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(54) Title: INHIBITORS OF B-RAF KINASE

(57) Abstract: The present invention relates to compounds and methods useful as inhibitors of B-Raf for the treatment or prevention of cancer, including hematological and non-hematologic malignancies, hematopoiesis, autoimmune diseases, dermatologic and ophthalmologic conditions.

INHIBITORS OF B-RAF KINASE

This application claims the priority of Untited States provisional application 60/680,328, filed May 12, 2005, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention is directed to new benzimidazole compounds, compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of Raf kinase activity in a human or animal subject are also provided for the treatment diseases such as cancer, chronic neurodegeneration, neurotraumatic conditions, pain, migraine and cardiac hypertrophy.

BACKGROUND OF THE INVENTION

The Raf genes code for highly conserved serine-threonine specific protein kinases. Raf kinases are essential components of the Ras/Mitogen-Activated Protein Kinase (MAPK) signaling module that controls complex cellular behavior in response to external stimuli. The Ras/MAPK signal transduction pathway is believed to consist of receptor tyrosine kinases (primarily, although other classes of receptors can activate this pathway), Ras family GTPases, Raf protein kinases, Mitogen-Activated Protein Kinase kinases (MAPKK, or Mek), and Extracellular signal-regulated kinases (MAPK, or Erk), which ultimately phosphorylate cytosolic and nuclear proteins (i.e., transcription factors). In this pathway, Raf kinases are recruited to the inner plasma membrane by interaction with active Ras and subsequently activated by phosphorylation. Raf kinases then phosphorylate and activate the two isoforms of MAPKK, Mek1 and Mek2, which are dual specificity threonine-tyrosine kinases. Mek kinases then phosphorylate and activate the two isoforms of MAPK, Erk1 and Erk2. In particular, Erk1 and Erk2 phosphorylate nuclear transcription factors that control gene expression in response to Ras/MAPK signaling. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular activities such as proliferation, differentiation, survival, oncogenic transformation and apoptosis (Wellbrock et al., Nat Rev Mol Cell Biol 5:875-885, 2004).

Raf kinases have three distinct isoforms, Raf-1 (C-Raf), A-Raf, and B-Raf, distinguished by their ability to interact with Ras, their ability to activate the MAPK pathway, and their tissue distribution and sub-cellular localization (Marias et al., Biochem J 351: 289-305, 2000) (Weber et al., Oncogene 19:169-176, 2000) (Pritchard et al., Mol Cell Biol 15:6430-6442, 1995). Both the essential role and the position of Raf in many signaling pathways have been demonstrated from studies using deregulated and dominant inhibitory Raf mutants in mammalian cells, as well as from studies employing biochemical and genetic techniques in model organisms. In many cases, the activation of Raf by receptors that stimulate cellular tyrosine phosphorylation is dependent on the activity of Ras, indicating that Ras functions upstream of Raf. Upon activation, Raf activates Mek1 and Mek2 by phosphorylation of two serines in the Mek kinase activation loop, resulting in the propagation of the signal to the downstream MAPK effectors (Crews, C. M. and Erikson, R. L., Cell 74:215-217, 1993). The Raf serine-threonine

kinases are considered to be the primary Ras effectors involved in the proliferation of animal cells (Avruch et al., Trends Biochem Sci 19:279-283, 1994). Further, among the Raf kinases, B-Raf is considered the primary effector of Ras activation and stimulation of the MAPK pathway in most cell types (Beeram et al., J Clin Oncol 23:6771-6790, 2005).

Activating mutation of one of the Ras genes is observed in greater than 20% of all human cancers, although they are much more prevalent in particular diseases, such as pancreatic cancer (90%) and colon cancer (50%). The Raf/Mek/Erk pathway is hyper-activated in about 30% of all tumors (Bos et al., Cancer Res 49:4682-4689, 1989) (Hoshino et al., Oncogene 18:813-822, 1999). Recent studies have shown that activating mutations in the catalytic domain of B-Raf occur in about 66% of melanomas, 12% of colorectal carcinomas and 14% of ovarian carcinomas, as well as smaller percentages in other tumor types (Davies et al., Nature 417:949-954, 2002) (Yuen et al., Cancer Res 62:6451-6455, 2002) (Brose et al., Cancer Res 62:6997-7000, 2002). These activating mutations generally increase, often substantially, basal B-Raf kinase activity in cells, and in all cases result in hyperactive MAPK signaling (Wan et al., Cell 116:855-867, 2004) (Garnett et al., Mol Cell 20:963-969, 2005). Greater than 80% of the B-Raf mutations in melanomas occur at a single residue, valine 600, which is substituted with a glutamate. Additional studies have shown that B-Raf is an oncogene, and that B-Raf mutation in the skin nevi is a critical step in the initiation of melanocytic neoplasia (Wellbrock et al., Cancer Res 64:2338-2342, 2004) (Mercer et al., Cancer Res 65:11493-11500, 2005) (Pollock et al., Nature Genetics 25:1-2, 2002).

Inhibitors of the Raf/Mek/Erk pathway at the level of Raf kinases can potentially be effective as therapeutic agents against tumors with over-expressed or mutated receptor tyrosine kinases, activated intracellular tyrosine kinases, aberrantly expressed Grb2 (an adapter protein that allows stimulation of Ras by the Sos exchange factor), and mutated Ras genes, as well as tumors harboring activating mutations of B-Raf itself. In early clinical trials, inhibitors of Raf kinases have shown promise as therapeutic agents in cancer therapy (Crump, M., Current Pharm Des 8:2243-2248, 2002) (Hotte, S.J. and Hirte, H. W., Current Pharm Des 8:2249-2253, 2002). Disruption of Raf expression in cell lines through the application of RNA antisense technology has been shown to suppress both Ras and Raf-mediated tumorigenicity (Kolch et al., Nature 349:416-428, 1991) (Monia et al., Nature Med 2:668-675, 1996). More recent studies using RNAi (RNA interference) to suppress expression of B-Raf (V600E mutant) in human melanoma cells have demonstrated inhibition of proliferation and induction of apoptosis (Karasarides et al., Oncogene 23:6292-6298, 2004) (Sharma et al., Cancer Res 65:2412-2421, 2005) (Hoeflich et al., Cancer Res 66:999-1006, 2006). These results have underscored the attractiveness of B-Raf as a target in tumor cells that bear B-Raf mutations or demonstrate hyperactivation of MAPK signaling upstream of B-Raf, especially in melanoma.

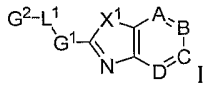
Several Raf kinase inhibitors have been described as exhibiting efficacy in inhibiting tumor cell proliferation in vitro and/or in vivo assays (see, e.g., U.S. Pat. Nos. 6,391,636, 6,358,932, 6,037,136, 5,717,100, 6,458,813, 6,204,467, and 6,268,391). Other patents and patent applications suggest the use

of Raf kinase inhibitors for treating leukemia (see, e.g., U.S. Pat. Nos. 6,268,391, and 6,204,467, and published U.S. patent application Ser. Nos. 20,020,137,774; 20,020,082,192; 20,010,016,194; and 20,010,006,975), or for treating breast cancer (see, e.g., U.S. Pat. Nos. 6,358,932, 5,717,100, 6,458,813, 6,268,391, and 6,204,467, and published U.S. patent application Ser. No. 20,010,014,679).

SUMMARY OF THE INVENTION

Novel compounds and pharmaceutical compositions that ameliorate disease by inhibiting B-Raf kinase have been found, together with methods of synthesizing and using the compounds including methods for inhibiting B-Raf kinase in a patient by administering the compounds.

The present invention discloses a class of compounds, useful in treating B-Raf-mediated disorders and conditions, defined by structural Formula I:



I

wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

A, B, C and D are each independently N or CR^2;

n is 0, 1 or 2;

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted;

L^1 is selected from the group consisting of a bond, optionally substituted alkyl, –O–, –S–, –C(O)–, –S(O)–, $–SO_2–$, $–N(R^3)–$, $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$, $–N(R^3)C(O)O–$, $–OC(O)N(R^3)–$ and –OC(O)O–;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

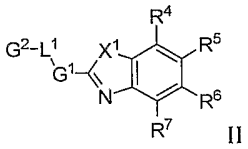
R^2 is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^3 is selected from the group consisting of alkyl and hydrogen.

Compounds according to the present invention possess useful B-Raf inhibiting or modulating activity, and may be used in the treatment or prophylaxis of a disease or condition in which B-Raf plays an active role. Thus, in broad aspect, the present invention also provides pharmaceutical compositions comprising one or more compounds of the present invention together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. In certain embodiments, the present invention provides methods for inhibiting B-Raf. In other embodiments, the present invention provides methods for treating a B-Raf-mediated disorder in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. The present invention also contemplates the use of compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of B-Raf.

DETAILED DESCRIPTION OF THE INVENTION

In certain embodiments, the compounds of the present invention have structural Formula II:



II

wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

n is 0, 1 or 2;

G^1 is selected from the group consisting of a bond, alkenyl, alkyl, alkylene, alkynyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted;

L^1 is selected from the group consisting of a bond, optionally substituted alkyl, –O–, –S–, –C(O)–, –S(O)–, $–SO_2–$, $–N(R^3)–$, $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$, $–N(R^3)C(O)O–$, $–OC(O)N(R^3)–$ and –OC(O)O–;

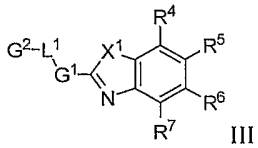
R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl,

alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula III:



III

wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

n is 0, 1 or 2;

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

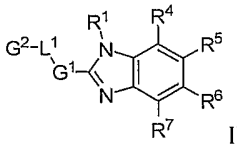
L^1 is selected from the group consisting of $-SO_2N(R^3)-$, $-N(R^3)SO_2-$, $-C(O)N(R^3)-$, $-N(R^3)C(O)-$, $-N(R^3)C(O)N(R^3)-$;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula IV:



IV

wherein:

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

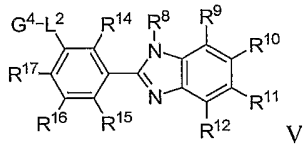
L^1 is selected from the group consisting of $-C(O)N(R^3)-$, $-N(R^3)C(O)-$, $-N(R^3)C(O)N(R^3)-$;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula V:



V

wherein:

G^4 is selected from the group consisting of aryl, which may be optionally substituted;

L^2 is selected from the group consisting of $-N(R^{13})C(O)-$ or $-N(R^{13})C(O)N(R^{13})-$;

R^8 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aryl, arylalkenyl, arylalkylthio, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

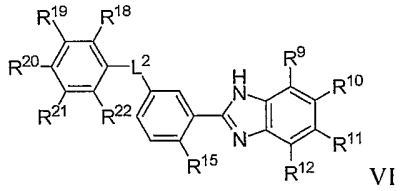
R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy,

hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted, with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

R^{13} is selected from the group consisting of alkyl and hydrogen; and

R^{14}, R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula VI:



VI

wherein:

L^2 is selected from the group consisting of $-C(O)N(R^{13})-$ or $-N(R^{13})C(O)N(R^{13})-$;

R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

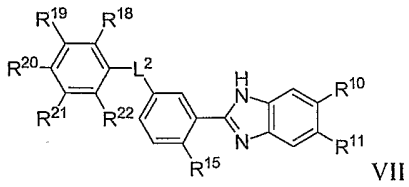
R^{13} is selected from the group consisting of alkyl and hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl,

arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula VII:



VII

wherein:

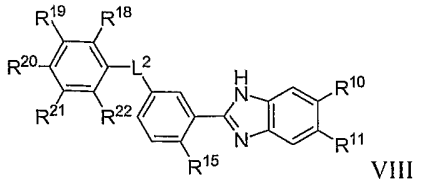
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, Bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula VIII:



VIII

wherein:

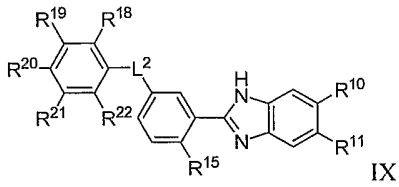
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula IX:



IX

wherein:

L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

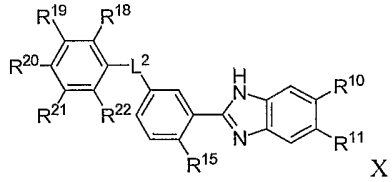
R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo,

haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention further provides for compounds of Formula X:



X

wherein:

L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, aminoalkyl, alkylaminocarbonyl, ester and heteroaryl, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

The invention provides for compounds of Formula VIII wherein R^{11} is optionally substituted alkylester, alkylaminocarbonyl or heteroaryl.

The invention provides for compounds of Formula VIII wherein R^{15} is optionally substituted alkyl or halo.

The invention provides for compounds of Formula VIII wherein R^{19}, R^{20} and R^{21} are each independently alkoxy, halo, haloalkyl and heteroaryl, any of which may be optionally substituted.

The invention provides for compounds of Formula I-IV and IX-XII for use in the inhibition of B-Raf kinase for the treatment of disease.

The invention provides for compounds of Formula I-IV and IX-XII administered in combination with another therapeutic agent.

As used herein, the terms below have the meanings indicated.

The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety were the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. Examples of acyl groups include formyl, alkanoyl and aroyl radicals.

The term "acylamino" embraces an amino radical substituted with an acyl group. An example of an "acylamino" radical is acetylamino ($CH_3C(O)NH-$).

The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20, preferably 2 to 6, carbon atoms. Alkenylene refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like.

The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy," as used herein, alone or in combination, refers to one or more alkoxy groups attached to the parent molecular moiety through another alkoxy group. Examples include ethoxyethoxy, methoxypropoxyethoxy, ethoxypentoxyethoxyethoxy and the like.

The term "alkoxyalkyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through an alkyl group. The term "alkoxyalkyl" also embraces alkoxyalkyl groups having one or more alkoxy groups attached to the alkyl group, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups.

The term "alkoxycarbonyl," as used herein, alone or in combination, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group. Examples of such "alkoxycarbonyl" groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The term "alkoxycarbonylalkyl" embraces radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower

alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl.

The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to and including 20, preferably 1 to 10, and more preferably 1 to 6, carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene (–CH_2–).

The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group.

The term "alkylaminocarbonyl" as used herein, alone or in combination, refers to an alkylamino group attached to the parent molecular moiety through a carbonyl group. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl.

The term "alkylcarbonyl" and "alkanoyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl.

The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

The term "alkylsulfinyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfinyl group. Examples of alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "alkylsulfonyl," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group. Examples of alkylsulfinyl groups include methanesulfonyl, ethanesulfonyl, tert-butanesulfonyl, and the like.

The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) radical wherein the term alkyl is as defined above. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, ethoxyethylthio, methoxypropoxyethylthio, ethoxypentoxyethoxyethylthio and the like.

The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. Alkylthioalkyl radicals include "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl.

The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20, preferably from 2 to 6, more preferably from 2 to 4, carbon atoms. "Alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl

radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl, and the like.

The term "amido," as used herein, alone or in combination, refers to an amino group as described below attached to the parent molecular moiety through a carbonyl group. The term "C-amido" as used herein, alone or in combination, refers to a $-C(=O)-NR_2$ group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein.

The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkenyl, arylalkyl, cycloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkenyl, and heterocycloalkyl, wherein the aryl, the aryl part of the arylalkenyl, the arylalkyl, the heteroaryl, the heteroaryl part of the heteroarylalkenyl and the heteroarylalkyl, the heterocycle, and the heterocycle part of the heterocycloalkenyl and the heterocycloalkyl can be optionally substituted as defined herein with one, two, three, four, or five substituents.

The term "aminoalkyl," as used herein, alone or in combination, refers to an amino group attached to the parent molecular moiety through an alkyl group. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Suitable "alkylamino" groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The terms "aminocarbonyl" and "carbamoyl," as used herein, alone or in combination, refer to an amino-substituted carbonyl group, wherein the amino group can be a primary or secondary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like.

The term "aminocarbonylalkyl," as used herein, alone or in combination, refers to an aminocarbonyl radical attached to an alkyl radical, as described above. An example of such radicals is aminocarbonylmethyl. The term "amidino" denotes an $-C(NH)NH_2$ radical. The term "cyanoamidino" denotes an $-C(N-CN)NH_2$ radical.

The term "aralkenyl" or "arylalkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

The term "aralkoxy" or "arylalkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "aralkyl" or "arylalkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

The term "aralkylamino" or "arylalkylamino," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a nitrogen atom, wherein the nitrogen atom is substituted with hydrogen.

The term "aralkylidene" or "arylalkylidene," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkylidene group

The term "aralkylthio" or "arylalkylthio," as used herein, alone or in combination, refers to an arylalkyl group attached to the parent molecular moiety through a sulfur atom.

The term "aralkynyl" or "arylalkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

The term "aralkoxycarbonyl," as used herein, alone or in combination, refers to a radical of the formula aralkyl-O–C(O)– in which the term "aralkyl," has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl (Z or Cbz) and 4-methoxyphenylmethoxycarbonyl (MOS).

The term "aralkanoyl," as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl" refers to an acyl radical derived from an arylcarboxylic acid, "aryl" having the meaning given below. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or napthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2-naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like.

The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as benzyl, phenyl, naphthyl, anthracenyl, phenanthryl, indanyl, indenyl, annulenyl, azulenyl, tetrahydronaphthyl, and biphenyl.

The term "arylamino" as used herein, alone or in combination, refers to an aryl group attached to the parent moiety through an amino group, such as N-phenylamino, and the like.

The terms "arylcarbonyl" and "aroyl," as used herein, alone or in combination, refer to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "arylsulfonyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The term "arylthio," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes --CO_2H.

The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent radical C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NR, group-with R as defined herein.

The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NH- group, with R as defined herein.

The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

The term "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

The term "cyano," as used herein, alone or in combination, refers to –CN.

The term "cycloalkyl," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 12, preferably five to seven, carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydonapthalene, octahydronapthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[2,2,2]octane, bicyclo[2,2,2]octane, bicyclo[1,1,1]pentane, camphor and bicyclo[3,2,1]octane.

The term "ester," as used herein, alone or in combination, refers to a carboxyl group bridging two moieties linked at carbon atoms.

The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl,

chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a halohydrocarbyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2–$), chloromethylene (–CHCl–) and the like. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, perfluorodecyl and the like.

The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, -CH2-NH-OCH3.

The term "heteroaryl," as used herein, alone or in combination, refers to 3 to 7 membered, preferably 5 to 7 membered, unsaturated heterocyclic rings wherein at least one atom is selected from the group consisting of O, S, and N. Heteroaryl groups are exemplified by: unsaturated 3 to 7 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.]tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.]etc.; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.]and isothiazolyl; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.]and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like.

The term "heteroaralkenyl" or "heteroarylalkenyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkenyl group.

The term "heteroaralkoxy" or "heteroarylalkoxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkoxy group.

The term "heteroarylalkyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkyl group.

The term "heteroaralkylidene" or "heteroarylalkylidene," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an alkylidene group.

The term "heteroaryloxy," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through an oxygen atom.

The term "heteroarylsulfonyl," as used herein, alone or in combination, refers to a heteroaryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic radical containing at least one, preferably 1 to 4, and more preferably 1 to 2 heteroatoms as ring members, wherein each said heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein there are preferably 3 to 8 ring members in each ring, more preferably 3 to 7 ring members in each ring, and most preferably 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Heterocycle groups of the invention are exemplified by aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

The term "heterocycloalkenyl," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkenyl group.

The term "heterocycloalkoxy," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular group through an oxygen atom.

The term "heterocycloalkyl," as used herein, alone or in combination, refers to an alkyl radical as defined above in which at least one hydrogen atom is replaced by a heterocyclo radical as defined above, such as pyrrolidinylmethyl, tetrahydrothienylmethyl, pyridylmethyl and the like.

The term "heterocycloalkylidene," as used herein, alone or in combination, refers to a heterocycle group attached to the parent molecular moiety through an alkylidene group.

The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

The term "hydroxy," as used herein, alone or in combination, refers to –OH.

The term "hydroxyalkyl" as used herein, alone or in combination, refers to a linear or branched alkyl group having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

The term "imino," as used herein, alone or in combination, refers to =N–.

The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of this invention.

The term "isocyanato" refers to a –NCO group.

The term "isothiocyanato" refers to a –NCS group.

The phrase "linear chain of atoms" refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

The term "lower," as used herein, alone or in combination, means containing from 1 to and including 6 carbon atoms.

The term "mercaptoalkyl" as used herein, alone or in combination, refers to an R'SR– group, where R and R' are as defined herein.

The term "mercaptomercaptyl" as used herein, alone or in combination, refers to a RSR'S– group, where R is as defined herein.

The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

The term "null" refers to a lone electron pair.

The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

The term "oxo," as used herein, alone or in combination, refers to =O.

The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

The term "oxo" as used herein, alone or in combination, refers to a doubly bonded oxygen.

The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

The term "sulfonyl," as used herein, alone or in combination, refers to $-SO_2-$.

The term "N-sulfonamido" refers to a $RS(=O)_2NH-$ group with R as defined herein.

The term "S-sulfonamido" refers to a $-S(=O)_2NR_2$, group, with R as defined herein.

The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

The term "thioether," as used herein, alone or in combination, refers to a thio group bridging two moieties linked at carbon atoms.

The term "thiol," as used herein, alone or in combination, refers to an –SH group.

The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

The term "N-thiocarbamyl" refers to an ROC(S)NH– group, with R as defined herein.

The term "O-thiocarbamyl" refers to a –OC(S)NR, group with R as defined herein.

The term "thiocyanato" refers to a –CNS group.

The term "trihalomethanesulfonamido" refers to a $X_3CS(O)_2NR-$ group with X is a halogen and R as defined herein.

The term "trihalomethanesulfonyl" refers to a $X_3CS(O)_2-$ group where X is a halogen.

The term "trihalomethoxy" refers to a X_3CO- group where X is a halogen.

The term "trisubstituted silyl," as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethysilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-menbered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., -CH2CH_3), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents are

recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particuar moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence.

The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified.

The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

B-Raf inhibitor is used herein to refer to a compound that exhibits an IC_{50} with respect to B-Raf activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the B-Raf Binding assay and B-Raf/Mek1 composite kinase assay described generally herein below. IC_{50} is that concentration of inhibitor which reduces the activity of an enzyme (e.g., B-Raf) to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibition activity against B-Raf. Compounds of the present invention preferably exhibit an IC_{50} with respect to B-Raf of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in the B-Raf assay(s) described herein.

The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

The term "prodrug" refers to a compound that is made more active in vivo. The present compounds can also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound. The term "therapeutically acceptable prodrug," refers to those prodrugs or zwitterions which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl,

lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the compounds of the present invention and the like.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

The compounds of the present invention can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, the subject invention provides a pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal,

transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

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

unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Compounds of the present invention may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

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

The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The compounds of the subject invention can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination

with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Specific, non-limiting examples of possible combination therapies include use of the compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic areaat present. Moreover, combination regimens may include a variety of routes of administration and should include intravenous, intraocular, subcutaneous, dermal, inhaled topical, oral.

For the treatment of oncologic diseases and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: aromatase inhibitors, antiestrogen, anti-androgen, or a gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, alkylating agents, antimeoplastic, antimetabolite, dacarbazine (DTIC), or platinum containing compound, lipid or protein kinase targeting agents, protein or lipid phosphatase targeting agents, anti-angiogentic agents, agents that induce cell differentiation, bradykinin 1 receptor and angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokines or cytokine inhibitors, bisphosphanates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, PPAR agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, aminopeptidase inhibitors.

For the treatment of oncologic diseases and solid tumors, compounds according to the present invention may be administered with an agent selected from the group comprising: dacarbazine (DTIC), alkylating agents (eg, melphalan) anthracyclines (eg. doxorubicin), corticosteroids (eg. dexamethasome), Akt inhibitor (eg. Perifosine), aromatase inhibitors, antiestrogen, anti-androgen, or a gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, alkylating agents (eg. cyclophophamide, temozolomide), antimeoplastic antimetabolite, or platinum containing compounds, MITC, nitrosoureas, taxanes, lipid or protein kinase targeting agents, protein or lipid phosphatase targeting agents, anti-angiogentic agents, IMiDs (eg. thalidomide, lenalidomide), protease inhibitors (eg. bortezomib, NPI0052), IGF-1 inhibitors, CD40 antibody, Smac mimetics (eg. telomestatin), FGF3 modulator (eg. CHIR258), mTOR inhibitor (Rad 001), HDAC inhibitors (eg. SAHA, Tubacin), IKK inhibitors, P38MAPK inhibitors, HSP90 inhibitor (eg 17-AAG), and other mutlikinase inhibitors (eg. sorafenib).

In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

Thus, in another aspect, the present invention provides methods for treating Braf-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of Braf-mediated disorders.

Diseases or disorders in which B-Raf kinase plays a role, include, without limitation: oncologic, hematologic, immunologic, dermatologic and ophthalmologic diseases.

Autoimmune diseases which may be prevented or treated include, without limitation: osteoarthritis, spondyloarthropathies, systemic lupus nephritis, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs. host disease, or psoriasis. The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Hematopoiesis diseases including, myelodysplastic disorders (MDS), and myeloproliferative disorders (polycythemia vera, myelofibrosis and essential thrombocythemia), sickle cell anemia.

Dermatologic diseases including, without limitation, melanoma, basel cell carcinoma, squamous cell carcinoma, and other non-epithelial skin cancer as well as psoriasis and persistent itch, and other diseases related to skin and skin structure, may be treated or prevented with p38 inhibitors of this invention.

Ophthalmologic dieases which may be treated or prevented include, without limitation, dry eye (including Sjögren's syndrome), macular degeneration, closed and wide angle glaucoma, inflammation, and pain of the eye.

Hematological and non-hematological malignancies which may be treated or prevented include but are not limited to multiple myeloma, acute and chronic leukemias including Acute Lymphocytic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), and Chronic Myelogenous Leukemia(CLL), lymphomas, including Hodgkin's lymphoma and non-Hodgkin's lymphoma (low, intermediate, and high grade), malignancies of the brain, head and neck, breast, lung, reproductive tract, upper digestive tract, pancreas, liver, renal, bladder, prostate and colorectal.

The present invention includes compounds listed above in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question.

Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

Asymmetric centers exist in the compounds of the present invention. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms,as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

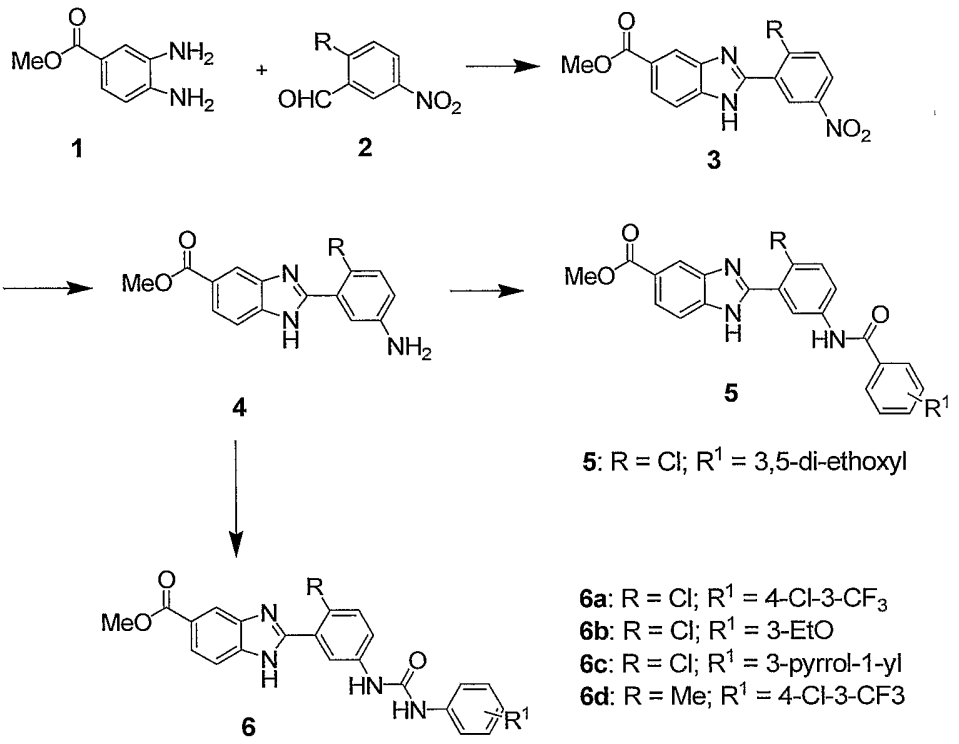
All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

The following schemes can be used to practice the present invention.

Examples 1-5 can be synthesized using the following general synthetic procedure set forth in Scheme I.

Scheme I

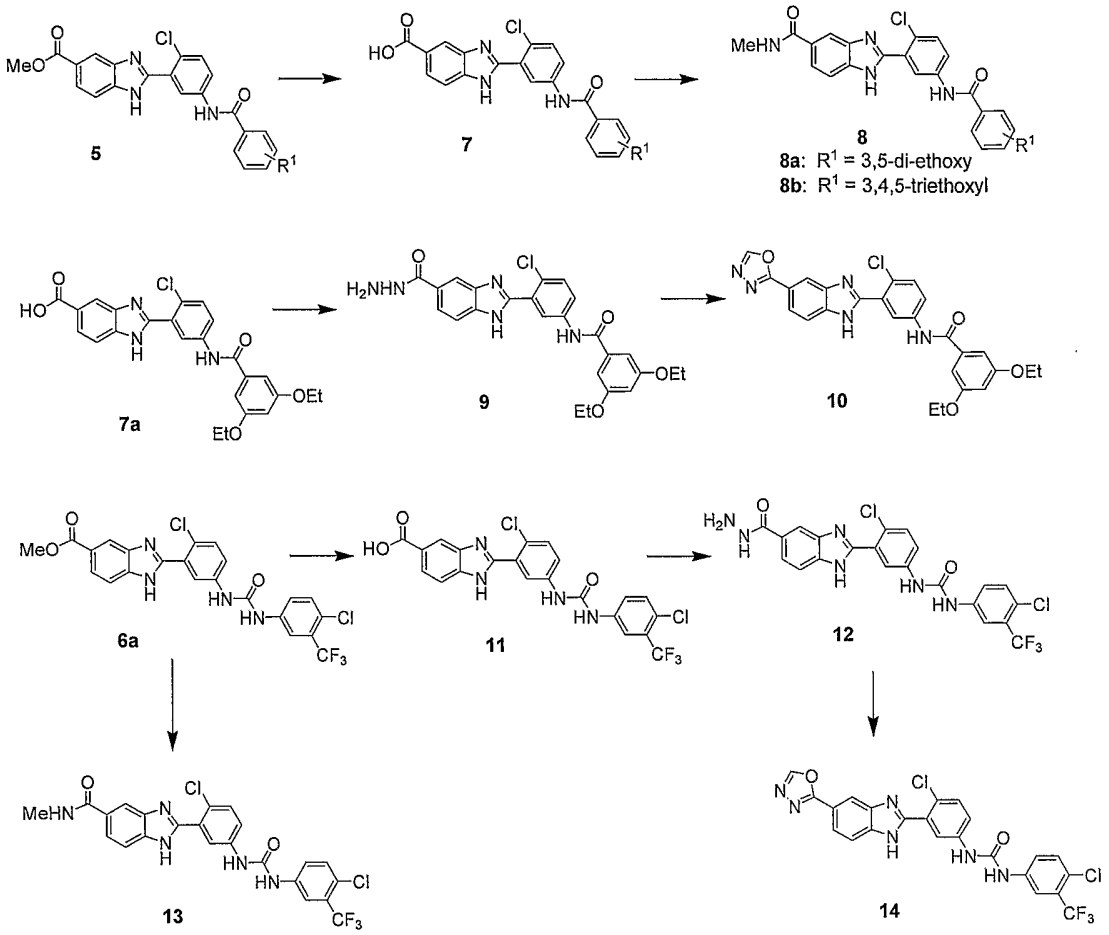


5: R = Cl; R^1 = 3,5-di-ethoxyl

6a: R = Cl; R^1 = 4-Cl-3-CF_3
6b: R = Cl; R^1 = 3-EtO
6c: R = Cl; R^1 = 3-pyrrol-1-yl
6d: R = Me; R^1 = 4-Cl-3-CF3

Examples 6-12 can be synthesized using the following general synthetic procedure set forth in Scheme II.

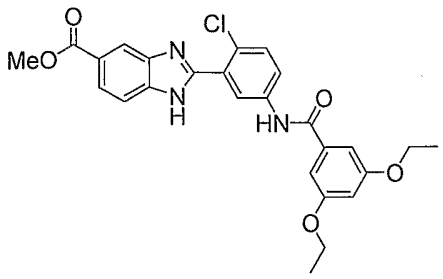
Scheme II



The invention is further illustrated by the following examples.

EXAMPLE 1

2-[2-Chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methyl ester (5)



Step 1

Synthesis of 2-(2-Chloro-5-nitro-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (3a)

A mixture of 3,4-diaminobenzoic acid methyl ester **1** (1.66g, 10 mmol)) and 2-chloro-5-nitrobenzaldehyde (**2**) (1.85g, 10 mmol) in acetic acid (15 ml) was heated at 125 °C for 2 h. The solvent was removed under reduced pressure and the residues were partitioned between brine and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column separation gave 1.6 g of the desired product **3a**. LCMS: Calc. MW = 331.71, Found (M/z) M+1 = 332.17, 334.17. HPLC r.t. = 2.48 min. ^{1}H-NMR (400 MHz, CDCl3) δ 9.10 (d, 1H, J = 2.8 Hz), 8.36 (s, 1H), 8.33 (d, 1H, J = 2.8 Hz), 8.31 (d, 1 H, J = 2.8 Hz), 8.16 (dd, 1H, J = 8.8, 1.6 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.79 (d, 1H, J = 8.8 Hz), 4.0 (s, 3H).

Step 2

Synthesis of 2-(5-Amino-2-chloro-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (4a)

A solution of 2-(2-chloro-5-nitro-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (**3a**) (0.55g)) and tin chloride dihydrate (2.5 g) in DMF (6 ml) was stirred at room temperature for 20 h. The mixture was then poured into EtOAc (150 ml) and triethyl amine (10 ml). The precipitate was filtered off on celite and washed with EtOAc/MeOH (30 ml /30 ml). The filtrate was washed with brine twice, dried over Na_2SO_4 and concentrated under reduced pressure. Column separation gave 0.47 g of the desired product **4a**. LCMS: Calc. MW = 301.73, Found (M/z) M+1 = 302.26, 304.72. HPLC r.t. = 0.22 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.97 (dd, 1H, J = 8.8, 1.6 Hz), 7.65 (d, 1H, J = 8.4 Hz), 7.25 (d, 1H, J = 8.4 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.82 (dd, 1 H, J = 8.4, 2.4 Hz), 3.93 (s, 3H).

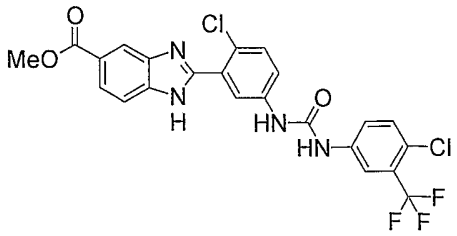
Step 3

Synthesis of 2-[2-Chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methyl ester (5)

To a solution of 2-(5-amino-2-chloro-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (**4a**) (50 mg, 0.17 mmol) in dry THF (4 ml) was added 3,5-diethoxybenzoyl chloride (38 mg, 0.17 mmol) and the solution was reacted overnight. The solvent was removed to give the desired product (82 mg). LCMS: Calc. MW = 493.94, Found (M/z) M+1 = 494.45, 496.65. HPLC r.t. = 2.87 min.

EXAMPLE 2

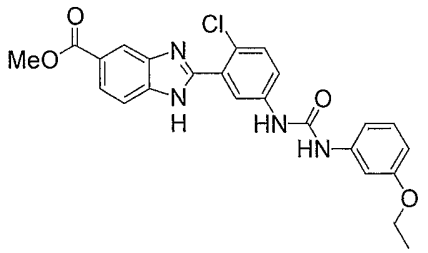
2-{2-Chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxyli c acid methyl ester (6a)



A mixture of 2-(5-amino-2-chloro-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (**4a**) (303 mg) and 4-chloro-3-trifluoromethylphenylisocyanate (229 mg) in THF (8 ml) was reacted at room temperature overnight. The ethyl acetate (8 ml) was added and the resulting precipitate was filtered (510mg). LCMS: Calc. MW = 523.29, Found (M/z) M+1 = 523.25, 525.70. HPLC r.t. = 2.96 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 7.97 (m, 3H), 7.65 (m, 3H), 7.50 (m, 3H), 3.94 (s, 3H).

EXAMPLE 3

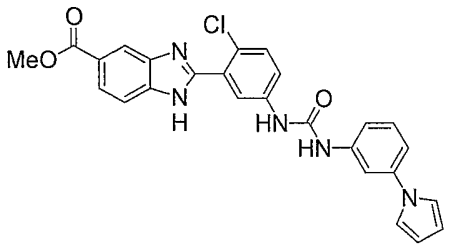
2-{2-Chloro-5-[3-(3-ethoxy-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid methyl ester (6b)



This compound was similarly prepared by following procedure of Example 2. LCMS: Calc. MW = 464.90, Found (M/z) M+1 = 465.60, 467.80. HPLC r.t. = 2.67 min.

EXAMPLE 4

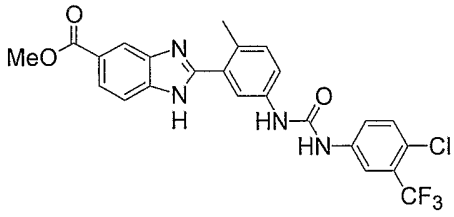
2-{2-Chloro-5-[3-(3-pyrrol-1-yl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid methyl ester (6c)



This compound was similarly prepared by following procedure of Example 2. LCMS: Calc. MW = 485.92, Found (M/z) M+1 = 486.46, 488.84. HPLC r.t. = 2.81 min.

EXAMPLE 5

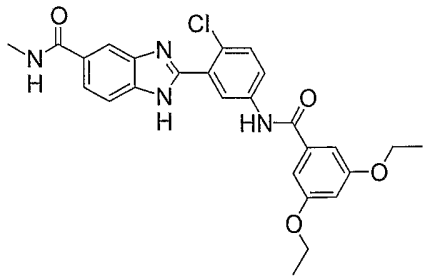
2-{5-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-2-methyl-phenyl}-1H-benzoimidazole-5-carboxylic acid methyl ester (6d)



This compound was prepared by a similar procedure of Example 2. LCMS: Calc. MW = 502.87, Found (M/z) M+1 = 503.38, 504.85. HPLC r.t. = 2.69 min.

EXAMPLE 6

2-[2-Chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methylamide (8a)



Step 1

Synthesis of 2-[2-Chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid (7a)

A mixture of 2-[2-chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methyl ester (**5**) (448 mg) and KOH (500 mg) in THF (4 ml), MeOH (4 ml) and water (5 ml) was heated at 60 °C for 20 h. The majority of solvent was removed and acetic acid (1.5 ml) and water (5 ml) were added. Then the resulting precipitate was filtered (410 mg). LCMS: Calc. MW = 479.91, Found (M/z) M+1 = 48015, 482.68. HPLC r.t. = 2.63 min.

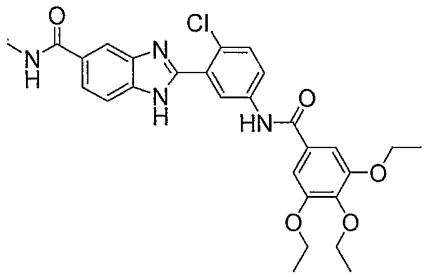
Step 2

Synthesis of 2-[2-Chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methylamide (8a)

To a solution of 2-[2-chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid (**7a**) (115 mg) in DMF (1.5 ml) at room temperature was add pentafluorophenyl trifluoroacetate (55 ul) and pyridine (100 ul) and the solution was reacted for 10 min. Then methylamine (1 ml, 2 M in THF) was added and the solution was reacted for another 1 hour. The solvent was removed and water (3 ml) was added. The mixture was extracted with ethyl acetate (3 X 3 ml), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column separation gave 95 mg of the desired product. LCMS: Calc. MW = 492.95, Found (M/z) M+1 = 493.73, 495.70. HPLC r.t. = 2.51 min.

EXAMPLE 7

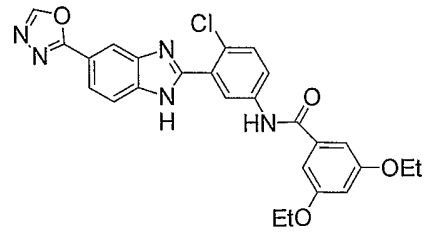
2-[2-Chloro-5-(3,4,5-triethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid methylamide (8 b)



This compound was similarly prepared according to the procedure for Example 6 (**8a**) LCMS: Calc. MW = 537.01, Found (M/z) M+1 = 537.43, 439.40. HPLC r.t. = 2.58 min. δ: 10.38(s, 1H); 8.40(d, 1H); 8.35(d, 1H); 8.21(s, 1H); 8.02(d, 1H); 8.01(s, 1H); 7.73(d, 1H); 7.28(s, 2H); .4.13-3.97(m, 6H); 2.81(s, 3H); 1.36-1.30(m, 9H).

EXAMPLE 8

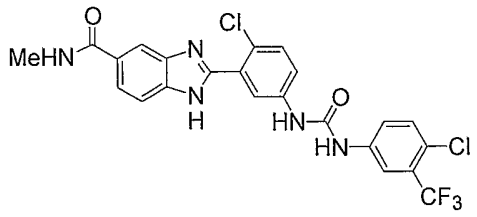
N-[4-Chloro-3-(5-[1,3,4]oxadiazol-2-yl-1H-benzoimidazol-2-yl)-phenyl]-3,5-diethoxy-benzamide (10)



To a solution of 2-[2-chloro-5-(3,5-diethoxy-benzoylamino)-phenyl]-1H-benzoimidazole-5-carboxylic acid (**7a**) (195 mg) in DMF (2 ml) at room temperature was add pentafluorophenyl trifluoroacetate (140 ul) and pyridine (200 ul) and the solution was reacted for 10 min. Then hydrazine anhydrous (200 ul) was added and the solution was reacted for another 1 hour. The majority of solvent was removed and water (5 ml) was added. The resulting precipitate was filtered. The material was heated in triethyl orthoformate (3 ml) and acetic acid (0.5 ml) at 117 °C for 35 min under microwave radiation. After the majority of solvent was removed under reduce pressure. The mixture was extracted with ethyl acetate (3 X 3 ml), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column separation gave 82 mg of the desired product. LCMS: Calc. MW = 503.94, Found (M/z) M+1 = 504.38, 505.95. HPLC r.t. = 2.71 min. ^{1}H-NMR (400 MHz, DMSO) δ 13.05 (s, 1H), 10.44 (s, 1H), 9.32 (s, 1H), 8.4 (m, 2 H), 8.0 (m, 3 H), 7.64 (d, 1H, J = 8.8 Hz), 7.11 (s, 2 H), 6.68 (s, 1 H), 4.08 (q, 4 H, J = 7.2 Hz), 1.33 (t, 6 H, J = 7.2 Hz).

EXAMPLE 9

2-{2-Chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid methylamide (13)

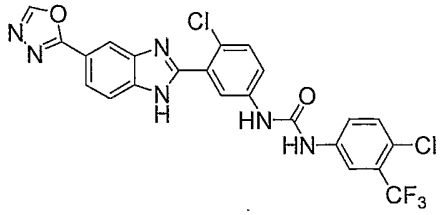


A mixture of 2-{2-chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid methyl ester (**6a**) (58 mg) and methylamine (3 ml, 33% in ethanol) was heated at 106 °C for 4.5 h. The solvent was removed and the residue was purified by column chromatography to give 18.5 mg of the desired product. LCMS: Calc. MW = 522.31, Found (M/z) M+1 = 522.23, 524.22. HPLC r.t. = 2.55 min. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 7.98 (d, 1 H, J =

2.8 Hz), 7.96 (d, 1 H, J = 2.4 Hz); 7.79 (dd, 1 H, J = 8.8, 1.6 Hz), 7.6(m, 3 H), 7.50 (m, 2 H), 2.96 (s, 3 H).

EXAMPLE 10

1-[4-Chloro-3-(5-[1,3,4]oxadiazol-2-yl-1H-benzoimidazol-2-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (14)



Step 1

Synthesis of 2-{2-Chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid (11)

A mixture of 2-{2-chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid methyl ester (**6a**) (1.35g) and KOH (0.77g) in THF (10 ml), MeOH (5 ml) and water (10 ml) was heated at 65 °C for 20 h. The majority of solvent was removed and acetic acid (1.5 ml) and brine (150 ml) were added. The mixture was extracted with ethyl acetate (2 X 150 ml), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column separation gave 1.25 g of the desired product. LCMS: Calc. MW = 509.26, Found (M/z) M+1 = 509.28, 511.19. HPLC r.t. = 2.66 min. ^{1}H-NMR (400 MHz, DMSO) δ 13.0 (s, 1H), 12.70 (s, 1H), 9.40 (s, 1H), 9.34 (s, 1H), 8.10 (m, 2 H), 7.85 (d, 1 H, J = 7.2 Hz), 7.60 (m, 4 H).

Step 2

Synthesis of 1-[4-Chloro-3-(5-hydrazinocarbonyl-1H-benzoimidazol-2-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (12)

To a solution of 2-{2-chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid (**11**) (0.96) in DMF (6ml) at room temperature was add pentafluorophenyl trifluoroacetate (0.4 ml) and pyridine (0.3 ml) and the solution was reacted for 10 min. Then hydrazine anhydrous (0.5 ml) was added and the solution was reacted for another 1 hour. Water (5 ml) was added and the mixture was stirred for 10 min. The resulting precipitate was filtered to give 0.85 g of the desired product. LCMS: Calc. MW = 523.29, Found (M/z) M+1 = 523.28. HPLC r.t. = 2.41 min.

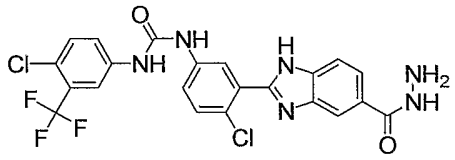
Step 3

Synthesis of 1-[4-Chloro-3-(5-[1,3,4]oxadiazol-2-yl-1H-benzoimidazol-2-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (14)

A mixture of 1-[4-chloro-3-(5-hydrazinocarbonyl-1H-benzoimidazol-2-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (**12**) (0.85 g) in triethyl orthoformate (12 ml) and acetic acid (1 ml) was heated at 115 °C for 25 min under microwave radiation. After the majority of solvent was removed under reduce pressure, ethyl acetate (10 ml) was added, the resulting precipitate was collected by filtration (0.52 g). LCMS: Calc. MW = 533.29, Found (M/z) M+1 = 533.39. HPLC r.t. = 2.79 min. ^{1}H-NMR (400 MHz, DMSO) δ 13.10 (s, 1H), 11.90 (s, 1 H), 9.26 (m, 3H), 8.10-8.40 (m, 2H), 7.75-8.00 (m, 2 H), 7.50-7.70 (m, 4 H).

EXAMPLE 11

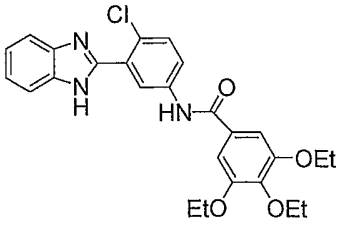
1-[4-Chloro-3-(5-hydrazinocarbonyl-1H-benzoimidazol-2-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea (12)



To a solution of 2-{2-chloro-5-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-benzoimidazole-5-carboxylic acid (**11**) (0.96) in DMF (6ml) at room temperature was add pentafluorophenyl trifluoroacetate (0.4 ml) and pyridine (0.3 ml) and the solution was reacted for 10 min. Then hydrazine anhydrous (0.5 ml) was added and the solution was reacted for another 1 hour. Water (5 ml) was added and the mixture was stirred for 10 min. The resulting precipitate was filtered to give 0.85 g of the desired product. LCMS: Calc. MW = 523.29, Found (M/z) M+1 = 523.28. HPLC r.t. = 2.41 min.

EXAMPLE 12

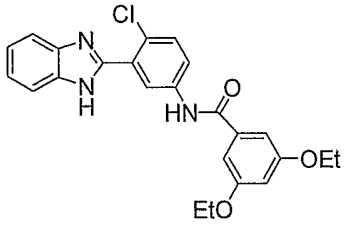
N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3,4,5-triethoxybenzamide



Example 12 is commercially available.

EXAMPLE 13

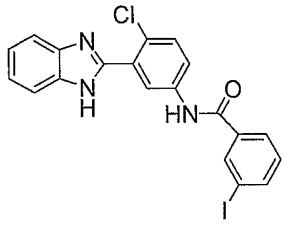
N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3,5-diethoxybenzamide



Example 13 is commercially available.

EXAMPLE 14

N-(3-(1H-benzo[d]imidazol-2-yl)-4-chlorophenyl)-3-iodobenzamide



Example 14 is commercially available.

The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

The following compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* **1988**, *28*, 31-36.

ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C(NC)=O)=CC=C5N4

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ClC%59=CC=C(NC(C%60=CC(CN%61CCN(C)CC%61)=CC(OCC)=C%60)=O)C=C%59C%62=NC%63=CC(C%64=NN=CO%64)=CC=C%63N%62C
ClC%65=CC=C(NC(C%66=CC(CN(CC)CC)=CC(OCC)=C%66)=O)C=C%65C%67=NC%68=CC(C%69=NC=NN%69C)=CC=C%68N%67C
ClC%70=CC=C(NC(C%71=CC(OCC)=CC(OCC)=C%71)=O)C=C%70C%72=NC%73=CC(C%74=NC=NN%74)=CC=C%73N%72C
ClC%75=CC=C(NC(C%76=CC(OCC)=CC(OCC)=C%76)=O)C=C%75C%77=NC%78=CC(C%79=NC=CN%79)=CC=C%78N%77C
ClC%80=CC=C(NC(C%81=CC(OCC)=CC(OCC)=C%81)=O)C=C%80C%82=NC%83=CC(C%84=NN=CO%84)=CC=C%83N%82C
ClC%85=CC=C(NC(C%86=CC(OCC)=CC(OCC)=C%86)=O)C=C%85C%87=NC%88=CC(C%89=NN=CO%89)=CC=C%88N%87C
ClC1=CC=C(NC(NC2=CC(C(F)(F)F)=C(Cl)C=C2)=O)C=C1C3=NC4=CC(C5=NN=CO5)=CC=C4N3
ClC6=CC=C(NC(NC7=CC(C(F)(F)F)=C(Cl)C=C7)=O)C=C6C8=NC9=CC(C%10=NC=CO%10)=CC=C9N8

ClC%11=CC=C(NC(NC%12=CC(C(F)(F)F)=C(Cl)C=C%12)=O)C=C%11C%13=NC%14=CC(C%15=NC=NN%15C)=CC=C%14N%13
ClC%16=CC=C(NC(NC%17=CC(C(F)(F)F)=C(Cl)C=C%17)=O)C=C%16C%18=NC%19=CC(C%20=NN=CO%20)=CC=C%19N%18C
ClC%21=CC=C(NC(NC%22=CC(C(F)(F)F)=C(Cl)C=C%22)=O)C=C%21C%23=NC%24=CC(C%25=NC=CO%25)=CC=C%24N%23C
ClC%26=CC=C(NC(NC%27=CC(C(F)(F)F)=C(Cl)C=C%27)=O)C=C%26C%28=NC%29=CC(C%30=NC=NN%30C)=CC=C%29N%28C
ClC%31=CC=C(NC(NC%32=CC(C(F)(F)F)=C(Cl)C=C%32)=O)C=C%31C%33=NC%34=CC(C%35=NN=CO%35)=CC=C%34N%33CCOC
ClC%36=CC=C(NC(NC%37=CC(C(F)(F)F)=C(Cl)C=C%37)=O)C=C%36C%38=NC%39=CC(C%40=NC=CO%40)=CC=C%39N%38CCOC
ClC%41=CC=C(NC(NC%42=CC(C(F)(F)F)=C(Cl)C=C%42)=O)C=C%41C%43=NC%44=CC(C%45=NC=NN%45C)=CC=C%44N%43CCOC
ClC%46=CC=C(NC(NC%47=CC(C(F)(F)F)=C(Cl)C=C%47)=O)C=C%46C%48=NC%49=CC(C%50=NN=CO%50)=CC=C%49N%48CCN(C)C
ClC%51=CC=C(NC(NC%52=CC(C(F)(F)F)=C(Cl)C=C%52)=O)C=C%51C%53=NC%54=CC(C%55=NC=CO%55)=CC=C%54N%53CCN(C)C
ClC%56=CC=C(NC(NC%57=CC(C(F)(F)F)=C(Cl)C=C%57)=O)C=C%56C%58=NC%59=CC(C%60=NC=NN%60C)=CC=C%59N%58CCN(C)C
ClC1=CC=C(NC(NC2=CC(C(F)(F)F)=CC(CN3CCN(C)CC3)=C2)=O)C=C1C4=NC5=CC(C6=NN=CO6)=CC=C5N4
ClC7=CC=C(NC(NC8=CC(C(F)(F)F)=CC(CN9CCN(C)CC9)=C8)=O)C=C7C%10=NC%11=CC(C%12=NC=CO%12)=CC=C%11N%10
ClC%13=CC=C(NC(NC%14=CC(C(F)(F)F)=CC(CN%15CCN(C)CC%15)=C%14)=O)C=C%13C%16=NC%17=CC(C%18=NC=NN%18C)=CC=C%17N%16
ClC%19=CC=C(NC(NC%20=CC(C(F)(F)F)=C(Cl)C=C%20OCCN(C)C)=O)C=C%19C%21=NC%22=CC(C%23=NN=CO%23)=CC=C%22N%21
ClC%24=CC=C(NC(NC%25=CC(C(F)(F)F)=C(Cl)C=C%25OCCN(C)C)=O)C=C%24C%26=NC%27=CC(C%28=NC=CO%28)=CC=C%27N%26
ClC%29=CC=C(NC(NC%30=CC(C(F)(F)F)=C(Cl)C=C%30OCCN(C)C)=O)C=C%29C%31=NC%32=CC(C%33=NC=NN%33C)=CC=C%32N%31
ClC%34=CC=C(NC(NC%35=CC(C(F)(F)F)=CC(CN%36CCN(C)CC%36)=C%35)=O)C=C%34C%37=NC%38=CC(C%39=NN=CO%39)=CC=C%38N%37C
ClC%40=CC=C(NC(NC%41=CC(C(F)(F)F)=CC(CN%42CCN(C)CC%42)=C%41)=O)C=C%40C%43=NC%44=CC(C%45=NC=CO%45)=CC=C%44N%43C
ClC%46=CC=C(NC(NC%47=CC(C(F)(F)F)=CC(CN%48CCN(C)CC%48)=C%47)=O)C=C%46C%49=NC%50=CC(C%51=NC=NN%51C)=CC=C%50N%49C
ClC%52=CC=C(NC(NC%53=CC(C(F)(F)F)=C(Cl)C=C%53OCCN%54CCCC%54)=O)C=C%52C%55=NC%56=CC(C%57=NN=CO%57)=CC=C%56N%55C
ClC%58=CC=C(NC(NC%59=CC(C(F)(F)F)=C(Cl)C=C%59OCCN%60CCCC%60)=O)C=C%58C%61=NC%62=CC(C%63=NC=CO%63)=CC=C%62N%61C
ClC%64=CC=C(NC(NC%65=CC(C(F)(F)F)=C(Cl)C=C%65OCCN%66CCN(C)CC%66)=O)C=C%64C%67=NC%68=CC(C%69=NC=NN%69C)=CC=C%68N%67C
ClC1=CC=C(NC(C2=CC(CN3CCNCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C6=CNN=C6)=CC=C5N4
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C6=CN=CO6)=CC=C5N4
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(OCC)=C2)=O)C=C1C4=NC5=CC(C6=NN=C(CCC(N)C)O6)=CC=C5N4
O=C(C1=CC(CN2CCNCC2)=CC(OCC)=C1)NC3=CC=C(OCCN(C)C)C(C4=NC5=CC(C6=NC=CN6)=CC=C5N4)=C3
O=C(C1=CC(OCC)=CC(OCC)=C1)NC2=CC(N(C)C)=CC(C3=NC4=CC(C5=NN=CO5)=CC=C4N3C)=C2

ClC1=CC=C(NC(C2=CC(CN3CCNCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C6=CN(C)N=C6)=CC=C5N4

ClC1=CC=C(NC(C2=CC(C(F)(F)F)=CC(C(F)(F)F)=C2)=O)C=C1C3=NC4=CC(C5=CN(CCNC)N=C5)=CC=C4N3

ClC1=CC=C(NC(C2=CC(C(F)(F)F)=CC(OCC)=C2)=O)C=C1C3=NC4=CC(C5=NN=C(CCN(C)C)O5)=CC=C4N3

ClC1=CC=C(NC(NC2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C(NC)=O)=CC=C5N4

ClC1=CC=C(C(NC2=CC(CN3CCNCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C(NC)=O)=CC=C5N4

ClC1=CC=C(C(NC2=CC(CN3CCNCC3)=CC(OCC)=C2)=O)C=C1C4=NC5=CC(C6=NN=CO6)=CC=C5N4C

ClC1=CC=C(C(N(C)C2=CC(CN3CCNCC3)=CC(OCC)=C2)=O)C=C1C4=NC5=CC(C6=NN=CO6)=CC=C5N4C

ClC1=CC=C(N(C)C(C2=CC(CN3CCOCC3)=CC(OCC)=C2)=O)C=C1C4=NC5=CC(C6=NC=CN6)=CC=C5N4C

ClC1=CC=C(N(C)C(C2=CC(CN3CCN(C)CC3)=CC(OCC)=C2)=O)C=C1C4=NC5=CC(C6=NN=CO6)=CC=C5N4C

ClC1=CC=C(NC(C2=CC(OCC)=CC(OCC)=C2)=O)C=C1C3=NC4=CC(C5=NC=NN5)=CC=C4N3CCN(C)C

ClC1=CC=C(NC(C2=CC(CN(CC)CC)=CC(OCC)=C2)=O)C=C1C3=NC4=CC(C5=NC=NN5C)=CC(OCCNC)=C4N3C

O=C(C1=CC(CN2CCOCC2)=CC(C(F)(F)F)=C1)NC3=CC=CC(C4=NC5=CC(C6=NN=CO6)=CC=C5N4)=C3

O=C(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)NC9=CC(C)=CC(C%10=NC%11=CC(C%12=NC=CO%12)=CC=C%11N%10)=C9

O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(C(F)(F)F)=C%13)NC%15=CC(F)=CC(C%16=NC%17=CC(C%18=CC=NN%18)=CC=C%17N%16)=C%15

O=C(C%19=CC(CN(CC)CC)=CC(C(F)(F)F)=C%19)NC%20=CC(C(OC)=O)=CC(C%21=NC%22=CC(C%23=NC=NN%23)=CC=C%22N%21)=C%20

O=C(C%24=CC(CN%25CCOCC%25)=CC(OCC)=C%24)NC%26=C(F)C=CC(C%27=NC%28=CC(C%29=NN=C(C)O%29)=CC=C%28N%27)=C%26

O=C(C%30=CC(CN%31CCNCC%31)=CC(OCC)=C%30)NC%32=C(C)C=CC(C%33=NC%34=CC(C%35=NC=CN%35)=CC=C%34N%33)=C%32

O=C(C%36=CC(CN%37CCN(C)CC%37)=CC(OCC)=C%36)NC%38=C(S)C=CC(C%39=NC%40=CC(C%41=CC=NO%41)=CC=C%40N%39)=C%38

O=C(C%42=CC(CN(CC)CC)=CC(OCC)=C%42)NC%43=C(OC)C=CC(C%44=NC%45=CC(C%46=NN=CO%46)=CC=C%45N%44)=C%43

O=C(C%47=CC(CN%48CCOCC%48)=CC(OCC)=C%47)NC%49=CC=CC(C%50=NC%51=CC(C%52=NC=CN%52)=CC=C%51N%50C)=C%49CC

O=C(C%53=CC(CN%54CCNCC%54)=CC(OCC)=C%53)NC%55=CC=CC(C%56=NC%57=CC(C%58=NN=CO%58)=CC=C%57N%56C)=C%55Br

O=C(C%59=CC(CN%60CCN(C)CC%60)=CC(OCC)=C%59)NC%61=CC=CC(C%62=NC%63=CC(C%64=NN=CO%64)=CC=C%63N%62C)=C%61O

O=C(C%65=CC(CN(CC)CC)=CC(OCC)=C%65)NC%66=CC=CC(C%67=NC%68=CC(C%69=NC=NN%69C)=CC=C%68N%67C)=C%66Cl

O=C(C%70=CC(OCC)=CC(OCC)=C%70)NC%71=CC=CC(C%72=NC%73=C(O)C(C%74=NC=NN%74)=CC=C%73N%72C)=C%71

O=C(C%75=CC(OCC)=CC(OCC)=C%75)NC%76=CC=CC(C%77=NC%78=CC(C%79=NC=CN%79)=CC(C(C)(C)C)=C%78N%77C)=C%76

O=C(C%80=CC(OCC)=CC(OCC)=C%80)NC%81=CC=CC(C%82=NC%83=CC(C%84=NN=CO%84)=C(F)C=C%83N%82C)=C%81

O=C(C%85=CC(OCC)=CC(OCC)=C%85)NC%86=CC=CC(C%87=NC%88=CC(C%89=NN=CO%89)=C(OC)C=C%88N%87C)=C%86

O=C(C1=CC(CN2CCOCC2)=CC(C(F)(F)F)=C1)NC3=CC=CC(C4=NC5=CC(C6=NN=CO6)=CC=C5O4)=C3

O=C(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)NC9=CC(C)=CC(C%10=NC%11=CC(C%12=NC=CO%12)=CC=C%11O%10)=C9

O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(C(F)(F)F)=C%13)NC%15=CC(F)=CC(C%16=NC%17=CC(C%18=CC=NN%18)=CC=C%17O%16)=C%15

O=C(C%19=CC(CN(CC)CC)=CC(C(F)(F)F)=C%19)NC%20=CC(C(OC)=O)=CC(C%21=NC%22=CC(C%23=NC=NN%23)=CC=C%22O%21)=C%20

O=C(C%24=CC(CN%25CCOCC%25)=CC(OCC)=C%24)NC%26=C(F)C=CC(C%27=NC%28=CC(C%29=NN=C(C)O%29)=CC=C%28O%27)=C%26

O=C(C%30=CC(CN%31CCNCC%31)=CC(OCC)=C%30)NC%32=C(C)C=CC(C%33=NC%34=CC(C%35=NC=CN%35)=CC=C%34O%33)=C%32

O=C(C%36=CC(CN%37CCN(C)CC%37)=CC(OCC)=C%36)NC%38=C(S)C=CC(C%39=NC%40=CC(C%41=CC=NO%41)=CC=C%40O%39)=C%38

O=C(C%42=CC(CN(CC)CC)=CC(OCC)=C%42)NC%43=C(OC)C=CC(C%44=NC%45=CC(C%46=NN=CO%46)=CC=C%45O%44)=C%43

O=C(C1=CC(CN2CCOCC2)=CC(C(F)(F)F)=C1)NC3=CC=CC(C4=NC5=CC(C6=NN=CO6)=CC=C5S4)=C3

O=C(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)NC9=CC(C)=CC(C%10=NC%11=CC(C%12=NC=CO%12)=CC=C%11S%10)=C9

O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(C(F)(F)F)=C%13)NC%15=CC(F)=CC(C%16=NC%17=CC(C%18=CC=NN%18)=CC=C%17S%16)=C%15

O=C(C%19=CC(CN(CC)CC)=CC(C(F)(F)F)=C%19)NC%20=CC(C(OC)=O)=CC(C%21=NC%22=CC(C%23=NC=NN%23)=CC=C%22S%21)=C%20

O=C(C%24=CC(CN%25CCOCC%25)=CC(OCC)=C%24)NC%26=C(F)C=CC(C%27=NC%28=CC(C%29=NN=C(C)O%29)=CC=C%28S%27)=C%26

O=C(C%30=CC(CN%31CCNCC%31)=CC(OCC)=C%30)NC%32=C(C)C=CC(C%33=NC%34=CC(C%35=NC=CN%35)=CC=C%34S%33)=C%32

O=C(C%36=CC(CN%37CCN(C)CC%37)=CC(OCC)=C%36)NC%38=C(S)C=CC(C%39=NC%40=CC(C%41=CC=NO%41)=CC=C%40S%39)=C%38

O=C(C%42=CC(CN(CC)CC)=CC(OCC)=C%42)NC%43=C(OC)C=CC(C%44=NC%45=CC(C%46=NN=CO%46)=CC=C%45S%44)=C%43

O=C(C1=CC(CN2CCOCC2)=CC(C(F)(F)F)=C1)NC3=CC=CC(C4=NC5=CC=C(C6=NN=CO6)C=C5O4)=C3

O=C(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)NC9=CC(C)=CC(C%10=NC%11=CC=C(C%12=NC=CO%12)C=C%11O%10)=C9

O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(C(F)(F)F)=C%13)NC%15=CC(F)=CC(C%16=NC%17=CC=C(C%18=CC=NN%18)C=C%17O%16)=C%15

O=C(C%19=CC(CN(CC)CC)=CC(C(F)(F)F)=C%19)NC%20=CC(C(OC)=O)=CC(C%21=NC%22=CC=C(C%23=NC=NN%23)C=C%22O%21)=C%20

O=C(C%24=CC(CN%25CCOCC%25)=CC(OCC)=C%24)NC%26=C(F)C=CC(C%27=NC%28=CC=C(C%29=NN=C(C)O%29)C=C%28O%27)=C%26

O=C(C%30=CC(CN%31CCNCC%31)=CC(OCC)=C%30)NC%32=C(C)C=CC(C%33=NC%34=CC=C(C%35=NC=CN%35)C=C%34O%33)=C%32

O=C(C%36=CC(CN%37CCN(C)CC%37)=CC(OCC)=C%36)NC%38=C(S)C=CC(C%39=NC%40=CC=C(C%41=CC=NO%41)C=C%40O%39)=C%38

O=C(C%42=CC(CN(CC)CC)=CC(OCC)=C%42)NC%43=C(OC)C=CC(C%44=NC%45=CC=C(C%46=NN=CO%46)C=C%45O%44)=C%43

O=C(C1=CC(CN2CCOCC2)=CC(C(F)(F)F)=C1)NC3=CC=CC(C4=NC5=CC=C(C6=NN=CO6)C=C5S4)=C3

O=C(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)NC9=CC(C)=CC(C%10=NC%11=CC=C(C%12=NC=CO%12)C=C%11S%10)=C9

O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(C(F)(F)F)=C%13)NC%15=CC(F)=CC(C%16=NC%17=CC=C(C%18=CC=NN%18)C=C%17S%16)=C%15

O=C(C%19=CC(CN(CC)CC)=CC(C(F)(F)F)=C%19)NC%20=CC(C(OC)=O)=CC(C%21=NC%22=CC=C(C%23=NC=NN%23)C=C%22S%21)=C%20
O=C(C%24=CC(CN%25CCOCC%25)=CC(OCC)=C%24)NC%26=C(F)C=CC(C%27=NC%28=CC=C(C%29=NN=C(C)O%29)C=C%28S%27)=C%26
O=C(C%30=CC(CN%31CCNCC%31)=CC(OCC)=C%30)NC%32=C(C)C=CC(C%33=NC%34=CC=C(C%35=NC=CN%35)C=C%34S%33)=C%32
O=C(C%36=CC(CN%37CCN(C)CC%37)=CC(OCC)=C%36)NC%38=C(S)C=CC(C%39=NC%40=CC=C(C%41=CC=NO%41)C=C%40S%39)=C%38
O=C(C%42=CC(CN(CC)CC)=CC(OCC)=C%42)NC%43=C(OC)C=CC(C%44=NC%45=CC=C(C%46=NN=CO%46)C=C%45S%44)=C%43
O=C(C1=CC(CN2CCOCC2)=CC(OCC)=C1)NC3=CC=CC(C4=NC5=CC=C(C6=NC=CN6)C=C5N4C)=C3CC
O=C(C7=CC(CN8CCNCC8)=CC(OCC)=C7)NC9=CC=CC(C%10=CC%11=CC=C(C%12=NN=CO%12)C=C%11N%10C)=C9Br
O=C(C%13=CC(CN%14CCN(C)CC%14)=CC(OCC)=C%13)NC%15=CC=CC(C%16=NC%17=CC=C(C%18=NN=CO%18)C=C%17N%16C)=C%15O
O=C(C%19=CC(CN(CC)CC)=CC(OCC)=C%19)NC%20=CC=CC(C%21=NC%22=CC=C(C%23=NC=NN%23C)C=C%22N%21C)=C%20Cl
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C(NC)=O)=CC=C5O4
ClC6=CC=C(NC(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)=O)C=C6C9=NC%10=CC(C(NC)=O)=CC=C%10O9
ClC%11=CC=C(NC(C%12=CC(CN%13CCN(C)CC%13)=CC(C(F)(F)F)=C%12)=O)C=C%11C%14=NC%15=CC(C(NC)=O)=CC=C%15O%14
ClC%16=CC=C(NC(C%17=CC(CN(CC)CC)=CC(C(F)(F)F)=C%17)=O)C=C%16C%18=NC%19=CC(C(NC)=O)=CC=C%19O%18
ClC%20=CC=C(NC(C%21=CC(CN%22CCOCC%22)=CC(OCC)=C%21)=O)C=C%20C%23=NC%24=CC(C(NC)=O)=CC=C%24O%23
ClC%25=CC=C(NC(C%26=CC(CN%27CCNCC%27)=CC(OCC)=C%26)=O)C=C%25C%28=NC%29=CC(C(NC)=O)=CC=C%29O%28
ClC%30=CC=C(NC(C%31=CC(CN%32CCN(C)CC%32)=CC(OCC)=C%31)=O)C=C%30C%33=NC%34=CC(C(NC)=O)=CC=C%34O%33
ClC%35=CC=C(NC(C%36=CC(CN(CC)CC)=CC(OCC)=C%36)=O)C=C%35C%37=NC%38=CC(C(NC)=O)=CC=C%38O%37
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC(C(NC)=O)=CC=C5S4
ClC6=CC=C(NC(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)=O)C=C6C9=NC%10=CC(C(NC)=O)=CC=C%10S9
ClC%11=CC=C(NC(C%12=CC(CN%13CCN(C)CC%13)=CC(C(F)(F)F)=C%12)=O)C=C%11C%14=NC%15=CC(C(NC)=O)=CC=C%15S%14
ClC%16=CC=C(NC(C%17=CC(CN(CC)CC)=CC(C(F)(F)F)=C%17)=O)C=C%16C%18=NC%19=CC(C(NC)=O)=CC=C%19S%18
ClC%20=CC=C(NC(C%21=CC(CN%22CCOCC%22)=CC(OCC)=C%21)=O)C=C%20C%23=NC%24=CC(C(NC)=O)=CC=C%24S%23
ClC%25=CC=C(NC(C%26=CC(CN%27CCNCC%27)=CC(OCC)=C%26)=O)C=C%25C%28=NC%29=CC(C(NC)=O)=CC=C%29S%28
ClC%30=CC=C(NC(C%31=CC(CN%32CCN(C)CC%32)=CC(OCC)=C%31)=O)C=C%30C%33=NC%34=CC(C(NC)=O)=CC=C%34S%33
ClC%35=CC=C(NC(C%36=CC(CN(CC)CC)=CC(OCC)=C%36)=O)C=C%35C%37=NC%38=CC(C(NC)=O)=CC=C%38S%37
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC=C(C(NC)=O)C=C5O4
ClC6=CC=C(NC(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)=O)C=C6C9=NC%10=CC=C(C(NC)=O)C=C%10O9

ClC%11=CC=C(NC(C%12=CC(CN%13CCN(C)CC%13)=CC(C(F)(F)F)=C%12)=O)C=C%11C%14=NC%15=CC=C(C(NC)=O)C=C%15O%14
ClC%16=CC=C(NC(C%17=CC(CN(CC)CC)=CC(C(F)(F)F)=C%17)=O)C=C%16C%18=NC%19=CC=C(C(NC)=O)C=C%19O%18
ClC%20=CC=C(NC(C%21=CC(CN%22CCOCC%22)=CC(OCC)=C%21)=O)C=C%20C%23=NC%24=CC=C(C(NC)=O)C=C%24O%23
ClC%25=CC=C(NC(C%26=CC(CN%27CCNCC%27)=CC(OCC)=C%26)=O)C=C%25C%28=NC%29=CC=C(C(NC)=O)C=C%29O%28
ClC%30=CC=C(NC(C%31=CC(CN%32CCN(C)CC%32)=CC(OCC)=C%31)=O)C=C%30C%33=NC%34=CC=C(C(NC)=O)C=C%34O%33
ClC%35=CC=C(NC(C%36=CC(CN(CC)CC)=CC(OCC)=C%36)=O)C=C%35C%37=NC%38=CC=C(C(NC)=O)C=C%38O%37
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC=C(C(NC)=O)C=C5S4
ClC6=CC=C(NC(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)=O)C=C6C9=NC%10=CC=C(C(NC)=O)C=C%10S9
ClC%11=CC=C(NC(C%12=CC(CN%13CCN(C)CC%13)=CC(C(F)(F)F)=C%12)=O)C=C%11C%14=NC%15=CC=C(C(NC)=O)C=C%15S%14
ClC%16=CC=C(NC(C%17=CC(CN(CC)CC)=CC(C(F)(F)F)=C%17)=O)C=C%16C%18=NC%19=CC=C(C(NC)=O)C=C%19S%18
ClC%20=CC=C(NC(C%21=CC(CN%22CCOCC%22)=CC(OCC)=C%21)=O)C=C%20C%23=NC%24=CC=C(C(NC)=O)C=C%24S%23
ClC%25=CC=C(NC(C%26=CC(CN%27CCNCC%27)=CC(OCC)=C%26)=O)C=C%25C%28=NC%29=CC=C(C(NC)=O)C=C%29S%28
ClC%30=CC=C(NC(C%31=CC(CN%32CCN(C)CC%32)=CC(OCC)=C%31)=O)C=C%30C%33=NC%34=CC=C(C(NC)=O)C=C%34S%33
ClC%35=CC=C(NC(C%36=CC(CN(CC)CC)=CC(OCC)=C%36)=O)C=C%35C%37=NC%38=CC=C(C(NC)=O)C=C%38S%37
ClC1=CC=C(NC(C2=CC(CN3CCOCC3)=CC(C(F)(F)F)=C2)=O)C=C1C4=NC5=CC=C(C(NC)=O)C=C5N4C
ClC6=CC=C(NC(C7=CC(CN8CCNCC8)=CC(C(F)(F)F)=C7)=O)C=C6C9=NC%10=CC=C(C(NC)=O)C=C%10N9C
ClC%11=CC=C(NC(C%12=CC(CN%13CCN(C)CC%13)=CC(C(F)(F)F)=C%12)=O)C=C%11C%14=NC%15=CC=C(C(NC)=O)C=C%15N%14C
ClC%16=CC=C(NC(C%17=CC(CN(CC)CC)=CC(C(F)(F)F)=C%17)=O)C=C%16C%18=NC%19=CC=C(C(NC)=O)C=C%19N%18C
ClC%20=CC=C(NC(C%21=CC(CN%22CCOCC%22)=CC(OCC)=C%21)=O)C=C%20C%23=NC%24=CC=C(C(NC)=O)C=C%24N%23C
ClC%25=CC=C(NC(C%26=CC(CN%27CCNCC%27)=CC(OCC)=C%26)=O)C=C%25C%28=NC%29=CC=C(C(NC)=O)C=C%29N%28C
ClC%30=CC=C(NC(C%31=CC(CN%32CCN(C)CC%32)=CC(OCC)=C%31)=O)C=C%30C%33=NC%34=CC=C(C(NC)=O)C=C%34N%33C
ClC%35=CC=C(NC(C%36=CC(CN(CC)CC)=CC(OCC)=C%36)=O)C=C%35C%37=NC%38=CC=C(C(NC)=O)C=C%38N%37C

The activity of the compounds in Examples 1-14 as Braf inhibitors is illustrated in the following assay(s). The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in these assay(s) as well.

Biological Activity Assay

In vitro B-Raf/Mek1 composite kinase assay

2.5µl of B-Raf kinase buffer (20mM MOPS [pH 7.2], 25mM sodium glycerophosphate, 2mM EGTA [pH 8.0], 1mM sodium orthovanadate, 1mM dithiothreitol, 10mM $MgCl_2$, 0.03% Brij-35, 0.3mg/ml bovine serum albumin) containing 1ng of recombinant, N-terminal GST-tagged human B-Raf protein kinase (Δ1-415, Upstate Cat. 14-530) is dispensed to wells of a 384 or 1536 multi-well white solid plate. 50nl of 100X concentration of test compound in DMSO is dispensed to the wells by passive pin transfer and incubated for 15 minutes at room temperature (approx. 22°C). 2.5µl of B-Raf kinase buffer containing 12.5ng of recombinant N-terminal GST-tagged, C-terminal His6-tagged human Mek1 (inactive, Upstate Cat. 14-420) and 2µM ATP is then dispensed and the kinase reaction allowed to incubate at 30°C for 2 hours. The assay plates are lidded and maintained in a humidified environment. After 2 hours, 2.5µl of PKLight protein kinase assay reagent (Cambrex) is dispensed. After an additional 5 minute incubation at room temperature, luminescence activity is measured on a suitable plate reader. Kinase inhibition results in less ATP consumption, and therefore increased luciferase-dependent luminescence. Negative control activity is measured with DMSO lacking any test compound. The positive control is [N-(3-trifluoromethyl-4-chlorophenyl)-N'-(4-(2-methylcarbamoyl-pyridin-4-yl)oxyphenyl)urea], aka Bay 43-9006. Efficacy is measured as a percentage of positive control activity.

IC_{50} data were obtained for the compounds provided herein. Data for selected compounds is shown in Table 1 below. Compounds not test were designated NT as shown in Table 1.

Table 1. Biological Activity

Example #	Kinase Assay IC50 mM + indicates ≤ 10 µM - indicates > 10 µM
1	-
2	-
3	+
4	+
5	-
6	-
7	-
8	-
9	-
10	-

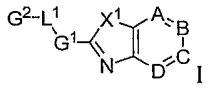
11	-
12	+
13	NT
14	+

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A method of inhibiting BRaf kinase comprising the administration of a compound of Formula I:



I

Or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

A, B, C and D are each independently N or CR^2;

n is 0, 1 or 2;

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted;

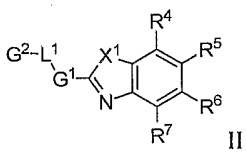
L^1 is selected from the group consisting of a bond, optionally substituted alkyl, –O–, –S–, –C(O)–, –S(O)–, $–SO_2–$, $–N(R^3)–$, $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$, $–N(R^3)C(O)O–$, $–OC(O)N(R^3)–$ and $–OC(O)O–$;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^2 is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^3 is selected from the group consisting of alkyl and hydrogen.

2. The method as recited in Claim 1 wherein, the compound has the Formula II:



II

Or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

n is 0, 1 or 2;

G^1 is selected from the group consisting of a bond, alkenyl, alkyl, alkylene, alkynyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted;

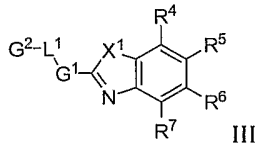
L^1 is selected from the group consisting of a bond, optionally substituted alkyl, –O–, –S–, –C(O)–, –S(O)–, $–SO_2–$, $–N(R^3)–$, $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$, $–N(R^3)C(O)O–$, $–OC(O)N(R^3)–$ and –OC(O)O–;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

3. The method as recited in Claim 2 wherein, the compound has the Formula III:



III

Or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

n is 0, 1 or 2;

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

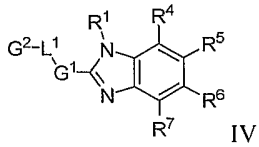
L^1 is selected from the group consisting of $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

4. The method as recited in Claim 3 wherein, the compound has the Formula IV:



IV

Or a salt, ester, or prodrug thereof, wherein:

G^1 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

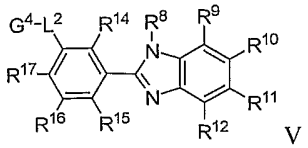
L^1 is selected from the group consisting of $-C(O)N(R^3)-$, $-N(R^3)C(O)-$, $-N(R^3)C(O)N(R^3)-$;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^3 is selected from the group consisting of alkyl and hydrogen; and

R^4, R^5, R^6, and R^7 are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

5. The method as recited in Claim 4 has the Formula V:



V

Or a salt, ester, or prodrug thereof, wherein:

G^4 is selected from the group consisting of aryl, which may be optionally substituted;

L^2 is selected from the group consisting of $-N(R^{13})C(O)-$ or $-N(R^{13})C(O)N(R^{13})-$;

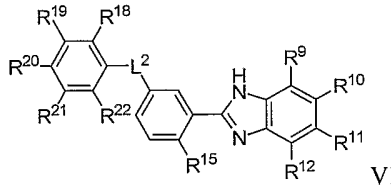
R^8 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aryl, arylalkenyl, arylalkylthio, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted, with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

R^{13} is selected from the group consisting of alkyl and hydrogen; and

R^{14}, R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

6. The method as recited in Claim 5 has the Formula VI:



VI

Or a salt, ester, or prodrug thereof, wherein:

L^2 is selected from the group consisting of $-C(O)N(R^{13})-$ or $-N(R^{13})C(O)N(R^{13})-$;

R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl,

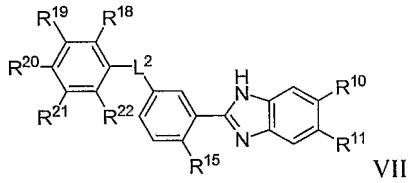
heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

R^{13} is selected from the group consisting of alkyl and hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

7. The method as recited in Claim 6 has the Formula VII:



VII

Or a salt, ester, or prodrug thereof, wherein:

L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

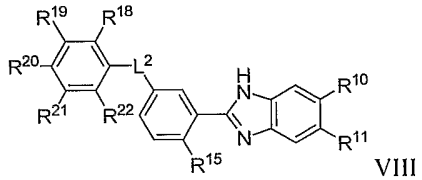
R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, Bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl,

aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

8. The method as recited in Claim 7 has the Formula VIII:



VIII

Or a salt, ester, or prodrug thereof, wherein:

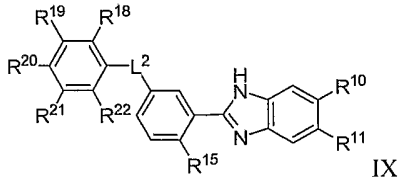
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

9. The method as recited in Claim 8 has the Formula IX:



IX

Or a salt, ester, or prodrug thereof, wherein:

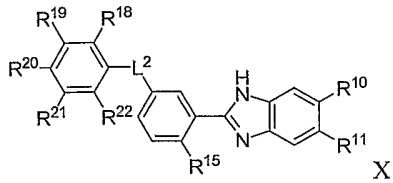
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

10. The method as recited in Claim 9 has the Formula X:



X

Or a salt, ester, or prodrug thereof, wherein:

L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

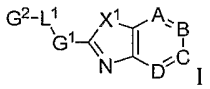
R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, aminoalkyl, alkylaminocarbonyl, ester and heteroaryl, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo,

haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

11. The method as recited in Claim 4, wherein R^6 is optionally substituted alkylester, amido, heteroaryl or hydrogen.
12. The method as recited in Claim 5, wherein R^1 is hydrogen.
13. The method as recited in Claim 5, wherein G^1 is optionally substituted aryl.
14. The method as recited in Claim 6, wherein G^2 is optionally substituted aryl.
15. The method as recited in Claim 1 selected from the group consisting of Examples 1-14.
16. A method of treatment of a BRaf-mediated disease in a patient in need thereof comprising the administration of a therapeutically effective amount of a compound of Formula I:



I

Or a salt, ester, or prodrug thereof, wherein:

X^1 is selected from the group consisting of NR^1, O and $S(O)_n$;

A, B, C and D are each independently N or CR^2;

n is 0, 1 or 2;

G^1 is selected from the group consisting of a bond, alkenyl, alkyl, alkylene, alkynyl, aryl, cycloalkyl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted;

G^2 is selected from the group consisting of alkenyl, alkyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl and hydrogen, any of which may be optionally substituted;

L^1 is selected from the group consisting of a bond, optionally substituted alkyl, –O–, –S–, –C(O)–, –S(O)–, $–SO_2–$, $–N(R^3)–$, $–SO_2N(R^3)–$, $–N(R^3)SO_2–$, $–C(O)N(R^3)–$, $–N(R^3)C(O)–$, $–N(R^3)C(O)N(R^3)–$, $–N(R^3)C(O)O–$, $–OC(O)N(R^3)–$ and –OC(O)O–;

R^1 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aminoalkyl, aryl, arylalkenyl, arylalkyl, arylalkylthio, arylalkynyl, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

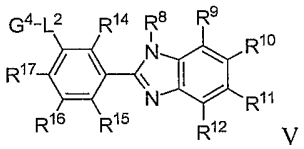
R^2 is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido,

amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^3 is selected from the group consisting of alkyl and hydrogen.

17. The method as recited in Claim 16 wherein said disease is selected from the group consisting of cancer, hematological and non-hematologic malignancies, autoimmune, hematopoiesis, malignancies of the skin, psoriasis, treatment of dry eye as well as glaucoma.

18. A compound of Formula V:



V

Or a salt, ester, or prodrug thereof, wherein:

G^4 is selected from the group consisting of aryl, which may be optionally substituted;

L^2 is selected from the group consisting of $-N(R^{13})C(O)-$ or $-N(R^{13})C(O)N(R^{13})-$;

R^8 is selected from the group consisting of alkenyl, alkyl, alkylsulfonyl, alkynyl, aryl, arylalkenyl, arylalkylthio, arylcarbonyl, arylsulfonyl, arylthio, carboxy, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydrogen, thio and sulfonyl, any of which may be optionally substituted;

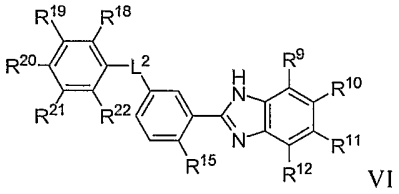
R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted, with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

R^{13} is selected from the group consisting of alkyl and hydrogen; and

R^{14}, R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl,

heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

19. The compound as recited in Claim 18 has the Formula VI:



VI

Or a salt, ester, or prodrug thereof, wherein:

L^2 is selected from the group consisting of $-C(O)N(R^{13})-$ or $-N(R^{13})C(O)N(R^{13})-$;

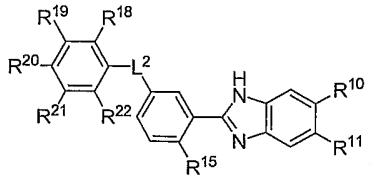
R^9, R^{10}, R^{11} and R^{12} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^9, R^{10}, R^{11} and R^{12} cannot be hydrogen;

R^{13} is selected from the group consisting of alkyl and hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

20. The compound as recited in Claim 19 has the Formula VII:



VII

Or a salt, ester, or prodrug thereof, wherein:

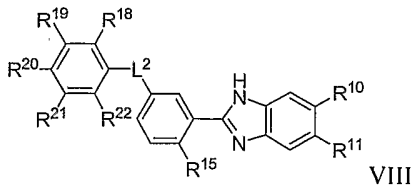
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, alkylene, alkylsulfonyl, alkynyl, alkylaminocarbonyl, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, Bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

21. The compound as recited in Claim 20 has the Formula VIII:



VIII

Or a salt, ester, or prodrug thereof, wherein:

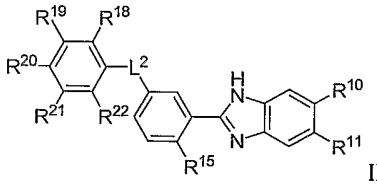
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted; with the proviso that at least one of R^{10} and R^{11} cannot be hydrogen;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

22. The compound as recited in Claim 21 has the Formula IX:



IX

Or a salt, ester, or prodrug thereof, wherein:

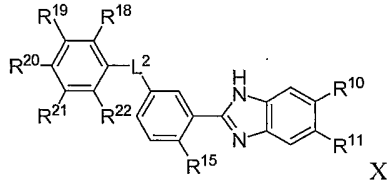
L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, C_2-C_6 alkyl, aminoalkyl, alkylaminocarbonyl, aryl, arylalkenyl, carboxy, cyanoalkenyl, cycloalkyl, ester, bromo, fluoro, iodo, haloalkyl, haloalkylcarbonyl, heteroaryl, heterocycloalkyl, hydroxy, hydroxyalkyl and thio, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

23. The compound as recited in Claim 22 has the Formula X:



X

Or a salt, ester, or prodrug thereof, wherein:

L^2 is selected from the group consisting of –C(O)NH– or –NHC(O)NH–;

R^{10} and R^{11} are each independently selected from the group consisting of acyl, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, aminoalkyl, alkylaminocarbonyl, ester and heteroaryl, any of which may be optionally substituted;

R^{15} is selected from the group consisting of acyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, amido, amino, aminoalkyl, carboxy, cyano, ester, halo, haloalkyl, haloalkylcarbonyl, heterocycloalkyl, hydrogen, hydroxy, nitro, sulfonyl and thio, any of which may be optionally substituted; and

R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each independently selected from the group consisting of acyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkylamine, alkoxyalkylheterocycloalkyl, alkyl, alkylene, alkylsulfonyl, alkynyl, amido, amino, aminoalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkylamino, arylalkynyl, aryloxy, carboxy, cyano, cyanoalkenyl, cycloalkyl, ester, halo, haloalkyl, haloalkylcarbonyl, heteroaryl, heteroarylalkenyl, heteroarylalkoxy, heteroarylalkyl, heteroaryloxy, heterocycloalkenyl, heterocycloalkoxy, heterocycloalkyl, hydrogen, hydroxy, hydroxyalkyl, nitro, sulfonyl and thio, any of which may be optionally substituted.

24. The compound as recited in Claim 23, wherein R^{11} is optionally substituted alkylester, alkylaminocarbonyl or heteroaryl.

25. The compound as recited in Claim 24, wherein R^{15} is optionally substituted alkyl or halo.

26. The compound as recited in Claim 25, wherein R^{10} is hydrogen.

27. The compound as recited in Claim 26, wherein R^{19}, R^{20} and R^{21} are each independently alkoxy, halo, haloalkyl and heteroaryl, any of which may be optionally substituted.

28. The compound as recited in Claim 18 selected from the group consisting of Examples 1-11.

29. A compound as recited in Claim 18 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of Braf kinase.
30. A pharmaceutical composition comprising a compound in Claim 18 together with a pharmaceutically acceptable carrier.
31. The pharmaceutical composition as recited in Claim 30, useful for the treatment or prevention of a Braf-mediated disease.
32. The method as recited in Claim 31 wherein said disease is melanoma.
33. A method of treatment of a B-Raf-mediated disease in a patient in need thereof comprising the administration of
    a. a therapeutically effective amount of a compound as recited in any one of Claims 18-28; and
    b. another therapeutic agent.
34. The method as recited in Claim 33 wherein said other agent is a compound selected from the group consisting of dacarbazine (DTIC), alkylating agents, anthracyclines, corticosteroids, Akt inhibitors, aromatase inhibitors, antiestrogen, anti-androgen, or a gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, antineoplastic antimetabolites, platinum containing compounds, MITC, nitrosoureas, taxanes, lipid or protein kinase targeting agents, protein or lipid phosphatase targeting agents, anti-angiogentic agents, IMiDs, protease inhibitors, IGF-1 inhibitors, CD40 antibodies, Smac mimetics, FGF3 modulators, mTOR inhibitors, HDAC inhibitors, IKK inhibitors, P38MAPK inhibitors, HSP90 inhibitors, and other mutlikinase inhibitors.
35. The method as recited in Claim 34 wherein said other agent is dacarbazine.