 15.8 mmol) in CHCl₃ (100 mL) was added acid chloride (3.41g, 15.8 mmol) as a solution in CHCl₃ (40 mL) and pyridine (12 mL). The resulting mixture was stirred at RT for 16 h. The mixture was then heated at 55 °C for 2 h. The volatiles were removed *in vacuo* and the residue was triturated with water/1N HCl resulting in a solid which was washed with 1N HCl and water. The solid was dried under vacuum and washed with CH₂Cl₂ and dried under vacuum to give the desired product which was used directly in the next step (3.0g). HPLC retention time 8.33 mins.

[0303] **Example 62.**

[0304] **2-(3-fluoro-4-(phenyl)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one**

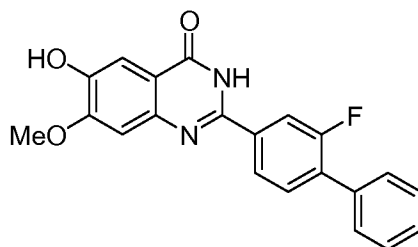


[0305] A suspension of the 4,5-Di-methoxy-2-(3-fluoro-4-(phenyl)phenyl)-benzamide (4.25g) in 2N NaOH (120 mL) was heated at 105 °C for 5h. The mixture was allowed to cool to

RT. The mixture was neutralized with 6N HCl with cooling. A solid separated out which was collected via filtration and washed with Et₂O and hexane to give the desired product 2-(3-fluoro-4-(phenyl)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one (4.00g, 10.6 mmol, 67% over two steps). HPLC retention time 7.9 mins.

[0306] Example 63.

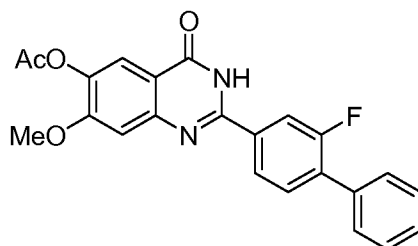
[0307] 2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4(3H)-one



[0308] A mixture of 2-(3-fluoro-4-(phenyl)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one (3.83g, 10.2 mmol) and methionine (2.1g, 14.1 mmol) in methanesulfonic acid was heated 110 °C for 4h. Additional methionine (0.75g) was added and heating was continued for another 1.5 h. The mixture was allowed to cool to RT and was poured into ice-water (300 mL). A solid separated out, which was collected *via* filtration. The solid was suspended in sat. NaHCO₃ and the after the effervescence subsided the solid was again collected via filtration. The solid was washed with water and EtOH to give the desired product 2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4(3H)-one (3.2g, 8.83 mmol, 87%). HPLC retention time 7.06 mins.

[0309] Example 64.

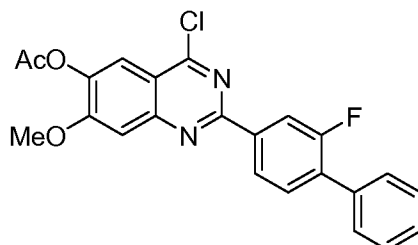
[0310] 2-(3-fluoro-4-(phenyl)phenyl)-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate



[0311] A mixture of 2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4(3H)-one (3.2g, 8.83 mmol), Ac₂O (40 mL) and pyridine (5 mL) was heated at 105 °C for 4 h. The mixture was poured onto ice-water (300 mL). The mixture was stirred for 1 h, upon which the solid which had formed was collected via filtration. The solid was washed with water and EtOH and dried under vacuum to give the desired product 2-(3-fluoro-4-(phenyl)phenyl)-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate. MS 405.2 (M+1) HPLC retention time 8.23 mins.

[0312] **Example 65.**

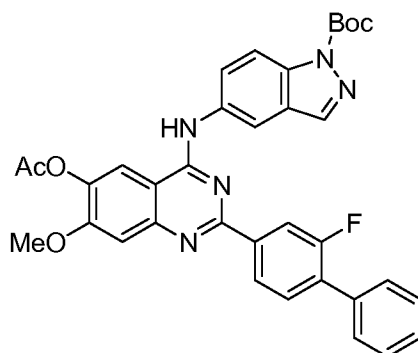
[0313] **4-chloro-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-6-yl acetate**



[0314] A suspension of 2-(3-fluoro-4-(phenyl)phenyl)-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (3.0g, 7.42 mmol) in SOCl₂ (60 mL) with DMF (1.4 mL) was heated at reflux for 5 h. the mixture was allowed to cool to RT and the volatiles were removed in *vacuo*. The residue was taken up in CHCl₃ (300 mL) and washed with water (100 mL), sat. NaHCO₃ (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated in *vacuo* to give the desired product 4-chloro-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-6-yl acetate (3.14g, 7.42 mmol, 100%). HPLC retention time 11.30 minutes (5-95-13 method).

[0315] **Example 66.**

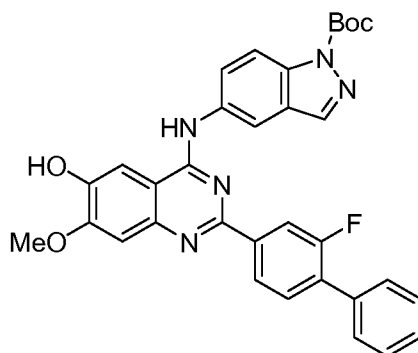
[0316] ***tert*-butyl 5-(6-acetoxy-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0317] A mixture of 4-chloro-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-6-yl acetate (3.14g, 7.42 mmol) and *tert*-butyl 5-amino-1H-indazole-1-carboxylate (1.85g, 7.93 mmol) in IPA (180 mL) was heated at 95 °C for 5 h. The mixture was allowed to cool to RT and the solid was collected *via* filtration. The solid was subjected to flash chromatography (SiO₂, CH₂Cl₂/MeOH) to give the desired compound *tert*-butyl 5-(6-acetoxy-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.70g, 4.36 mmol, 59%). MS 620.4 (M+1). HPLC retention time 8.10 mins (5-95-13 method).

[0318] **Example 67.**

[0319] ***tert*-butyl 5-(2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**

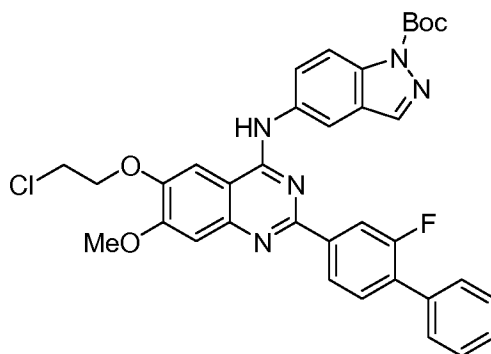


[0320] A mixture of *tert*-butyl 5-(6-acetoxy-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.6g) and 28% NH₄OH (2.8 mL) in MeOH (160 mL) was stirred at RT for 24 h. A solid separated out which was collected *via* filtration. The solid was triturated with hexane and dried under vacuum to give the desired

compound *tert*-butyl 5-(2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.6g). MS 578.4 (M+1). HPLC retention time 7.66 mins.

[0321] **Example 68.**

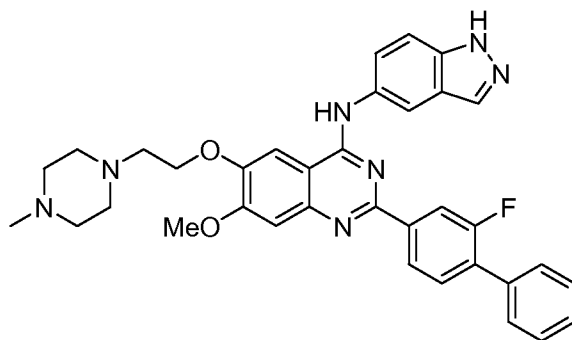
[0322] ***tert*-butyl 5-(6-(2-chloroethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0323] A mixture of *tert*-butyl 5-(2-(3-fluoro-4-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.61g, 1.06 mmol), 1-bromo-2-chloro ethane (0.475g, 3.31 mmol) and K₂CO₃ (0.533g, 3.86 mmol) in DMF (5 mL) was heated at 85 °C for 2.5 h. the mixture was allowed to cool to RT upon which, it was poured into water. A solid separated out which was collected *via* filtration and dried under vacuum. The residue was purified *via* preparative TLC (SiO₂, CH₂Cl₂:MeOH 9:1) to give the desired compound *tert*-butyl 5-(6-(2-chloroethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.37g, 0.578 mmol, 55%). MS 640.3 (M+1 Cl isotope pattern).

[0324] **Example 69.**

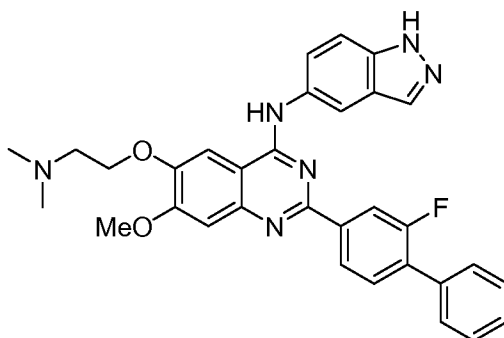
[0325] **2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-amine**



[0326] A mixture of 5-(6-(2-chloroethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.35g, 0.55 mmol) and 4-methyl piperazine in DMSO (1.5 mL) was heated at 85 °C for 3 h. The mixture was allowed to cool to RT, upon which it was poured into water (100 mL). The solid that formed was collected via filtration and purified by preparative TLC (SiO₂, CH₂Cl₂:MeOH 9:1) to give the desired compound. The lower running spot was isolated and then taken up in CH₂Cl₂ (6 mL) and TFA (5 mL). The mixture was stirred for 2.5 h at RT. The volatiles were removed in *vacuo* to give a solid which was triturated with Et₂O, filtered and dried under vacuum to give the desired product 2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-amine (0.111g, 0.184 mmol, 33%). MS 604.5 (M+1). HPLC retention time 5.10 mins.

[0327] Example 70.

[0328] 6-(2-(dimethylamino)ethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxyquinazolin-4-amine



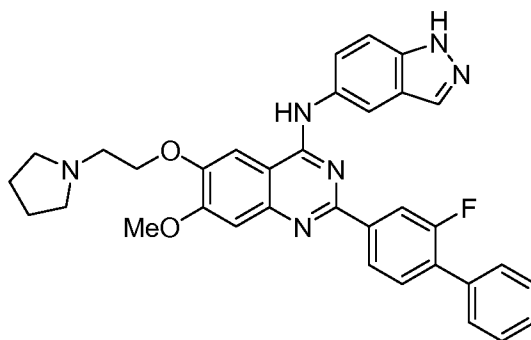
[0329] To an ice-cold solution of 5-(6-(2-chloroethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.26g, 0.55 mmol) in DMSO (3 mL)

was bubbled dimethylamine for 3-4 minutes. The mixture was heated at 85 °C for 2 h. The mixture was allowed to cool to RT, upon which it was poured into water (100 mL). The solid that formed was collected *via* filtration and purified by preparative TLC (SiO₂, CH₂Cl₂:MeOH 9:1) to give the desired compound.

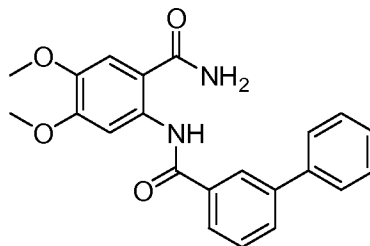
The purified compound was taken up in CH₂Cl₂ (5 mL) and TFA (5 mL). The mixture was stirred for 3 h at RT. The volatiles were removed in *vacuo* to give a solid which was dried under vacuum to give the desired product 6-(2-(dimethylamino)ethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxyquinazolin-4-amine (0.173g, 0.315mmol, 57%). MS 548.5 (M⁺). HPLC retention time 5.38 mins.

[0330] **Example 71.**

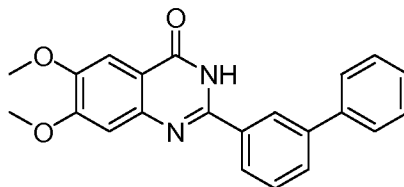
[0331] **2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-amine**



[0332] A mixture of 5-(6-(2-chloroethoxy)-2-(3-fluoro-4-(phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.200g, 0.31 mmol) and pyrrolidine (0.385g, 5.41 mmol) in DMSO (1.5 mL) was heated at 75 °C for 1.5 h. The mixture was allowed to cool to RT, upon which it was poured into water (100 mL). The solid that formed was collected *via* filtration and purified by preparative TLC (SiO₂, CH₂Cl₂:MeOH 9:1) to give the desired compound 2-(3-fluoro-4-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-amine (0.15g, 0.261mmol, 84%). MS 575.4 (M+1) HPLC retention time 5.40 mins.

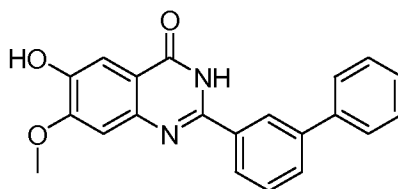
[0333] Example 72.**[0334] 4,5-Di-methoxy-2-(3-phenyl)phenyl)benzamide**

[0335] To a mixture of 2-amino-4,5-dimethoxybenzamide (8.42g, 38.86 mmole) and pyridine (11.64g, 147.4 mmole) in CHCl_3 (180 mL) was added 3-phenylbenzoyl chloride (7.23g, 36.86 mmole) and the reaction was stirred at RT for 5 h. The volatiles were removed *in vacuo* and the product 2-(benzoylamino)-4,5-dimethoxybenzamide was used immediately without future purification. HPLC retention time 7.92 mins.

[0336] Example 73.**[0337] 2-[(3-phenyl)phenyl]-6,7-dimethoxyquinazolin-4(3H)-one**

[0338] A mixture of 2 N NaOH (185 mL, 370 mmole) and 4,5-di-methoxy-2-(3-phenyl)phenyl)benzamide (38.9 mmole) was stirred under reflux for 16 h. The mixture was cooled and then pH adjusted to 7 with 1 N HCl. The crude product was filtered from solution, and the cake was washed with ether, hexane and dried under vacuum to give 2-[(3-phenyl)phenyl]-6,7-dimethoxyquinazolin-4(3H)-one (9.97g, 27.82 mmole, 76 % over two steps). HPLC retention time 7.23 mins.

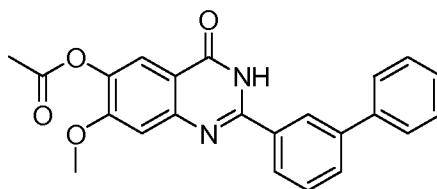
[0339] Example 74.**[0340] 2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquiazolin-4(3H)-one**



[0341] To a solution of 2-[(3-phenyl)phenyl]-6,7-dimethoxyquinazolin-4(3H)-one (9.97g, 27.8 mmole) in methanesulfonic acid (100 mL) was added L-methionine (5.00g, 33.49 mmoles) and the reaction was stirred at 100 °C for 24 h. The solution was cooled to RT and poured onto ice-water (800 mL) and the resulting precipitate was filtered and washed with water. To the crude product was added ethanol (400 mL) and the suspension was stirred at 60 °C for 1 h. The product was then filtered and the cake was washed with ether, hexane and dried under vacuum to afford 2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4(3H)-one (3.84g, 11.15 mmole, 40%). HPLC retention time 6.37 mins.

[0342] **Example 75.**

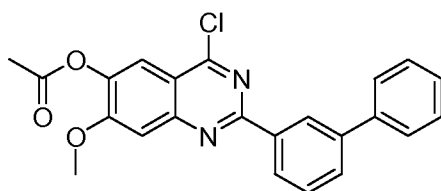
[0343] **2-[(3-phenyl)phenyl]-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate**



[0344] To a mixture of 2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4(3H)-one (3.40g, 9.87 mmole) in acetic anhydride (40 mL, 43.2g, 423.16 mmole) was added pyridine (4 mL, 3.91g, 49.46 mmole) and the reaction was stirred at 105 °C for 3 h. The suspension was cooled to RT and poured onto ice-water (800 mL) and stirred for 20 min. The crude product was filtered, washed with water and dried under vacuum to give 2-[(3-phenyl)phenyl]-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (186-036, 3.6g, 9.32 mmole, 94%). HPLC retention time 7.81 mins.

[0345] **Example 76.**

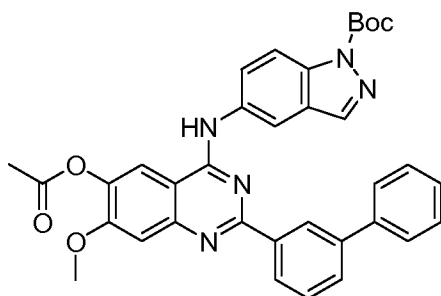
[0346] **4-chloro-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yl acetate**



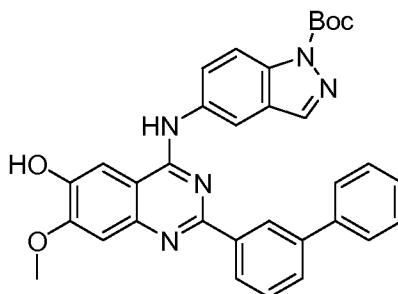
[0347] To a mixture of 2-[(3-phenyl)phenyl]-7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (3.6 g, 9.32 mmole) in SOCl_2 (40 mL) was added DMF (1 mL) and the reaction was stirred at reflux for 16 h. The mixture was cooled to RT and then the volatiles were removed in *vacuo*. The crude product was dissolved in CHCl_3 (300 mL) and washed with saturated NaHCO_3 solution (3x150 mL), water (2x150 mL) and brine (1 x150 mL) and dried with Na_2SO_4 . The solution was concentrated *in vacuo* to yield 4-chloro-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yl acetate (4.0g, 9.88 mmole). HPLC retention time 11.12 mins. (5-95-13 method).

[0348] **Example 77.**

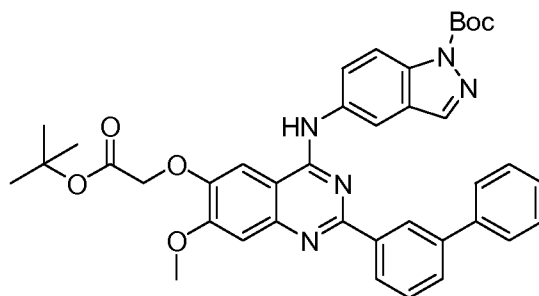
[0349] ***tert*-butyl 5-(6-acetoxy-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0350] A mixture of 4-chloro-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yl acetate (4.00g, 9.88 mmole), *tert*-butyl 5-amino-1H-indazole-1-carboxylate (2.42g, 10.37 mmole) in *iso*-propanol (130 mL) was stirred at 95 °C for 2 h. The reaction was cooled to RT and the crude product was filtered and then washed with ether, *iso*-propanol, and hexane and dried under vacuum to give *tert*-butyl 5-(6-acetoxy-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (4.33g, 7.20 mmole, 77% over two steps). MS 602 (M+1). HPLC retention time 6.47 mins.

[0351] Example 78.**[0352] 5-(2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**

[0353] To a mixture of *tert*-butyl 5-(6-acetoxy-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (4.30g, 7.15 mmole) in CH₃OH (300 mL) was added 28 % NH₄OH, and the reaction was stirred at RT for 16 h. The solution was concentrated *in vacuo* and the resulting solid was triturated with toluene and then hexane, followed by filtration to give *tert*-butyl 5-(2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (4.40g, 7.87 mmole). MS 560 (M+1). HPLC retention time 7.62 mins.

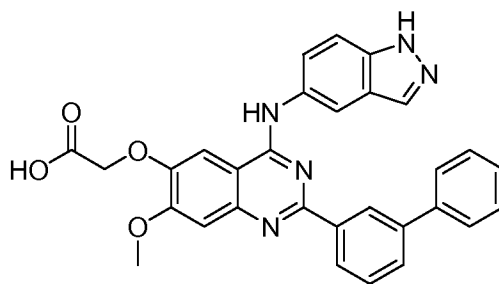
[0354] Example 79.**[0355] *tert*-butyl 5-[6-(2-*tert*-butoxy-2-oxoethoxy)-2-(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**

[0356] A mixture of *tert*-butyl 5-(2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.0g, 1.79 mmole), *tert*-butylbromoacetate (0.174g, 0.132 mL, 0.895 mmole), potassium carbonate (0.99g, 7.16 mmole) in DMF (20 mL) was stirred at 80 °C for 2 h. Then, a second portion of *tert*-butylbromoacetate (0.174g, 0.132 mL, 0.895

mmole) was added and the reaction for stirred for an additional 2 h at 80 °C. The mixture was cooled to RT and the volatiles were removed *in vacuo*. The crude product was partitioned between dichloromethane and water and the organic layer was dried with sodium sulfate and concentrated *in vacuo*. The crude product *tert*-butyl 5-[6-(2-*tert*-butoxy-2-oxoethoxy)-2-(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate was used immediately without further purification. MS 618 (M-^tBu+1). HPLC retention time 8.48 mins.

[0357] **Example 80.**

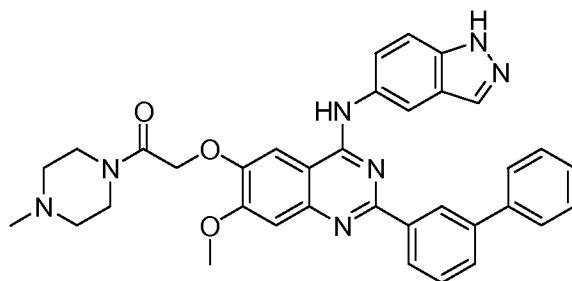
[0358] **2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy)acetic acid**



[0359] To *tert*-butyl 5-[6-(2-*tert*-butoxy-2-oxoethoxy)-2-(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.79 mmole) was added TFA (15 mL) at RT, and the solution was stirred for 2 h. The volatiles were removed *in vacuo* and the crude product was then triturated with ether, filtered and dried under vacuum to give 2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy) acetic acid (0.775g, 1.50 mmole, 84 % over 2 steps). MS 518 (M+1). HPLC retention time 5.95 mins.

[0360] **Example 81.**

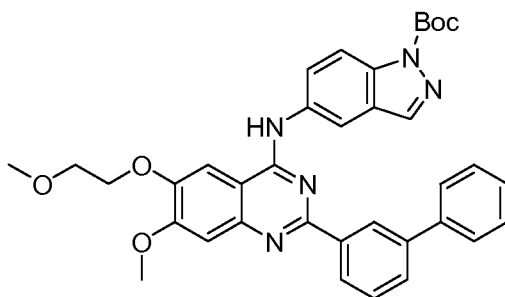
[0361] **2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy)-1-(4-methylpiperazin-1-yl)ethanone**



[0362] To a mixture of 2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy)acetic acid (0.25g, 0.48 mmole) in DMF (1 mL) / CH₂Cl₂ (7 mL) was added PyBOP® (0.25g, 0.48 mmole), and DIEA (0.186g, 0.251 mL, 1.44 mmole). The mixture was then stirred for 15 minutes and 1-methylpiperazine (0.048g, 0.053 mL, 0.48 mmole) was added and the reaction was stirred at RT for 3 h. The volatiles were then removed *in vacuo*. Upon adding CH₂Cl₂, the crude product precipitated and was subsequently filtered. The cake was washed with ether, hexane, CH₃OH, CH₂Cl₂ and finally hexane. The crude product was purified by reverse phase HPLC (25 to 55 % CH₃CN / H₂O, 90 minute run time) to yield 2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy)-1-(4-methylpiperazin-1-yl)ethanone (0.015g, 5%). MS 600 (M+1). HPLC retention time 5.22 mins.

[0363] **Example 82.**

[0364] *tert*-butyl 5-(2-[(3-(phenyl)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate

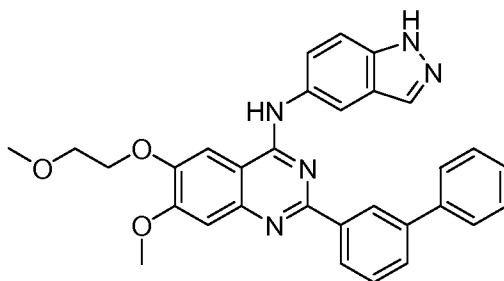


[0365] A mixture of *tert*-butyl 5-(2-[(3-(phenyl)phenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.055 g, 0.098 mmole), 2-bromoethyl methyl ether (0.031g, 0.021 mL, 0.226 mmole), K₂CO₃ (0.036g, 0.26 mmole), and DMF (2.5 mL) was stirred at 85 °C for 3.5 h. The mixture was poured onto ice-water (200 mL) and the crude product was filtered. The product was then dissolved in ether and was washed with water and the organic

layer was concentrated in *vacuo*. The crude product was purified by preparative TLC (SiO₂, 7 : 2.6 : 0.4 (CH₂Cl₂ : EtOAc : CH₃OH) to give *tert*-butyl 5-(2-[(3-(phenyl)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.110g). HPLC retention time 7.89 mins.

[0366] **Example 83.**

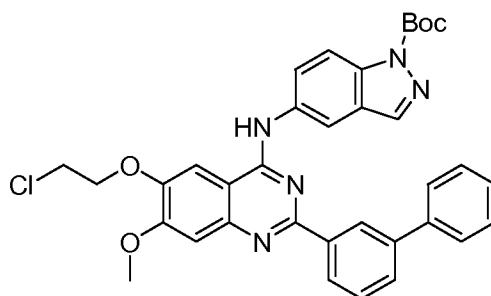
[0367] **2-[(3-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-amine**



[0368] TFA (4 mL) was added to *tert*-butyl 5-(2-[(3-(phenyl)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.110g, mmole) and the reaction was stirred at RT for 2 h. The solution was concentrated *in vacuo* and then azeotroped from hexane (1 X). The crude product was triturated with ether and filtered, dried under vacuum to give 2-[(3-(phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-amine (0.024g, 0.046 mmole, 47 % over 2 steps). MS 518.4 (M+1). HPLC retention time 6.47 mins.

[0369] **Example 84.**

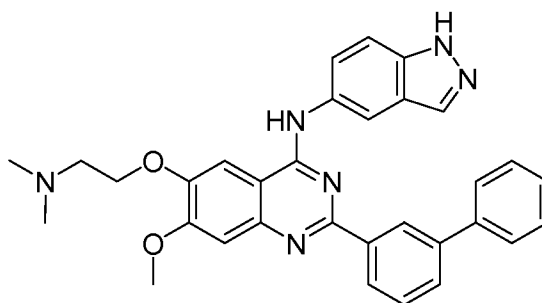
[0370] ***tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0371] A mixture of *tert*-butyl 5-(2-[(3-phenyl)phenyl]-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.5 g, 2.68 mmole), 1-bromo-2-chloroethane (1.32g, 0.76 mL, 9.17 mmole), K₂CO₃ (1.55g, 11.21 mmole), and DMF (15 mL) was stirred at 85 °C for 2.5 h. The mixture was poured onto ice-water and the crude product was filtered. The product was then dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo* to give *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.55g, 2.49mmol, 93 %). HPLC retention time 8.22 mins.

[0372] **Example 85.**

[0373] **6-(2-(dimethylamino)ethoxy)-N-(1H-indazol-5-yl)-7-methoxy-2-(3-(phenyl)phenyl)quinazolin-4-amine**

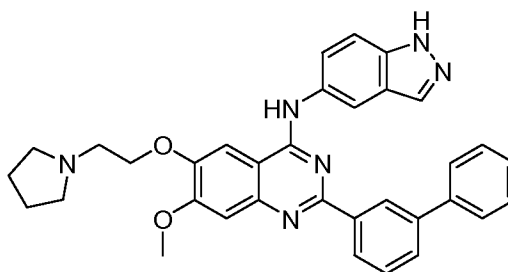


[0374] A solution of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.25g, 0.40 mmole) in DMSO (3 mL) was cooled to 0 °C. To this was added dimethylamine gas (bubbled into solution for 15 minutes) and the reaction was slowly heated to 85 °C and stirred for 2 h. The mixture was poured onto ice-water and the crude product was filtered. The product was then dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo*. The residue was

purified via preparative TLC (SiO₂, 10% CH₂Cl₂ / CH₃OH). To the crude product was added TFA (5 mL) and the reaction was stirred at RT for 1 h. The solution was concentrated *in vacuo* and the residue was triturated with ether, filtered and dried under vacuum to give 6-(2-(dimethylamino)ethoxy)-N-(1H-indazol-5-yl)-7-methoxy-2-(3-(phenyl) phenyl)quinazolin-4-amine (0.096g, 0.18 mmole, 45 % over 2 steps). MS 531 (M+1). HPLC retention time 5.18 mins.

[0375] Example 86.

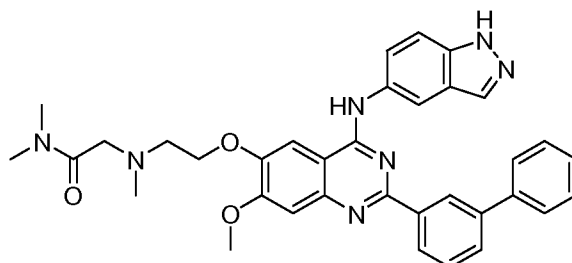
[0376] 2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-amine



[0377] To a mixture of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.25g, 0.040 mmole) in DMSO (2 mL) was added pyrrolidine (0.143g, 0.16 mL, 2.00 mmole) and the reaction was stirred at 85 °C for 4 h. The mixture was poured onto ice-water and the crude product was filtered. The product was then dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo*. The residue was purified via preparative TLC (SiO₂, 10% CH₂Cl₂ / CH₃OH) to give 2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-4-amine (0.042g, 0.075 mmole, 19 %). MS 557 (M+1). HPLC retention time 5.34 mins.

[0378] Example 87.

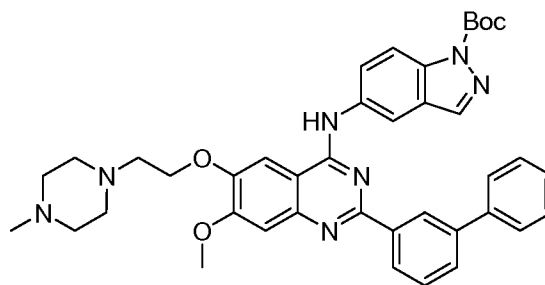
[0379] 2-((2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy)ethyl)(methyl)amino)-N,N-dimethylacetamide



[0380] To a mixture of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.25g, 0.40 mmole) in DMSO (2 mL) was added N,N-dimethyl-2-(methylamino)acetamide (0.232g, 2.00 mmole) and the reaction was stirred at 85 °C for 4 h. The mixture was poured onto ice-water and the crude product was filtered. The product was then dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo*. The residue was purified *via* preparative TLC (SiO₂, 10% CH₂Cl₂ / CH₃OH). To the product was added TFA (4 mL) and the reaction was stirred at RT for 2 h. The solution was concentrated *in vacuo* and the residue was triturated with ether, filtered and dried under vacuum to give 2-((2-(4-(1H-indazol-5-ylamino)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-6-yloxy) ethyl)(methyl)amino)-N,N-dimethylacetamide (0.178g, 0.30 mmole, 74 %). MS 602.6 (M+1). HPLC retention time 5.24 mins.

[0381] **Example 88.**

[0382] *tert*-butyl 5-(2-[(3-phenyl)phenyl]-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate

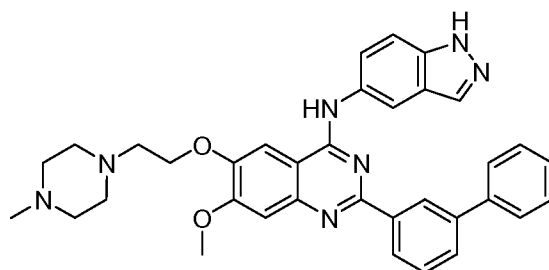


[0383] To a mixture of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.30g, 0.44 mmole) in DMSO (2 mL) was added 1-methylpiperazine (0.903g, 1.00 mL, 9.02 mmole) and the reaction was stirred at 85 °C for 3 h. The mixture was poured onto ice-water (100 mL) and the crude product was

filtered. The product was then dissolved in a mixture of CH_2Cl_2 and CH_3OH and the solution was concentrated *in vacuo*. The residue was purified via preparative TLC (SiO_2 , 10% CH_2Cl_2 / CH_3OH -with 0.1% NH_4OH) to give *tert*-butyl 5-(2-[(3-phenyl)phenyl]-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate which was taken on to the next step. HPLC retention time 6.00 mins.

[0384] **Example 89.**

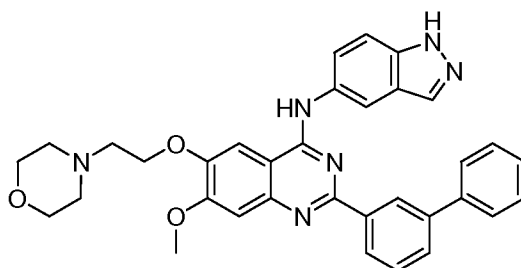
[0385] **2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-amine**



[0386] TFA (4 mL) was added to 5-(2-[(3-phenyl)phenyl]-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate and the reaction was stirred at RT for 1.5 h. The solution was concentrated *in vacuo* and the crude product was triturated with ether and filtered, dried under vacuum to give 2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-4-amine (0.166g, 0.283 mmole, 64 % over two steps). MS 586.4 (M+1). HPLC retention time 5.06 mins.

[0387] **Example 90.**

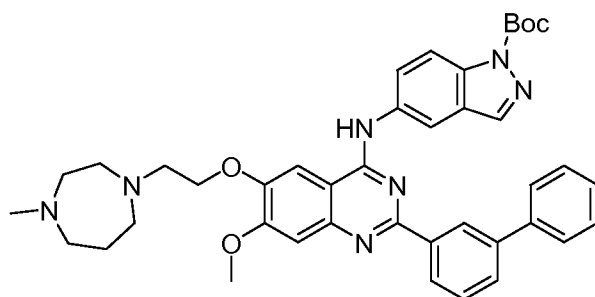
[0388] **2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-amine**



[0389] To a mixture of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.25g, 0.40 mmole) in DMSO (2 mL) was added morpholine (1.32g, 1.33 mL, 15.2 mmole) and the reaction was stirred at 85 °C for 48 h. The mixture was poured onto ice-water and the crude product was filtered. The product was then dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo*. The residue was purified *via* preparative TLC (SiO₂, 10% CH₂Cl₂ / CH₃OH) to give 2-[(3-phenyl)phenyl)-N-(1H-indazol-5-yl)-7-methoxy-6-(2-morpholinoethoxy)quinazolin-4-amine (0.131g, 0.20 mmole, 50 %). MS 572.2 (M⁺). HPLC retention time 5.27 mins.

[0390] **Example 91.**

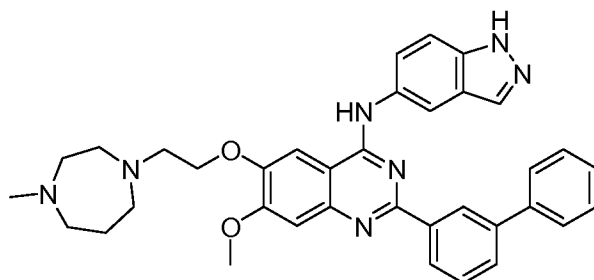
[0391] *tert*-butyl 5-(2-[(3-phenyl)phenyl)-7-methoxy-6-(2-(4-methyl-1,4-diazepan-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0392] A mixture of *tert*-butyl 5-(6-(2-chloroethoxy)-2-[(3-phenyl)phenyl]-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.25g, 0.402 mmole), 1-methyl-1,4-diazepane (0.23g, 0.25 mL, 2.00 mmoles) in DMSO was stirred at 85 °C for 2.5 h. The suspension was poured onto ice-water, filtered and re-dissolved in a mixture of CH₂Cl₂ and CH₃OH and the solution was concentrated *in vacuo*. The residue was purified *via* preparative TLC (SiO₂, 10% CH₂Cl₂ / CH₃OH-with 0.1% NH₄OH) to give *tert*-butyl 5-(2-[(3-phenyl)phenyl)-7-methoxy-6-(2-(4-methyl-1,4-diazepan-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate which taken on directly to the next step. HPLC retention time 5.96 mins.

[0393] Example 92.

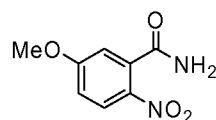
[0394] 2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methyl-1,4-diazepan-1-yl)ethoxy)quinazolin-4-amine



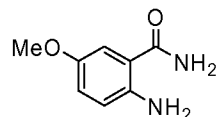
[0395] To a solution of 5-(2-[(3-phenyl)phenyl]-7-methoxy-6-(2-(4-methyl-1,4-diazepan-1-yl)ethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate in CH₂Cl₂ (2 mL) was added HCl as a 4.0 M solution in 1,4 dioxane (8 mL) and the reaction was stirred at RT for 5 h. The volatiles were removed *in vacuo* and the crude product was washed with hexane and dried under vacuum to yield 2-[(3-phenyl)phenyl]-N-(1H-indazol-5-yl)-7-methoxy-6-(2-(4-methyl-1,4-diazepan-1-yl)ethoxy)quinazolin-4-amine (0.063g, 0.105 mmole, 26 % over 2 steps.). MS 600.4 (M+1). HPLC retention time 5.01 mins.

[0396] Example 93.

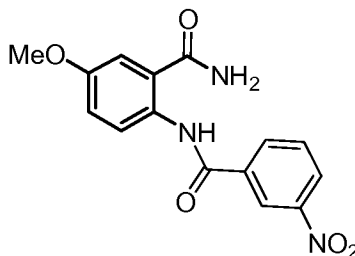
[0397] 5-Methoxy-2-nitrobenzamide



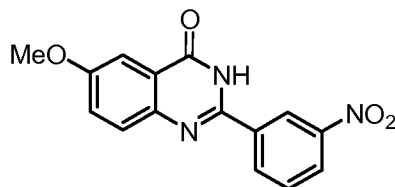
[0398] To a suspension of 5-methoxy-2-nitrobenzoic acid (7.5 g, 38.0 mmol) in anhydrous benzene (50 mL), was added thionyl chloride (3.8 mL, 52.05 mmol) followed by the addition of anhydrous DMF (0.4 mL). The resulting reaction mixture was refluxed for 5 h, upon which the volatiles were removed *in vacuo*. The residue was dissolved in anhydrous THF (60 mL) and added to an ice-cold saturated solution of ammonia in THF (60 mL). The resulting heterogeneous reaction mixture was allowed to warm room temperature and stirring was continued at RT for 48 h. The volatiles were removed *in vacuo* and the residue was used without further purification for next step. HPLC retention time 3.29 mins.

[0399] Example 94.**[0400] 5-Methoxy-2-aminobenzamide**

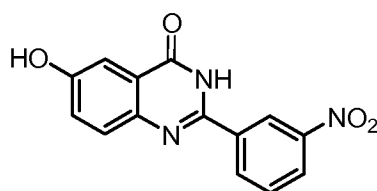
[0401] To a suspension of 5-methoxy-2-nitrobenzamide (38.0 mmol) in methanol (150 mL), was added 10% Pd-C (1.2 g) under an atmosphere of argon followed by addition of ammonium formate (18.0 g, 285.4 mmole). The resulting reaction mixture was refluxed for 2.5 h, upon which, the mixture was allowed to cool to RT and was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and the residue was washed with water to give a solid (4.74g). The filtrate, was extracted with ethyl acetate (2x300 mL), dried (Na₂SO₄), filtered, concentrated in *vacuo* and combined with the previous solid. The resulting solid was dried under vacuum to give 5-methoxy-2-aminobenzamide (4.74 g, 35.7 mmol, 94%). HPLC retention time 3.16 mins.

[0402] Example 95.**[0403] 5-Methoxy-2-(3-nitrophenyl)aminobenzamide**

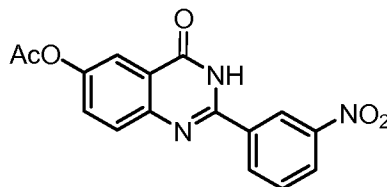
[0404] To a suspension of 2-amino-5-methoxybenzamide (2.42g, 14.6 mmol) and pyridine (6 mL) in CHCl₃ (120 mL) was added 3-nitrobenzoyl chloride (3.0g, 16.1 mmol). The resulting mixture was stirred at RT for 6 h. The volatiles were removed in *vacuo* and the resultant solid was washed with Et₂O to give the 5-Methoxy-2-(3-nitrobenzoyl)aminobenzamide (6.15g) which was taken directly on to the next step. HPLC retention time 6.58 mins.

[0405] Example 96.**[0406] 6-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**

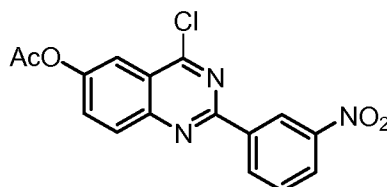
[0407] A suspension of the amide from the previous step (6.0g) in 3N NaOH (160 mL) was heated at 100°C for 9 h. The mixture was allowed to cool to RT and stirring was continued overnight at RT. The mixture was neutralized with 6N HCl to pH 7. A solid precipitated out and was collected *via* filtration and dried under vacuum to give the desired product 6-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (4.0g, 13.5 mmol, 95%). HPLC retention time 6.721 min.

[0408] Example 97.**[0409] 6-hydroxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**

[0410] To a suspension of 6-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (3.90g, 13.1 mmol), in CH₂Cl₂ (30 mL) cooled to -78 °C under an atmosphere of N₂ was added BBr₃ as a 1.0M solution in CH₂Cl₂ (20 mL, 20.0 mmol). The resulting mixture was stirred at -78 °C for 1 h, then allowed to warm to RT upon which it was stirred for a further 3 h. The mixture was re-cooled to -78 °C and stirred overnight. The reaction was quenched by the addition of EtOH (60 mL) and allowed to warm to RT. Stirring was continued for 1 h at RT, upon which a precipitate formed. Sat. NaHCO₃ solution was added and the yellow solid was collected via filtration and washed with Et₂O and EtOH and dried under vacuum to give 6-hydroxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (2.96g, 10.5 mmol, 80%). HPLC retention time 5.588 min.

[0411] Example 98.**[0412] 2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate**

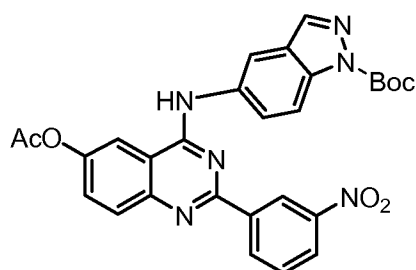
[0413] A mixture of 6-hydroxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (2.92g, 10.3mmol) Ac₂O (30 mL) and pyridine (4 mL) was heated at 105 °C for 4h.. The mixture was allowed to cool to RT and was poured into ice-water (300mL). The resulting slurry was stirred for 2-3 h at RT, then the solid was collected via filtration, washed with water, EtOH and Et₂O and dried under vacuum to give the product 2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (3.35g, 10.3 mmol, 100%). HPLC retention time 6.559 min.

[0414] Example 99.**[0415] 4-chloro-2-(3-nitrophenyl)quinazolin-6-yl acetate**

[0416] A suspension of 2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (3.30g, 10.1mmol) in SOCl₂ (65 mL) was added DMF (2 mL). The mixture was refluxed for 2.5 h, upon which the volatiles were removed in *vacuo*. The residue was taken up in CHCl₃ (450 mL) and washed with sat NaHCO₃ (200 ml) and water (200 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated in *vacuo* to give the product 4-chloro-2-(3-nitrophenyl)quinazolin-6-yl acetate (3.53g, 10.3 mmol). HPLC retention time 9.748 min.

[0417] Example 100.

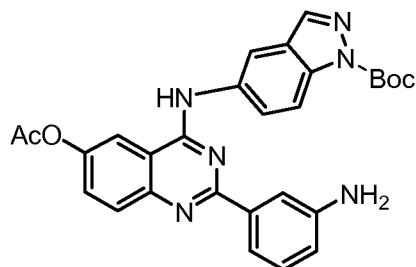
[0418] *tert*-butyl 5-(6-acetoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0419] A mixture of 4-chloro-2-(3-nitrophenyl)quinazolin-6-yl acetate (1.63g, 4.74 mmol) and *tert*-butyl 5-amino-1H-indazole-1-carboxylate (1.16g, 4.28 mmol) in IPA (80 mL) were heated at 95 °C for 5h. The mixture was allowed to cool to RT, the yellow solid was collected via filtration and washed with Et₂O to give the product *tert*-butyl 5-(6-acetoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.14g, 3.96mmol, 84%). HPLC retention time 9.649 min.

[0420] **Example 101.**

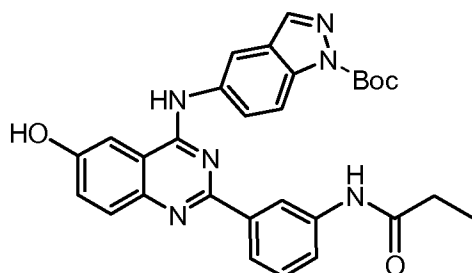
[0421] *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0422] A mixture of *tert*-butyl 5-(6-acetoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.84g, 1.55mmol) in MeOH (200 mL) was added 10% Pd/C under an atmosphere of N₂. The mixture was stirred under an atmosphere of H₂ (balloon pressure) for 48 h at RT. The mixture was filtered through a pad of Celite® washing with MeOH. The volatiles were removed in *vacuo* to give *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.811g, 1.59 mmol). HPLC retention time 5.51 min.

[0423] Example 102.

[0424] *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate

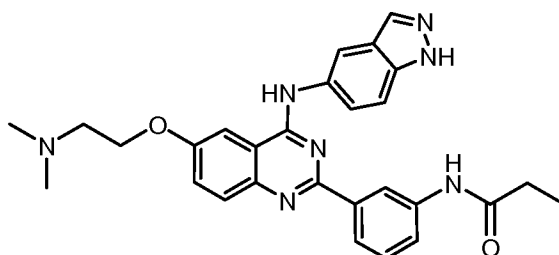


[0425] A mixture of *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.570g, 1.12 mmol), butyl chloride (0.18g, 1.69 mmol), and DIEA (0.65g, 5.03 mmol) in CH₂Cl₂ (20 mL) was stirred at RT for 7 h. the volatiles were removed in *vacuo* and the residue was triturated with water. The resultant solid was collected by filtration, washed with water and dried under vacuum.

[0426] The residue was taken up in MeOH (50 mL) and 28% NH₄OH (0.9 mL) was added. The mixture was stirred at RT for 24 h. The volatiles were removed in *vacuo* and the residue was triturated with MeOH/Et₂O to give the product *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.354g, 0.657mmol, 59%). HPLC retention time 6.342 min.

[0427] Example 103.

[0428] N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(dimethylamino)ethoxy)quinazolin-2-yl)phenyl)butyramide



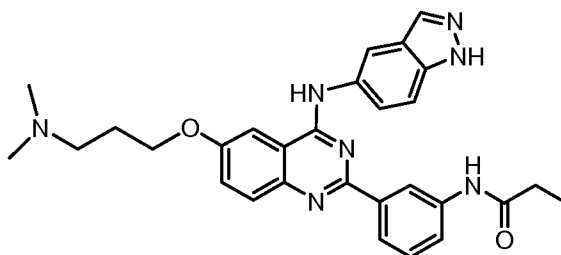
[0429] To a mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.107g, 0.199 mmol), 2-chloro-N,N-dimethylethanamine

hydrochloride (0.065g, 0.451 mmol), K_2CO_3 (0.065g, 0.451 mmol) in DMF (1.2 mL) was heated at 70 °C for 2.5 h. The mixture was allowed to cool to RT upon which, the mixture was diluted with CH_2Cl_2 (75 mL), washed with water (10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*.

[0430] The material was taken up in CH_2Cl_2 (2 mL) and TFA (3 mL) was added. The mixture was stirred at RT for 3 h. The volatiles were removed in *vacuo* and the residue was triturated with Et_2O and dried under vacuum to give the desired product N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(dimethylamino)ethoxy)quinazolin-2-yl)phenyl) butyramide (0.037g, 72.6 μ mol, 36%). MS 510.4 (M+1). HPLC retention time 5.16 min.

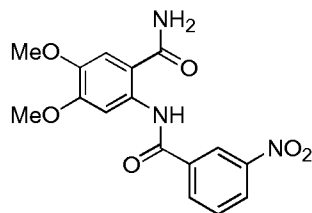
[0431] **Example 104.**

[0432] **N-(3-(4-(1H-indazol-5-ylamino)-6-(3-(dimethylamino)propoxy)quinazolin-2-yl)phenyl)butyramide**

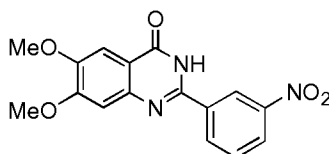


[0433] To a mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.106g, 0.197 mmol), 3-chloro-N,N-dimethylpropan-1-amine (0.081g, 0.451 mmol), K_2CO_3 (0.065g, 0.512 mmol) in DMF (1.2 mL) was heated at 70 °C for 2.5 h. The mixture was allowed to cool to RT upon which, the mixture was diluted with CH_2Cl_2 (75 mL), washed with water (10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The material was purified by preparative TLC (SiO_2 , CH_2Cl_2 :MeOH 9:1).

[0434] The purified material was taken up in CH_2Cl_2 (2 mL) and TFA (3 mL) was added. The mixture was stirred at RT for 3 h. The volatiles were removed in *vacuo* and the residue was triturated with Et_2O and dried under vacuum to give the desired product N-(3-(4-(1H-indazol-5-ylamino)-6-(3-(dimethylamino)propoxy)quinazolin-2-yl)phenyl) butyramide (0.057g, 0.109mmol, 55%). MS 524.6 (M+1). HPLC retention time.

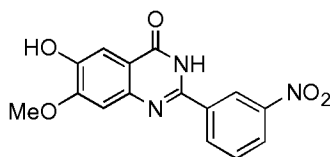
[0435] Example 105.**[0436] 4,5-Dimethoxy-2-(3-nitrophenyl)aminobenzamide**

[0437] To a suspension of 2-amino-4,5-dimethoxybenzamide (5.05 g, 25.7 mmole) and 3-nitro benzoyl chloride (5.2 g, 28.0 mmole) CHCl_3 (120 ml) was added pyridine (50 ml) drop wise at RT. The reaction mixture was stirred at RT for 24 h. The solvent was removed *in vacuo* and residue was triturated with Et_2O , filtered and dried under high vacuum to give 4, 5-dimethoxy-2-(3-nitrophenyl)aminobenzamide, which was used directly in the next step.

[0438] Example 106.**[0439] 6,7-Dimethoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**

[0440] A suspension of 4, 5-dimethoxy-2-(3-nitrophenyl)aminobenzamide (9.5g) was taken up in 2 N NaOH (200 mL) and was refluxed for 8 h. The reaction mixture was cooled to RT and left to stand overnight. The pH adjusted to 7 with 3 N HCl and the mixture was filtered. The filtered solid washed with water and dried under high vacuum to give 6,7-dimethoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one. (6.2g, 18.9mmol, 74% over two steps) HPLC retention time 6.15 mins.

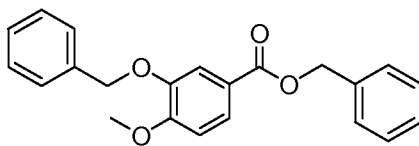
[0441] Example 107.**[0442] 6-Hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**



[0443] A mixture of 6,7-dimethoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (5.72g, 17.5 mmol) and L-methionine (3.1g, 20.7mmol) in methanesulfonic acid (40 mL) was heated at 100 °C for 4.5 h. An additional aliquot of L-methionine (0.45g, 1.36mmol) and methanesulfonic acid (10 mL) were added and the mixture was heated for a further 2 h. The mixture was allowed to cool to RT, poured into ice water (ca. 500 mL) and was neutralized with sat. NaHCO₃ solution. A solid separated out which was collected by filtration and dried under vacuum to give the desired 6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one. (7.3g). HPLC retention time 5.486 min.

[0444] **Example 108.**

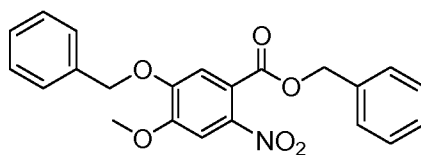
[0445] **Benzyl 3-(benzyloxy)-4-methoxybenzoate**



[0446] To an ice cold mixture of isovanillic acid **1** (4.3 g, 25.5 mmol) and K₂CO₃ (10.5 g, 0.152 mol) in anhydrous DMF (40 mL) was added benzyl bromide (8.7g, 6.05 mL, 51.1 mmol). The resulting reaction mixture stirred at RT overnight. An additional aliquot of benzyl bromide was added (1.0 ml) and stirring was continued for 1.5 h. The reaction mixture was poured into brine (100 mL) and the solid was collected *via* filtration, washed with water and dried under high vacuum to give benzyl 3-(benzyloxy)-4-methoxybenzoate as a white solid (7.99g, 23.0 mmol, 90%).

[0447] **Example 109.**

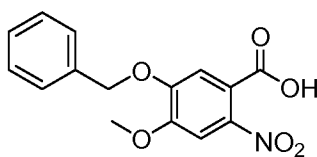
[0448] **Benzyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate**



[0449] To a solution of benzyl 3-(benzyloxy)-4-methoxybenzoate (6.32g, 18.1 mmol) in Ac₂O (62 mL) cooled to -10 °C under an atmosphere of N₂ was added fuming HNO₃ (1.5 mL, 37.1 mmol) in one portion. Stirring was continued at -10 °C for 10 minutes, then at RT for 3 hours. The reaction mixture was carefully poured into ice-water and the pH adjusted to ca. pH=5 with 5N NaOH, sat. NaHCO₃ and 0.5 NaOH. The mixture was extracted with CH₂Cl₂ (3x200 mL). The combined organics were dried (Na₂SO₄), filtered and concentrated in *vacuo*. The residue was azeotroped with heptane to give benzyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate as red colored oil (6.55g, 16.7 mmol, 93%).

[0450] **Example 110.**

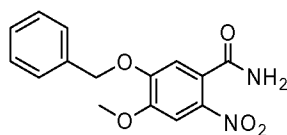
[0451] **5-(Benzyloxy)-4-methoxy-2-nitrobenzoic acid**



[0452] To a solution of benzyl 5-(benzyloxy)-4-methoxy-2-nitrobenzoate (1.4g, 3.56 mmol) in EtOH (10 mL) was added 1N NaOH (4.27 mL, 4.27 mmol). The mixture was stirred at RT for 1h, upon which an additional aliquot of NaOH (4.27 mL, 4.27 mmol) was added. Stirring was continued at RT overnight. The mixture was diluted with water (20 mL) and washed with CH₂Cl₂ (2x25 mL). The aqueous layer was acidified to pH=2 with 0.5 N HCl and extracted with EtOAc (3 x50 mL). The combined organics were dried (Na₂SO₄), filtered and concentrated in *vacuo* to give 5-(benzyloxy)-4-methoxy-2-nitrobenzoic acid (1.02g, 3.37 mmol, 94%).

[0453] **Example 111.**

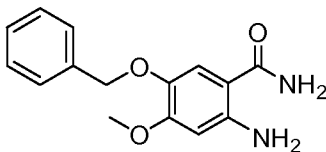
[0454] **4-Methoxy-5-benzyloxy-2-nitrobenzamide**



[0455] To a suspension of 4-methoxy-5-benzyloxy-2-nitrobenzoic acid (10.0 g, 33.3 mmol) in anhydrous THF (100 mL) was added oxalyl chloride (4.90 mL, 56.2 mmol) followed by one drop of anhydrous DMF. The mixture was stirred at RT for 16 h, upon which the mixture was poured into water (300 mL) and ammonium hydroxide (50 mL). A solid was separated out, which was collected by filtration and dried under *vacuo*. The solid was taken up in refluxing methanol (500 mL) and the insoluble solid was collected via filtration and dried under vacuum to give 4-methoxy-5-benzyloxy-2-nitrobenzamide (6.50g, 21.5 mmol, 65 %). HPLC retention time 6.154 min.

[0456] **Example 112.**

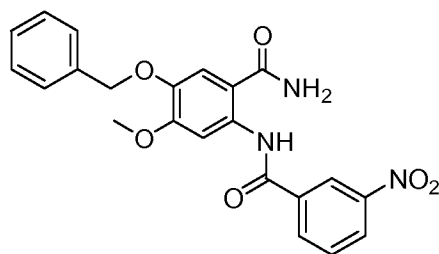
[0457] **4-Methoxy-5-benzyloxy-2-aminobenzamide**



[0458] A mixture of 4-methoxy-5-benzyloxy-2-nitrobenzamide (6.60 g, 21.9 mmol) and iron powder (8.14 g, 0.146 mol) in acetic acid/methanol (80 mL/80mL) was heated at $85 \pm 5^\circ\text{C}$ for 1.5 h. The reaction mixture was allowed to cool to RT and the iron was removed by filtration, and volatiles were removed in *vacuo*. The residue was taken up in sat. sodium bicarbonate and the mixture was extracted with ethyl acetate (600 mL x 3). The combined organic layers were washed with water (1x150 mL), brine (1x150 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give 4-methoxy-5-benzyloxy-2-aminobenzamide (5.2 g, 19.1 mmol, 87%). MS 273.2. (M^+). HPLC retention time 4.585 min.

[0459] **Example 113.**

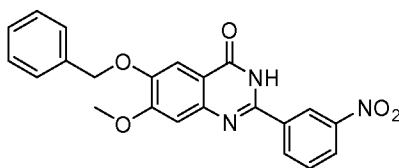
[0460] **4-Methoxy-5-benzyloxy-2-(3-nitrobenzoylamino)benzamide**



[0461] To a suspension of 6-methoxy-7-benzyloxy-2-aminobenzamide (4.86 g, 17.9 mmol) and pyridine (10 mL) in chloroform (600 mL), was added 3-nitrobenzoyl chloride (3.60 g, 19.4 mmol) slowly. The resulting reaction mixture was stirred at room temperature for 24 h, upon which the volatiles were removed under reduced pressure, and resulting residue was dried under vacuum. The residue upon trituration with Et₂O gave a light yellow colored solid in quantitative yield (Note: Possesses some pyridine. HCl). HPLC retention time 8.384 min.

[0462] **Example 114.**

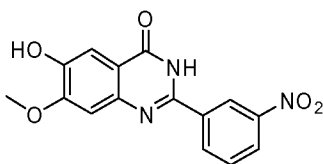
[0463] **6-(Benzyloxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**



[0464] A suspension of 4-methoxy-5-benzyloxy-2-(3-nitrobenzoylamino) benzamide (8.00 g, possesses some pyridine.HCl) in 4N NaOH (200 mL) was heated at 100±5°C for 10 h. The reaction mixture was allowed to cool to room temperature and pH was adjusted to 7 - 7.5 with 6 N HCl. A solid separated out, which was collected by filtration, washed with water (100 mL) and dried under vacuum to give 6-(benzyloxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (3.22g, 7.99 mmol, 47% over two steps). MS 404 (M+1) HPLC retention time 8.026 min.

[0465] **Example 115.**

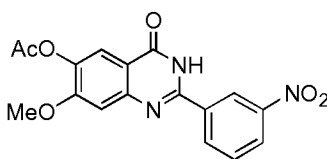
[0466] **6-Hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one**



[0467] To a suspension of 6-(benzyloxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (3.21 g, 7.95 mmol) in trifluoroacetic acid (45 mL) was heated at 75 ± 5 °C for 2.5 h. The volatiles were removed in *vacuo* and residue was taken up with sat. NaHCO_3 solution. A light yellow colored solid separated out, which was collected via filtration. The solid was washed with water and dried under vacuum to give 6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (2.38g, 7.60 mmol, 96%). HPLC retention time 5.486 min.

[0468] **Example 116.**

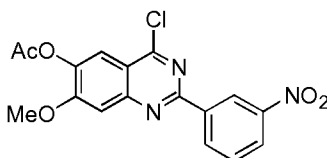
[0469] **7-Methoxy-2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate**



[0470] A mixture of 6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4(3H)-one (2.3g, 7.34mmol), Ac_2O (40mL) and pyridine (4 mL) were heated at 105 °C for 3.5 h. The reaction mixture was allowed to cool and poured into ice-water (ca. 300 mL) and the resulting slurry was stirred for 2 h. The solid was collected by filtration and washed with water, EtOH and Et_2O and dried under high vacuum to give 7-methoxy-2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate. (2.6g, 7.31 mmol, 99%). HPLC retention time 6.24 min.

[0471] **Example 117.**

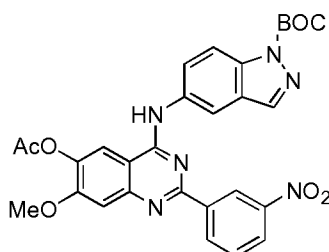
[0472] **4-Chloro-7-methoxy-2-(3-nitrophenyl)quinazolin-6-yl acetate**



[0473] A mixture of the 7-methoxy-2-(3-nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (1.70g, 4.79 mmol), thionyl chloride (30 mL) and anhydrous DMF (0.6 mL) were refluxed for 2.5 h. The volatiles were removed in *vacuo* and the residue dissolved in CH₂Cl₂ (500 mL) and was washed with water, sat. NaHCO₃, water and brine, dried (Na₂SO₄), filtered and concentrated in *vacuo* to 4-chloro-7-methoxy-2-(3-nitrophenyl)quinazolin-6-yl acetate. (1.6g, 4.23 mmol, 88%). HPLC retention time 9.75 min.

[0474] **Example 118.**

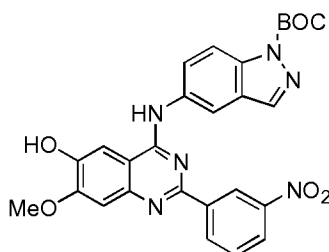
[0475] ***tert*-Butyl 5-(6-acetoxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0476] A mixture of 4-chloro-7-methoxy-2-(3-nitrophenyl)quinazolin-6-yl acetate (1.60g, 4.23 mmol) and *tert*-butyl 5-amino-1H-indazole-1-carboxylate (1.0g, 4.28 mmol) were refluxed in anhydrous *iso*-propanol (60mL) for 5 h. The mixture was allowed to cool to RT, upon which the solid was collected *via* filtration and was washed with Et₂O to give *tert*-butyl 5-(6-acetoxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (2.2g, 4.23mmol, 100%). HPLC retention time = 7.75 mins.

[0477] **Example 119.**

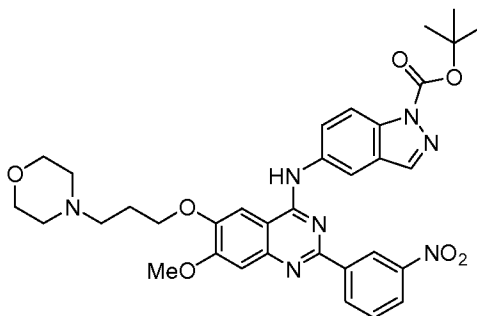
[0478] ***tert*-Butyl 5-(6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0479] To a suspension of *tert*-butyl 5-(6-acetoxy-7-methoxy-2-(3-nitrophenyl)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.150g, 2.01mmol) in MeOH (100 mL) was added 28% aq. NH₄OH solution (0.7 mL). The mixture was stirred at RT for 20 h. The solid was collected via filtration and dried under vacuum to give *tert*-butyl 5-(6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.800g, 1.51mmol, 75%). HPLC retention time 6.57 mins.

[0480] **Example 120.**

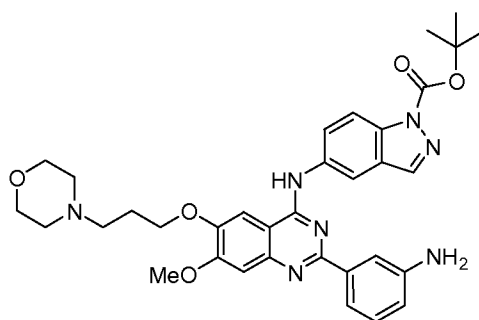
[0481] ***tert*-butyl 5-(7-methoxy-6-(3-morpholinopropoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0482] A mixture of *tert*-Butyl 5-(6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.70g, 1.32 mmol), 4-(3-chloropropyl)morpholine (0.32g, 1.96 mmol) and K₂CO₃ (1.33g, 9.62 mmol) in DMF (10mL) was heated at 80°C for 2.5 h. The mixture was allowed to cool to RT and the volatiles were removed in *vacuo*. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂ 97:3 to 94:6 to 90:10) to give the desired compound *tert*-butyl 5-(7-methoxy-6-(3-morpholinopropoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. HPLC retention time (5.76 min).

[0483] **Example 121.**

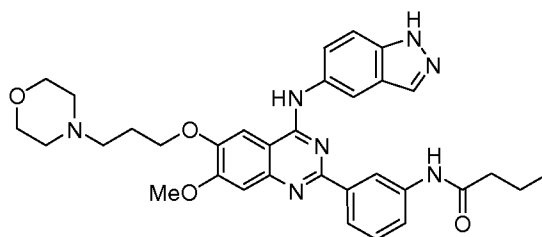
[0484] ***tert*-butyl 5-(2-(3-aminophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0485] To a mixture of 5-(7-methoxy-6-(3-morpholinopropoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.215g) in MeOH (60mL) was added Pd/C (0.21g) and NH_4CO_2 (0.21g). The mixture was heated at 60 °C for 40 mins, upon which an additional portion of NH_4CO_2 (0.095g) was added, heating was continued for a further 20 minutes. The mixture was filtered to remove the Pd/C and the filtrate was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (300 mL) and was washed with water and brine. The mixture was dried (Na_2SO_4) and the volatiles removed in *vacuo*. The material was combined with an identical experiment using 0.2g and the residue was subjected to preparative TLC (SiO_2 , CH_2Cl_2 : MeOH 9:1) to give the desired product *tert*-butyl 5-(2-(3-aminophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. HPLC retention time 4.67 mins.

[0486] **Example 122.**

[0487] **N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-2-yl)phenyl)butyramide**



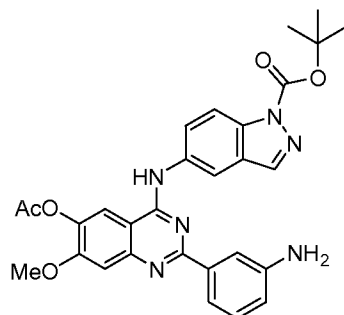
[0488] To a solution of *tert*-butyl 5-(2-(3-aminophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.076g, 0.121 mmol) in CH_2Cl_2 (4mL), DIEA (0.040g, 0.30 mmol) and butyryl chloride (0.026g) were added.

The resulting mixture was stirred at RT for 2.5h. The volatiles were removed in *vacuo* and the residue was taken up in CH₂Cl₂ (15 mL), washed with NaHCO₃ solution, water and brine, dried (Na₂SO₄) and filtered.

[0489] The residue was taken up in CH₂Cl₂ (3 mL) and TFA (3 mL) was added. The mixture was stirred at RT for 2.5 h. The volatiles were removed in *vacuo* and the residue was washed with Et₂O and hexane. The solid was dried under vacuum to give the desired product N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-2-yl)phenyl)butyramide (0.066g, 0.110mmol, 91%). MS 596.3 (M+1). HPLC retention time 4.60 mins.

[0490] **Example 123.**

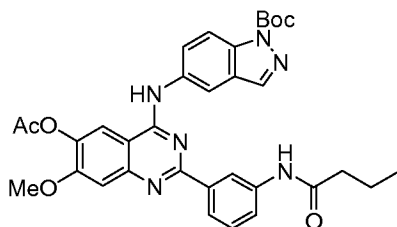
[0491] ***tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0492] To a mixture of *tert*-butyl 5-(6-acetoxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.40g, 0.70 mmol) in MeOH (100mL) was added Pd/C (0.15g) under an atmosphere of N₂. The mixture was then stirred under an atmosphere of H₂ (balloon pressure) for 48h at RT. The mixture was filtered through a pad of Celite® washing with MeOH. The filtrate was concentrated in *vacuo* to give the desired product *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.23g, 0.43mmol, 61%). HPLC retention time 5.748 mins.

[0493] **Example 124.**

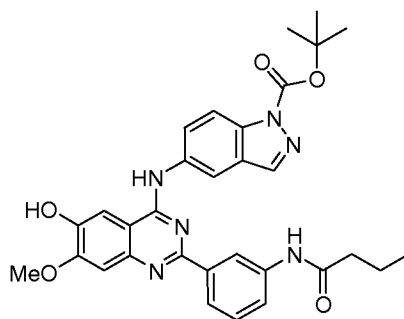
[0494] ***tert*-Butyl 5-(6-acetoxy-2-(3-butyramidophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0495] To a solution of *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.51 g, 4.65 mmol) and DIEA (3.08 mL, 17.7 mmol) in dichloromethane (60 mL) was added butyryl chloride (0.72 g, 6.76 mmol). The resulting reaction mixture was stirred at room temperature for 84 h upon which a solid separated out. The solid was collected by filtration and dried under vacuum (1.32 g). The filtrate was concentrated in *vacuo* and upon trituration with water gave an additional product (1.0g). Combination of the two solids gave *tert*-butyl 5-(6-acetoxy-2-(3-butyramidophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.32g, 3.80 mmol, 82%). HPLC retention time 7.079 min.

[0496] **Example 125.**

[0497] ***tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**

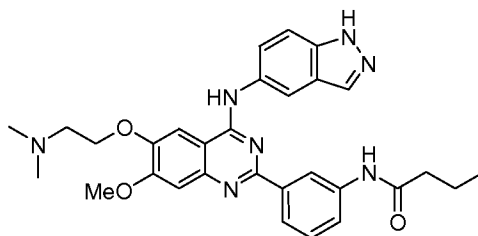


[0498] To a mixture of *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.205g, 0.38 mmol) in CH₂Cl₂ (10mL) was added DIEA (0.180g, 1.4 mmol) and butyryl chloride (0.055g, 0.52 mmol) respectively. The mixture was stirred at RT for 2 h. The mixture was concentrated in *vacuo* and taken up in CH₂Cl₂ (60 mL), the organic layer was washed with water and brine, dried (Na₂SO₄), filtered and concentrated in *vacuo*.

[0499] The residue was taken up in MeOH (40mL) and 28% NH₄OH (0.25 mL) was added to the mixture. The mixture was stirred at RT for 24 h. The volatiles were removed in *vacuo* and the residue was triturated with Et₂O to give *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.130g, 0.24mmol, 63%). HPLC retention time 6.49 min.

[0500] **Example 126.**

[0501] **N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(dimethylamino)ethoxy)-7-methoxyquinazolin-2-yl)phenyl)butyramide**

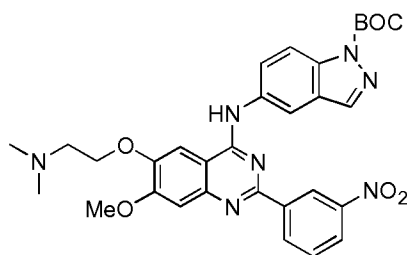


[0502] To a mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.102g, 0.168 mmol), 2-chloro-N,N-dimethylethanamine hydrochloride (0.053g, 0.37 mmol) and K₂CO₃ (0.090g, 0.65 mmol) in DMF (2.5 mL) was heated at 85 °C for 3 h. The mixture was allowed to cool to RT and was concentrated in *vacuo*. The residue was subjected to preparative TLC (SiO₂, CH₂Cl₂ 9:1).

[0503] After isolation, the product was immediately taken up CH₂Cl₂ (1 mL) and TFA (2 mL) was added. The mixture was stirred at RT for 3.5 h, the volatiles were removed in *vacuo* and the residue was triturated with Et₂O and dried under vacuum to give the desired product N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(dimethylamino)ethoxy)-7-methoxyquinazolin-2-yl)phenyl)butyramide. MS 540.5 (M+1). (HPLC retention time 4.55 mins).

[0504] **Example 127.**

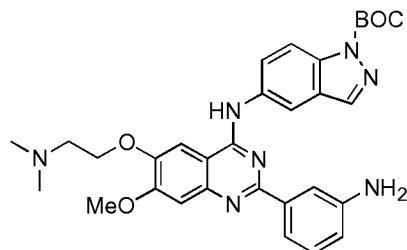
[0505] ***tert*-Butyl 5-(6-(2-(dimethylamino)ethoxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



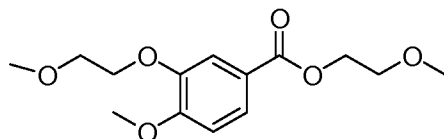
[0506] A mixture of *tert*-butyl 5-(6-hydroxy-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.475g, 0.898mmol), 2-chloro-N,N-dimethylethanamine (0.28g, 1.94 mmol) and K₂CO₃ (1.18g, 2.54 mmol) in DMF (8 mL) was heated at 85°C for 3 h. The volatiles were removed in *vacuo* and the residue was taken up in CHCl₃/MeOH. The solid was removed *via* filtration and the filtrate was concentrated in *vacuo*. The residue was purified by column chromatography (SiO₂, CHCl₃/MeOH 93:7 then 90:10) to give *tert*-butyl 5-(6-(2-(dimethylamino)ethoxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.087g, 0.145 mmol, 16%). MS 600.4 (M+1).

[0507] **Example 128.**

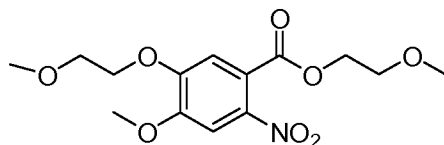
[0508] ***tert*-Butyl 5-(2-(3-aminophenyl)-6-(2-(dimethylamino)ethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**



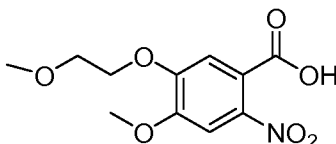
[0509] A mixture of *tert*-butyl 5-(6-(2-(dimethylamino)ethoxy)-7-methoxy-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.085g, 0.142mmol) and 10 % Pd / C (0.100g) in MeOH (20 ml) was hydrogenated at RT using a balloon filled with hydrogen gas. The reaction was heated at 55 °C for 1 h. The reaction mixture filtered through Celite® washing with MeOH. The filtrate was concentrated in *vacuo* to give *tert*-butyl 5-(2-(3-aminophenyl)-6-(2-(dimethylamino)ethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate. (0.065g, 0.128mmol, 90%). HPLC retention time 3.42 mins.

[0510] Example 129.**[0511] 2-Methoxyethyl 4-methoxy-3-(2-methoxyethoxy)benzoate**

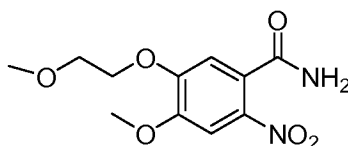
[0512] To a mixture of 3-hydroxy-4-methoxy benzoic acid (9.6g, 57.1 mmol) in DMF (110 mL) cooled to 0°C under an atmosphere of N₂ was added K₂CO₃ slowly. The mixture was stirred for 30 minutes upon which 2-bromoethyl methyl ether (10.7 mL, 114.2 mmol) was added slowly. The mixture was stirred at RT for 1 h and then at 80 °C for 12 hours, upon which another portion of 2-bromoethyl methyl ether (8.0 mL, 85.7 mmol) was added. Heating was continued for 2 h., upon which TLC indicated complete reaction. The reaction mixture was allowed to cool to RT and poured into ice-water. The mixture was extracted with EtOAc:hexane (4:1 v/v, 3x300 mL). The combined extracts were washed with brine (1x 300 mL), dried (Na₂SO₄), filtered and concentrated in *vacuo* to give 2-methoxyethyl 4-methoxy-3-(2-methoxyethoxy)benzoate as a dark colored oil. (15.05g, 52.9mmol, 93%). MS 307.3 (M+Na). HPLC retention time 5.80 mins.

[0513] Example 130.**[0514] 2-Methoxyethyl 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoate**

[0515] To a solution of 2-methoxyethyl 4-methoxy-3-(2-methoxyethoxy)benzoate (15.05g, 52.9 mmol) in AcOH (54 mL) under an atmosphere of N₂ was added conc. HNO₃ (13.5 mL) in one portion. The reaction was stirred at RT for 72 h. The mixture was poured into ice-water (ca. 800mL) and extracted with EtOAc (2x400 mL). The combined organics were washed with water (2x 200 mL) and brine (1x 200 mL), dried (Na₂SO₄) and conc. in *vacuo*. The residue was azeotroped with heptane (2x300 mL) to remove residual AcOH giving 2-methoxyethyl 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoate as a dark colored oil. (15.5g, 47.1mmol, 89%). HPLC retention time 6.24 mins.

[0516] Example 131.**[0517] 4-Methoxy-5-(2-methoxyethoxy)-2-nitrobenzoic acid**

[0518] To a solution of 2-methoxyethyl 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoate (5.0g, 15.2 mmol) in EtOH (40mL) was added 2N NaOH (40mL, 76.0 mmol, 5 eq.). The mixture was stirred at RT for 12 h. The mixture was diluted with water (100 mL) and washed with CH₂Cl₂ (1x100 mL). The aqueous layer was acidified to pH=1 using 1N HCl (A solid began to precipitate, this was dissolved by the addition of EtOAc). The aqueous mixture was extracted with EtOAc (2x200 mL). The combined organics were washed with brine (1x100mL), dried (Na₂SO₄), filtered and concentrated in *vacuo* to give 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoic acid as an off white solid (3.55g, 12.4 mmol, 86%). HPLC retention time 4.94 mins.

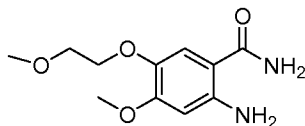
[0519] Example 132.**[0520] 4-Methoxy-5-(2-methoxyethoxy)-2-nitrobenzamide**

[0521] To a solution of 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzoic acid (3.35g, 12.4mmol) under an atmosphere of N₂ in anhydrous THF (50 mL) was added oxalyl chloride (2.25 mL, 1.7 eq. 25.5 mmol) and two drops of DMF. The mixture was stirred at RT for 30 minutes, upon which two more drops of DMF were added and stirring at RT was continued for 1 h. Tlc and HPLC analysis indicated complete formation of the acid chloride intermediate and the mixture was concentrated in *vacuo* to give the acid chloride intermediate as a yellow solid. The solid was dissolved in anhydrous THF (50 mL) and to this solution was added a saturated solution of NH₃ in THF (15 mL) *via* a cannula. A precipitate began to form and stirring was continued at RT for 12 h. The mixture was concentrated in *vacuo* to give 4-methoxy-5-(2-

methoxyethoxy)-2-nitrobenzamide as an off-white solid. (4.5g, contains some NH₄Cl, the mixture was taken on directly to the next step). HPLC retention time 8.55 mins.

[0522] **Example 133.**

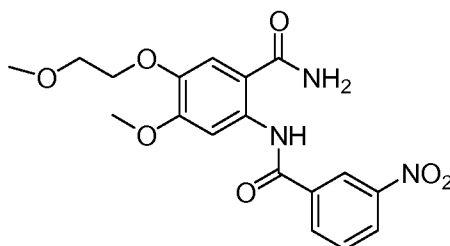
[0523] **2-Amino-4-methoxy-5-(2-methoxyethoxy)benzamide**



[0524] A mixture of 4-methoxy-5-(2-methoxyethoxy)-2-nitrobenzamide (4.5g, contains some NH₄Cl) and 10% Pd/C (ca. 0.5g) in DME (200mL) and MeOH (200mL) was hydrogenated under a balloon of H₂ at RT for 12 h. The mixture was filtered through a pad of Celite® and concentrated in *vacuo* to give 2-amino-4-methoxy-5-(2-methoxyethoxy)benzamide as an off white solid (2.8g, 11.6 mmol). HPLC retention time 2.80 mins.

[0525] **Example 134.**

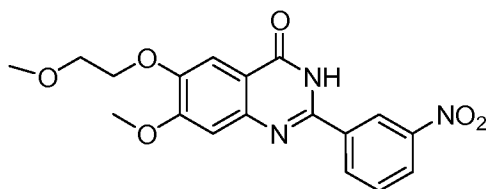
[0526] **4-Methoxy-5-(2-methoxyethoxy)-(3-nitrophenyl)aminobenzamide**



[0527] To a mixture of 2-amino-4-methoxy-5-(2-methoxyethoxy)benzamide (1.78g, 7.40 mmol) and pyridine (2.40 mL, 29.6 mmol) in CHCl₃ (40 mL) was added 3-nitrobenzoyl chloride (1.44g, 7.8 mmol). The mixture was stirred at RT for 2.5 h upon which the mixture was concentrated in *vacuo* to give the desired product, which was used directly in the next step without purification.

[0528] **Example 135.**

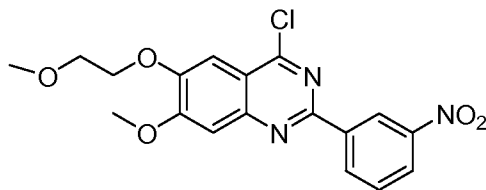
[0529] **7-Methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4(3H)-one**



[0530] The crude product from the previous step (7.4 mmol theoretically) was taken up in 2N NaOH (40 mL) and refluxed for 4 h. the mixture was allowed to cool to RT and neutralized to pH=7 with 6 and 1 N HCl. Upon neutralization a precipitate appeared which was collected *via* filtration and washed with Et₂O. The solid was azeotroped with toluene (2x50mL) to remove any residual water and dried under high vacuum to give 7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4(3H)-one as an off white solid (2.60g, 7.00 mmol, 95% over two steps). HPLC retention time 6.2 mins.

[0531] **Example 136.**

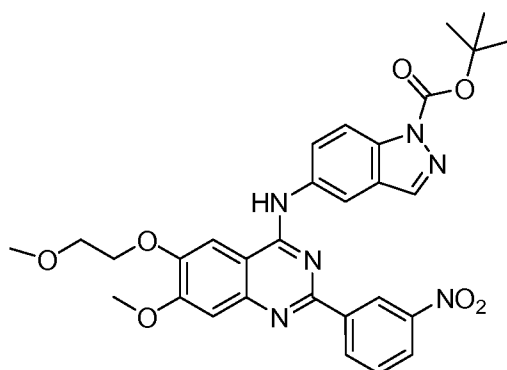
[0532] **4-Chloro-7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazoline**



[0533] To a suspension of 7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4(3H)-one (1.65g, 4.46 mmol) in anhydrous THF (30mL) was added oxalyl chloride (1.3 mL, 14.7 mmol) and 2 drops of DMF. The mixture was refluxed for 2 h, upon which the mixture was concentrated in *vacuo*, taken up in CHCl₃ (100 mL) and washed with sat. NaHCO₃ (3x 50 mL), water (2x50 mL) and brine (1x50 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated in *vacuo* to give 4-chloro-7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazoline (1.18g, 3.03 mmol, 68%). HPLC retention time 9.55 mins.

[0534] **Example 137.**

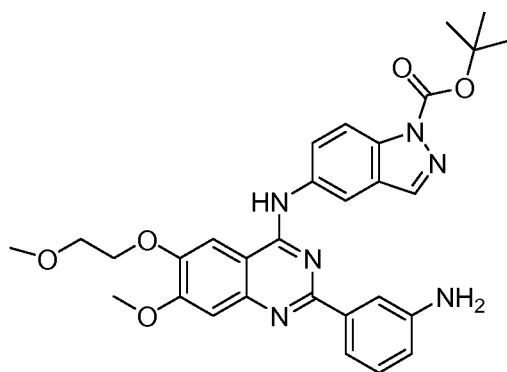
[0535] ***tert*-Butyl 5-(7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0536] A mixture of 4-chloro-7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazoline (0.500g, 1.28 mmol) and 5-amino-1H-indazole-1-carboxylate (0.314g, 1.34mmol) in iso-propanol (30 mL) was heated at 95°C for 30 minutes and at 95 °C for 8 h. The mixture was allowed to cool to RT and the solid was collected via filtration. The cake was washed with iso-propanol and Et₂O, triturated with CH₂Cl₂ and EtOAc and dried in *vacuo* to give *tert*-Butyl 5-(7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.560g, 0.955 mmol, 71%). MS 587 (M+1). HPLC retention time 7.21 mins.

[0537] **Example 138.**

[0538] ***tert*-Butyl 5-(2-(3-aminophenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

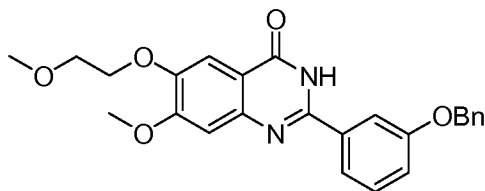


[0539] A mixture of *tert*-butyl 5-(7-methoxy-6-(2-methoxyethoxy)-2-(3-nitrophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.560g, 0.95 mmol) and 10% Pd/C (ca. 0.1g) in DME (100mL) and MeOH (100mL) was hydrogenated under a balloon of H₂ at RT for 12 h. The mixture was filtered through a pad of Celite® and concentrated in *vacuo* to

give *tert*-butyl 5-(2-(3-aminophenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate as an off white solid (0.510g, 0.92 mmol, 97%). HPLC retention time 5.62 mins.

[0540] **Example 139.**

[0541] **2-(3-(benzyloxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4(3H)-one**

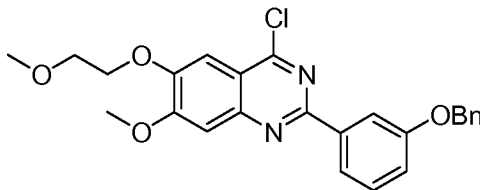


[0542] To mixture of 2-amino-4-methoxy-5-(2-methoxyethoxy)benzamide (2.20g, 9.16 mmol) and 3-(benzyloxy)benzoyl chloride (2.50 g, 10.1 mmol) in CHCl_3 (50 mL) was added pyridine 2.9 mL). The mixture was stirred at RT for 3 h, upon which the volatiles were removed in *vacuo*.

[0543] The residue was taken up in 2N NaOH (60 mL) and heated at reflux overnight. The mixture was allowed to cool to RT, upon which it was neutralized with 1N HCl to pH=7. The mixture was allowed to stand for 2 h upon which the precipitate was collected via filtration. The solid was dried under high vacuum to give 2-(3-(benzyloxy)-phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4(3H)-one (3.28g, 7.58 mmol, 83%). MS 433 (M+1). HPLC retention time 7.41 mins.

[0544] **Example 140.**

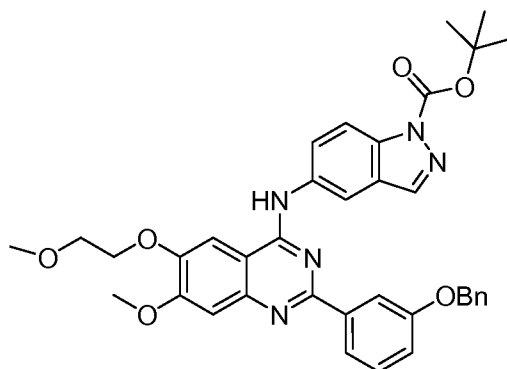
[0545] **2-(3-(benzyloxy)phenyl)-4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline**



[0546] To a suspension of 2-(3-(benzyloxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4(3H)-one (3.28g, 7.58 mmol) in CH₂Cl₂ (100mL) was added oxalyl chloride (2.20 mL, 24.8 mmol) and 2 drops of DMF. The mixture was stirred at RT for 6 h. An additional aliquot of oxalyl chloride (1.20 mL, 13.5 mmol) was added. Stirring was continued at RT overnight, upon which the mixture was concentrated in *vacuo*, taken up in CHCl₃ (100 mL) and washed with sat. NaHCO₃ (3x 50 mL), water (2x50 mL) and brine (1x50 mL). The organic layer was dried (Na₂SO₄), filtered and concentrated in *vacuo* to give 2-(3-(benzyloxy)phenyl)-4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline (1.52g, 3.37 mmol, 45%). MS 451 (M+1 Cl isotope pattern). HPLC retention time 10.84 mins. (10-95-13 method).

[0547] **Example 141.**

[0548] ***tert*-butyl 5-(2-(3-(benzyloxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**

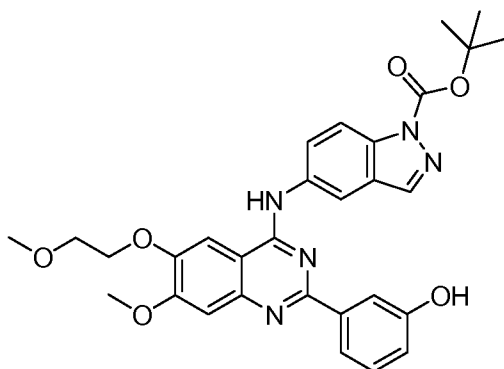


[0549] A mixture of 2-(3-(benzyloxy)phenyl)-4-chloro-7-methoxy-6-(2-methoxyethoxy)quinazoline (1.55g, 3.44 mmol) and *tert*-butyl 5-amino-1H-indazole-1-carboxylate (0.842g, 3.61 mmol) in iso-propanol (100 mL) was heated at 95 °C for 2h, upon which the an additional aliquot of *tert*-butyl 5-amino-1H-indazole-1-carboxylate (0.100g, 0.43 mmol) was added. Stirring was continued at 95 °C for a further 3 h upon which a third aliquot of *tert*-butyl 5-amino-1H-indazole-1-carboxylate (0.050g, 0.22 mmol) was added. Stirring was continued at 95 °C for a further 1 h upon which the mixture was allowed to cool to RT and the precipitate was collected via filtration. The solid was washed with iso-propanol and dried under vacuum to give *tert*-butyl 5-(2-(3-(benzyloxy)phenyl)-7-methoxy-6-(2-

methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.35g, 3.44 mmol, 100%). MS 648 (M+1). HPLC retention time 7.79 mins.

[0550] **Example 142.**

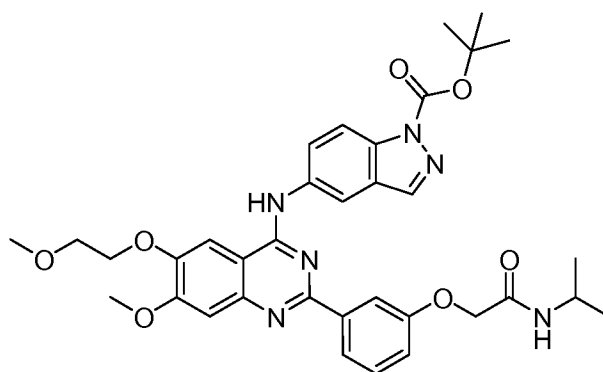
[0551] ***tert*-Butyl 5-(2-(3-hydroxyphenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0552] A suspension of *tert*-butyl 5-(2-(3-(benzyloxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.70g, 4.17 mmol) in MeOH (400 mL) and DME (200 mL) was added Pd/C (10%, wet, 0.500g) under an atmosphere of N₂. The N₂ was exchanged for H₂ and the mixture was stirred under an atmosphere of H₂ (balloon pressure) overnight. The mixture was filtered through a pad of Celite® and the filtrate was concentrated in *vacuo* to give *tert*-Butyl 5-(2-(3-hydroxyphenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (2.25g, 4.04 mmol, 97 %). MS 558 (M+1). HPLC retention time 6.44 mins.

[0553] **Example 143.**

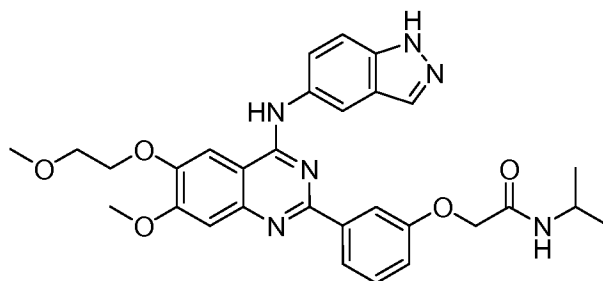
[0554] ***tert*-butyl 5-(2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate**



[0555] To a solution of *tert*-Butyl 5-(2-(3-hydroxyphenyl)-7-methoxy-6-(2-methoxyethoxy) quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.400g, 0.72 mmol) and 2-chloro-N-isopropylacetamide (0.107g, 0.79 mmol) in DMF (16 mL) was added K₂CO₃ (0.297g, 1.44 mmol). The mixture was heated at 80 °C for 72 h. The mixture was concentrated in *vacuo* and taken on directly into the next step. HPLC retention time 6.76mins.

[0556] **Example 144.**

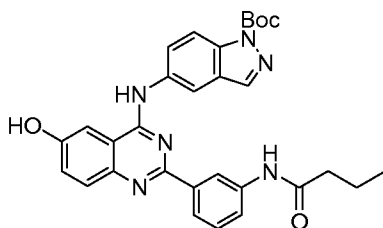
[0557] **2-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-methoxyethoxy)quinazolin-2-yl)phenoxy)-N-isopropylacetamide**



[0558] The crude *tert*-butyl 5-(2-(3-(2-(isopropylamino)-2-oxoethoxy)phenyl)-7-methoxy-6-(2-methoxyethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate from the previous step was taken up in CH₂Cl₂ (2 mL) and TFA (5 mL). The mixture was stirred at RT for 2 h. The mixture was concentrated in *vacuo* and a portion of the residue was purified by preparative HPLC (10-35-90, 10-30-90, 0-15-90, 5-20-90 and 20-40-90 methods) to give 2-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-methoxyethoxy)-quinazolin-2-yl)phenoxy)-N-isopropylacetamide (0.039g, 68.4 μmol). MS 557 (M+1). HPLC retention time 5.48 mins.

[0559] Example 145.

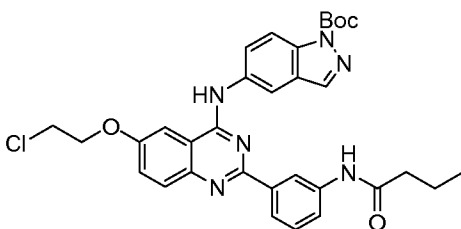
[0560] *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0561] To a solution of *tert*-butyl 5-(6-acetoxy-2-(3-aminophenyl)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.57 g, 1.12 mmol) and DIEA (0.65 g, 5.03 mmol) in dichloromethane (20 mL) was added butryl chloride (0.180 g, 1.69 mmol). The resulting reaction mixture was stirred at room temperature for 4 h. The volatiles were removed under reduced pressure and the residue was triturated with water causing formation of a precipitate. The solid was collected via filtration and dried under vacuum. The solid was suspended in anhydrous methanol (50 mL) and 28% ammonium hydroxide (0.9 mL) was added. The resulting reaction mixture was stirred at room temperature for 24 h. The volatiles were removed under reduced pressure and the residue upon trituration with ether gave *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.354 g, 0.66 mmol, 59% over two steps). HPLC retention time 6.342 min.

[0562] Example 146.

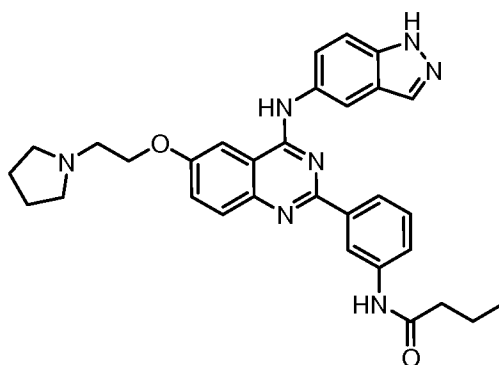
[0563] *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate



[0564] To a mixture of 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (1.50 g, 2.79 mmol) and potassium carbonate (1.64 g, 11.8 mmol) in anhydrous DMF (5 mL) was added 1-bromo-2-chloroethane (1.6 g, 11.2 mmol). The subsequent mixture was heated at 85°C for 4 h, upon which it was allowed to cool to RT and it was poured onto ice-water. A solid was precipitated out, which collected via filtration and dried under vacuum. The solid was purified via silica gel column chromatography to give *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.94g, 1.56 mmol, 60%). HPLC retention time 7.479.

[0565] **Example 147.**

[0566] **N-(3-(4-(1H-Indazol-5-ylamino)-6-(2-(pyrrolidin-1-yl)ethoxy)-quinazolin-2-yl)phenyl)butyramide**

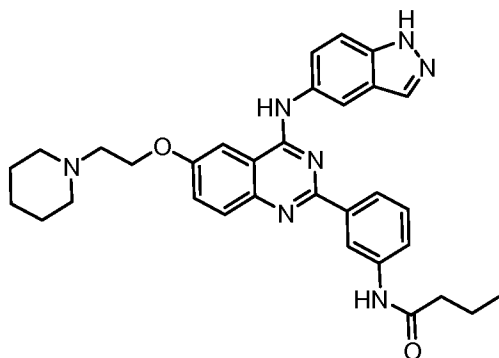


[0567] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.170g, 0.282 mmol) in DMSO (2 mL) was added pyrrolidine (0.5 mL). The subsequent mixture was heated at 80 °C for 1.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 8:1).

[0568] The purified solid was taken up in HCl (4M in 1,4 dioxane, 2 mL) and stirred at RT for 2 h. The volatiles were removed in *vacuo* to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(pyrrolidin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide di-hydrochloride salt (0.120g, 0.198 mmol, 70% over two steps). MS 536 (M+1). HPLC retention time 4.61 mins.

[0569] Example 148.

[0570] N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(piperidin-1-yl)ethoxy)-quinazolin-2-yl)phenyl)butyramide

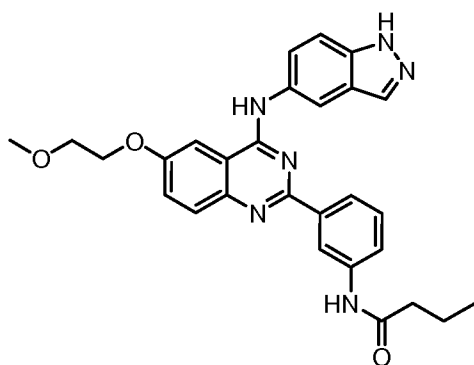


[0571] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.174g, 0.290 mmol) in DMSO (1.5 mL) was added piperidine (0.5 mL). The subsequent mixture was heated at 80 °C for 1.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 8:1).

[0572] The purified solid was taken up in HCl (4M in 1,4 dioxane, 2 mL) and stirred at RT for 2 h. The volatiles were removed in *vacuo* to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(piperidin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide di-hydrochloride salt (0.085g, 0.137 mmol, 47% over two steps). MS 550 (M+1). HPLC retention time 4.67 mins.

[0573] Example 149.

[0574] N-(3-(4-(1H-indazol-5-ylamino)-6-(2-methoxyethoxy)quinazolin-2-yl)phenyl)butyramide

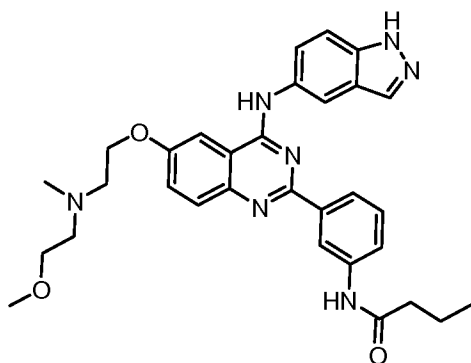


[0575] A mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.167g, 0.31 mmol), 1-bromo-2-methoxyethane (0.118g, 0.85 mmol) and K₂CO₃ (0.172g, 1.25 mmol) in DMF (2 mL) was heated at 80 °C for 2.5 h. The mixture was allowed to cool to RT, upon which it was poured into water. A precipitate formed which was collected via filtration, dried under vacuum and purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 95:5).

[0576] The purified solid was taken up in HCl (4M in 1,4 dioxane, 30 mL) and stirred at RT for 4.5 h. The volatiles were removed in *vacuo* and the residue was triturated with Et₂O to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-methoxyethoxy)quinazolin-2-yl)phenyl) butyramide hydrochloride (0.091g, 0.171mmol, 55% over two steps). MS 497 (M+1). HPLC retention time 5.547 mins.

[0577] Example 150.

[0578] N-(3-(4-(1H-indazol-5-ylamino)-6-(2-((2-methoxyethyl)(methyl)amino)ethoxy)quinazolin-2-yl)phenyl)butyramide

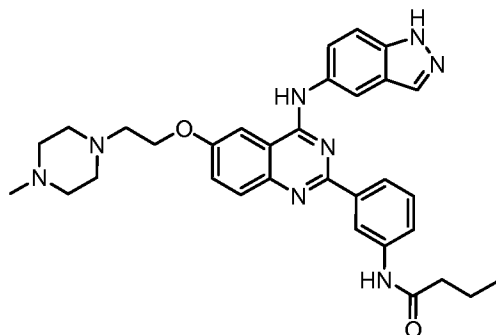


[0579] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.150g, 0.250 mmol) in DMSO (2 mL) was added 2-methoxy-N-methylethanamine (0.5 mL). The subsequent mixture was heated at 75 °C for 1.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 8:1). Two compounds were isolated and combined.

[0580] The combined compounds were taken up in CH₂Cl₂ (2mL) and HCl (4M in 1,4 dioxane, 25 mL) and stirred at RT for 7 h. The volatiles were removed in *vacuo* and the residue was washed with CH₂Cl₂ and Et₂O. The solid was dried under vacuum to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-((2-methoxyethyl)(methyl)amino)ethoxy)-quinazolin-2-yl)phenyl)butyramide di-hydrochloride salt (0.100g, 0.160 mmol, 64% over two steps). MS 554 (M+1). HPLC retention time 4.52 mins.

[0581] **Example 151.**

[0582] **N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(4-methylpiperazin-1-yl)ethoxy)-quinazolin-2-yl)phenyl)butyramide**



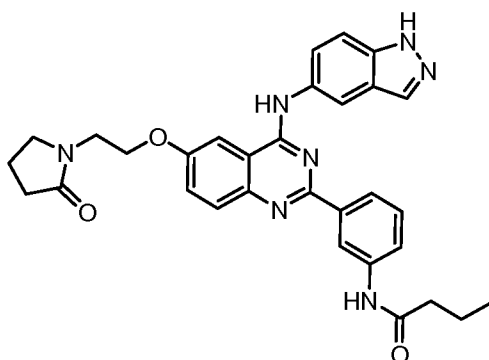
[0583] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.150g, 0.250 mmol) in DMSO (2 mL) was added 1-methylpiperazine (0.5 mL). The subsequent mixture was heated at 85 °C for 2 h upon which an additional aliquot of 1-methylpiperazine (0.2 mL). Heating at 85 °C was continued for a further 1.5 h, upon which the mixture was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried

under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH:NH₄OH 9:1:0.1) to give two compounds.

[0584] The combined compounds were taken up in CH₂Cl₂ (2mL) TFA (4mL) was added. The resulting mixture was stirred at RT for 4 h, upon which the volatiles were removed in *vacuo*. The residue was neutralized with sat. NaHCO₃ and extracted with THF (3x25 mL). The combined organics were washed with brine (1x20 mL), dried (Na₂SO₄) and purified by preparative TLC (SiO₂, CH₂Cl₂:MeOH:NH₄OH 9:1:0.1). The purified compound was taken up in CH₂Cl₂ (2 mL) and HCl (4M in 1,4 dioxane, 10 mL) and was stirred at RT for 4 h. The volatiles were removed in *vacuo* and the residue was triturated with Et₂O, filtered and dried under vacuum to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide di-hydrochloride salt (0.067g, 0.105 mmol, 42% over two steps). MS 565 (M+1). HPLC retention time 4.30 mins.

[0585] **Example 152.**

[0586] **N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)-quinazolin-2-yl)phenyl)butyramide**

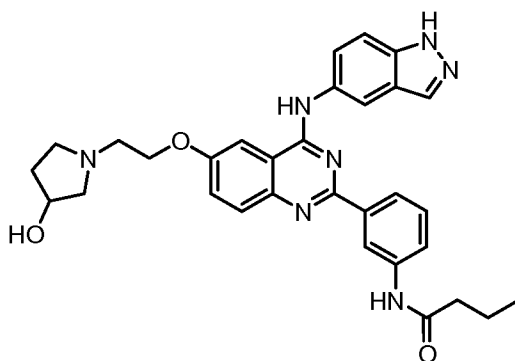


[0587] A mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.120g, 0.186 mmol), 1-(2-bromoethyl)pyrrolidin-2-one (0.25 g, 1.31 mmol) and K₂CO₃ (0.415g, 3.0 mmol) in DMF (1.5 mL) was heated at 75 °C for 5 h. The mixture was allowed to cool to RT, upon which it was poured into water. A precipitate formed which was collected via filtration, dried under vacuum and purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 95:5).

[0588] The purified solid was taken up in HCl (4M in 1,4 dioxane, 30 mL) and stirred at RT for 4 h. The volatiles were removed in *vacuo* and the residue was washed with CH₂Cl₂ to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide hydrochloride (0.025g, 0.043mmol, 23% over two steps). MS 550 (M+1). HPLC retention time 5.30 mins.

[0589] **Example 153.**

[0590] **N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(3-hydroxypyrrolidin-1-yl)ethoxy)-quinazolin-2-yl)phenyl)butyramide**

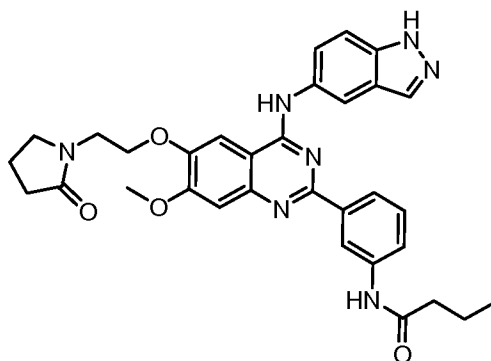


[0591] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-quinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.143 g, 0.240 mmol) in DMSO (1.5 mL) was added pyrrolidin-3-ol (0.5 mL). The subsequent mixture was heated at 75 °C for 1.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH NH₄OH 9:1:0.1).

[0592] The purified solid was taken up in MeOH/CH₂Cl₂ (3 mL 1:1) and HCl (4M in 1,4 dioxane, 2 mL) was added. The mixture was stirred at RT for 4 h. The volatiles were removed in *vacuo* and the residue was washed with CH₂Cl₂ to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-(3-hydroxypyrrolidin-1-yl)ethoxy)quinazolin-2-yl)phenyl) butyramide di-hydrochloride salt (0.095g, 0.153 mmol, 64% over two steps). MS 552 (M+1). HPLC retention time 4.389 mins.

[0593] **Example 154.**

[0594] **N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide**

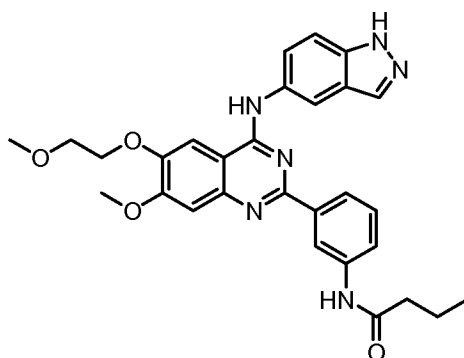


[0595] A mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.200 g, 0.35 mmol), 2-(2-oxopyrrolidin-1-yl)ethyl methanesulfonate (0.300 g, 1.48 mmol) and K₂CO₃ (0.410g, 2.97 mmol) in DMF (3 mL) was heated at 75 °C for 5 h. The mixture was allowed to cool to RT, upon which it was poured into water 50-80 mL). A precipitate formed which was collected via filtration, dried under vacuum and purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH 95:5).

[0596] The purified solid was taken up in CH₂Cl₂/MeOH (3 mL 1:1) and HCl (4M in 1,4 dioxane, 30 mL) was added. The mixture was stirred at RT for 5 h. The volatiles were removed *in vacuo* to give N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide hydrochloride (0.108, 0.176 mmol, 50% over two steps). MS 580 (M+1). HPLC retention time 5.523 mins.

[0597] **Example 155.**

[0598] **N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-methoxyethoxy)-quinazolin-2-yl)phenyl)butyramide**

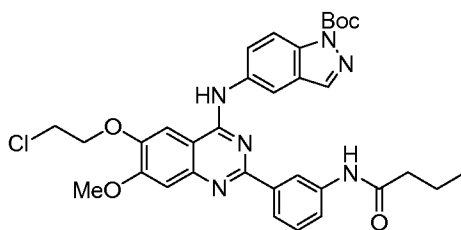


[0599] A mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.176g, 0.31 mmol), 1-bromo-2-methoxyethane (0.120g, 0.86 mmol) and K₂CO₃ (0.120 g, 2.8 mmol) in DMSO (1.5 mL) was heated at 75 °C for 1.5 h. The mixture was allowed to cool to RT, upon which it was poured into water. A precipitate formed which was collected via filtration and dried under vacuum.

[0600] The solid was taken up CH₂Cl₂ (8 mL) and HCl (4M in 1,4 dioxane, 18 mL) was added. The subsequent mixture was stirred at RT for 4 h. The volatiles were removed in *vacuo* and the residue was triturated with Et₂O to give N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-methoxyethoxy)quinazolin-2-yl)phenyl) butyramide hydrochloride (0.09g, 0.160 mmol, 52 % over two steps). MS 527 (M+1). HPLC retention time 5.71 mins.

[0601] **Example 156.**

[0602] ***tert*-Butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate**

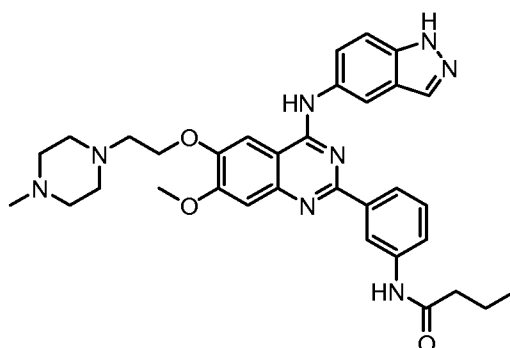


[0603] To a mixture of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-hydroxy-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.855 g, 1.50 mmol) and potassium carbonate (0.950g, 6.87 mmol) in anhydrous DMF (8 mL) was added, 1-bromo-2-chloroethane (0.89 g, 6.20 mmol) and resulting reaction mixture was stirred at 85°C for 3.5 h. The mixture was

allowed to cool to room temperature upon which, it was poured into ice-water. A solid was precipitated out, which was collected via filtration and dried under vacuum to give *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.864g, 1.37 mmol, 91%). HPLC retention time 7.694 min.

[0604] **Example 157.**

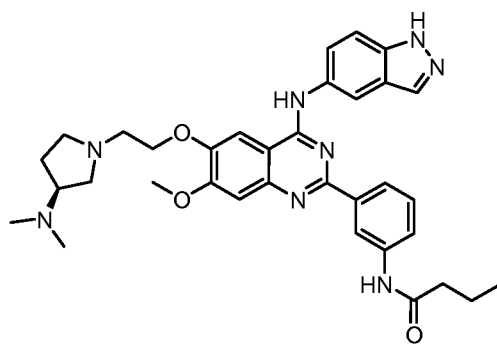
[0605] **N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)quinazolin-2-yl)phenyl)butyramide**



[0606] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.170g, 0.299 mmol) in DMSO (2 mL) was added 1-methylpiperazine (0.5 mL). The subsequent mixture was heated at 85 °C for 2.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH:NH₄OH 9:1:0.1). The purified compound was taken up in CH₂Cl₂ (2mL) and HCl (4M in 1,4 dioxane, 10 mL) and stirred at RT for 4 h. The volatiles were removed in *vacuo* and the residue was triturated with Et₂O, filtered and dried under vacuum to give N-(3-(4-(1H-indazol-5-ylamino)-7-methoxy-6-(2-(4-methylpiperazin-1-yl)ethoxy)-quinazolin-2-yl)phenyl) butyramide di-hydrochloride salt (0.085g, 0.128 mmol, 43% over two steps). MS 595 (M+1). HPLC retention time 4.337 mins.

[0607] **Example 158.**

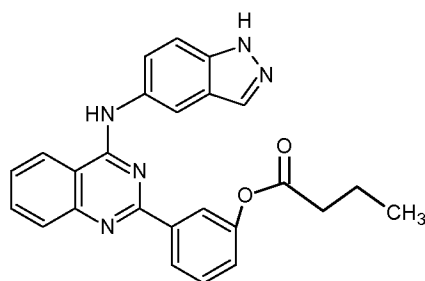
[0608] **N-(3-(4-(1H-indazol-5-ylamino)-6-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)ethoxy)-7-methoxyquinazolin-2-yl)phenyl)butyramide**

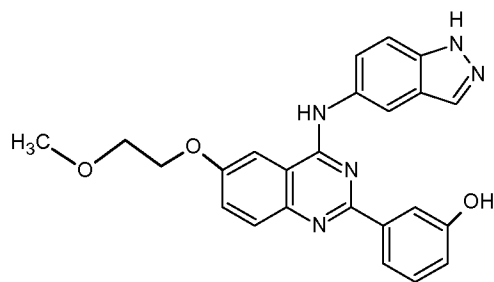
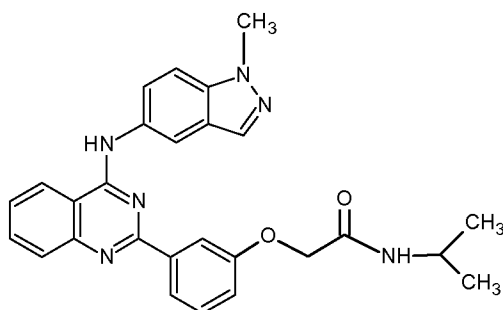
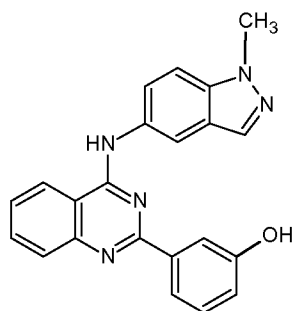
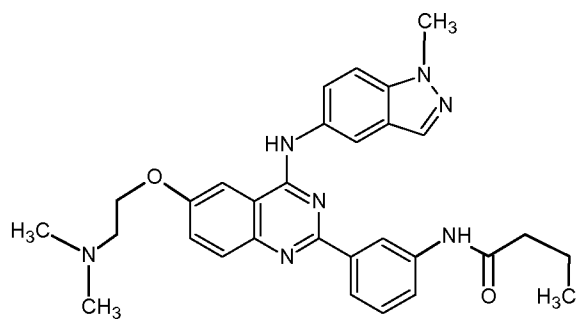


[0609] To a solution of *tert*-butyl 5-(2-(3-butyramidophenyl)-6-(2-chloroethoxy)-7-methoxyquinazolin-4-ylamino)-1H-indazole-1-carboxylate (0.180g, 0.300 mmol) in DMSO (2 mL) was added (S)-N,N-dimethylpyrrolidin-3-amine (0.5 mL). The subsequent mixture was heated at 80 °C for 1.5 h upon which it was allowed to cool to RT and poured into ice-water (100 mL). A precipitate formed which was collected via filtration and it was dried under vacuum. The precipitate was purified via preparative TLC (SiO₂, CH₂Cl₂:MeOH:NH₄OH 9:1:0.1).

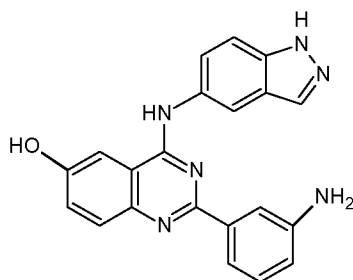
[0610] The purified solid was taken up in HCl (4M in 1,4 dioxane, 2 mL) and stirred at RT for 2 h. The volatiles were removed in *vacuo* to give N-(3-(4-(1H-indazol-5-ylamino)-6-(2-((S)-3-(dimethylamino)pyrrolidin-1-yl)ethoxy)-7-methoxyquinazolin-2-yl) phenyl) butyramide di-hydrochloride salt (0.090g, 0.132 mmol, 44% over two steps). MS 609 (M+1). HPLC retention time 4.30 mins.

[0611] Example 159.

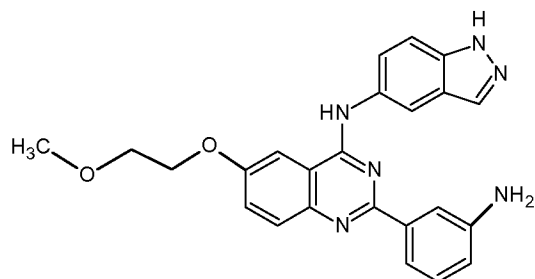


[0612] Example 160.**[0613] Example 161.****[0614] Example 162.****[0615] Example 163.**

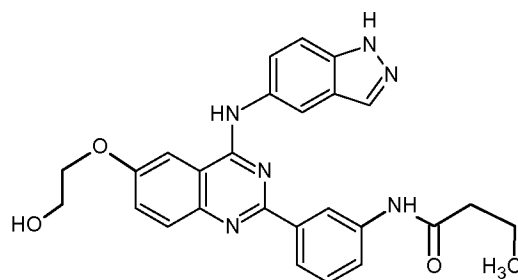
[0616] **Example 164.**



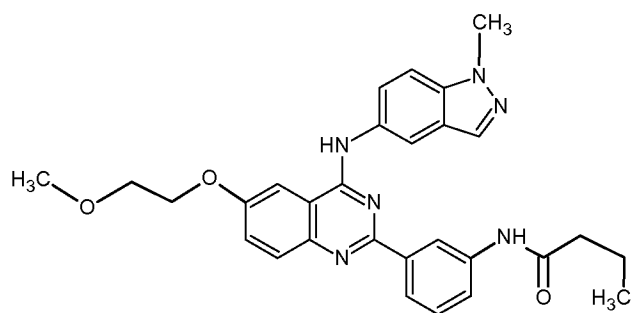
[0617] **Example 165.**

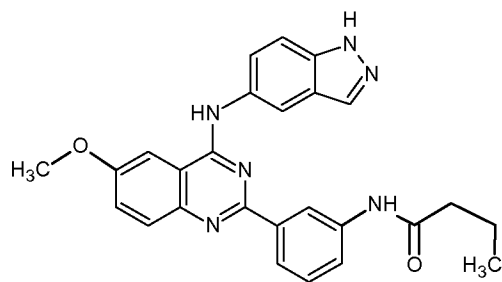
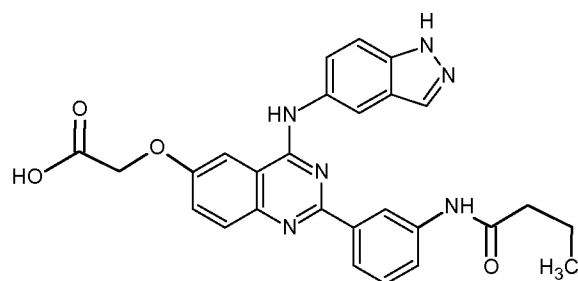
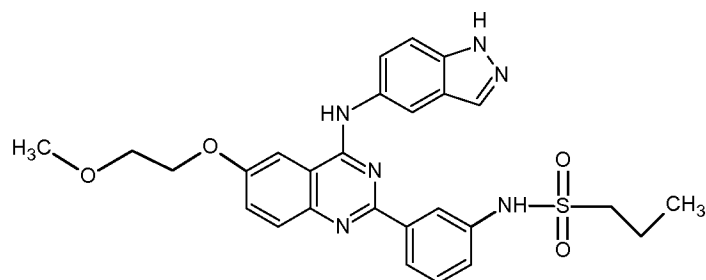
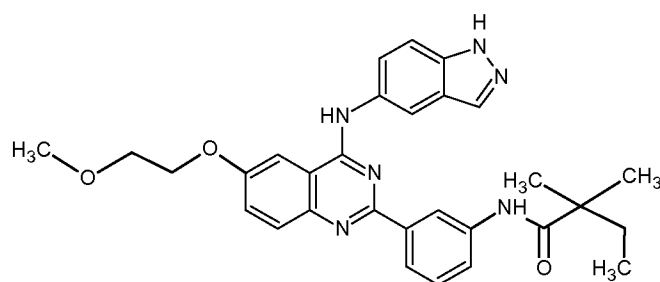


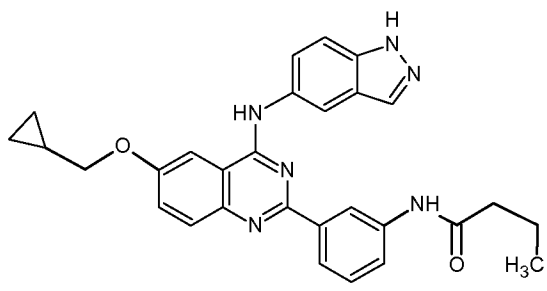
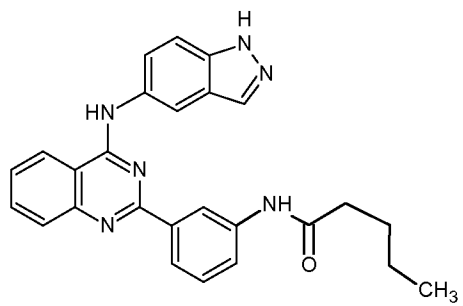
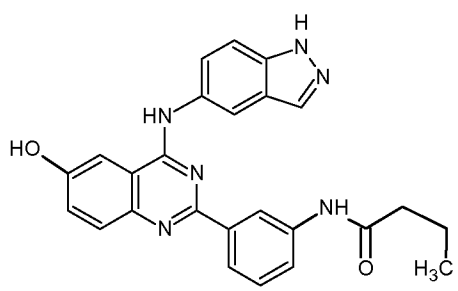
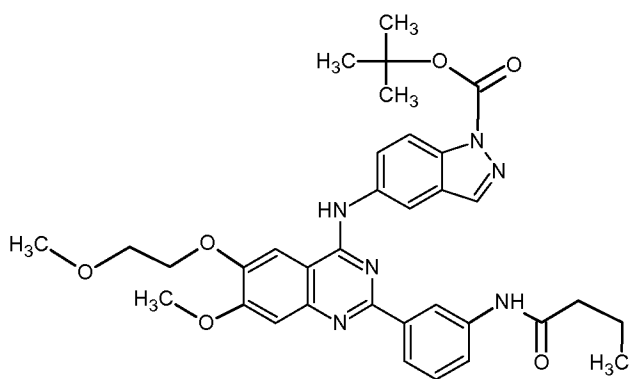
[0618] **Example 166.**

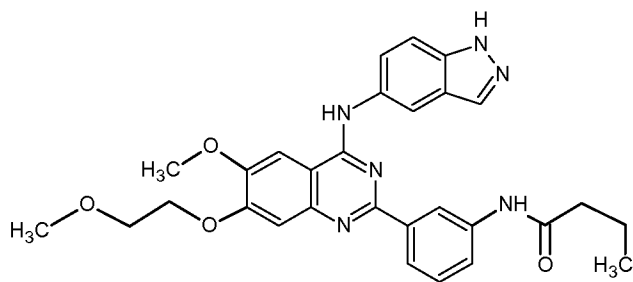
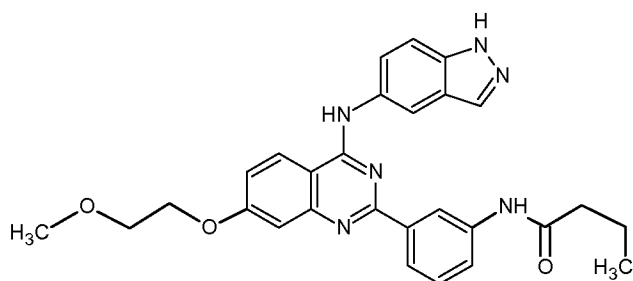
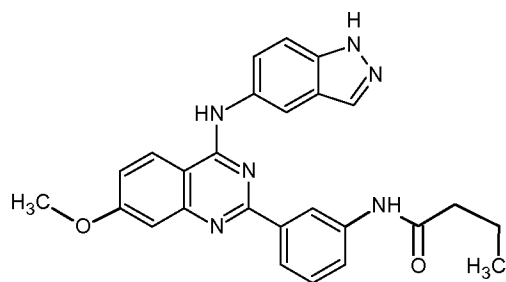
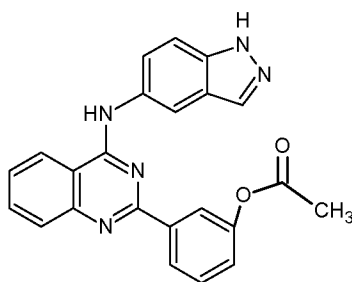


[0619] **Example 167.**

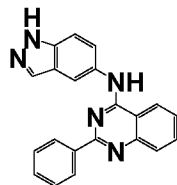


[0620] Example 168.**[0621] Example 169.****[0622] Example 170.****[0623] Example 171.**

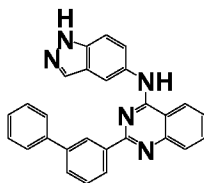
[0624] Example 172.**[0625] Example 173.****[0626] Example 174.****[0627] Example 175.**

[0628] Example 176.**[0629] Example 177.****[0630] Example 178.****[0631] Example 179.**

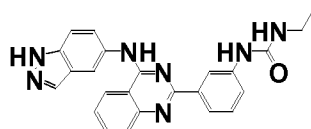
[0632] Example 180.



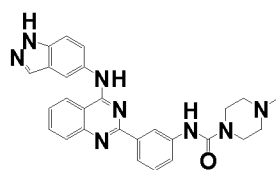
[0633] Example 181.



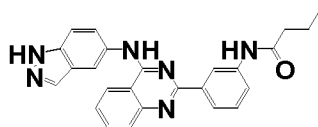
[0634] Example 182.



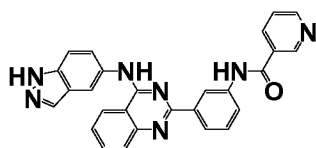
[0635] Example 183.



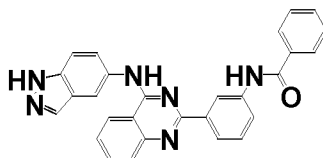
[0636] Example 184.



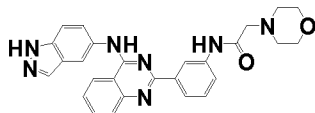
[0637] Example 185.



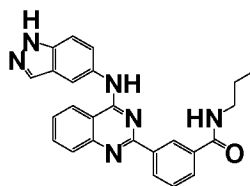
[0638] Example 186.



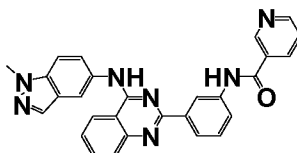
[0639] Example 187.



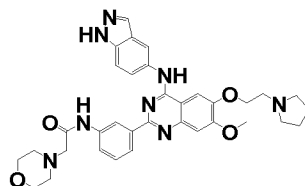
[0640] Example 188.



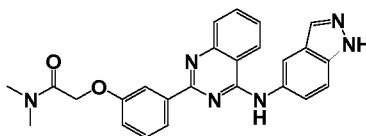
[0641] Example 189.



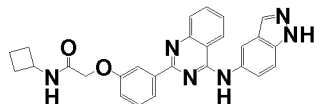
[0642] Example 190.



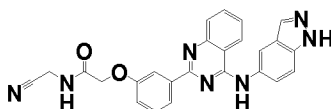
[0643] Example 191.



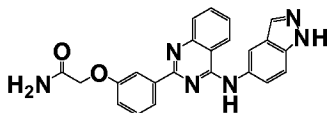
[0644] Example 192.



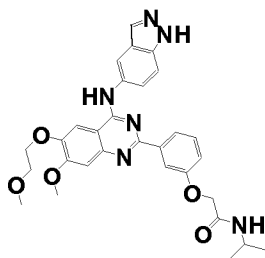
[0645] Example 193.



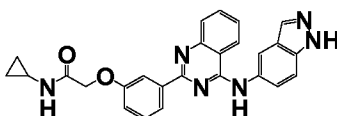
[0646] Example 194.



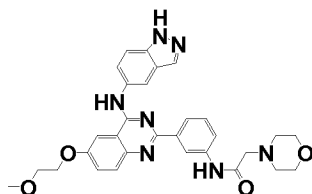
[0647] Example 195.



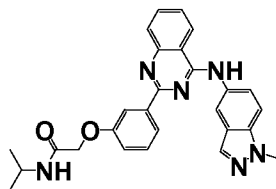
[0648] Example 196.



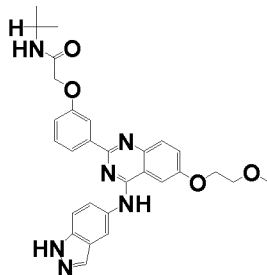
[0649] Example 197.

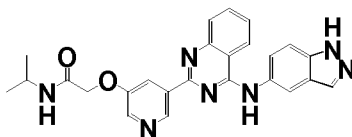
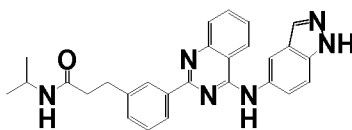
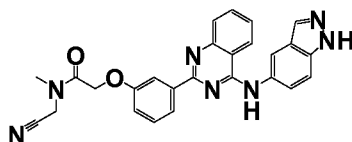
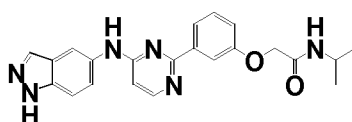
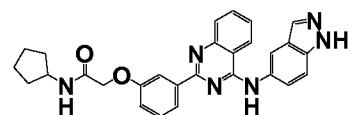
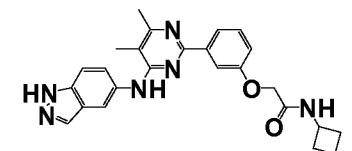
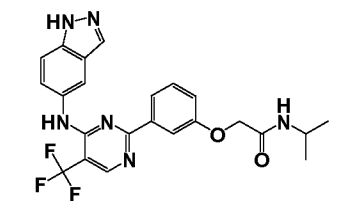


[0650] Example 198.

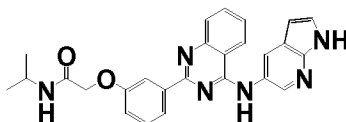


[0651] Example 199.

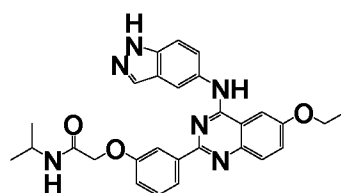


[0652] Example 200.[0653] Example 201.[0654] Example 202.[0655] Example 203.[0656] Example 204.[0657] Example 205.[0658] Example 206.

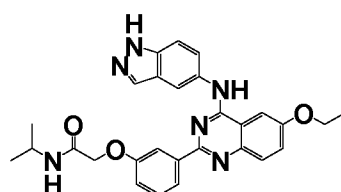
[0659] Example 207.



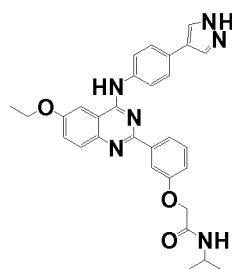
[0660] Example 208.



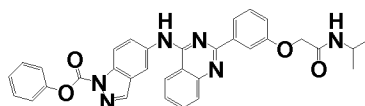
[0661] Example 209.



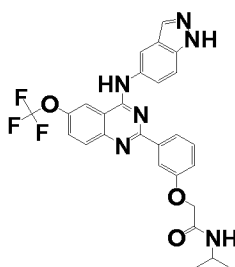
[0662] Example 210.



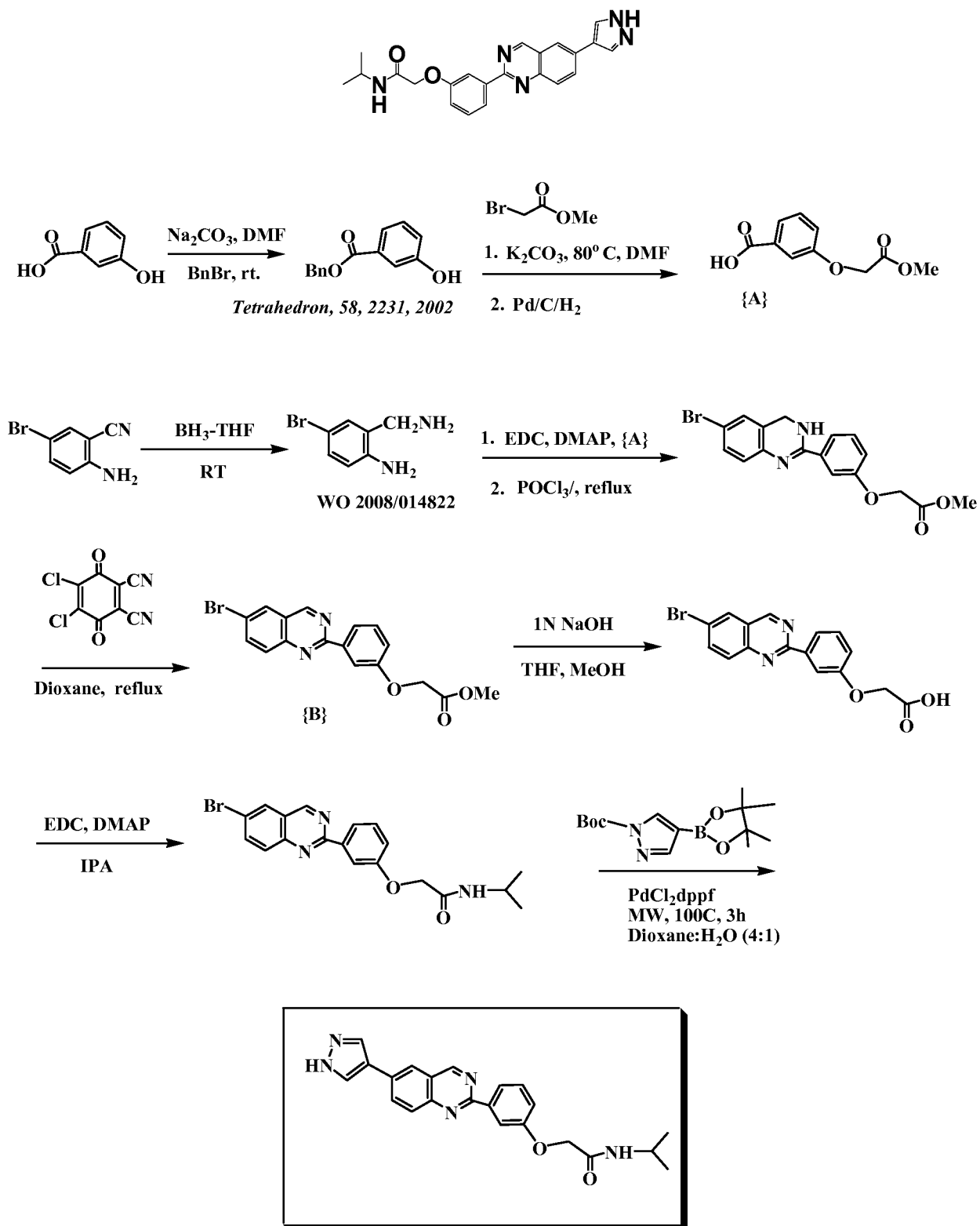
[0663] Example 211.



[0664] Example 212.



[0665] Example 213.



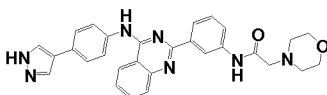
[0666] The acid coupling partner 3-(2-methoxy-2-oxoethoxy)benzoic acid {A} was synthesized via a protection / de-protection protocol as follows. Commercially available 3-hydroxybenzoic acid was esterified following the literature protocol utilizing benzyl bromide and sodium carbonate in DMF at room temperature. *See Tetrahedron*, 58, 2231, 2002. The resulting phenol was then alkylated using methyl-2-bromoacetate in the presence of potassium carbonate in DMF at 80 °C. The benzyl protecting group was then removed via hydrogenation using palladium carbon conditions using the parr apparatus to provide 3-(2-methoxy-2-oxoethoxy)benzoic acid compound {A}.

[0667] Commercially available 2-amino-5-bromobenzonitrile was reduced using 1M-borane-THF solution according the literature procedure to provide 2-(aminomethyl)-4-bromobenzenamine. *See WO 2008/014822*. The bis-amine was then coupled with 3-(2-methoxy-2-oxoethoxy)benzoic acid compound {A} using EDC as a peptide coupling agent and DMAP as the base. The resultant crude product was then cyclized using phosphorous oxychloride to provide methyl 2-(3-(6-bromo-3,4-dihydroquinazolin-2-yl)phenoxy)acetate. Oxidation using DDQ provides the required quinazoline ring scaffold IN methyl 2-(3-(6-bromoquinazolin-2-yl)phenoxy)acetate {B}. The methyl ester in the phenoxy side chain of {B} was converted to the isopropyl amide by a series of hydrolysis (utilizing 1N NaOH), followed by peptide coupling reaction (with isopropylamine as the nucleophile). The final compound was assembled via a Microwave promoted Suzuki conditions at 100 °C using PdCl₂ dppf as the catalyst and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate as the boronate coupling partner and cesium carbonate as the base. Under the microwave conditions the Boc protecting group is removed and the final compound 2-(3-(6-(1H-pyrazol-4-yl)quinazolin-2-yl)phenoxy)-N-isopropylacetamide is obtained upon aqueous workup and ISCO purification.

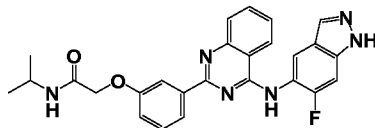
HPLC: 6.2 mins (95_5_10 min method, YMC column)

LCMS: ESI (388.0, M+) 6.10 mins (95_5_10 min method, YMC column).

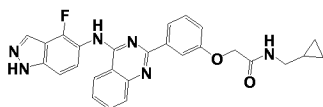
[0668] **Example 214.**



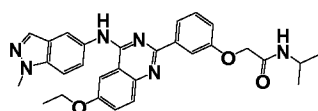
[0669] Example 215.



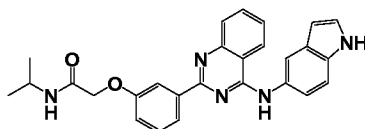
[0670] Example 216.



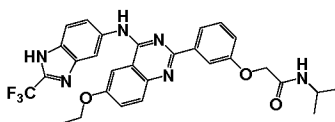
[0671] Example 217.



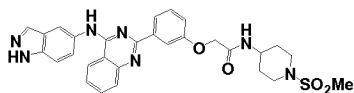
[0672] Example 218.



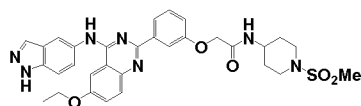
[0673] Example 219.



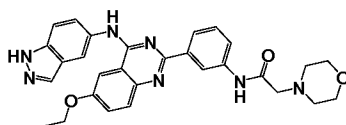
[0674] Example 220.



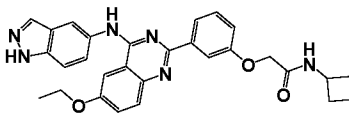
[0675] Example 221.



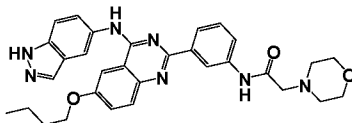
[0676] Example 222.



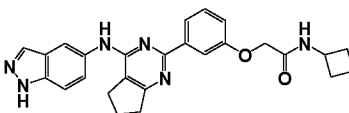
[0677] Example 223.



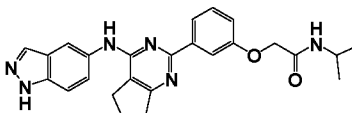
[0678] Example 224.



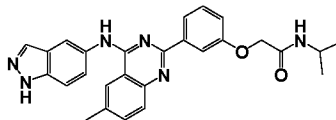
[0679] Example 225.



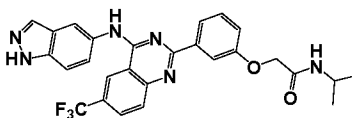
[0680] Example 226.



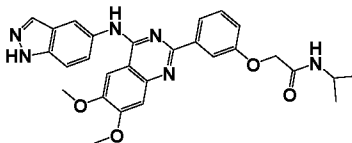
[0681] Example 227.



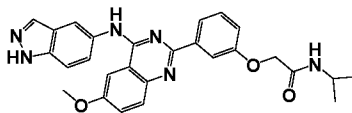
[0682] Example 228.



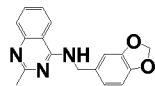
[0683] Example 229.



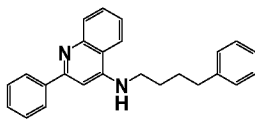
[0684] Example 230.



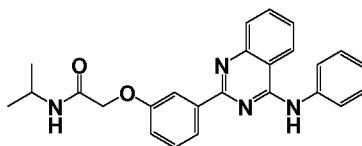
[0685] Example 231.



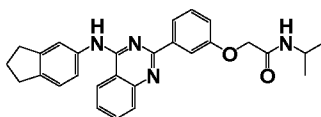
[0686] Example 232.



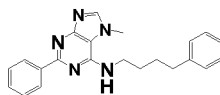
[0687] Example 233.



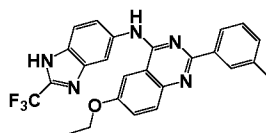
[0688] Example 234.



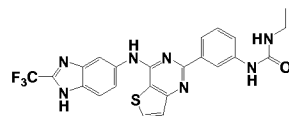
[0689] Example 235.



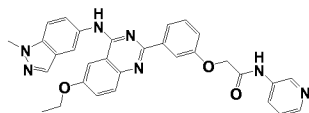
[0690] Example 236.

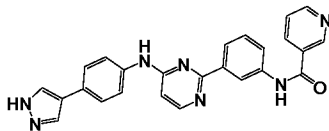
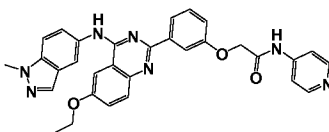
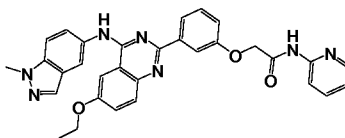
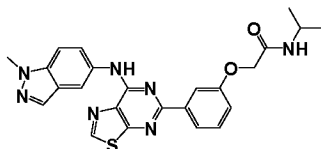
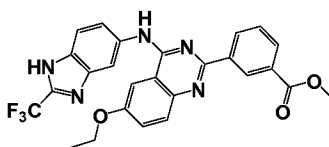
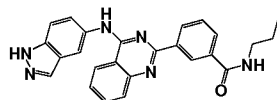


[0691] Example 237.



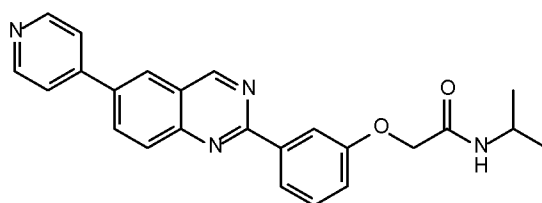
[0692] Example 238.



[0693] Example 239.[0694] Example 240.[0695] Example 241.[0696] Example 242.[0697] Example 243.[0698] Example 244.

The following compounds were prepared according to the method of Example 213.

[0699] Example 245. N-isopropyl-2-(3-(6-(pyridin-4-yl)quinazolin-2-yl)phenoxy)acetamide

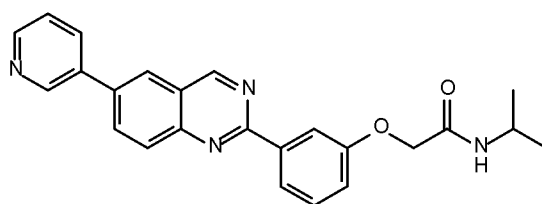


[0700] N-isopropyl-2-(3-(6-(pyridin-4-yl)quinazolin-2-yl)phenoxy)acetamide was synthesized following the representative Suzuki procedure above utilizing 2-(3-(6-bromoquinazolin-2-yl)phenoxy)-N-isopropylacetamide as the aryl bromide and pyridin-4-ylboronic acid as the boronic acid coupling partner.

HPLC retention time: 4.2 mins (95% pure @254nm).

LCMS: ES^+ 399.2 (M+1).

[0701] **Example 246.** N-isopropyl-2-(3-(6-(pyridin-3-yl)quinazolin-2-yl)phenoxy)acetamide

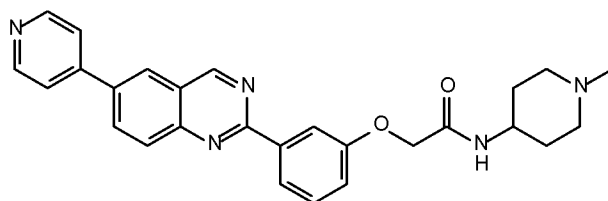


[0702] N-isopropyl-2-(3-(6-(pyridin-3-yl)quinazolin-2-yl)phenoxy)acetamide was synthesized following the representative Suzuki procedure above utilizing 2-(3-(6-bromoquinazolin-2-yl)phenoxy)-N-isopropylacetamide as the aryl bromide and pyridin-3-ylboronic acid as the boronic acid coupling reagent.

HPLC retention time: 5.4 mins (95% pure @254nm).

LCMS: ES^+ 399.2 (M+1).

[0703] **Example 247.** N-(1-methylpiperidin-4-yl)-2-(3-(6-(pyridin-4-yl)quinazolin-2-yl)phenoxy)acetamide

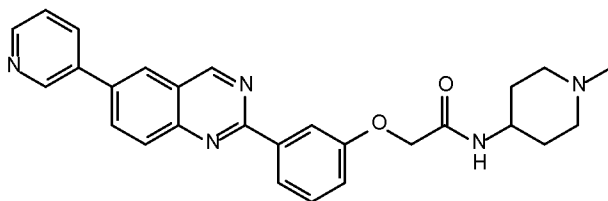


[0704] N-(1-methylpiperidin-4-yl)-2-(3-(6-(pyridin-4-yl)quinazolin-2-yl)phenoxy)acetamide was synthesized following the representative Suzuki procedure above utilizing 2-(3-(6-bromoquinazolin-2-yl)phenoxy)-N-(1-methylpiperidin-4-yl)acetamide as the aryl bromide and pyridin-3-ylboronic acid as the boronic acid coupling reagent.

HPLC retention time: 2.9 mins (95% pure @254nm).

LCMS: ES⁺ : 454.2 (M+1).

[0705] **Example 248.** N-(1-methylpiperidin-4-yl)-2-(3-(6-(pyridin-3-yl)quinazolin-2-yl)phenoxy)acetamide



[0706] N-(1-methylpiperidin-4-yl)-2-(3-(6-(pyridin-3-yl)quinazolin-2-yl)phenoxy)acetamide was synthesized following the representative Suzuki procedure above utilizing 2-(3-(6-bromoquinazolin-2-yl)phenoxy)-N-(1-methylpiperidin-4-yl)acetamide as the aryl bromide and pyridin-3-ylboronic acid as the boronic acid coupling reagent.

HPLC retention time: 3.3 mins (95% pure @254nm).

LCMS: ES⁺ : 454.2 (M+1).

[0707] Table 1 summarizes AMPK activation, CK2 inhibition, ROCK2 inhibition, and GLUT1 inhibition activities for the compounds exemplified above.

Table 1. – Activities				
Ex.	AMPK activation	CK2 inhibition	ROCK2 inhibition	GLUT1 inhibition
186			+	+
187			+	+
188			+	+

Table 1. – Activities				
Ex.	AMPK activation	CK2 inhibition	ROCK2 inhibition	GLUT1 inhibition
48	+	+	+	+
189	+		-	-
190			+	+
191				+
192			+	+
193			+	+
194	+		+	+
195				+
196			+	+
197	+	-	+	+
198	+		-	-
199	+		+/-	+
200	+		+	+
201	+		+	+
202	+		+	+
203	+		+	-
204	+		+	+
205	+	+	+	-
206	+			-
207	+		-	
208	+		+	+
209	+	-	-	+
210	+	-	-	+
211	+		-	-
212	+		-	-
213	+		-	-
214	+			+
215	+		-	+
216	+			-

Table 1. – Activities				
Ex.	AMPK activation	CK2 inhibition	ROCK2 inhibition	GLUT1 inhibition
217	+			-
218	+			-
219	+			-
220	+			-
221				-
222				
223	+			-
224	+			-
225	+			-
226				
227				
228	+			
229	+			+
230	+			-
231				-
232	+/-			-
233	+			-
234	+			-
235	-			-
236	-			-
237	+			-
238	+			-
239	+			-
240	-			-
241	+			-
242	+			-
243	-			-

[0708] Cell culture: HT1080 cells (human fibrosarcoma line, ATCC #CCL-121) were grown in a Growth Media containing MEM media (ATCC #30-2003) with 1 g/l glucose, 10% fetal bovine serum (Gibco/Invitrogen #16140) and 1% penicillin-streptomycin (Gibco/Invitrogen #15070). To plate the cells for assays, the cells growing in T175 plates were washed with D-PBS (Gibco/Invitrogen #14040), trypsinized for 5-10 minutes at 37°C with TrypLE (Gibco/Invitrogen #12604) and suspended at 250,000 cells/ml with Growth Media. 200 µl of the cells were transferred to each well of a 96 well tissue culture treated microtiter plate (Becton Dickinson #353072 for glucose consumption and Perkin Elmer #6005181 for 2-deoxyglucose transport) and the cells were incubated at 37°C overnight.

[0709] Glucose Consumption Assay: The media in the microtiter wells was replaced with 240 µl of Growth Media with compounds plus 0.2% DMSO or just 0.2% DMSO and the cells were incubated for various time points (20 hours for routine screening). 10 µl of the supernatant was removed for glucose determination using a glucose assay kit (Sigma-Aldrich #GAHK20).

[0710] [³H]-2-Deoxyglucose Uptake Assay: [³H]-2-Deoxy-D-glucose uptake was measured in an Assay Buffer containing glucose free DMEM (Gibco/Invitrogen #11966) with 1 mM Na pyruvate (Gibco/Invitrogen #11360), 1% fetal bovine serum (ATCC #30-2020) and 25 mM HEPES (Gibco/Invitrogen). The wells were first washed with 280 µl D-PBS (Gibco/Invitrogen 14040) and 245 µl/well of Assay Buffer containing varying concentrations of compounds and 0.2% DMSO was added. The cells were incubated at room temperature for 30 minutes and 5 µl/well of 25 µCi/ml [³H]-2-deoxy-D-glucose (Perkin Elmer #NET32800) in Assay Buffer with 1.25 mM cold 2-deoxy-D-glucose (Sigma Aldrich #D6134) was added. After a 60 minute incubation, the assay was stopped by aspirating the media and washing each well twice with 280 µl D-PBS. 50 µl of EchoLume scintillation fluid (MP Biomedicals #882470) was added to each well and the plate was counted in a Perkin Elmer Microbeta Jet.

[0711] **Example 249.**

[0712] Compounds of the invention were tested in studies of Rho kinase inhibition (ROCK1 and ROCK2), 2-deoxy-D-glucose uptake, glucose consumption, AMPK activation (phosphorylation), and ACC phosphorylation.

Example	ROCK1 IC ₅₀	ROCK2 IC ₅₀	ROCK2 % inhib @ 500 nM	2-DG % inhib @ 500 nM C6 cells	Glucose consumption % inhib @ 10μM HT1080 cells		pAMPK	pACC
					Assay 1	Assay 2		
180			0.06	19%	18	12		
181			.43		57	50	+	+
182	>3	0.03, 0.138		3.71	87	75	+	+
183	0.956	0.029, 0.046		0.64	89	86		
184			0.3	44%	106	107		
185	>10	0.03, 0.02		0.47	81 (57% @ 1μM)	81 (62% @ 1μM)		
186	>10	0.19, 0.145			77	80		
187	>10	0.071		0.085	120	107		
188		0.132		0.462	107	98		
48		0.082		0.302	>90	>90	+	+
189	-	-		0.491	56	65	+	+
190	7.2 3.1 3.73	0.063		60%	108 @ 5 μM	101		
191					100	93		
192			0.84	44%	92	91		
193			0.82	34%	75	76		
194			0.84	46%	89	79	+	+
195					107 (103% @ 1 μM)	94 (90% @ 1 μM)		
196	-	0.059			86	86		
197	~7.0	0.108		0.018	99	97 (77% @ 1 μM)	+	+
198			-0.049	29%	32	41	+	+

Example	ROCK1 IC ₅₀	ROCK2 IC ₅₀	ROCK2 % inhib @ 500 nM	2-DG % inhib @ 500 nM C6 cells	Glucose consumption % inhib @ 10μM HT1080 cells		pAMPK	pACC
					Assay 1	Assay 2		
199			0.38	36%	102% @ 6 μ M (56% @ 1 μM)	93% @ 6 μ M (60% @ 1 μM)	+	+
200			0.64	60%	74	86		
201	>10		0.67		78	107	+	+
202	-	0.182		8%	71	74	+	+
203	>3 μm	0.07			40	51	+	+
204			0.92	43%	6	92	+	+
205	>10	0.026		>3	38	42	+	+
206			0.64		17	23	+	+
207	-	-	-0.14				+	+
208	>10	1.3 2.23		10.00	81	72	+	+
209	-	-		0.22	78	72	+	+
210	-	8.11		0.143	102% (86% @ 1 μM)	102% (86% @ 1 μM)	+	+
211		-	-		39	41	+	+
212	>10	1.31			16	33	+	+
213					10% @ 5 μM	9% @ 5 μm	+	+
214	-	-			53	77	+	+
215					27% @ 5 μM	27	+	+
216						7	+	+

[0713] **Example 250.** Activation of AMPK.

[0714] HT1080 cells were treated with compounds of the invention or a known AMPK activator. Phosphothreonine antibodies were used to assess phosphorylation of threonine 172 of the α -subunit of AMPK by the upstream kinase, AMPK kinase. Phosphoserine antibodies was used to assess specific phosphorylation of skeletal muscle acetyl-CoA carboxylase (ACC) at the activity-modulating AMPK target site (Ser79). Compounds 48 and 196 (10 μ M) induced substantial phosphorylation (activation) of AMPK and downstream phosphorylation (inactivation) of ACC at Ser79. (Fig. 1). The level of phosphorylation was substantially greater than AICAR (500 μ M) which served as a positive control.

[0715] **Example 251.** Selectivity – Compound 48 demonstrated activity against 3 targets in addition to AMPK: ROCK2, CK2, and GLUT1 uptake. (Fig. 2). Otherwise, 10 μ M Compound 48 was tested using a Novascreen panel of receptors and ion channels and found not to modulate their activity. 10 μ M Compound 48 was also inactive against a panel of kinases including PKC, PKA, MAP, MLCK, and PKG as well as an Upstate panel of 212 kinases (ACG, CMGC, TK, TKL, STE, CAMK, and CK1 families. 30 μ M Compound 48 was inactive against mTOR kinase.

[0716] **Example 252.** HT1080 fibrosarcoma cells were incubated with various concentrations of Compound 48, 2 mM AICAR (a known GLUT1 inhibitor) and DMSO (vehicle control). As shown in Fig. 3, activation of AMPK by Compound 48 was specific (phosphorylation of Thr172) and dose dependent. The dose dependent response in ACC phosphorylation is depicted in Fig. 4.

[0717] **Example 253.** Human skeletal muscle cells were incubated with various concentrations of Compound 48, 1 mM or 2 mM AICAR (GLUT1 inhibitor) and DMSO (vehicle control). Activation of AMPK by Compound 48 was specific (phosphorylation of Thr172) and dose dependent (Fig. 5).

[0718] **Example 254.** Human adipocytes were incubated with various concentrations of Compound 48, and DMSO (vehicle control). As shown in Fig. 6, activation of AMPK by Compound 48 was specific (phosphorylation of Thr172) and dose dependent. AMPK activation was not observed in hepatocytes.

[0719] **Example 255.** AMPK activation by Compound 48 is rapid and reversible. Fig. 7 shows the time course of AMPK activation in HT-1080 cells. AMPK phosphorylation at Thr172 was observed within 15 min. after treatment with Compound 48. In contrast, activation of AMPK by AICAR was not evident until 1 hour after treatment. AMPK activation by Compound 48 is also reversible. One set of HT-1080 cells (controls) was incubated with DMSO, 10 μ M Compound 48, or 2 mM AICAR and examined for AMPK phosphorylation and ACC phosphorylation after 3, 4, or six hours (controls). A second set of HT-1080 cells was incubated with DMSO, 10 μ M Compound 48, or 2 mM AICAR for 2 hours, washed, and sampled after an additional 1, 2, or 4 hours. One hour following removal of Compound 48, AMPK phosphorylation at Thr172 and ACC phosphorylation at Ser79 were greatly diminished. (Fig. 8).

[0720] **Example 256.** [AMP]/[ATP] ratio. Cells expressing high levels of GLUT1 were treated with Compound 48. In tumor cells treated with Compound 48, a significant increase in the [AMP]/[ATP] ratio was observed, along with increased levels of AMP. No increase was observed in muscle cells. (Fig. 9).

[0721] **Example 257.** AMPK activation was observed in a fibrosarcoma tumor line deprived of glucose. HT1080 cells were incubated with glucose or transferred to glucose-free media. Cells under both conditions were then treated with Compound 48, AICAR, or DMSO (control). (Fig. 10). AMPK and ACC activation by Compound 48 was rapid, with significant phosphorylation observed within 15 minutes of treatment. Glucose deprivation alone resulted in observable ACC phosphorylation only after 2-6 hr. following the shift to glucose-free media, and increased AMPK phosphorylation was not observed. A separate experiment was performed using glucose-pyruvate free media. Under those conditions, rapid activation of AMPK was observed.

[0722] **Example 258.** CAM kinase kinase inhibition reduces AMPK phosphorylation below basal levels. Compound 48 overcomes the inhibition and raises phosphorylation amounts. Downstream ACC phosphorylation is consistent with increased AMPK activity. (Fig. 11)

[0723] **Example 259.** Diet-induced obese (DIO) C57/BL/6J mice were fed a high fat diet with and without Compound 48 (90 mg/kg) or low-fat chow. In mice supplemented with Compound 48, there was an immediate increase in fatty acid oxidation, which was maintained throughout the dosing period (8 days). (Fig. 12).

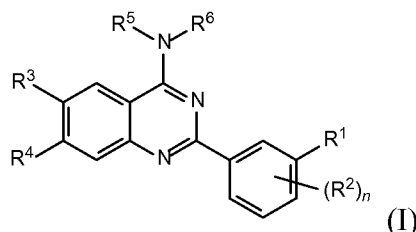
[0724] **Example 260.** Ob knockout mice (ob/ob) were fed a high fat diet with or without Compound 48. Administration of Compound 48 resulted in improvements in serum insulin, blood glucose, serum cholesterol, visceral fat, liver weight, and serum ALT. (Fig. 13).

[0725] **Example 261.** AMPK activation (phosphorylation) is correlated with GLUT1 inhibition in muscle and adipose tissue. However, in hepatocytes, GLUT1 inhibition, for example using Compound 48, is not accompanied by increased AMPK phosphorylation. Moreover, glucose uptake is not inhibited by cytochalasin or phloretin/phlorizin. The likely explanation is that hepatocytes utilize GLUT2 instead. Nevertheless, liver steatosis (fatty liver), which is observed in Apo E^{-/-} mice maintained on a high fat diet is not observed in those mice when the high fat diet is supplemented with Compound 48. This is attributed to ROCK2 inhibition, which blocks differentiation of hepatic stellate cells.

[0726] **Example 262.** Kidney function was assessed by measuring urinary protein excretion. Administration of Compound 48 greatly reduced urinary protein/albumin levels, indicating reduced impairment of kidney function (Fig. 14).

WE CLAIM:

1. A compound having the formula I:



wherein:

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$, $-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$, $-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl, $-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $NR^{16}R^{17}$, aryl, $-(C_1$ - C_6 alkyl)- O -(aryl), aralkyl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$, $-(C_1$ - C_6 alkyl)- $NR^{16}R^{17}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, $-SO_2$ -alkyl, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{13} and R^{14} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents

independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, -SO₂-alkyl, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

each R² is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

n is selected from 0 to 4;

R^3 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, $-(CH_2)_a-NR^{33}R^{34}$, $-Y-R^{32}$, $-O-(CH_2)_a-CO_2R^{32}$, $-O-(CH_2)_a-C(=O)NR^{33}R^{34}$, $-O-(CH_2)_a$ -heteroaryl, $-O-(CH_2)_a$ -cycloalkyl, $-O-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-O-(CH_2)_c-NR^{33}R^{34}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-NH-C(=O)-Y-R^{35}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$;

R^{32} is selected from the group consisting of C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{33} and R^{34} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{33} and R^{34} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

Y is selected from a covalent bond, O, NH, and C_1 - C_6 alkyl;

R^{35} is selected from the group consisting of H, aryl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-CO_2R^{38}$, $-O-(CH_2)_b-CO_2R^{38}$, and $-C(=O)NR^{36}R^{37}$,

R^{36} and R^{37} independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{36} and R^{37} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{38} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoroalkyl;

R^4 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, $-(CH_2)_a-NR^{43}R^{44}$, $-Z-R^{42}$, $-O-(CH_2)_a-CO_2R^{42}$, $-O-(CH_2)_a-C(=O)NR^{43}R^{44}$, $-O-(CH_2)_a$ -heteroaryl, $-O-(CH_2)_a$ -cycloalkyl, $-O-C(=O)-(CH_2)_a-NR^{43}R^{44}$, $-O-(CH_2)_c-NR^{43}R^{44}$, $-NH-C(=O)-(CH_2)_a-NR^{43}R^{44}$, $-NH-C(=O)-Z-R^{45}$, $-NH-C(=O)-(CH_2)_a-NR^{43}R^{44}$;

R^{42} is selected from the group consisting of C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{46}R^{47}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{46}R^{47}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{43} and R^{44} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{46}R^{47}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{46}R^{47}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{43} and R^{44} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

Z is selected from a covalent bond, O, NH, and C_1 - C_6 alkyl;

R^{45} is selected from the group consisting of H, aryl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{46}R^{47}$, $-CO_2R^{48}$, $-O-(CH_2)_b-CO_2R^{48}$, and $-C(=O)NR^{46}R^{47}$;

R^{46} and R^{47} independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, aryl, aralkyl, heteroaryl, C_3-C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, hydroxy, amino, cyano and C_1-C_3 perfluoro alkyl;

or R^{46} and R^{47} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1-C_3 perfluoro alkyl;

R^{48} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{46}R^{47}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkoxy, hydroxy, amino, cyano and C_1-C_3 perfluoroalkyl;

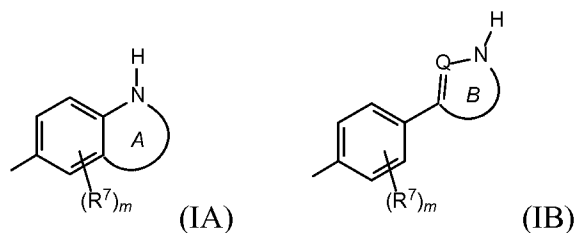
each a is independently selected from 0 to 6;

each b is independently selected from 0 to 6;

each c is independently selected from 2 to 6;

R^5 is selected from the group consisting of H and C_1-C_6 alkyl;

R^6 is selected from the group of formula (IA) and (IB):



wherein

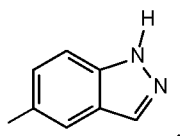
Ring A is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

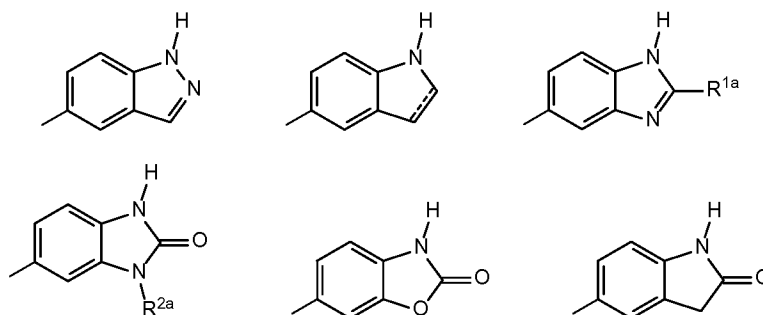
R^7 is selected from the group consisting of halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

m is 0 to 2;

wherein Formula IA is not

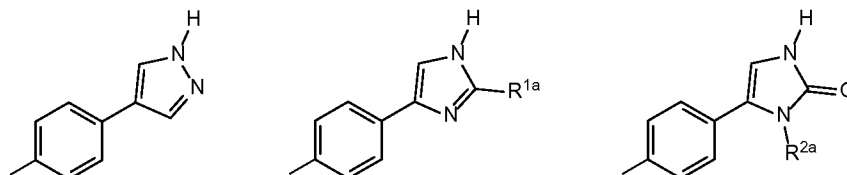


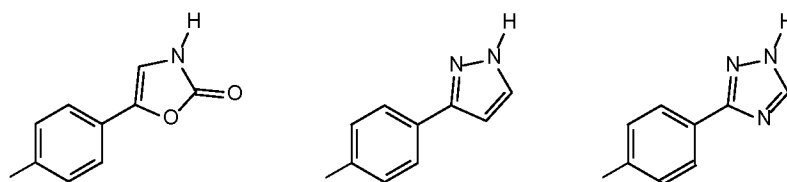
2. The compound of claim 1, wherein R^6 is formula IA, and formula IA is selected from the group consisting of:



wherein the dotted line represents an optional double bond; R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

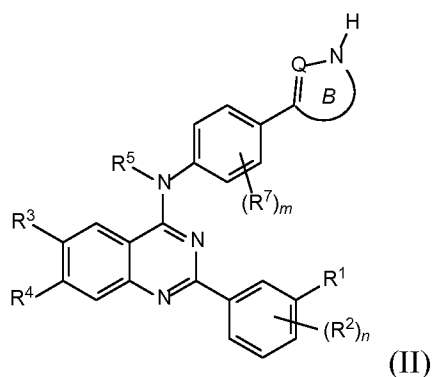
3. The compound of claim 1, wherein R^6 is formula IB, and formula IB is selected from the group consisting of:





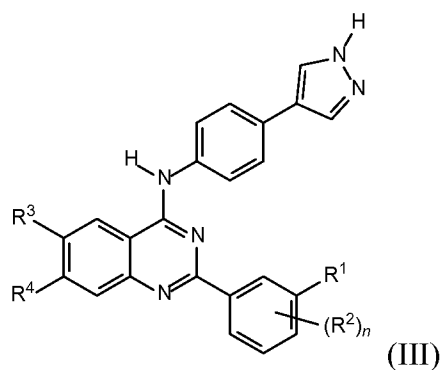
wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

4. The compound of claim 1, having the formula II:



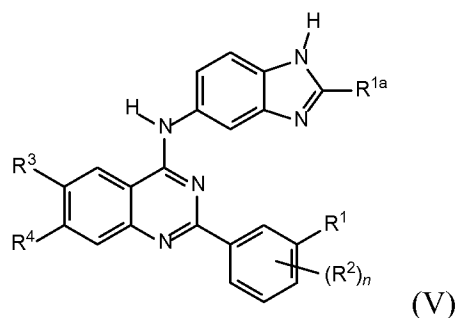
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , *Ring B*, *Q*, n and m are as stated for formula I.

5. The compound of claim 4, having the formula III:



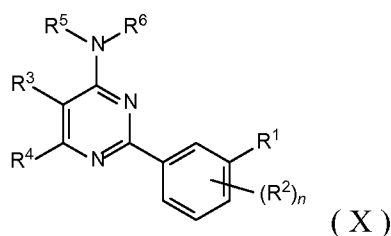
wherein R^1 , R^2 , R^3 , R^4 , and n are as stated for formula I.

6. The compound of claim 1, having I the formula V:



wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^1 , R^2 , R^3 , R^4 , and n and are as stated for formula I.

7. A compounds having the formula X:



wherein:

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$, $-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$, $-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl, $-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $NR^{16}R^{17}$, aryl, $-(C_1$ - C_6 alkyl)- O -(aryl), aralkyl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$,

aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹³ and R¹⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, -SO₂-alkyl, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

each R^2 is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

n is selected from 0 to 4;

R^3 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, $-(CH_2)_a-NR^{33}R^{34}$, $-Y-R^{32}$, $-O-(CH_2)_a-CO_2R^{32}$, $-O-(CH_2)_a-C(=O)NR^{33}R^{34}$, $-O-(CH_2)_a$ -heteroaryl, $-O-(CH_2)_a$ -cycloalkyl, $-O-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-O-(CH_2)_c-NR^{33}R^{34}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$, $-NH-C(=O)-Y-R^{35}$, $-NH-C(=O)-(CH_2)_a-NR^{33}R^{34}$;

R^{32} is selected from the group consisting of C_1 - C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

R^{33} and R^{34} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{36}R^{37}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

or R^{33} and R^{34} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, oxo, hydroxy, amino, cyano and C_1 - C_3 perfluoro alkyl;

Y is selected from a covalent bond, O, NH, and C_1 - C_6 alkyl;

R^{35} is selected from the group consisting of H, aryl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{36}R^{37}$, $-CO_2R^{38}$, $-O-(CH_2)_b-CO_2R^{38}$, and $-C(=O)NR^{36}R^{37}$;

- R^{36} and R^{37} independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;
- or R^{36} and R^{37} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;
- R^{38} is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR³⁶R³⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;
- R^4 is selected from the group consisting of H, lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, perfluoro lower alkyl, -(CH₂)_a-NR⁴³R⁴⁴, -Z-R⁴², -O-(CH₂)_a-CO₂R⁴², -O-(CH₂)_a-C(=O)NR⁴³R⁴⁴, -O-(CH₂)_a-heteroaryl, -O-(CH₂)_a-cycloalkyl, -O-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -O-(CH₂)_c-NR⁴³R⁴⁴, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴, -NH-C(=O)-Z-R⁴⁵, -NH-C(=O)-(CH₂)_a-NR⁴³R⁴⁴;
- R^{42} is selected from the group consisting of C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;
- R^{43} and R^{44} are independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-C(=O)NR⁴⁶R⁴⁷, aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo,

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R⁴³ and R⁴⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

alternatively, R³ and R⁴ may be taken together to form a 5- or 6-membered ring;

Z is selected from a covalent bond, O, NH, and C₁-C₆ alkyl;

R⁴⁵ is selected from the group consisting of H, aryl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -CO₂R⁴⁸, -O-(CH₂)_b-CO₂R⁴⁸, and -C(=O)NR⁴⁶R⁴⁷;

R⁴⁶ and R⁴⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

or R⁴⁶ and R⁴⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, amino, cyano and C₁-C₃ perfluoro alkyl;

R⁴⁸ is selected from the group consisting of H, aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR⁴⁶R⁴⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, amino, cyano and C₁-C₃ perfluoroalkyl;

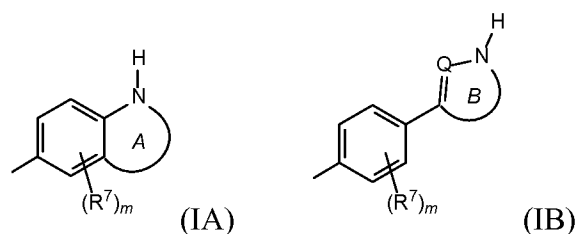
each *a* is independently selected from 0 to 6;

each *b* is independently selected from 0 to 6;

each *c* is independently selected from 2 to 6;

R⁵ is selected from the group consisting of H and C₁-C₆ alkyl;

R⁶ is selected from the group of formula (IA) and (IB):



wherein

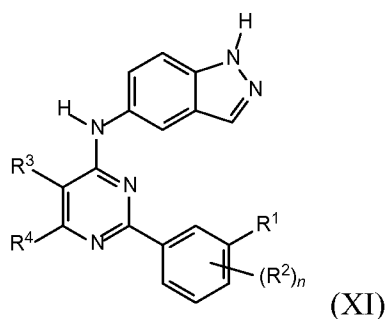
Ring A is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

R^7 is selected from the group consisting of halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

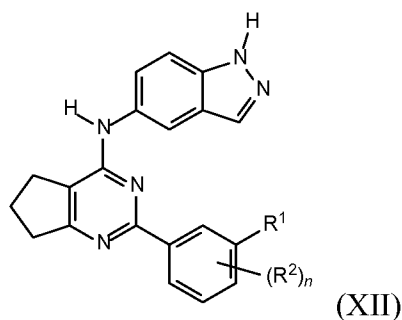
m is 0 to 2.

8. The compound of claim 7 having the formula XI:



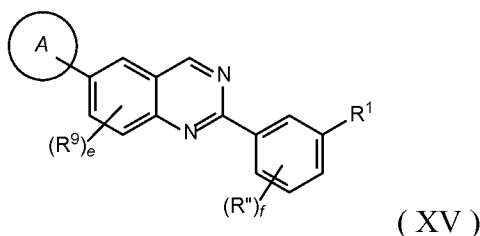
wherein R^1 , R^2 , R^3 , R^4 , and n are as stated for formula X.

9. The compound of claim 7, having the formula XII:



wherein R^1 , R^2 , and n are as stated above for formula X.

10. A compounds having the formula XV:



wherein

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$, $-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$, $-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl, $-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, aryl, $-(C_1-C_6 \text{ alkyl})-O-(\text{aryl})$, aralkyl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted at one or more carbon atoms by from 1 to 3 substituents independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring

containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;
 or R¹³ and R¹⁴ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆, alkenyl, C₁-C₆ alkoxy, C₃-C₇ cycloalkyl, oxo, -SO₂-alkyl, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

X is selected from a covalent bond, O, and C₁-C₆ alkyl;

R¹⁵ is selected from the group consisting of H, C₁-C₈ alkyl, aryl, heteroaryl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-O-(aryl), -(C₁-C₆ alkyl)-C(=O)NR¹⁶R¹⁷, -O-(CH₂)_x-CO₂R¹⁸, -O-(CH₂)_x-C(=O)NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-CO₂R¹⁸; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁶ and R¹⁷ independently selected from the group consisting of H, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), aryl, aralkyl, heteroaryl, C₃-C₇ cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

or R¹⁶ and R¹⁷ may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, oxo, hydroxy, cyano and C₁-C₃ perfluoro alkyl;

R¹⁸ is selected from the group consisting of aryl, aralkyl, heteroaryl, C₁-C₆ alkyl, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -(C₁-C₆ alkyl)-NR¹⁶R¹⁷, -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C₁-C₆ alkoxy, hydroxy, cyano and C₁-C₃ perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

each R^9 is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

e is selected from 0 to 3;

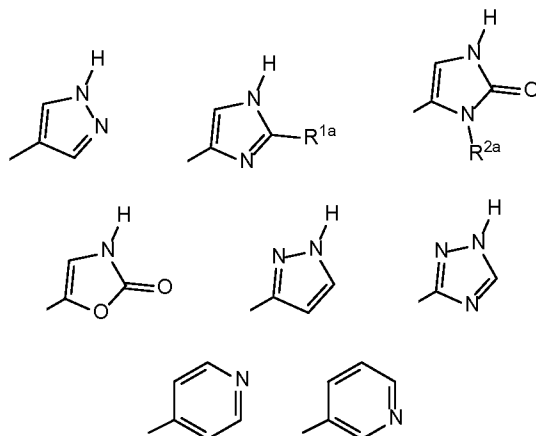
Ring A is a 5- or 6-membered ring which may comprise 0-3 ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy;

R'' is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl; and

f is selected from 0 to 2.

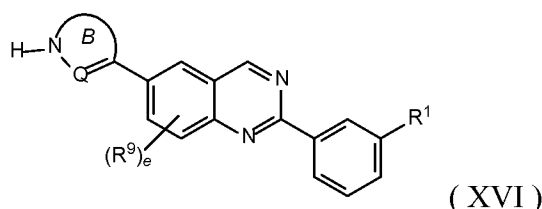
11. The compound of claim 10, wherein the *Ring A* of compound XV is a 5- or 6-membered aromatic ring which comprises 1-3 ring heteroatoms selected from N, O and S.

12. The compound of claim 10, wherein *Ring A* of compound XV has the structure selected from the group consisting of:



wherein R^{1a} is selected from the group consisting of H, lower alkyl, and perfluoro lower alkyl; and R^{2a} is selected from the group consisting of H and lower alkyl.

13. The compounds of claim 10 having the formula XVI:



wherein

R^1 is selected from the group consisting of aryl, $-(CH_2)_y-NR^{13}R^{14}$, $-X-R^{12}$,

$-(CH_2)_y-C(=O)NR^{13}R^{14}$, $-O-(CH_2)_y-CO_2R^{12}$, $-O-(CH_2)_y-C(=O)NR^{13}R^{14}$,

$-O-(CH_2)_y$ -cycloalkyl, $-(CH_2)_y-O-C(=O)-NR^{13}R^{14}$, $-NH-C(=O)-(CH_2)_y-NR^{13}R^{14}$,

$-NH-C(=O)-X-R^{15}$, $-(CH_2)_y-S(=O)_2NR^{13}R^{14}$, $-O-(CH_2)_y-S(=O)_2NR^{13}R^{14}$,

$-NH-S(=O)_2-X-R^{15}$, $-NH-(CH_2)_y-NR^{13}R^{14}$, $-O-(CH_2)_y$ -heteroaryl,

$-O-C(=O)-(CH_2)_y-NR^{13}R^{14}$, and $-O-(CH_2)_z-NR^{13}R^{14}$;

R^{12} is selected from the group consisting of C_1 - C_{10} alkyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl),

$-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl)- O -(C_1 - C_6 alkyl),

$-(C_1$ - C_6 alkyl)- $NR^{16}R^{17}$, aryl, $-(C_1$ - C_6 alkyl)- O -(aryl), aralkyl, C_3 - C_7 cycloalkyl, a three to

twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may

be optionally substituted at one or more carbon atoms by from 1 to 3 substituents

independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

R^{13} and R^{14} are independently selected from the group consisting of H, C_1 - C_8 alkyl, C_2 - C_8

alkenyl, C_2 - C_8 alkynyl, $-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- $C(=O)NR^{16}R^{17}$,

aryl, aralkyl, heteroaryl, C_3 - C_7 cycloalkyl, a three to twelve membered heterocyclic ring

containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to

3 substituents independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_3 - C_7

cycloalkyl, C_1 - C_6 alkoxy, $-SO_2$ -alkyl, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

or R^{13} and R^{14} may be taken together form a three to twelve membered heterocyclic ring

having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents

independently selected from halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, C_3 - C_7

cycloalkyl, $-SO_2$ -alkyl, oxo, hydroxy, cyano and C_1 - C_3 perfluoro alkyl;

X is selected from a covalent bond, O, and C_1 - C_6 alkyl;

R^{15} is selected from the group consisting of H, C_1 - C_8 alkyl, aryl, heteroaryl, C_3 - C_7 cycloalkyl,

$-(C_1$ - C_6 alkyl)- O -(C_1 - C_6 alkyl), $-(C_1$ - C_6 alkyl)- O -(aryl),

$-(C_1-C_6 \text{ alkyl})-C(=O)NR^{16}R^{17}$, $-O-(CH_2)_x-CO_2R^{18}$, $-O-(CH_2)_x-C(=O)NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-CO_2R^{18}$; and a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, hydroxy, cyano and C_1-C_3 perfluoro alkyl;

R^{16} and R^{17} independently selected from the group consisting of H, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, aryl, aralkyl, heteroaryl, C_3-C_7 cycloalkyl, a three to twelve membered heterocyclic ring containing up to 3 heteroatoms, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, hydroxy, cyano and C_1-C_3 perfluoro alkyl;

or R^{16} and R^{17} may be taken together form a three to twelve membered heterocyclic ring having up to 3 heteroatoms which is optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, oxo, hydroxy, cyano and C_1-C_3 perfluoro alkyl;

R^{18} is selected from the group consisting of aryl, aralkyl, heteroaryl, C_1-C_6 alkyl, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, $-(C_1-C_6 \text{ alkyl})-NR^{16}R^{17}$, $-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, each of which may be optionally substituted by from 1 to 3 substituents independently selected from halo, C_1-C_6 alkoxy, hydroxy, cyano and C_1-C_3 perfluoroalkyl;

x is selected from 1 to 6;

y is selected from 0 to 6;

z is selected from 2 to 6;

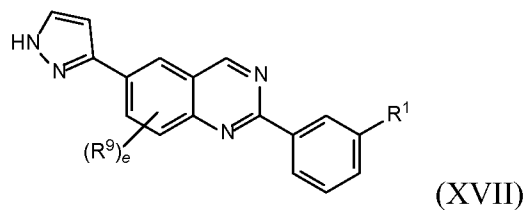
each R^9 is independently selected from the group consisting of lower alkyl, CN, halo, hydroxy, lower alkoxy, amino, and perfluoro lower alkyl;

e is selected from 0 to 3;

Ring B is a 5- or 6-membered ring which may comprise 0-2 additional ring heteroatoms selected from N, O and S, and may be unsubstituted or may be substituted with 1 to 3 substituents selected from halo, CN, oxo, hydroxy, amino, lower alkyl, perfluoro lower alkyl, and lower alkoxy; and

Q is selected from CH or N.

14. The compound of claim 10 having the formula XVII:

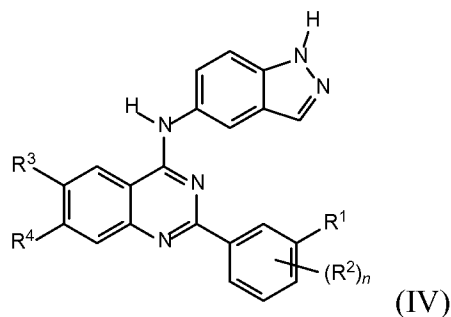


wherein R^1 , R^9 and e are as stated above for formula XV.

15. A method of treating neoplastic diseases comprising administering to a patient an effective amount of a compound according to claims 1 to 14.

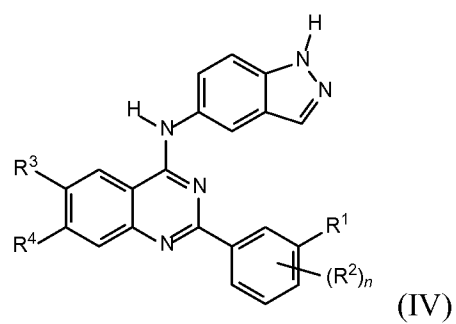
16. A method of treating metabolic diseases comprising administering to a patient an effective amount of a compound according to claims 1 to 14.

17. A method of treating neoplastic diseases comprising administering to a patient an effective amount of a compound of the formula IV:



wherein R^1 , R^2 , R^3 , R^4 , n and m are as stated above for formula I.

18. A method of treating metabolic diseases comprising administering to a patient an effective amount of a compound of the formula IV:



wherein R¹, R², R³, R⁴, *n* and *m* are as stated above for formula I.

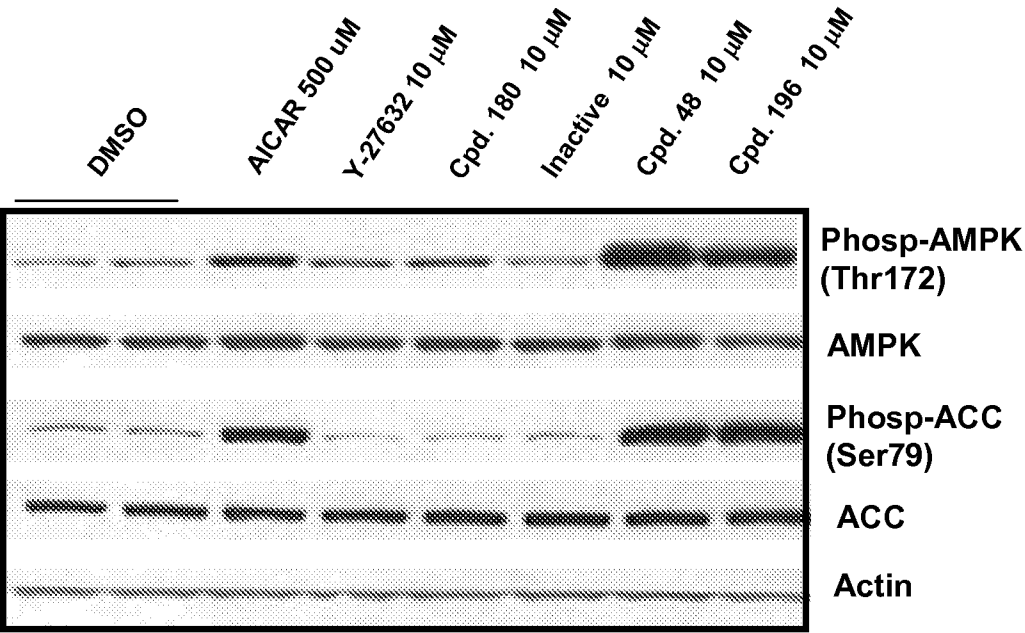


Fig. 1

2/12

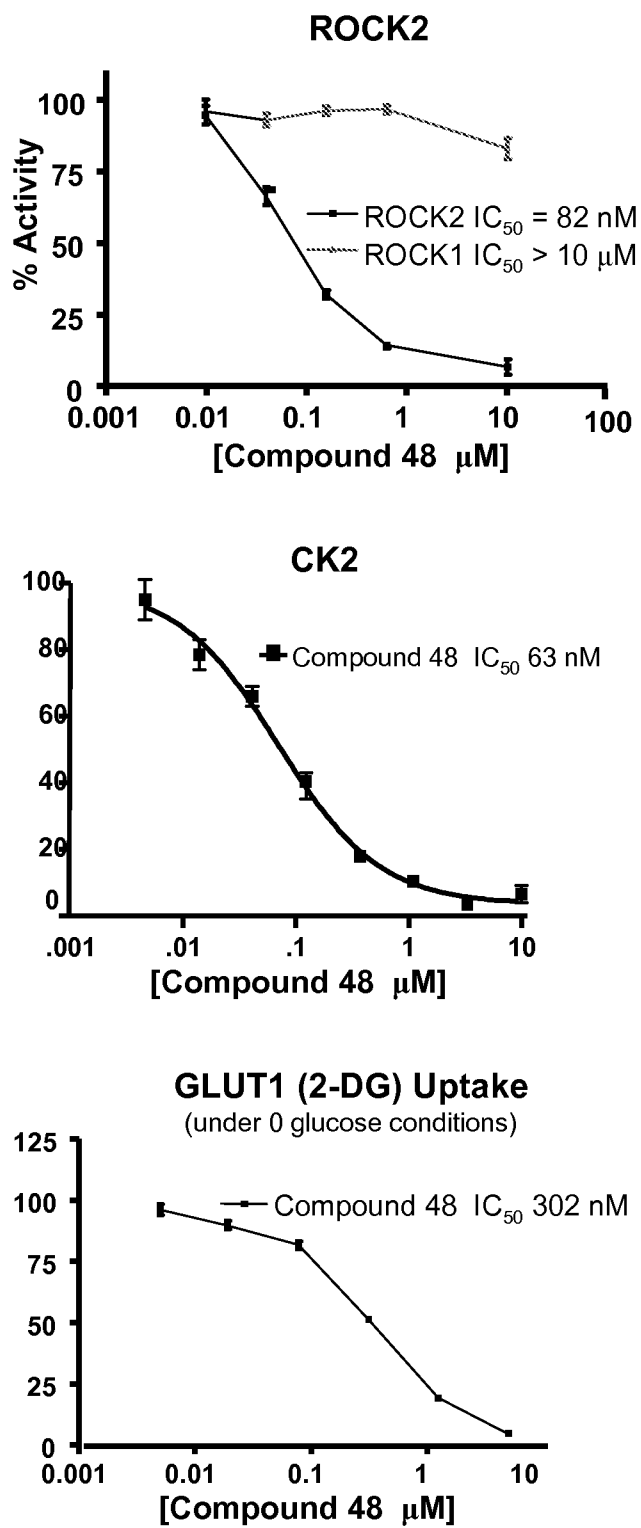


Fig. 2

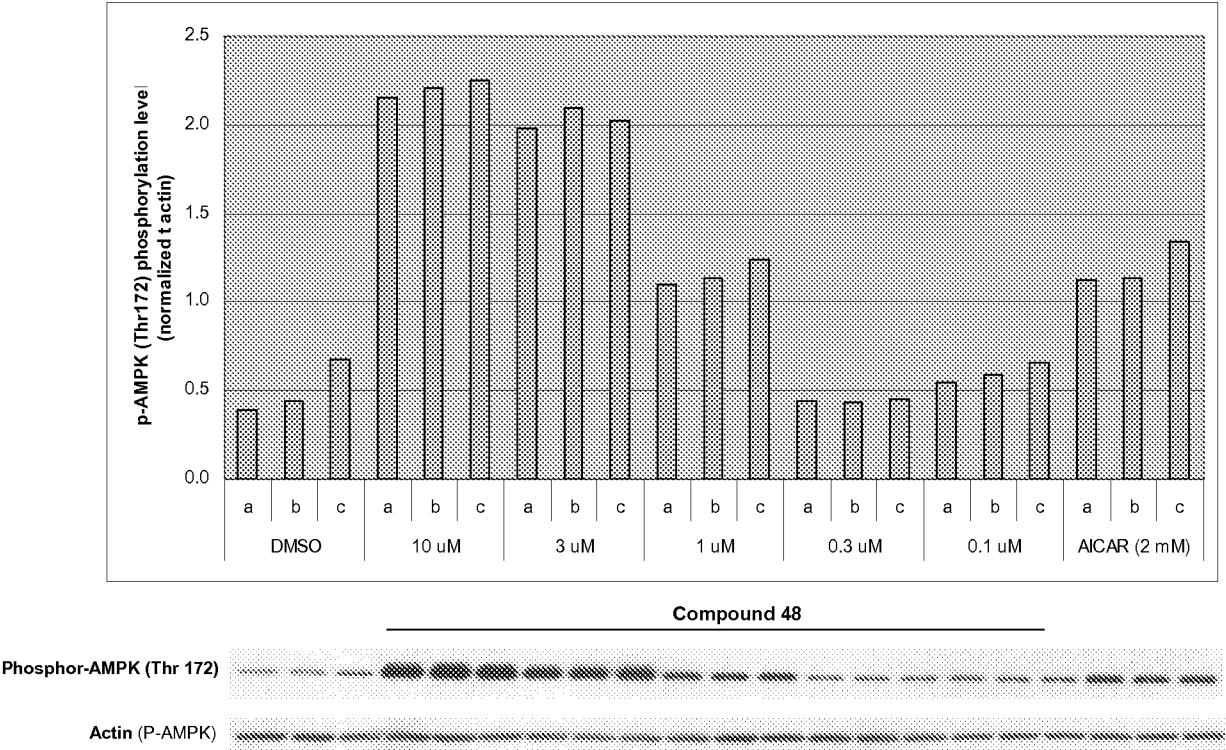


Fig. 3

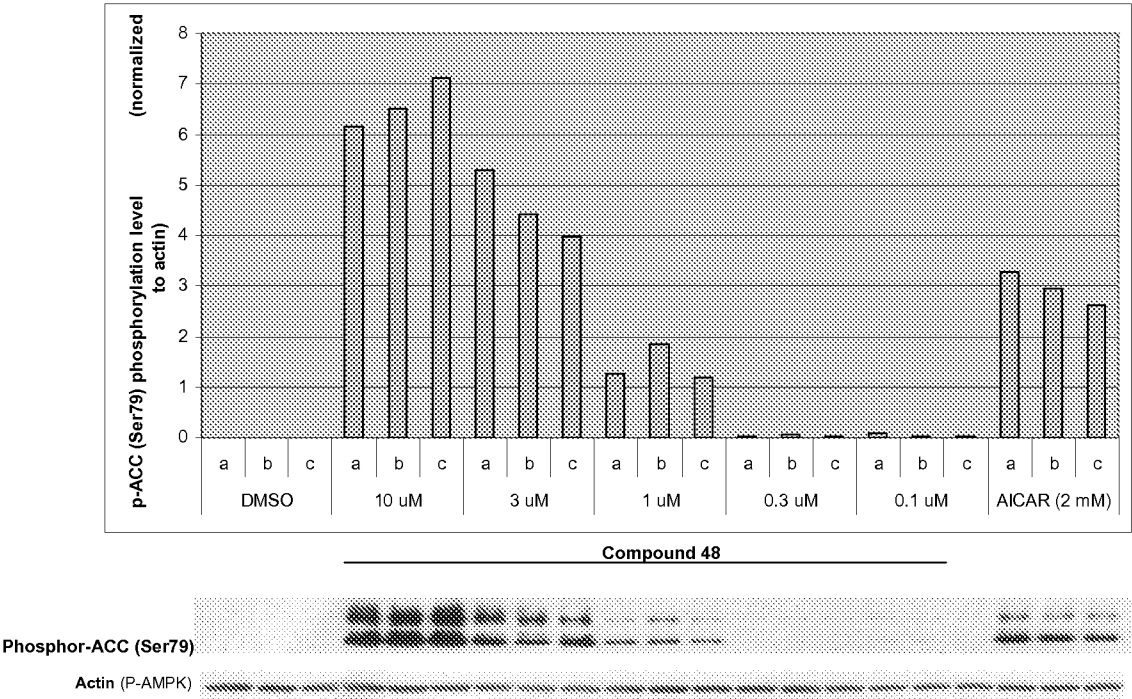


Fig. 4

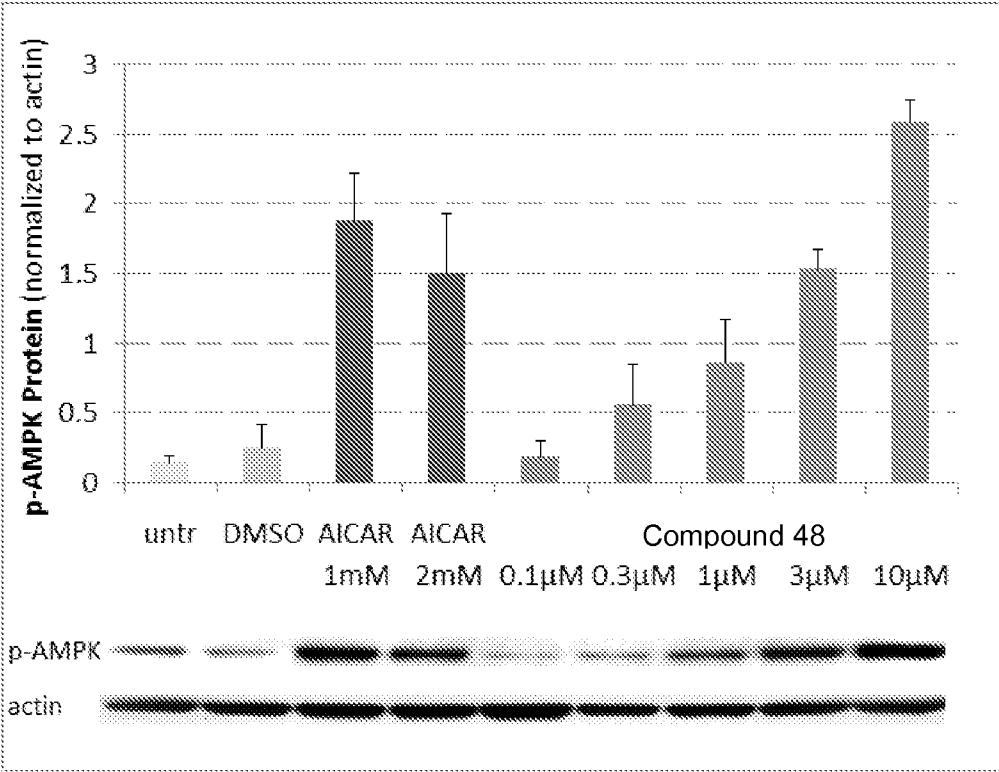


Fig. 5

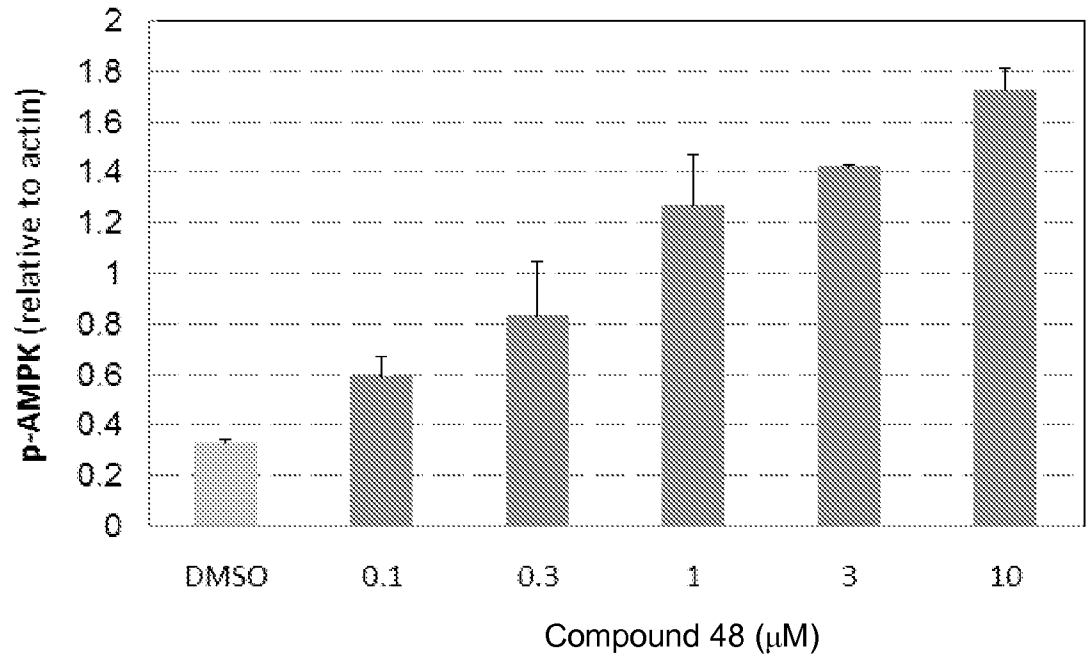


Fig. 6

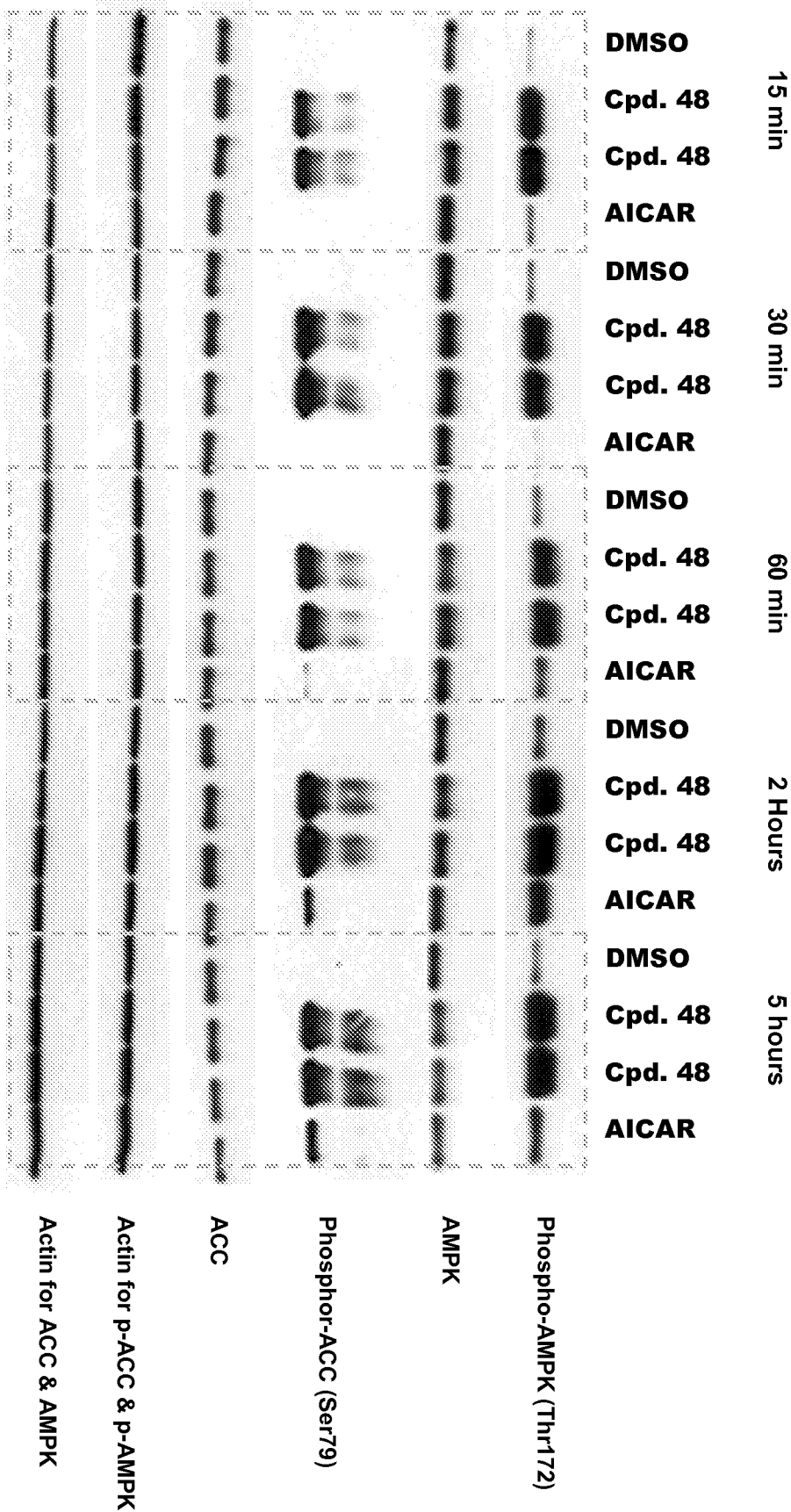


Fig. 7

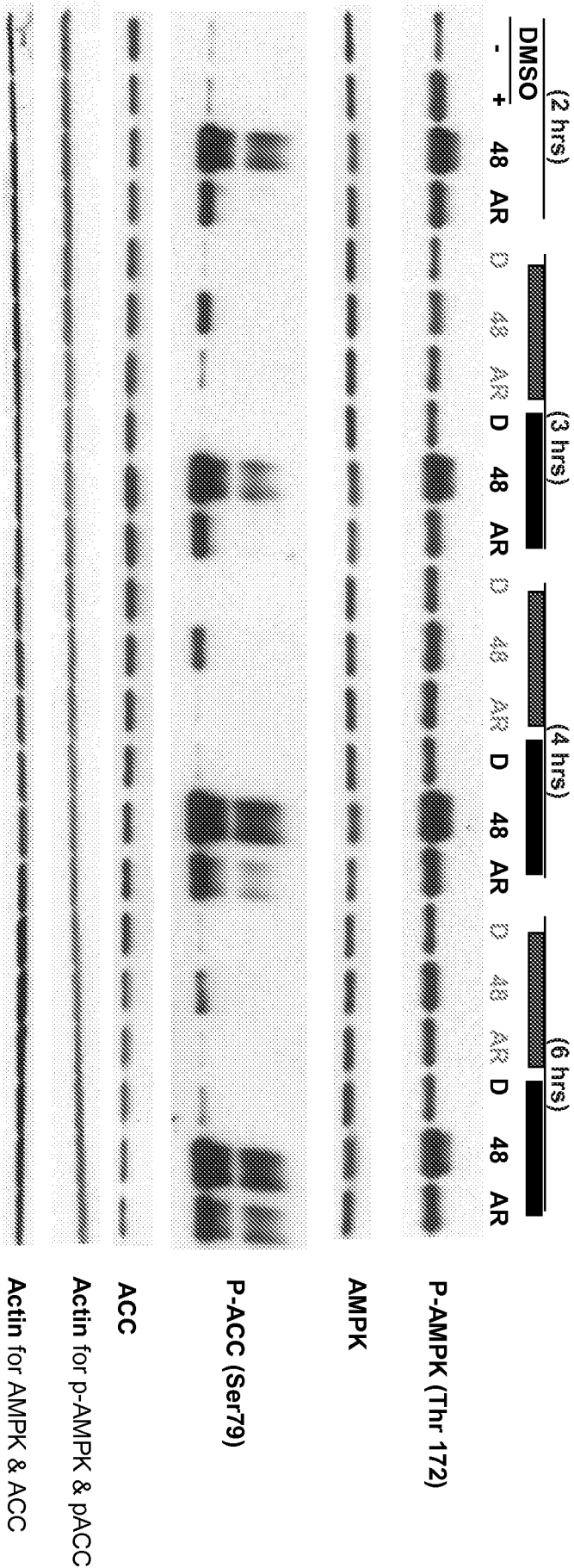


Fig. 8

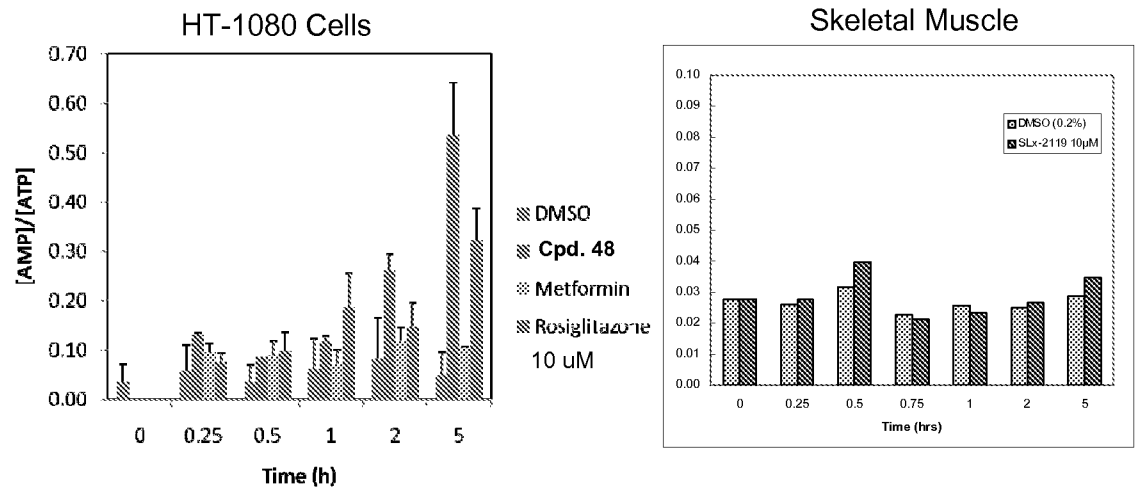


Fig. 9

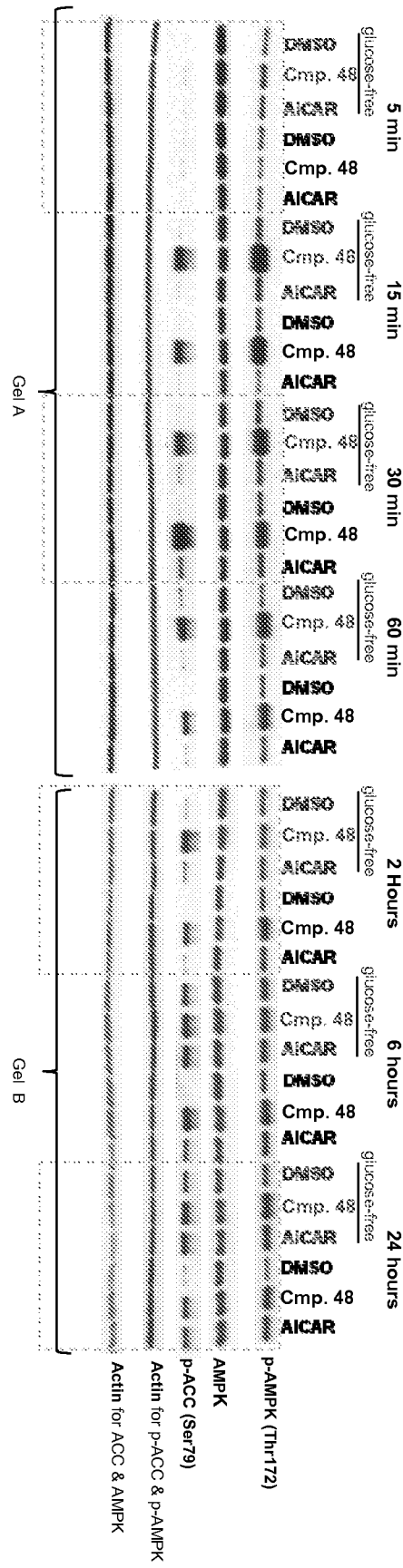


Fig. 10

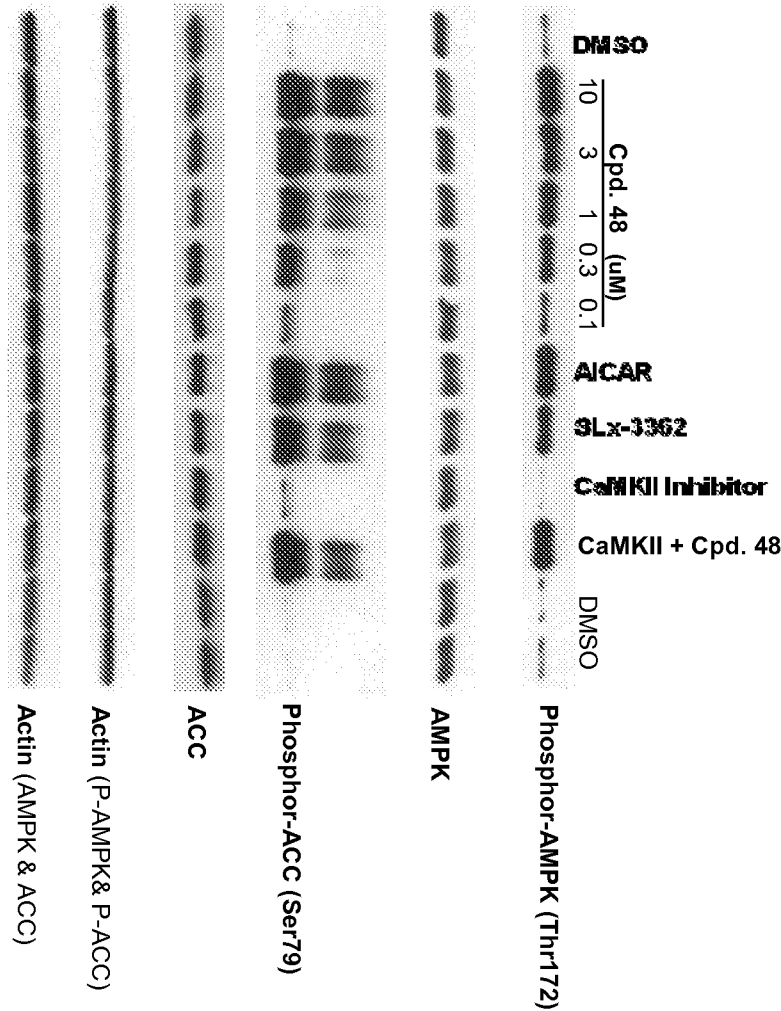


Fig. 11

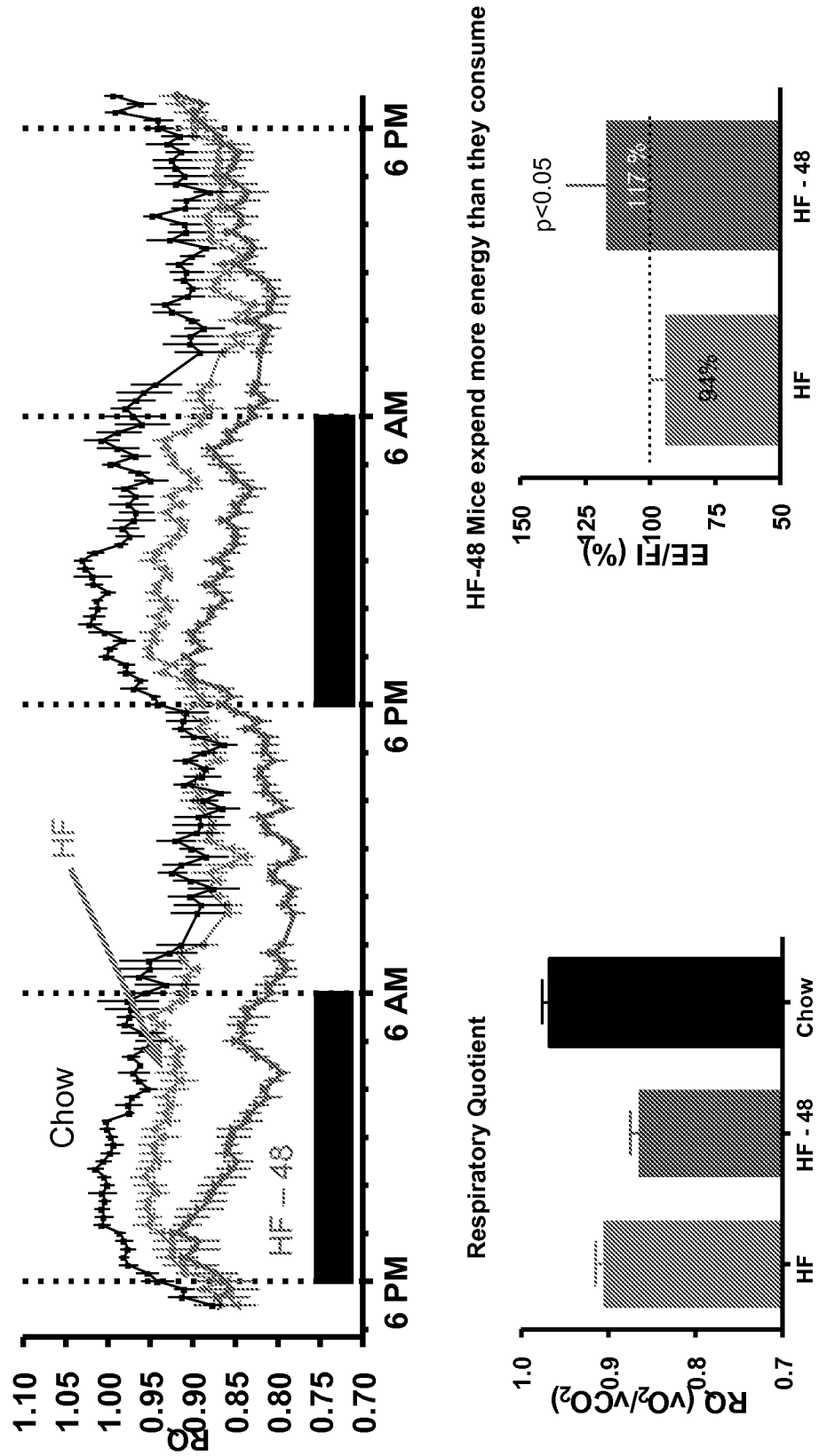


Fig. 12

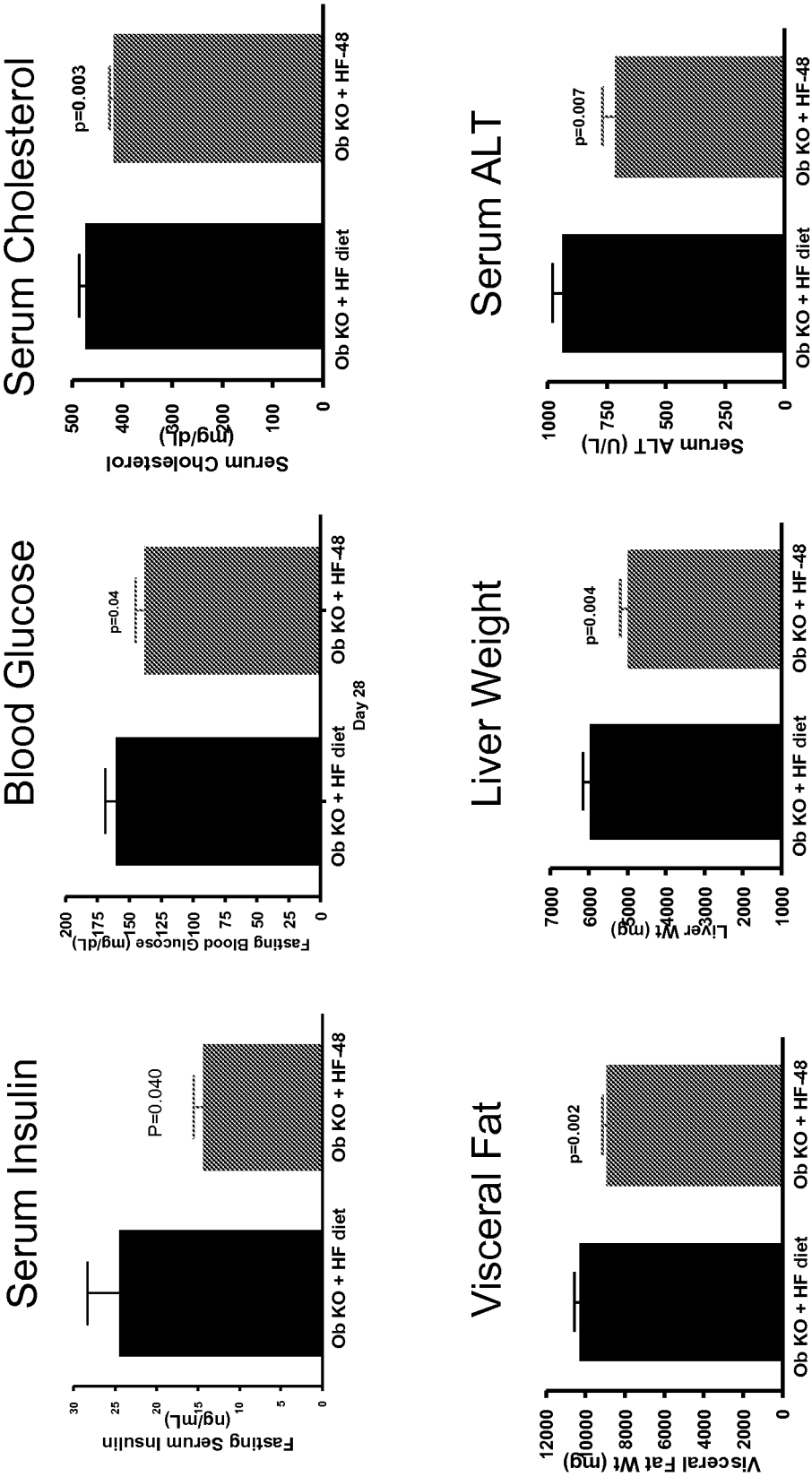


Fig. 13

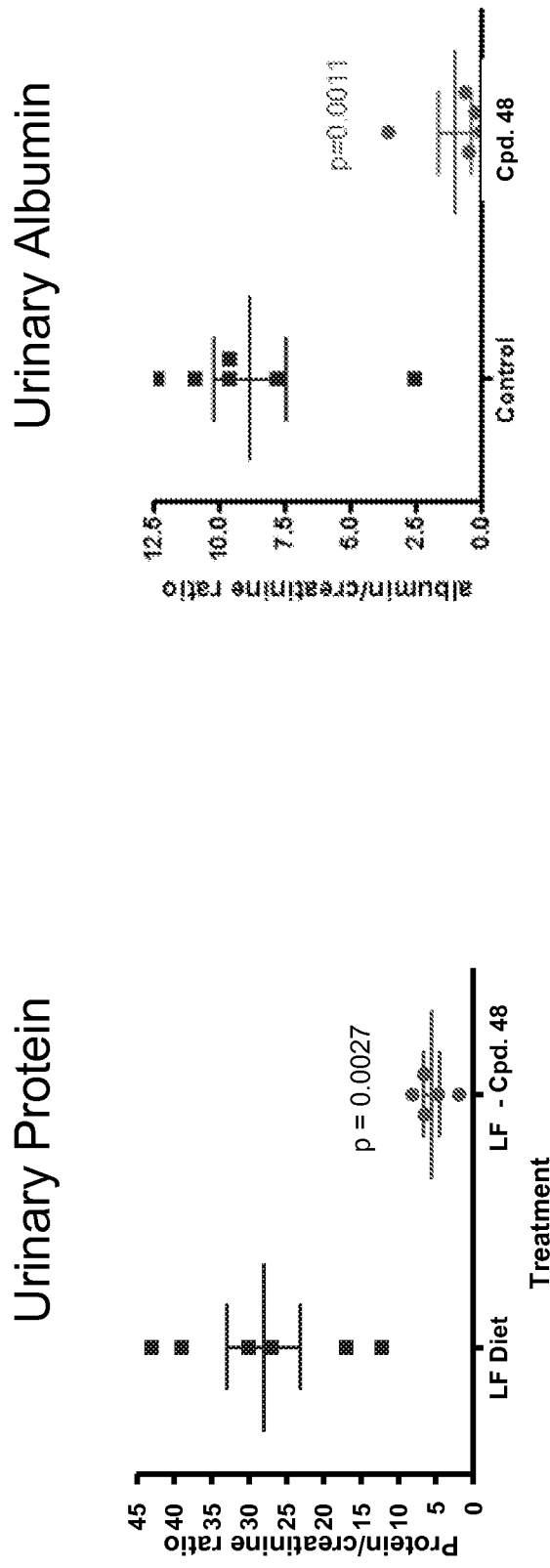


Fig. 14