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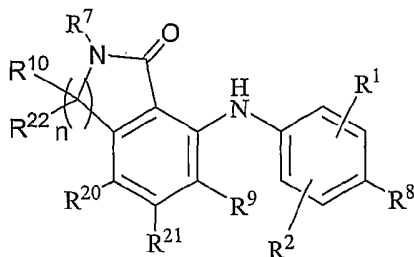
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(54) Title: BICYCLIC INHIBITORS OF MEK AND METHODS OF USE THEREOF



(I)

(57) Abstract: Disclosed are compounds of the Formula (I) and pharmaceutically acceptable salts and prodrugs thereof, wherein R¹, R², R⁷, R⁸, R⁹, R¹⁰, R²⁰, R²¹, and R²² are as defined in the specification. Such compounds are MFK inhibitors and useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals, and inflammatory conditions. Also disclosed are methods of using such compounds in the treatment of hyperproliferative diseases in mammals and pharmaceutical compositions containing such compounds.

BICYCLIC INHIBITORS OF MEK AND METHODS OF USE THEREOF

[0001] This application claims benefit of U.S. Provisional Application Serial No. 60/523,270, filed November 19, 2003, incorporated herein in its entirety by this reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0002] This invention relates to a series of novel heterocyclic compounds that are useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

2. Description of the state of the art

[0003] Cell signaling through growth factor receptors and protein kinases is an important regulator of cell growth, proliferation and differentiation. In normal cell growth, growth factors, through receptor activation (i.e., PDGF or EGF and others), activate MAP kinase pathways. One of the most important and most well understood MAP kinase pathways involved in normal and uncontrolled cell growth is the Ras/Raf kinase pathway. Active GTP-bound Ras results in the activation and indirect phosphorylation of Raf kinase. Raf then phosphorylates MEK1 and 2 on two serine residues (S218 and S222 for MEK1 and S222 and S226 for MEK2) (Ahn *et al.*, *Methods in Enzymology*, **2001**, 332, 417-431). Activated MEK then phosphorylates its only known substrates, the MAP kinases, ERK1 and 2. ERK phosphorylation by MEK occurs on Y204 and T202 for ERK1 and Y185 and T183 for ERK2 (Ahn *et al.*, *Methods in Enzymology*, **2001**, 332, 417-431). Phosphorylated ERK dimerizes and then translocates to the nucleus where it accumulates (Khokhlatchev *et al.*, *Cell*, **1998**, 93, 605-615). In the nucleus, ERK is involved in several important cellular functions, including, but not limited to, nuclear transport, signal transduction, DNA repair, nucleosome assembly and translocation, and mRNA processing and translation (Ahn *et al.*, *Molecular Cell*, **2000**, 6, 1343-1354). Overall, treatment of cells with growth factors leads to the activation of ERK1 and 2 which results in proliferation and, in some cases, differentiation (Lewis *et al.*, *Adv. Cancer Res.*, **1998**, 74, 49-139).

[0004] In proliferative diseases, genetic mutations and/or overexpression of the growth factor receptors, downstream signaling proteins, or protein kinases involved in the ERK kinase pathway lead to uncontrolled cell proliferation and, eventually, tumor formation. For example, some cancers contain mutations which result in the continuous activation of this pathway due to continuous production of growth factors. Other mutations can lead to defects in the deactivation of the activated GTP-bound Ras complex, again resulting in activation of the MAP kinase pathway. Mutated, oncogenic forms of Ras are found in 50% of colon and >90% pancreatic cancers as well as many others types of cancers (Kohl *et al.*, *Science*, **1993**, 260, 1834-1837). Recently, bRaf mutations have been identified in more than 60% of malignant melanoma (Davies, H. *et al.*, *Nature*, **2002**, 417, 949-954). These mutations in bRaf result in a constitutively active MAP kinase cascade. Studies of primary tumor samples and cell lines have also shown constitutive or overactivation of the MAP kinase pathway in cancers of pancreas, colon, lung, ovary and kidney (Hoshino, R. *et al.*, *Oncogene*, **1999**, 18, 813-822). Hence, there is a strong correlation between cancers and an overactive MAP kinase pathway resulting from genetic mutations.

[0005] As constitutive or overactivation of MAP kinase cascade plays a pivotal role in cell proliferation and differentiation, inhibition of this pathway is believed to be beneficial in hyperproliferative diseases. MEK is a key player in this pathway as it is downstream of Ras and Raf. Additionally, it is an attractive therapeutic target because the only known substrates for MEK phosphorylation are the MAP kinases, ERK1 and 2. Inhibition of MEK has been shown to have potential therapeutic benefit in several studies. For example, small molecule MEK inhibitors have been shown to inhibit human tumor growth in nude mouse xenografts, (Sebolt-Leopold *et al.*, *Nature-Medicine*, **1999**, 5 (7), 810-816; Trachet *et al.*, AACR April 6-10, 2002, Poster #5426; Tecle, H., IBC 2nd International Conference of Protein Kinases, September 9-10, 2002), block static allodynia in animals (WO 01/05390 published January 25, 2001) and inhibit growth of acute myeloid leukemia cells (Milella *et al.*, *J. Clin. Invest.*, **2001**, 108 (6), 851-859).

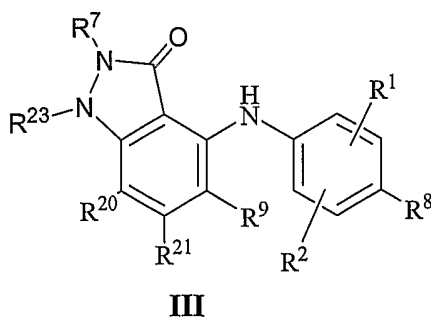
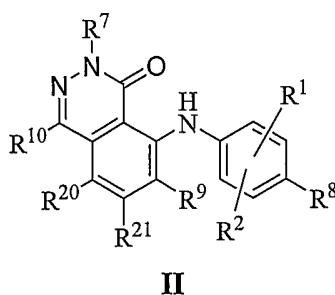
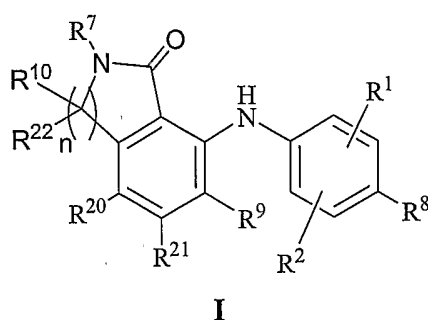
[0006] Small molecule inhibitors of MEK have been disclosed, including in U.S. Patent Publication Nos. 2003/0232869, 2004/0116710, and 2003/0216460, and U.S. Patent Application Serial Nos. 10/654,580 and 10/929,295, each of which is hereby incorporated by reference. At least fifteen additional patent applications have appeared in the last several years. See, for example: U.S. Patent No. 5,525,625; WO 98/43960; WO 99/01421; WO

99/01426; WO 00/41505; WO 00/42002; WO 00/42003; WO 00/41994; WO 00/42022; WO 00/42029; WO 00/68201; WO 01/68619; WO 02/06213; WO 03/077914; and WO 03/077855.

SUMMARY OF THE INVENTION

[0007] This invention provides for novel heterocyclic compounds, and pharmaceutically acceptable salts and prodrugs thereof that are useful in the treatment of hyperproliferative diseases. Specifically, one aspect the present invention relates to compounds of Formulas **I-III** that act as MEK inhibitors.

[0008] More specifically, one embodiment of the present invention provides compounds of the Formulas **I-III**:



[0009] and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein:

[0010] R^1 , R^2 , R^8 , R^9 , R^{20} and R^{21} are independently hydrogen, hydroxy, halogen,

cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-SR^{11}$, $-OR^3$, $-C(O)R^3$, $-C(O)OR^3$, $-NR^4C(O)OR^6$, $-OC(O)R^3$, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-NR^3R^4$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, $-S(O)_j(C_1-C_6 \text{ alkyl})$, $-S(O)_j(CR^4R^5)_m\text{-aryl}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-O(CR^4R^5)_m\text{-aryl}$, $-NR^4(CR^4R^5)_m\text{-aryl}$, $-O(CR^4R^5)_m\text{-heteroaryl}$, $-NR^4(CR^4R^5)_m\text{-heteroaryl}$, $-O(CR^4R^5)_m\text{-heterocyclyl}$ or $-NR^4(CR^4R^5)_m\text{-heterocyclyl}$, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0011] R^7 is hydrogen, trifluoromethyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from

halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³;

[0012] where for Formula I, R¹⁰ and R²² are independently hydrogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, -C(O)R³, -C(O)OR³, -SO₂NR³R⁴, -C(O)NR³R⁴, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, -S(O)_j(C₁-C₆ alkyl), -S(O)_j(CR⁴R⁵)_m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -C(O)R³, -C(O)OR³, -OC(O)R³, -NR⁴C(O)OR⁶, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -OR³, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³;

[0013] and where for Formula II, R¹⁰ is hydrogen, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, -SR¹¹, -OR³, -C(O)R³, -C(O)OR³, -NR⁴C(O)OR⁶, -OC(O)R³, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -NR³R⁴, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, -S(O)_j(C₁-C₆ alkyl), -S(O)_j(CR⁴R⁵)_m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -O(CR⁴R⁵)_m-aryl, -NR⁴(CR⁴R⁵)_m-aryl, -O(CR⁴R⁵)_m-heteroaryl, -NR⁴(CR⁴R⁵)_m-heteroaryl, -O(CR⁴R⁵)_m-heterocyclyl or -NR⁴(CR⁴R⁵)_m-heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro,

trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^4\text{SO}_2\text{R}^6$, $-\text{SO}_2\text{NR}^3\text{R}^4$, $-\text{C}(\text{O})\text{R}^3$, $-\text{C}(\text{O})\text{OR}^3$, $-\text{OC}(\text{O})\text{R}^3$, $-\text{NR}^4\text{C}(\text{O})\text{OR}^6$, $-\text{NR}^4\text{C}(\text{O})\text{R}^3$, $-\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{C}(\text{O})\text{NR}^3\text{R}^4$, $-\text{NR}^5\text{C}(\text{NCN})\text{NR}^3\text{R}^4$, $-\text{OR}^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0014] R^{23} is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0015] R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, -

$\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl,

[0016] or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0017] R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

[0018] R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0019] R^6 is trifluoromethyl, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0020] R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

[0021] or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are

attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0022] m is 0, 1, 2, 3, 4 or 5;

[0023] n is 1 or 2; and

[0024] j is 0, 1 or 2.

[0025] In a further aspect the present invention provides compositions that inhibit MEK comprising compounds of Formulas **I-III**.

[0026] The invention is also directed to pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of compounds of Formula **I-III**. Methods of making the compounds of Formula **I-III** are also described.

[0027] In a further aspect the present invention provides a method of using the compounds of this invention to treat diseases or medical conditions mediated by MEK, such as cancer. For example, this invention provides a method for treatment of a hyperproliferative disorder or an inflammatory condition in a mammal, comprising administering to said mammal one or more compounds of Formulas **I-III** or a pharmaceutically acceptable salt or prodrug thereof in an amount effective to treat said hyperproliferative disorder.

[0028] In a further aspect the present invention provides treating or preventing an MEK-mediated condition, comprising administering to a human or animal in need thereof a pharmaceutical composition comprising a compound of Formula **I-III** or a pharmaceutically-acceptable salt or in vivo cleavable prodrug thereof in an amount effective to treat or prevent said MEK-mediated condition.

[0029] The inventive compounds may further be used advantageously in combination with other known therapeutic agents.

[0030] The invention also relates to pharmaceutical compositions comprising an effective amount of a compound selected from compounds of Formulas **I-III**, or pharmaceutically acceptable prodrugs, pharmaceutically active metabolites or pharmaceutically acceptable salt thereof.

[0031] Additional advantages and novel features of this invention shall be set forth in

part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the invention. The advantages of the invention may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0032] The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate non-limiting embodiments of the present invention, and together with the description, serve to explain the principles of the invention.

In the Figures:

[0033] Figure 1 shows a reaction scheme for the synthesis of compounds 5-6.

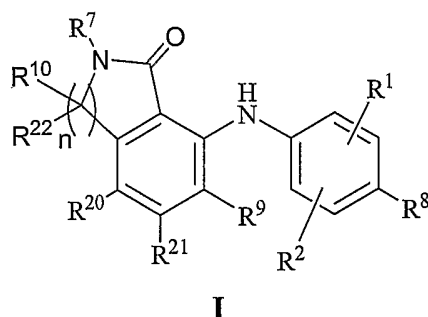
[0034] Figure 2 shows a reaction scheme for the synthesis of compound 6.

[0035] Figure 3 and 4 show reaction schemes for the synthesis of compound 8.

[0036] Figure 5 shows a reaction scheme for the synthesis of compounds 11-12.

DETAILED DESCRIPTION OF THE INVENTION

[0037] The inventive compounds of the Formulas **I-III** and the pharmaceutically acceptable salts and prodrugs thereof of this invention are useful in the treatment of hyperproliferative diseases. Specifically, one aspect the present invention relates to compounds of Formula **I-III** that act as MEK inhibitors. In general, one embodiment of the invention relates to compounds having the general Formula **I**:



[0038] and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein:

[0039] R^1 , R^2 , R^8 , R^9 , R^{20} and R^{21} are independently hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-SR^{11}$, $-OR^3$, $-C(O)R^3$, $-C(O)OR^3$, $-NR^4C(O)OR^6$, $-OC(O)R^3$, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10}

cycloalkylalkyl, $-S(O)_j(C_1-C_6 \text{ alkyl})$, $-S(O)_j(CR^4R^5)_m\text{-aryl}$, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-O(CR^4R^5)_m\text{-aryl}$, $-NR^4(CR^4R^5)_m\text{-aryl}$, $-O(CR^4R^5)_m\text{-heteroaryl}$, $-NR^4(CR^4R^5)_m\text{-heteroaryl}$, $-O(CR^4R^5)_m\text{-heterocyclyl}$ or $-NR^4(CR^4R^5)_m\text{-heterocyclyl}$, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0040] R^7 is hydrogen, trifluoromethyl, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, C_3-C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0041] R^{10} and R^{22} are independently hydrogen, cyano, nitro, trifluoromethyl,

difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-C(O)R^3$, $-C(O)OR^3$, $-SO_2NR^3R^4$, $-C(O)NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1-C_6 \text{ alkyl})$, $-S(O)_j(CR^4R^5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0042] R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl,

[0043] or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$,

$-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0044] R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

[0045] R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0046] R^6 is trifluoromethyl, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0047] R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

[0048] or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0049] m is 0, 1, 2, 3, 4 or 5;

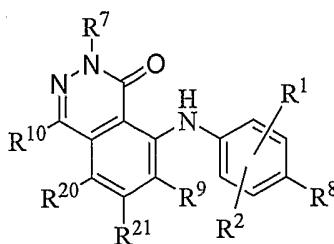
[0050] n is 1 or 2; and

[0051] j is 0, 1 or 2.

[0052] Figures 1-2 show non-limiting examples of the synthesis of compounds of this

invention having the general Formula I.

[0053] In addition to compounds of the general Formula I, this invention further includes compounds of the general Formula II:



II

[0054] and pharmaceutically accepted salts, prodrugs and solvates thereof, where:

[0055] R¹, R², R⁸, R⁹, R¹⁰, R²⁰ and R²¹ are independently hydrogen, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, -SR¹¹, -OR³, -C(O)R³, -C(O)OR³, -NR⁴C(O)OR⁶, -OC(O)R³, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -NR³R⁴, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, -S(O)_j(C₁-C₆ alkyl), -S(O)_j(CR⁴R⁵)_m-aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, -O(CR⁴R⁵)_m-aryl, -NR⁴(CR⁴R⁵)_m-aryl, -O(CR⁴R⁵)_m-heteroaryl, -NR⁴(CR⁴R⁵)_m-heteroaryl, -O(CR⁴R⁵)_m-heterocyclyl or -NR⁴(CR⁴R⁵)_m-heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -C(O)R³, -C(O)OR³, -OC(O)R³, -NR⁴C(O)OR⁶, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR³R⁴, -NR⁵C(O)NR³R⁴, -NR⁵C(NCN)NR³R⁴, -OR³, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³;

[0056] R⁷ is hydrogen, trifluoromethyl, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,

heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_6$ heterocycloalkyl, NR^3R^4 and OR^3 ;

[0057] R^3 is hydrogen, trifluoromethyl, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl,

[0058] or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl,

heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

[0059] R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

[0060] R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

[0061] R^6 is trifluoromethyl, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

[0062] R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

[0063] or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

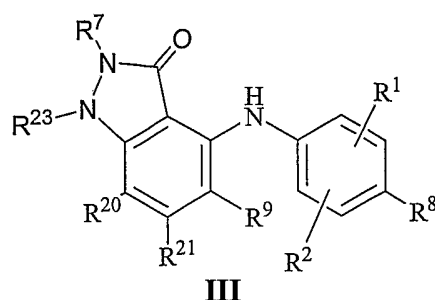
[0064] m is 0, 1, 2, 3, 4 or 5; and

[0065] j is 0, 1 or 2.

[0066] Figures 3-4 show non-limiting examples of the synthesis of compounds of this invention having the general Formula II.

[0067] In another embodiment, this invention relates to compounds of the general

Formula III:



[0068] and pharmaceutically accepted salts, prodrugs and solvates thereof, where:

[0069] R^1 , R^2 , R^8 , R^9 , R^{20} and R^{21} are independently hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-SR^{11}$, $-OR^3$, $-C(O)R^3$, $-C(O)OR^3$, $-NR^4C(O)OR^6$, $-OC(O)R^3$, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1$ - C_6 alkyl), $-S(O)_j(CR^4R^5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-O(CR^4R^5)_m$ -aryl, $-NR^4(CR^4R^5)_m$ -aryl, $-O(CR^4R^5)_m$ -heteroaryl, $-NR^4(CR^4R^5)_m$ -heteroaryl, $-O(CR^4R^5)_m$ -heterocyclyl or $-NR^4(CR^4R^5)_m$ -heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0070] R^7 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, OR^3 , NR^3R^4 , aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and

heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclalkyl and heterocyclalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0071] R^{23} is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, or heterocyclalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclalkyl and heterocyclalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

[0072] R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl, heterocyclalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclalkyl

and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocycl, and heterocyclalkyl;

[0073] or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocycl, and heterocyclalkyl;

[0074] R^4 and R^5 independently are hydrogen or $\text{C}_1\text{-C}_6$ alkyl, or

[0075] R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocycl, and heterocyclalkyl;

[0076] R^6 is trifluoromethyl, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycl or heterocyclalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycl and heterocyclalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl,

heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0077] R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

[0078] or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

[0079] m is 0, 1, 2, 3, 4 or 5; and

[0080] j is 0, 1 or 2.

[0081] Figure 5 shows a non-limiting example of the synthesis of compounds of this invention having the general Formula **III**.

[0082] The terms " C_1 - C_{10} alkyl", "alkyl" and "lower alkyl" as used herein refer to a saturated linear or branched-chain monovalent hydrocarbon radical having one to ten carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, heptyl, octyl, and the like.

[0083] The terms " C_2 - C_{10} alkenyl", "lower alkenyl" and "alkenyl" refer to linear or branched-chain monovalent hydrocarbon radical having two to 10 carbon atoms and at least one double bond, and include, but is not limited to, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0084] The terms " C_2 - C_{10} alkynyl", "lower alkynyl" and "alkynyl" refer to a linear or branched monovalent hydrocarbon radical of two to twelve carbon atoms containing at least one triple bond. Examples include, but are not limited to, ethynyl, propynyl, butynyl, pentyn-2-yl and the like, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein.

[0085] The term "allyl" refers to a radical having the formula $RC=CHCHR$, wherein R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or any substituent

as defined herein, wherein the allyl may be optionally substituted independently with one or more substituents described herein.

[0086] The terms "carbocycle," "carbocyclyl," "cycloalkyl" or "C₃-C₁₀ cycloalkyl" refer to saturated or partially unsaturated cyclic hydrocarbon radical having from three to ten carbon atoms. The term "cycloalkyl" includes monocyclic and polycyclic (e.g., bicyclic and tricyclic) cycloalkyl structures, wherein the polycyclic structures optionally include a saturated or partially unsaturated cycloalkyl fused to a saturated or partially unsaturated cycloalkyl or heterocycloalkyl ring or an aryl or heteroaryl ring. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. The cycloalkyl may be optionally substituted independently in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

[0087] The term "heteroalkyl" refers to saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms, wherein at least one of the carbon atoms is replaced with a heteroatom selected from N, O, or S, and wherein the radical may be a carbon radical or heteroatom radical (i.e., the heteroatom may appear in the middle or at the end of the radical). The heteroalkyl radical may be optionally substituted independently with one or more substituents described herein. The term "heteroalkyl" encompasses alkoxy and heteroalkoxy radicals.

[0088] The terms "heterocycloalkyl," "heterocycle" or "heterocyclyl" refer to a saturated or partially unsaturated carbocyclic radical of 3 to 8 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen and sulfur, the remaining ring atoms being C, where one or more ring atoms may be optionally substituted independently with one or more substituent described below. The radical may be a carbon radical or heteroatom radical. The term further includes bicyclic and tricyclic fused ring systems which include a heterocycle fused one or more carbocyclic or heterocyclic rings. "Heterocycloalkyl" also includes radicals where heterocycle radicals are fused with aromatic or heteroaromatic rings. Examples of heterocycloalkyl rings include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl,

dihydropyran-yl, tetrahydrothiopyran-yl, piperidino, morpholino, thiomorpholino, thioxan-yl, piperazin-yl, homopiperazin-yl, azetid-yl, oxetan-yl, thietan-yl, homopiperidin-yl, oxepan-yl, thiopan-yl, oxazepin-yl, diazepin-yl, thiazepin-yl, 1,2,3,6-tetrahydropyridin-yl, 2-pyrrolin-yl, 3-pyrrolin-yl, indolin-yl, 2H-pyran-yl, 4H-pyran-yl, dioxan-yl, 1,3-dioxolan-yl, pyrazolin-yl, dithian-yl, dithiolan-yl, dihydropyran-yl, dihydrothien-yl, dihydrofuran-yl, pyrazolidinylimidazol-yl, imidazolidin-yl, 3-azabicyclo[3.1.0]hexan-yl, 3-azabicyclo[4.1.0]heptan-yl, azabicyclo[2.2.2]hexan-yl, 3H-indol-yl and quinolizin-yl. Spiro moieties are also included within the scope of this definition. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties is 1,1-dioxo-thiomorpholin-yl. The heterocycle groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alken-yl, C₂-C₆alkyn-yl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

[0089] The term "aryl" refers to a monovalent aromatic carbocyclic radical having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, trifluoromethyl, aryl, heteroaryl, and hydroxy.

[0090] The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings which includes fused ring systems (at least one of which is aromatic) of 5-10 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Examples of heteroaryl groups are pyridin-yl, imidazol-yl, pyrimidin-yl, pyrazol-yl, triazol-yl, pyrazin-yl, tetrazol-yl, furyl, thien-yl, isoxazol-yl, thiazol-yl, oxazol-yl, isothiazol-yl, pyrrol-yl, quinolin-yl, isoquinolin-yl, indol-yl, benzimidazol-yl, benzofuran-yl, cinnolin-yl, indazol-yl, indolizin-yl, phthalazin-yl, pyridazin-yl, triazin-yl, isoindol-yl, pteridin-yl, purin-yl, oxadiazol-yl, triazol-yl, thiadiazol-yl, thiadiazol-yl, furazan-yl, benzofurazan-yl, benzothiophen-yl,

benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Spiro moieties are also included within the scope of this definition. Heteroaryl groups are optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, haloalkyl, aryl, heteroaryl, and hydroxy.

[0091] The term "halogen" represents fluorine, bromine, chlorine, and iodine.

[0092] The term "arylalkyl" means an alkyl moiety (as defined above) substituted with one or more aryl moiety (also as defined above). More preferred arylalkyl radicals are aryl-C₁₋₃-alkyls. Examples include benzyl, phenylethyl, and the like.

[0093] The term "heteroarylalkyl" means an alkyl moiety (as defined above) substituted with a heteroaryl moiety (also as defined above). More preferred heteroarylalkyl radicals are 5- or 6-membered heteroaryl-C₁₋₃-alkyls. Examples include oxazolymethyl, pyridylethyl and the like.

[0094] The term "heterocyclalkyl" means an alkyl moiety (as defined above) substituted with a heterocyclalkyl moiety (also defined above). More preferred heterocyclalkyl radicals are 5- or 6-membered heterocyclalkyl-C₁₋₃-alkyls. Examples include tetrahydropyranylmethyl.

[0095] The term "cycloalkylalkyl" means an alkyl moiety (as defined above) substituted with a cycloalkyl moiety (also defined above). More preferred heterocyclalkyl radicals are 5- or 6-membered cycloalkyl-C₁₋₃-alkyls. Examples include cyclopropylmethyl.

[0096] The term "Me" means methyl, "Et" means ethyl, "Bu" means butyl and "Ac" means acetyl.

[0097] The term "amino acid residue" includes, but is not limited to, the 20 naturally occurring amino acids commonly designated by three letter symbols, and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone.

[0098] In general, the various moieties or functional groups of the compounds of Formulas I-III may be optionally substituted by one or more substituents. Examples of substituents suitable for purposes of this invention include, but are not limited to, oxo (with the proviso that it is not on an aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -NR⁴SO₂R⁶, -SO₂NR³R⁴, -C(O)R³, -C(O)OR³, -OC(O)R³, -NR⁴C(O)OR⁶, -NR⁴C(O)R³, -C(O)NR³R⁴, -NR³R⁴, -NR⁵C(O)NR³R⁴,

$-\text{NR}^5\text{C}(\text{NCN})\text{NR}^3\text{R}^4$, $-\text{OR}^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, where R^3 , R^4 , R^5 and R^6 are as defined herein.

[0099] It is to be understood that in instances where two or more radicals are used in succession to define a substituent attached to a structure, the first named radical is considered to be terminal and the last named radical is considered to be attached to the structure in question. Thus, for example, the radical arylalkyl is attached to the structure in question by the alkyl group.

[00100] In the compounds of the present invention, where a term such as $(\text{CR}^4\text{R}^5)_m$ is used, R^4 and R^5 may vary with each iteration of m above 1. For instance, where m is 2, the term $(\text{CR}^4\text{R}^5)_m$ may equal $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)\text{C}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{CH}_2\text{CH}_3)-$ or any number of similar moieties falling within the scope of the definitions of R^4 and R^5 .

[00101] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers, diastereomers mixtures, racemic or otherwise, thereof. Accordingly, this invention also includes all such isomers, including diastereomeric mixtures and pure enantiomers of the Formulas I-III. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomer mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. The methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition, J. March, John Wiley and Sons, New York, 1992).

[00102] This invention also encompasses pharmaceutical compositions containing a compound of Formula I-III and methods of treating proliferative disorders, or abnormal cell growth, by administering compounds of the present invention. Compounds of the present invention having free amino, amido, hydroxy or carboxylic groups can be converted into pharmaceutically acceptable prodrugs.

[00103] A "pharmaceutically acceptable prodrug" is a compound that may be

converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. One preferred prodrug of this invention is a compound of Formula **I-III** covalently joined to a valine residue.

[00104] Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. As another example, compounds of this invention comprising free hydroxy groups may be derivatized as prodrugs by converting the hydroxy group groups including to a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl, as outlined in *Advanced Drug Delivery Reviews*, **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.*, **1996**, *39*, 10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[00105] Free amines can also be derivatized as amides, sulfonamides or phosphoramides. All of these prodrug moieties may incorporate groups including, but not limited to, ether, amine and carboxylic acid functionalities. For example, a prodrug can be

formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇)cycloalkyl, benzyl, or R-carbonyl is a natural α -aminoacyl or natural α -aminoacyl-natural α -aminoacyl, -C(OH)C(O)OY wherein Y is H, (C₁-C₆)alkyl or benzyl, -C(OY₀)Y₁ wherein Y₀ is (C₁-C₄) alkyl and Y₁ is (C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N- (C₁-C₆)alkylaminoalkyl, -C(Y₂)Y₃ wherein Y₂ is H or methyl and Y₃ is mono-N- or di-N,N-(C₁-C₆)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[00106] In addition, the invention also includes solvates, pharmaceutically active metabolites, and pharmaceutically acceptable salts of compounds of Formulas I-III.

[00107] The term "solvate" refers to an aggregate of a molecule with one or more solvent molecules.

[00108] A "pharmaceutically active metabolite" is a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein.

[00109] Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see, for example, a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) *A Textbook of Drug Design and Development*, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs," by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8, 1-38 (1992); d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, 77:285 (1988); and e) N. Kakeya, et al., *Chem. Pharm. Bull.*, 32: 692 (1984), each of which is specifically incorporated herein by reference.

[00110] A "pharmaceutically acceptable salt" as used herein, unless otherwise indicated, includes salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds

of the present invention with a mineral or organic acid or an inorganic base, such salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyn-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitromenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, pheylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycollates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. Since a single compound of the present invention may include more than one acidic or basic moieties, the compounds of the present invention may include mono, di or tri-salts in a single compound.

[00111] If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an acidic compound, particularly an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alphahydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[00112] If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base. Preferred inorganic salts are those formed with alkali and alkaline earth metals such as lithium, sodium, potassium, barium and calcium. Preferred organic base salts include, for example, ammonium, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylamine, dibenzylethylenediamine, and the like salts. Other salts of acidic moieties may include, for example, those salts formed with procaine, quinine and N-methylglucosamine, plus salts formed with basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine.

[00113] The inventive compounds may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available or can be synthesized using methods known in the art.

[00114] Illustrations of the preparation of compounds of the present invention are shown in Figures 1-5.

[00115] Figure 1 illustrates the synthesis of compounds of Formula I of the present invention. 2-Bromo-6-fluorobenzoic acid analog **2** can be prepared by deprotonation of 1-bromo-3-fluoro-benzene analog **1** with an amide base followed by quench with either solid or gaseous CO₂ in a suitable organic solvent such as THF, diethyl ether or MTBE at temperatures ranging from -78 °C to ambient temperature. Preferably, the benzoic acid **2** can be made by deprotonation with freshly prepared LDA at low temperature (-20 to -78 °C) in THF following by a solid CO₂ quench. Preparation of ester **3** is accomplished in a two-step procedure. In the first step, the appropriate aniline moiety can be incorporated by S_NAr reaction. This can be done in a suitable organic solvent such as THF using an amide base such as LDA, LiHMDS, NaHMDS or KHMDS at appropriate temperatures (-78 °C to room temperature). Preferably, the S_NAr addition is achieved by adding the benzoic acid **2** to a mixture of freshly prepared LDA and the appropriate aniline in THF at low temperature (-20 to -78 °C) and then allowing the reaction mixture to warm to room temperature.

[00116] With continued reference to Figure 1, the next step in the synthesis of compound **6** is a standard esterification, which can be achieved by standard methods including but not limited to Fisher esterification (MeOH, H₂SO₄), reaction with TMSCHN₂ or TMSCl in MeOH. The synthesis of keto acid derivative **4** can be accomplished in a three-step sequence. In the first step, palladium mediated alkyne cross-coupling reaction is used to generate the corresponding alkyne intermediate. This palladium mediated cross-coupling reaction can be achieved by standard methods including, but not limited to, treating bromide **3** with desired alkyne, a palladium catalyst such as Pd(OAc)₂ and Ph₃P, PdCl₂(dppf), Pd(Ph₃P)₂Cl₂, Pd(Ph₃P)₄, Pd₂dba₃ and Ph₃P, CuI, and amine base such as Et₃N, Et₂NH, or *i*-Pr₂NH, in a suitable organic solvent such as THF, DMF, PhMe, DME or MeCN at elevated temperature. More preferably, the bromide **3** and alkyne are treated with Pd(Ph₃P)₂Cl₂, CuI and amine base in THF or DMF at 50 to 100 °C. In the second step, the intermediate alkyne is hydrolysed to the corresponding ketone by standard methods including, but not limited to,

H₂SO₄, TFA, trifluorosulfonamide, FeCl₃ or HgSO₄/H₂SO₄. In the third step, the keto acid **4** is prepared by basic hydrolysis under standard conditions using either LiOH or NaOH in standard mixed aqueous/organic solvent systems. Dihydro-isoindol-1-one **5** can be prepared by treatment of the ketone with hydroxylamine followed by reduction under standard conditions including, but not limited to, Zn dust in AcOH, or H₂ and catalytic Pd/C or PtO₂, or Raney nickel. Preferably, this reduction can be accomplished with Zn dust in AcOH at elevated temperature (50 to 85 °C). To prepare derivatives where R⁸ is iodo or bromo, this can be accomplished at this stage under standard halogenation conditions including, but not limited to, NIS or NBS in DMF with or without catalytic aqueous acid. Alkylation of dihydro-isoindol-1-one **5** to form substituted dihydro-isoindol-1-one **6** can be accomplished by use of an alkylating agent such as an alkyl halide and base such as LiH, NaH, or K₂CO₃ in suitable organic solvent such as DMF, MeCN, or THF at temperatures ranging from 0 to 80 °C. Alternatively, substituted dihydro-isoindol-1-one **13** can be prepared directly from keto acid **4** under standard reduction amination conditions including, but not limited to, treatment with the appropriate amine, and reducing agent such as NaBH(OAc)₃, NaBH₃CN, or NaBH₄ with or without AcOH in a suitable organic solvent such as THF, methylene chloride, dichloroethane, MeCN or dioxane.

[00117] In Figure 2, preparation of compounds of the Formula **I** of the present invention is illustrated. Ester **7** can be prepared from bromide **3** by palladium mediated cross-coupling reaction with a variety of nucleophiles and palladium catalysts. Some of these methods include but not limited to Bu₃SnCHR¹⁰R²², Pd(PPh₃)₄ in PhMe, R¹⁰R²²CHB(OR)₂, Pd(PPh₃)₄ or PdCl₂(dppf) in dioxane or THF/water and K₂CO₃, R¹⁰R²²CHBF₃K, PdCl₂(dppf) in *i*-PrOH/water and *t*-BuNH₂, R¹⁰R²²CHZnR, PdCl₂(dppf) in dioxane or R¹⁰R²²CH-Al-R₂, PdCl₂(dppf) and CeCl₃ in THF. All of these cross-coupling reactions are run at elevated temperatures (50 to 120 °C). Dihydro-isoindol-1-one **6** can be prepared by bromination of ester **7** followed by treatment with ammonia or a primary amine. Bromination of ester **7** can be accomplished using standard conditions such as NBS in a suitable organic solvent. Cyclization to form dihydro-isoindol-1-one **6** can be achieved by treatment with ammonia or a primary amine in a suitable organic solvent at temperatures ranging from ambient to slightly elevated. Preferably, this cyclization is accomplished in an alcoholic solvent such as MeOH or EtOH. To prepare derivatives where R⁸ is iodo or bromo, this can be accomplished at this stage under standard halogenation conditions including, but not limited to, NIS or NBS

in DMF with or without catalytic aqueous acid.

[00118] Figure 3 illustrates the synthesis of compounds of Formula **II** of the present invention. Cyclization to form phthalazin-1-one **8** can be accomplished by treating ketone **4** with substituted or unsubstituted hydrazine in a suitable organic solvent such as EtOH, *i*-PrOH, DMF, DME or mixtures thereof at temperatures ranging from ambient temperature to about 100 °C. To prepare derivatives where R⁸ is iodo or bromo, this can be accomplished at this stage under standard halogenation conditions including, but not limited to, NIS or NBS in DMF with or without catalytic aqueous acid.

[00119] Figure 4 shows an alternative preparation of compounds of Formula **II** of the present invention. Aldehyde **9** can be formed in a two-step procedure from bromide **3**. In the first step, Suzuki type palladium mediated vinyl boronic acid cross-coupling reaction of bromide **3** gives the corresponding styrene derivative. This reaction can be accomplished with a variety of vinyl boronic acids and palladium catalysts in the presence of base in a suitable organic solvent such as PhMe, DME, DMF or THF at elevated temperature. Preferably, *trans*-2-phenylboronic acid is used with Pd(PPh₃)₄ and K₂CO₃ in a mixture of DME and water at temperatures ranging from 60 to 105 °C. In the second step, the aldehyde is prepared by standard oxidative conditions including, but not limited to, O₃/Me₂S, O₃/Ph₃P or OsO₄/NaIO₄. The aldehyde **9** can then be converted to phthalazin-1-one **8** by treatment with the appropriate hydrazine. To prepare derivatives where R⁸ is iodo or bromo, this can be accomplished at this stage under standard halogenation conditions including, but not limited to, NIS or NBS in DMF with or without catalytic aqueous acid.

[00120] In Figure 5, preparation of compounds of the Formula **III** of the present invention is illustrated. Hydrazide **10** can be prepared from bromide **3** by palladium mediated cross-coupling reaction. Preferably, this is accomplished by treatment of the bromide **3** with the appropriate *t*-butylcarbazate, Cs₂CO₃ and catalytic Pd₂(dba)₃/dppf in PhMe at elevated temperature. Removal of the BOC protecting group under standard acidic conditions such as TFA in methylene chloride or HCl in dioxane or diethyl ether generates dihydro-indazol-3-one **11**. To prepare derivatives where R⁸ is iodo or bromo, this can be accomplished at this stage under standard halogenation conditions including, but not limited to, NIS or NBS in DMF with or without catalytic aqueous acid. Alkylation of dihydro-indazol-3-one **11** to form substituted dihydro-indazol-3-one **12** can be accomplished by use of an alkylating agent such as an alkyl halide and base such as LiH, NaH, or K₂CO₃ in suitable

organic solvent such as DMF, MeCN, or THF at temperatures ranging from 0 to 80 °C.

[00121] The invention also relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for the treatment of cancer such as brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, esophageal, testicular, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

[00122] The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) or the treatment of pain in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

[00123] The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier.

[00124] The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease or other inflammatory condition such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00125] The invention also relates to a method of treating a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method relates to the treatment of cancer such as brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, esophageal, testicular, gynecological or thyroid cancer. In another embodiment, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign prostatic hypertrophy (BPH)).

[00126] The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[00127] The invention also relates to a method of treating pancreatitis or kidney disease in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

[00128] The invention also relates to a method of preventing blastocyte implantation in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

[00129] The invention also relates to a method of treating diseases related to vasculogenesis or angiogenesis in a mammal that comprises administering to said mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof. In one embodiment, said method is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic

retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

[00130] The invention also relates to a pharmaceutical composition for treating a disease or condition related to inflammatory disease, autoimmune disease, destructive bone disorders, proliferative disorders, infectious disease, viral disease, fibrotic disease or neurodegenerative disease in a mammal which comprises a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, prodrug or hydrate thereof, and a pharmaceutically acceptable carrier. Examples of the above diseases and/or conditions include but is not limited to rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, skin diseases such as psoriasis, eczema, and scleroderma, diabetes and diabetic complications, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, allergic responses including asthma allergic rhinitis and atopic dermatitis, renal disease and renal failure, polycystic kidney disease, acute coronary syndrome, congestive heart failure, osteoarthritis, neurofibromatosis, organ transplant rejection, cachexia and pain.

[00131] Patients that can be treated with compounds of the present invention, or pharmaceutically acceptable salts, prodrugs and hydrates of said compounds, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, restenosis, atherosclerosis, BPH, lung cancer, bone cancer, CMML, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, testicular, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

[00132] This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[00133] This invention further relates to a method for inhibiting abnormal cell growth in a mammal or treating a hyperproliferative disorder which method comprises administering to the mammal an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate or prodrug thereof, in combination with radiation therapy, wherein the amounts of the compound, salt, solvate, or prodrug, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

[00134] It is believed that the compounds of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present invention or pharmaceutically acceptable salt or solvate or prodrug thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

[00135] The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of the present invention, or a pharmaceutically acceptable salt or solvate thereof, a prodrug

thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

[00136] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172, WO 96/27583, EP 818442, EP 1004578, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, EP 606,046, EP 931788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO 99/07675, EP 945864, U.S. Patent No. 5,863,949, U.S. Patent No. 5,861,510, and EP 780,386, all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e., MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

[00137] The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application.

[00138] "Abnormal cell growth," as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes, for example, the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate by receptor tyrosine kinases; (4) any tumors that proliferate by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases in which aberrant serine/threonine kinase activation occurs.

[00139] The term "treating," as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment," as used herein, unless otherwise indicated, refers to the act of treating as

"treating" is defined immediately above.

[00140] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e. g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. "Treating" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is affected, at least in part, by the activity of MEK, and includes, but is not limited to, preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

[00141] In order to use a compound of the Formula **I-III** or a pharmaceutically acceptable salt or prodrug thereof, for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition that comprises a compound of the Formula **I-III**, or a pharmaceutically acceptable salt or prodrug thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

[00142] To prepare the pharmaceutical compositions according to this invention, a therapeutically or prophylactically effective amount of a compound of Formula **I-III** or a pharmaceutically acceptable salt, solvate, metabolite or prodrug thereof (alone or together with an additional therapeutic agent) is preferably intimately admixed with a pharmaceutically acceptable carrier according to conventional pharmaceutical compounding techniques to produce a dose. A carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. Examples of suitable carriers include any and all solvents, dispersion media, adjuvants, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, sweeteners, stabilizers (to promote long term storage), emulsifiers, binding agents, thickening agents, salts, preservatives, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, flavoring agents, and miscellaneous materials such as buffers and absorbents that may be needed in order to prepare a particular therapeutic composition. The use of such media and agents with pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with a compound of

Formula **I-III**, its use in the therapeutic compositions and preparations is contemplated. Supplementary active ingredients can also be incorporated into the compositions and preparations as described herein.

[00143] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing or as a suppository for rectal dosing). For example, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[00144] Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

[00145] Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

[00146] Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), coloring agents, flavoring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

[00147] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00148] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

[00149] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

[00150] Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

[00151] The pharmaceutical compositions may also be in the form of a sterile

injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

[00152] Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

[00153] Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

[00154] Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50 mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

[00155] Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

[00156] For further information on formulations, see Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990, which is specifically incorporated herein by reference.

[00157] The amount of a compound of this invention that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the subject treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an

effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day. For further information on routes of administration and dosage regimes, see Chapter 25.3 in Volume 5 of *Comprehensive Medicinal Chemistry* (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990, which is specifically incorporated herein by reference.

[00158] The size of the dose for therapeutic or prophylactic purposes of a compound of Formula **I-III** will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

[00159] The compounds of this invention may be used alone in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of MEK. Such treatment may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents:

[00160] (i) antiproliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example, cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); anti-metabolites (for example, antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, or, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid); antitumor antibiotics (for example, anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example, vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin):

[00161] (ii) cytostatic agents such as antiestrogens (for example, tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), estrogen receptor down regulators (for example, fulvestrant) antiandrogens (for example, bicalutamide, flutamide, nilutamide, cyproterone acetate and CasodexTM (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide)), LHRH antagonists or LHRH agonists (for example, goserelin, leuporelin and buserelin), progestogens (for example, megestrol acetate), aromatase inhibitors (for example, asanastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

[00162] (iii) agents which inhibit cancer cell invasion (for example, metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

[00163] (iv) inhibitors of growth factor function like growth factor antibodies, growth factor receptor antibodies (for example, the anti-erbB2 antibody trastuzumab [HerceptinTM] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine-threonine kinase inhibitors (for example, inhibitors of the epidermal growth factor family tyrosine kinases such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), inhibitors of the platelet-derived growth factor family and inhibitors of the hepatocyte growth factor family;

[00164] (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor (for example, the anti-vascular endothelial cell growth factor antibody bevacizumab [AvastinTM], compounds such as those disclosed in PCT Publication Nos. WO 97/22596, WO 97/30035, WO 97/32856, and WO 98/13354) and compounds that work by other mechanisms (for example, linomide, inhibitors of integrin $\alpha v \beta 3$ function, MMP inhibitors, COX-2 inhibitors and angiostatin);

[00165] (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in PCT Publication Nos. WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434, and WO 02/08213;

[00166] (vii) antisense therapies (for example, those which are directed to the targets listed above such as ISIS 2503, and anti-ras antisense);

[00167] (viii) gene therapy approaches, including for example GVAXTM, approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;

[00168] (ix) interferon; and

[00169] (x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches to using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies.

[00170] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment. Such combination products employ the compounds of this invention within the dose range described hereinbefore and the other pharmaceutically active agent within its approved dose range.

[00171] According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of Formula I-III as defined hereinbefore and an additional anti-tumor agent as defined hereinbefore for the conjoint treatment of cancer.

[00172] Although the compounds of Formula I-III are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of MEK. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

[00173] The activity of the compounds of the present invention may be determined by the following procedure. N-terminal 6 His-tagged, constitutively active MEK-1 (2-393) is expressed in *E. coli* and protein is purified by conventional methods (*Ahn et al., Science* 1994, 265, 966-970). The activity of MEK1 is assessed by measuring the incorporation of γ -³³P-phosphate from γ -³³P-ATP onto N-terminal His tagged ERK2, which is expressed in *E. coli* and is purified by conventional methods, in the presence of MEK-1. The assay is carried out in 96-well polypropylene plate. The incubation mixture (100 μ L) comprises of 25 mM Hepes, pH 7.4, 10 mM MgCl₂, 5 mM β -glycerolphosphate, 100 μ M Na-orthovanadate, 5 mM

DTT, 5 nM MEK1, and 1 μ M ERK2. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1% DMSO. Reactions are initiated by the addition of 10 μ M ATP (with 0.5 μ Ci γ - 33 P-ATP/well) and incubated at ambient temperature for 45 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP washed off using a Tomtec MACH III harvester. Plates are allowed to air-dry prior to adding 30 μ L/well of Packard Microscint 20, and plates are counted using a Packard TopCount. In this assay, compounds of the invention exhibited an IC_{50} of less than 50 micromolar.

[00174] Representative compounds of the present invention, which are encompassed by the present invention include, but are not limited to the compounds of the examples and their pharmaceutically acceptable acid or base addition salts or prodrugs thereof. The examples presented below are intended to illustrate particular embodiments of the invention, and are not intended to limit the scope of the specification or the claims in any way.

[00175] The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

EXAMPLES

[00176] In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other MEK inhibitors of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[00177] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further

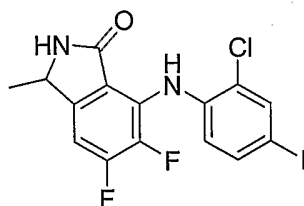
purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane, toluene, dioxane and 1,2-difluoroethane were purchased from Aldrich in Sure seal bottles and used as received.

[00178] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00179] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters).

[00180] ¹H-NMR spectra were recorded on a Varian instrument operating at 400 MHz. ¹H-NMR spectra were obtained as CDCl₃ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Example 1



7-(2-Chloro-4-iodophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one

[00181] Step A: Preparation of 6-bromo-2,3,4-trifluorobenzoic acid. To a solution of i-Pr₂NH (3.65 mL, 25.8 mmol) in THF (50 mL) was added n-BuLi (10.3 mL, 25.8 mmol, 2.50 M solution in hexanes) at 0 °C. After stirring for 15 minutes, the reaction mixture was cooled to -78 °C. A solution of 5-bromo-1,2,3-trifluorobenzene (5.00 g, 23.7 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 2 hours at -78 °C, poured into an excess of freshly crushed dry ice, and stirred for 30 minutes. To this mixture was added 10% aqueous HCl to adjust its pH to 1. The resulting mixture was extracted with ether (3x). The combined organic layers were washed with 5% aqueous NaOH (2x). The combined basic aqueous layers were acidified to pH 1 with concentrated HCl, and extracted with ether (2x). The combined organic layers were washed with water, dried over MgSO₄, filtered, and

concentrated *in vacuo* to give the desired product (5.06 g, 84%) that was used directly without further purification.

[00182] Step B: Preparation of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid. To a solution of *i*-Pr₂NH (5.83 mL, 41.2 mmol) in THF (16 mL) at 0 °C was added *n*-BuLi (16.4 mL, 41.1 mmol, 2.5 M solution in hexanes). After stirring for 15 minutes, the reaction mixture was cooled to -78 °C. 2-Chloroaniline (2.89 mL, 27.5 mmol) was added. After vigorous stirring for 10 minutes, a solution of 6-bromo-2,3,4-trifluorobenzoic acid (3.51 g, 13.8 mmol) in THF (4 mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 hours at room temperature. The reaction mixture was concentrated, treated with 10% aqueous HCl (15 mL) until the aqueous phase was acidic, and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude material that was triturated three times with boiling CH₂Cl₂ to afford the desired product (3.18 g, 64%).

[00183] Step C: Preparation of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester. To a solution of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid (3.18 g, 8.77 mmol) in THF-MeOH (16 mL/5 mL) was added TMSCHN₂ (5.30 mL, 10.6 mmol, 2M solution in hexanes) at room temperature. The resulting mixture was stirred for 1 hour, quenched with AcOH, and diluted with EtOAc. The organic layer was washed with water, saturated NaHCO₃ (2x), and brine. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the desired product (3.31 g, 100%) that was used directly without further purification.

[00184] Step D: Preparation of 2-(2-chlorophenylamino)-3,4-difluoro-6-trimethylsilanylethynyl-benzoic acid methyl ester. A mixture of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester (2.61 g, 6.93 mmol), TMS-acetylene (1.18 mL, 8.32 mmol), Pd(PPh₃)₂Cl₂ (496 mg, 0.693 mmol), CuI (132 mg, 0.693 mmol), and *i*-Pr₂NH (1.95 mL, 13.9 mmol) in THF (11 mL) was stirred for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, and washed with saturated aqueous NH₄Cl and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to give the crude material that was purified by silica gel flash column chromatography (100% hexanes to 1% to 2% EtOAc in hexanes) to afford the desired product (2.15 g, 79%).

[00185] Step E: Preparation of 6-acetyl-2-(2-chlorophenylamino)-3,4-difluorobenzoic

acid methyl ester. A mixture of 2-(2-chlorophenylamino)-3,4-difluoro-6-trimethylsilanylethynylbenzoic acid methyl ester (1.00 g, 2.54 mmol), HgSO₄ (761 mg, 2.54 mmol), and concentrated H₂SO₄ (0.27 mL) in acetone-water (22 mL/4 mL) was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc-THF, and washed with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated to give the crude material that was purified by silica gel flash column chromatography (8% EtOAc in hexanes) to afford the desired product (496 mg, 58%).

[00186] Step F: Preparation of 6-acetyl-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid. To a solution of 6-acetyl-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester (200 mg, 0.59 mmol) in THF-water (2 mL/0.5 mL) was added 1 M aqueous LiOH (1.21 mL, 1.21 mmol) at room temperature. The reaction mixture was stirred for 30 minutes, acidified to pH 1 with 1 N aqueous HCl, and extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo* to give the desired acid (166 mg, 86%) that was used directly without further purification.

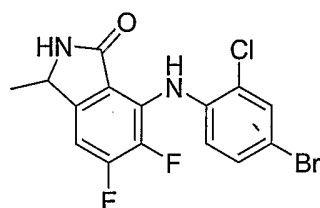
[00187] Step G: Preparation of 8-(2-chlorophenylamino)-6,7-difluoro-4-methylbenzo[d][1,2]oxazin-1-one. To a solution of 6-acetyl-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid (50 mg, 0.15 mmol) and hydroxylamine hydrochloride (11 mg, 0.15 mmol) in MeOH-H₂O (1 mL/0.5 mL) was added TEA (0.022 mL, 0.15 mmol) at room temperature. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude material that was purified by silica gel flash column chromatography (100% CH₂Cl₂) to afford the desired product (26.8 mg, 54%).

[00188] Step H: Preparation of 7-(2-chlorophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one. A mixture solution of 8-(2-chlorophenylamino)-6,7-difluoro-4-methyl-benzo[d][1,2]oxazin-1-one (26 mg, 0.079 mmol) and Zn (30 mg, 0.46 mmol) in AcOH (2 mL) was heated for 1 hour at 85 °C. The reaction mixture was filtered and the solid was washed with additional AcOH. The filtrate was concentrated *in vacuo*, diluted with EtOAc, and washed with saturated aqueous NaHCO₃ and water. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the desired product (18 mg, 74%) that was used directly without further purification.

[00189] Step I: Preparation of 7-(2-chloro-4-iodophenylamino)-5,6-difluoro-3-methyl-

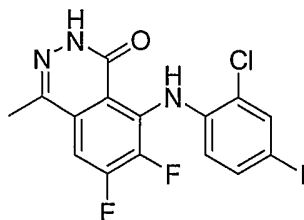
2,3-dihydro-isoindol-1-one. A solution of 7-(2-chlorophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one (18 mg, 0.059 mmol), NIS (17 mg, 0.074 mmol), and p-TsOH-H₂O (24 mg, 0.12 mmol) in THF-MeOH (1 mL/1 mL) was stirred for 1 hour at room temperature. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaHCO₃ and water. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude material that was purified by silica gel flash column chromatography (100% CH₂Cl₂ to 1% MeOH in CH₂Cl₂) to afford 7-(2-chloro-4-iodophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one (5.4 mg, 21%). MS APCI (-) *m/z* 433, 435 (M-, Cl pattern) detected; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 7.70 (d, 1H), 7.48 (dd, 1H), 6.75 (m, 2H), 6.04 (s, 1H), 4.63 (q, 1H), 1.49 (d, 3H).

Example 2



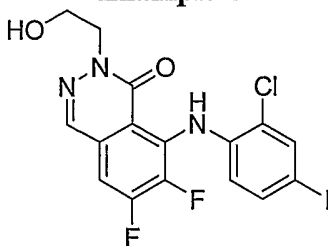
7-(4-Bromo-2-chlorophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one

[00190] A mixture of 7-(2-chlorophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one (68 mg, 0.22 mmol, prepared by the procedures described in Example 1) and NBS (46 mg, 0.26 mmol) in DMF (2 mL) was stirred for 3 hours at room temperature. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude material which was purified by silica gel flash column chromatography (100% hexanes to 25% EtOAc in hexanes) to afford 7-(4-bromo-2-chlorophenylamino)-5,6-difluoro-3-methyl-2,3-dihydro-isoindol-1-one (40 mg, 47%). MS APCI (-) *m/z* 385, 387 (M-, Br, Cl pattern) detected; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 7.54 (d, 1H), 7.31 (dd, 1H), 6.89 (t, 1H), 6.75 (dd, 1H), 6.05 (s, 1H), 4.63 (q, 1H), 1.49 (d, 3H).

Example 3**8-(2-Chloro-4-iodophenylamino)-6,7-difluoro-4-methyl-2H-phthalazin-1-one**

[00191] Step A: Preparation of 8-(2-chlorophenylamino)-6,7-difluoro-4-methyl-2H-phthalazin-1-one. To a solution of 6-acetyl-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid (62 mg, 0.19 mmol, prepared by the procedures described in Example 1) and hydrazine monohydrate (0.031 mL, 0.63 mmol) in THF (3 mL) was added catalytic amount of 1 N aqueous HCl (0.15 mL, 0.15 mmol) at room temperature. After stirring for 16 hours at room temperature, the reaction mixture was diluted with EtOAc, and washed with water (2x) and brine. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the desired product (53 mg, 86%) that was used directly without further purification.

[00192] Step B: Preparation of 8-(2-chloro-4-iodophenylamino)-6,7-difluoro-4-methyl-2H-phthalazin-1-one. A mixture of 8-(2-chlorophenylamino)-6,7-difluoro-4-methyl-2H-phthalazin-1-one (30 mg, 0.093 mmol) and NIS (24 mg, 0.11 mmol) in AcOH-THF (2 mL/0.5 mL) was heated at 85 °C for 3 minutes. The reaction mixture was concentrated *in vacuo* and washed with water. The organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude material that was purified by silica gel flash column chromatography (100% hexanes to 15% EtOAc in hexanes) to afford 8-(2-chloro-4-iodophenylamino)-6,7-difluoro-4-methyl-2H-phthalazin-1-one (7.7 mg, 17%). MS APCI (-) *m/z* 446, 448 (M⁻, Cl pattern) detected; ¹H NMR (400 MHz, DMSO-d₆) δ 12.74 (s, 1H), 10.96 (s, 1H), 7.86 (s, 1H), 7.60 (d, 1H), 7.53 (dd, 1H), 6.94 (t, 1H), 2.47 (s, 3H).

Example 4

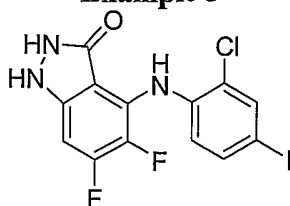
8-(2-Chloro-4-iodophenylamino)-6,7-difluoro-2-(2-hydroxy-ethyl)-2H-phthalazin-1-one

[00193] Step A: Preparation of 2-(2-chlorophenylamino)-3,4-difluoro-6-styryl-benzoic acid methyl ester: Pd(PPh₃)₄ (0.313 g, 0.271 mmol) and *trans*-2-phenylvinylboronic acid (1.105 g, 7.468 mmol) were added to a mixture of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester (2.00 g, 5.31 mmol) in 35 mL DME and 8 mL 2.0 M aqueous K₂CO₃ solution. The reaction mixture was heated under a N₂ atmosphere to 90 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and water and the layers separated. The organic layer was dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography gave 1.20 g (56%) clean desired product.

[00194] Step B: Preparation of 2-(2-chlorophenylamino)-3,4-difluoro-6-formylbenzoic acid methyl ester: A mixture of 2-(2-chlorophenylamino)-3,4-difluoro-6-styrylbenzoic acid methyl ester (1.20 g, 3.00 mmol), 2.5% OsO₄ solution in *t*-BuOH (2.0 mL, 0.165 mmol) and NMO (0.435 g, 3.60 mmol) in 30 mL of 1:1 THF/water was stirred for 1 hour. Sodium periodate (0.963 g, 4.50 mmol) was added. After 1 hour, the reaction mixture was diluted with ethyl acetate and water and the layers separated. The organic layer was dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (1:1 methylene chloride/hexanes) gave 0.406 g (42%) pure desired product.

[00195] Step C: Preparation of 8-(2-chlorophenylamino)-6,7-difluoro-2-(2-hydroxyethyl)-2H-phthalazin-1-one: A mixture of 2-(2-chlorophenylamino)-3,4-difluoro-6-formyl benzoic acid methyl ester (0.400 mg, 1.228 mmol) and 2-hydroxyethyl hydrazine (0.102 mL, 1.351 mmol) in EtOH (10 mL) was heated at reflux under N₂ for 16 hours. After cooling to room temperature, a yellow precipitate formed which was collected by filtration. The yellow solid was washed with EtOH and dried to yield 0.128 g (30%) pure desired product.

[00196] Step D: 8-(2-Chloro-4-iodophenylamino)-6,7-difluoro-2-(2-hydroxyethyl)-2H-phthalazin-1-one was prepared from 8-(2-chlorophenylamino)-6,7-difluoro-2-(2-hydroxyethyl)-2H-phthalazin-1-one by the method described in Step B of Example 3. MS APCI (-) *m/z* 476, 478 (M-, Cl pattern) detected; ¹H NMR (400 MHz, CDCl₃) δ 10.90 (s, 1H), 8.39 (s, 1H), 7.43 (d, 1H), 7.22 (t, 1H), 7.07 (m, 2H), 4.42 (t, 2H), 4.08 (t, 2H).

Example 5**4-(2-Chloro-4-iodophenylamino)-5,6-difluoro-1,2-dihydro-indazol-3-one**

[00197] Step A: Preparation of 6-(N'-tert-butoxycarbonyl-hydrazino)-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester: $\text{Pd}_2(\text{dba})_3$ (4 mol %), *t*-butylcarbazate (4.00 equivalents), dppf (12 mol %) and Cs_2CO_3 (1.00 equivalent) are added to a solution of 6-bromo-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester (1.00 equivalent) in PhMe. The reaction mixture is heated in a sealed vial charged under a N_2 atmosphere to 100 °C and stirred for 16 hours. After cooling to room temperature, the reaction mixture is diluted with methylene chloride and filtered. The filtrate is concentrated under reduced pressure. The product is purified by trituration or flash column chromatography if further purification is necessary.

[00198] Step B: Preparation of 4-(2-chlorophenylamino)-5,6-difluoro-1,2-dihydroindazol-3-one: 6-(N'-tert-Butoxycarbonylhydrazino)-2-(2-chlorophenylamino)-3,4-difluorobenzoic acid methyl ester (1.00 equivalent) is treated with a 1:1 mixture of methylene chloride and TFA and stirred for 2 hours. The reaction mixture is concentrated under reduced pressure and the product is purified by trituration or flash column chromatography if needed.

[00199] Step C: 4-(2-Chloro-4-iodophenylamino)-5,6-difluoro-1,2-dihydro-indazol-3-one is prepared from 4-(2-chlorophenylamino)-5,6-difluoro-1,2-dihydro-indazol-3-one by the method described in Step B of Example 3.

[00200] The foregoing description is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will be readily apparent to those skilled in the art, it is not desired to limit the invention to the exact construction and process shown as described above. Accordingly, all suitable modifications and equivalents may be resorted to falling within the scope of the invention as defined by the claims that follow.

[00201] The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the

presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

R^7 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^{10} and R^{22} are independently hydrogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-C(O)R^3$, $-C(O)OR^3$, $-SO_2NR^3R^4$, $-C(O)NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1-C_6 \text{ alkyl})$, $-S(O)_j(CR^4R^5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl,

or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^6 is trifluoromethyl, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the

proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclalkyl;

m is 0, 1, 2, 3, 4 or 5;

n is 1 or 2; and

j is 0, 1 or 2.

2. The compound of claim 1, where R^9 is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl.

3. The compound of claim 2, where R^7 is $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl or $\text{C}_2\text{-C}_4$ alkynyl, wherein any of said $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl and $\text{C}_2\text{-C}_4$ alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_3\text{-C}_6$ heterocycloalkyl, NR^3R^4 and OR^3 .

4. The compound of claim 3, where R^{10} and R^{22} are independently $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl or $\text{C}_2\text{-C}_4$ alkynyl, wherein any of said $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl and $\text{C}_2\text{-C}_4$ alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl,

methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³.

5. The compound of claim 4, where R¹ and R² are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl; and R⁸ is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethyl, ethoxy or SR¹¹.

6. The compound of claim 5, where R¹ is halogen or methyl, R² is hydrogen and R⁸ is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or SR¹¹.

7. The compound of claim 6, where R¹ is halogen, R⁸ is halogen, R⁹ is alkyl or halogen, and R² is in the position adjacent to Y, wherein R² is hydrogen.

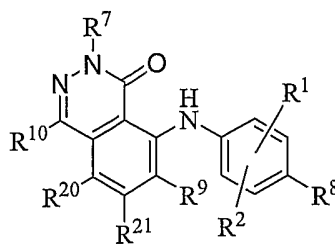
8. A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

9. A method of inhibiting MEK activity in a mammal comprising administering to said mammal one or more compounds of claim 1 in an amount effective to inhibit said MEK activity.

10. A method for treatment of a hyperproliferative disorder in a mammal comprising administering to said mammal one or more compounds of claim 1 in an amount effective to treat said hyperproliferative disorder.

11. A method for treatment of an inflammatory condition in a mammal comprising administering to said mammal one or more compounds of claim 1 in an amount effective to treat said inflammatory condition.

12. A compound including resolved enantiomers, diastereomers, solvates and pharmaceutically acceptable salts thereof, said compound having the Formula II:



II

where:

R^1 , R^2 , R^8 , R^9 , R^{10} , R^{20} and R^{21} are independently hydrogen, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy difluoromethoxy, trifluoromethoxy, azido, $-SR^{11}$, $-OR^3$, $-C(O)R^3$, $-C(O)OR^3$, $-NR^4C(O)OR^6$, $-OC(O)R^3$, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1$ - C_6 alkyl), $-S(O)_j(CR^4R^5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-O(CR^4R^5)_m$ -aryl, $-NR^4(CR^4R^5)_m$ -aryl, $-O(CR^4R^5)_m$ -heteroaryl, $-NR^4(CR^4R^5)_m$ -heteroaryl, $-O(CR^4R^5)_m$ -heterocyclyl or $-NR^4(CR^4R^5)_m$ -heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^7 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it

is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl,

or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic,

heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^6 is trifluoromethyl, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

m is 0, 1, 2, 3, 4 or 5; and

j is 0, 1 or 2.

13. The compound of claim 12, where R^9 is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl.

14. The compound of claim 13, where R^7 is $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl or $\text{C}_2\text{-C}_4$ alkynyl, wherein any of said $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl and $\text{C}_2\text{-C}_4$ alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy,

cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³.

15. The compound of claim 14, where R¹⁰ is independently C₁-C₄ alkyl, C₂-C₄ alkenyl or C₂-C₄ alkynyl, wherein any of said C₁-C₄ alkyl, C₂-C₄ alkenyl and C₂-C₄ alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³.

16. The compound of claim 15, where R¹ and R² are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl; and R⁸ is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethyl, ethoxy or SR¹¹.

17. The compound of claim 16, where R¹ is halogen or methyl, R² is hydrogen and R⁸ is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or SR¹¹.

18. The compound of claim 17, where R¹ is halogen, R⁸ is halogen, R⁹ is alkyl or halogen, and R² is in the position adjacent to Y, wherein R² is hydrogen.

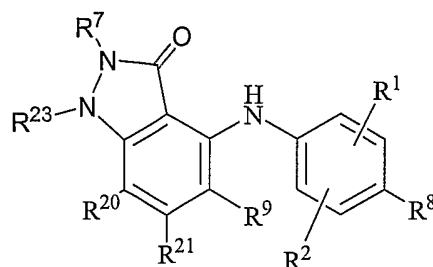
19. A composition comprising a compound of claim 12 and a pharmaceutically acceptable carrier.

20. A method of inhibiting MEK activity in a mammal comprising administering to said mammal one or more compounds of claim 12 in an amount effective to inhibit said MEK activity.

21. A method for treatment of a hyperproliferative disorder in a mammal comprising administering to said mammal one or more compounds of claim 12 in an amount effective to treat said hyperproliferative disorder.

22. A method for treatment of an inflammatory condition in a mammal comprising administering to said mammal one or more compounds of claim 12 in an amount effective to treat said inflammatory condition.

23. A compound including resolved enantiomers, diastereomers, solvates and pharmaceutically acceptable salts thereof, said compound having the Formula III:



III

and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein:

R^1 , R^2 , R^8 , R^9 , R^{20} and R^{21} are independently hydrogen, hydroxy, halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-SR^{11}$, $-OR^3$, $-C(O)R^3$, $-C(O)OR^3$, $-NR^4C(O)OR^6$, $-OC(O)R^3$, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-NR^3R^4$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, $-S(O)_j(C_1$ - C_6 alkyl), $-S(O)_j(CR^4R^5)_m$ -aryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-O(CR^4R^5)_m$ -aryl, $-NR^4(CR^4R^5)_m$ -aryl, $-O(CR^4R^5)_m$ -heteroaryl, $-NR^4(CR^4R^5)_m$ -heteroaryl, $-O(CR^4R^5)_m$ -heterocyclyl or $-NR^4(CR^4R^5)_m$ -heterocyclyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^4SO_2R^6$, $-SO_2NR^3R^4$, $-C(O)R^3$, $-C(O)OR^3$, $-OC(O)R^3$, $-NR^4C(O)OR^6$, $-NR^4C(O)R^3$, $-C(O)NR^3R^4$, $-NR^3R^4$, $-NR^5C(O)NR^3R^4$, $-NR^5C(NCN)NR^3R^4$, $-OR^3$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^7 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, OR^3 , NR^3R^4 , aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^{23} is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, or heterocyclylalkyl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethyl, fluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl, and wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be further substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 ;

R^3 is hydrogen, trifluoromethyl, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, phosphate or an amino acid residue, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

or R^3 and R^4 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said carbocyclic, heteroaryl or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^4 and R^5 independently are hydrogen or C_1 - C_6 alkyl, or

R^4 and R^5 together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein said alkyl or any of said carbocyclic, heteroaryl and heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-NR^{11}SO_2R^{14}$, $-SO_2NR^{11}R^{12}$, $-C(O)R^{11}$, $C(O)OR^{11}$, $-OC(O)R^{11}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, $-SR^{11}$, $-S(O)R^{14}$, $-SO_2R^{14}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-NR^{11}C(NCN)NR^{12}R^{13}$, $-OR^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^6 is trifluoromethyl, C_1 - C_{10} alkyl, C_3 - C_{10} cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl, wherein any of said alkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl and heterocyclylalkyl portions are optionally substituted with one or more groups independently selected from oxo (with the

proviso that it is not substituted on a aryl or heteroaryl), halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, $-\text{NR}^{11}\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{O})\text{OR}^{11}$, $-\text{OC}(\text{O})\text{R}^{11}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$, $-\text{NR}^{11}\text{C}(\text{NCN})\text{NR}^{12}\text{R}^{13}$, $-\text{OR}^{11}$, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

R^{11} , R^{12} and R^{13} independently are hydrogen, lower alkyl, lower alkenyl, aryl or arylalkyl, and R^{14} is lower alkyl, lower alkenyl, aryl or arylalkyl;

or any two of R^{11} , R^{12} , R^{13} or R^{14} together with the atom to which they are attached form a 4 to 10 membered carbocyclic, heteroaryl or heterocyclic ring, wherein any of said alkyl, alkenyl, aryl, arylalkyl carbocyclic rings, heteroaryl rings or heterocyclic rings are optionally substituted with one or more groups independently selected from halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, aryl, heteroaryl, arylalkyl, heteroarylalkyl, heterocyclyl, and heterocyclylalkyl;

m is 0, 1, 2, 3, 4 or 5; and

j is 0, 1 or 2.

24. The compound of claim 23, where R^9 is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl.

25. The compound of claim 24, where R^7 is C_1 - C_4 alkyl, C_2 - C_4 alkenyl or C_2 - C_4 alkynyl, wherein any of said C_1 - C_4 alkyl, C_2 - C_4 alkenyl and C_2 - C_4 alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 heterocycloalkyl, NR^3R^4 and OR^3 .

26. The compound of claim 25, where R^{23} is independently C_1 - C_4 alkyl, C_2 - C_4 alkenyl or C_2 - C_4 alkynyl, wherein any of said C_1 - C_4 alkyl, C_2 - C_4 alkenyl and C_2 - C_4 alkynyl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl,

diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl rings may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, azido, fluoromethyl, difluoromethyl, trifluoromethyl, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, NR³R⁴ and OR³.

27. The compound of claim 26, where R¹ and R² are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl; and R⁸ is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethyl, ethoxy or SR¹¹.

28. The compound of claim 27, where R¹ is halogen or methyl, R² is hydrogen and R⁸ is hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or SR¹¹.

29. The compound of claim 28, where R¹ is halogen, R⁸ is halogen, R⁹ is alkyl or halogen, and R² is in the position adjacent to Y, wherein R² is hydrogen.

30. A composition comprising a compound of claim 23 and a pharmaceutically acceptable carrier.

31. A method of inhibiting MEK activity in a mammal comprising administering to said mammal one or more compounds of claim 23 in an amount effective to inhibit said MEK activity.

32. A method for treatment of a hyperproliferative disorder in a mammal comprising administering to said mammal one or more compounds of claim 23 in an amount effective to treat said hyperproliferative disorder.

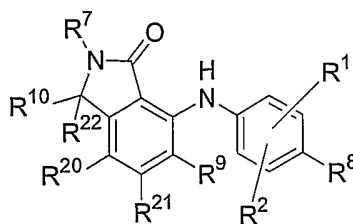
33. A method for treatment of an inflammatory condition in a mammal comprising administering to said mammal one or more compounds of claim 23 in an amount effective to treat said inflammatory condition.

34. A compound according to any one of claims 1, 12, and 23 for use as a medicament.

35. A compound according to any one of claims 1, 12, and 23 for use as a medicament for the treatment of a hyperproliferative disorder or an inflammatory condition.

36. The use of a compound according to any one of claims 1, 12, and 23 in the manufacture of a medicament for the treatment of a hyperproliferative disorder or an inflammatory condition.

37. A method for preparing a compound of formula 6



6

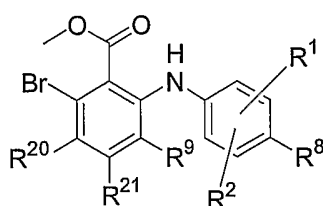
wherein

R^1 , R^2 and R^9 are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^7 , R^{10} , R^{20} , R^{21} and R^{22} are independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, amino, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

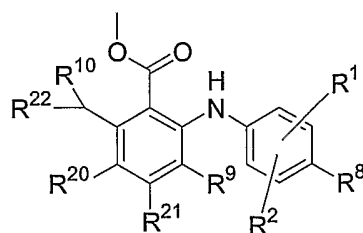
R^8 is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, SR^1 , ethyl, or ethoxy; said method comprising:

(a) reacting a compound of formula 3



3

with an appropriate nucleophile to provide a compound of formula 7

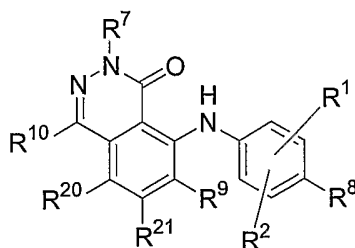


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; and

(b) reacting a compound of formula 7 with a brominating agent followed by an amine to provide a compound of formula 6.

38. A method for preparing a compound of formula 8



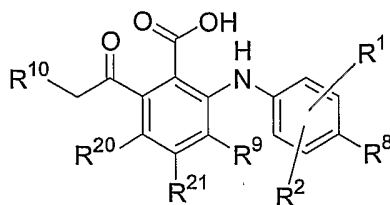
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wherein

R^1 , R^2 and R^9 are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^7 , R^{10} , R^{20} and R^{21} are independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, amino, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

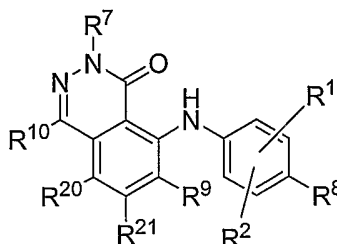
R^8 is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, SR^1 , ethyl, or ethoxy; said method comprising reacting a compound of formula 4



4

with a hydrazine to provide a compound of formula 8.

39. A method for preparing a compound of formula 8



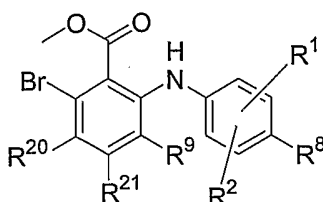
wherein

R^1 , R^2 and R^9 are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^7 , R^{10} , R^{20} and R^{21} are independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, amino, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

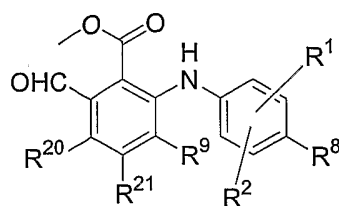
R^8 is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, SR^1 , ethyl, or ethoxy; said method comprising:

(a) reacting a compound of formula 3



3

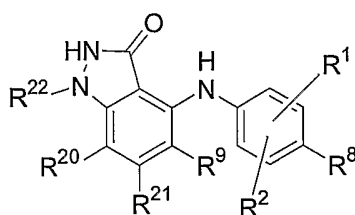
with a vinyl boronic acid derivative to provide a compound of formula 9



9 ; and

(b) reacting a compound of formula 9 with a hydrazine to provide a compound of formula 8.

40. A method for preparing a compound of formula 11



11

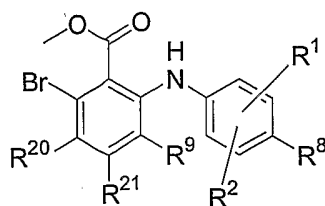
wherein

R^1 , R^2 and R^9 are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

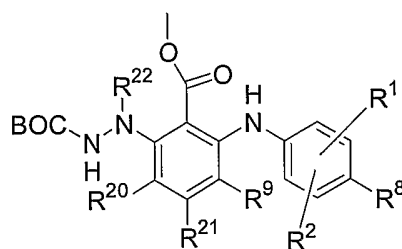
R^{20} , R^{21} and R^{22} are independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, amino, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

R^8 is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, SR^1 , ethyl, or ethoxy; said method comprising:

(a) reacting a compound of formula 3

**3**

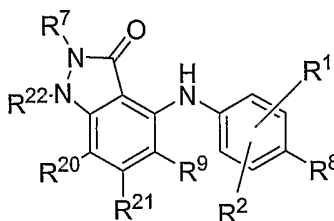
with a carbazate to provide a compound of formula **10**

**10**

; and

(b) deprotecting a compound of formula **10** to provide a compound of formula **11**.

41. A method for preparing a compound of formula **12**

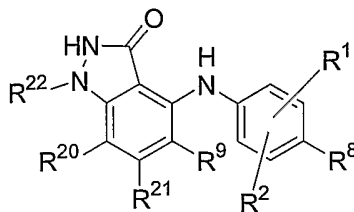
**12**

wherein

R^1 , R^2 and R^9 are independently hydrogen, halogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^7 , R^{20} , R^{21} and R^{22} are independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein any of said alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be optionally substituted with one or more groups independently selected from halogen, hydroxyl, cyano, nitro, amino, azido, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, ethoxy, cycloalkyl, heterocycloalkyl, aryl or heteroaryl; and

R^8 is halogen, hydroxyl, cyano, nitro, azido, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, amino, aminomethyl, dimethylamino, aminoethyl, diethylamino, SR^1 , ethyl, or ethoxy; said method comprising reacting a compound of formula **11**

**11**

with an alkylating agent to provide a compound of formula **12**.

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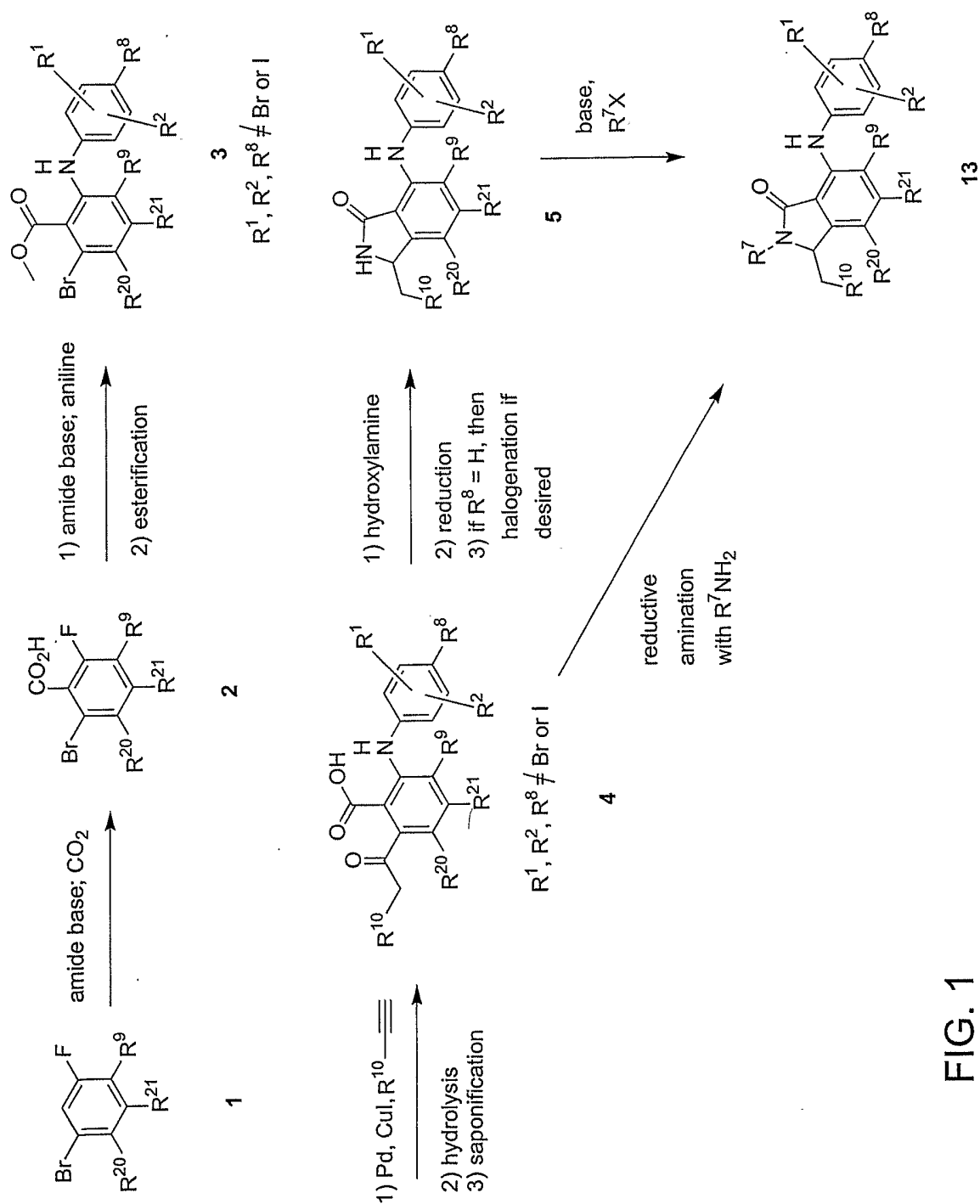


FIG. 1

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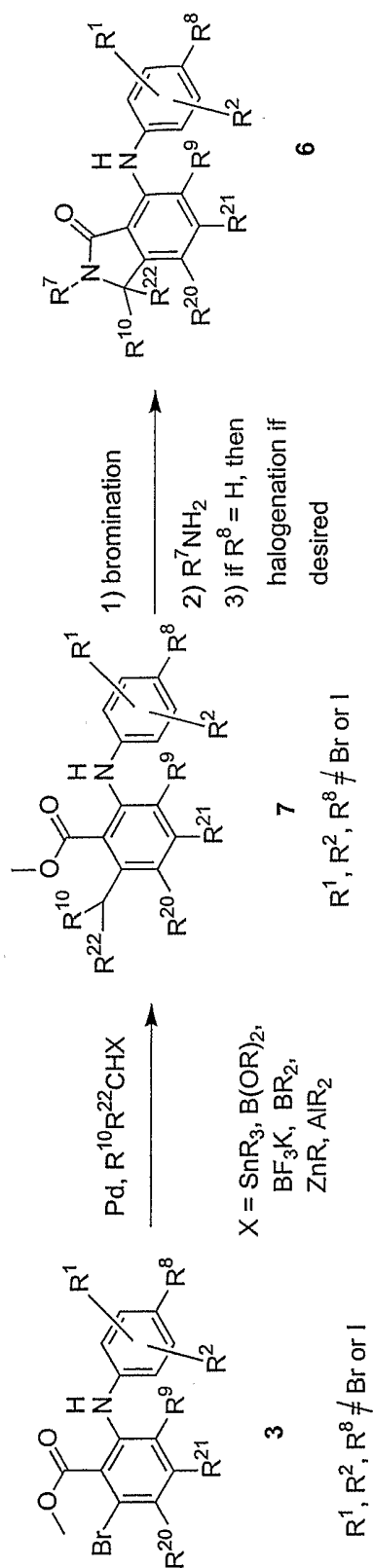
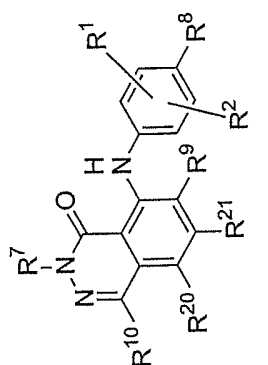
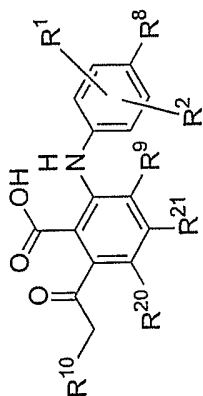
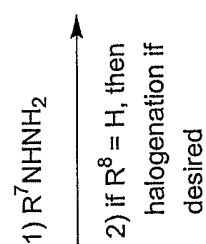


FIG. 2

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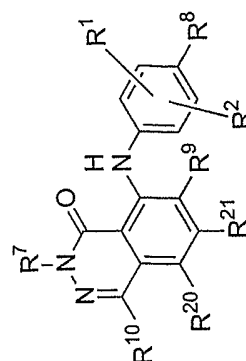
8



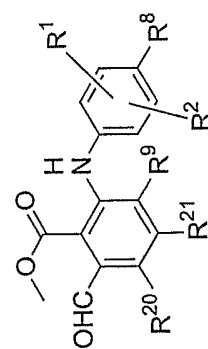
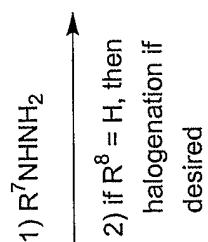
4

 $R^1, R^2, R^8 \neq \text{Br or I}$

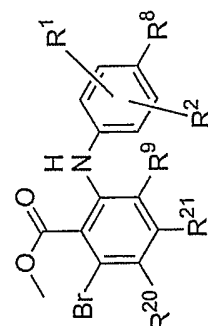
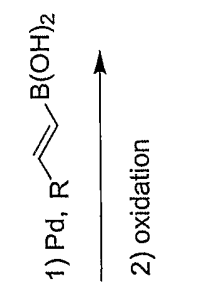
FIG. 3



8



9



3

 $R^1, R^2, R^8 \neq \text{Br or I}$

FIG. 4

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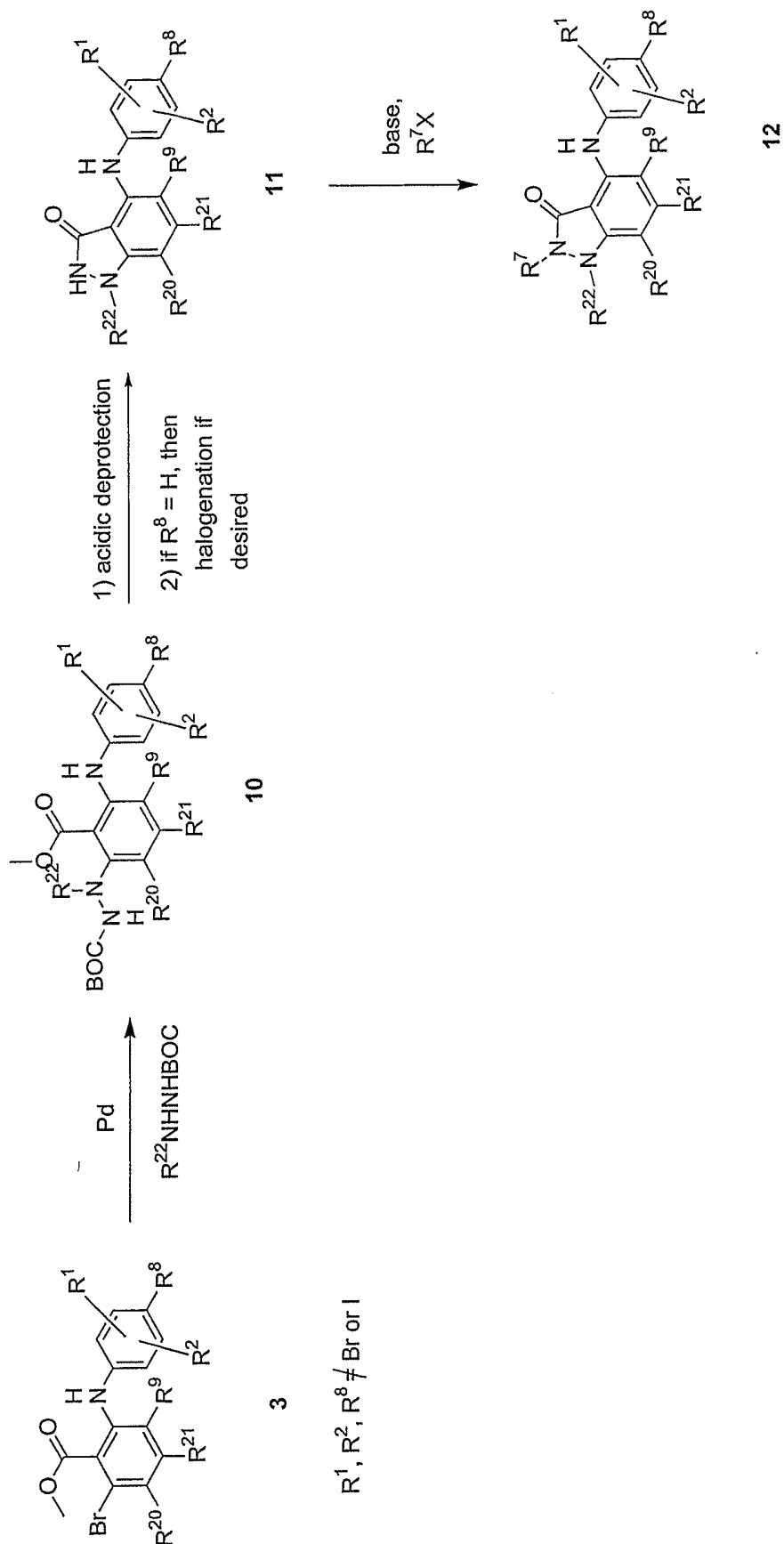


FIG. 5