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Inhibitors of Akt activity

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(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: The present invention is directed to compounds which contain substituted pyridazines and pyrimidines moieties which inhibit the activity of Akt, a serine/threonine protein kinase. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for treating cancer comprising administration of the compounds of the invention.

TITLE OF THE INVENTION

INHIBITORS OF AKT ACTIVITY

BACKGROUND OF THE INVENTION

- 5 The present invention relates to compounds which contain substituted pyridazines and pyrimidines that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB; hereinafter referred to as "Akt"). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer.
- 10 Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand,
- 15 expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase-1 related proteinases, including caspase-3, caspase-7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*, 281:1312-1316 (1998)).
- 20 The phosphatidylinositol 3'-OH kinase (PI3K)/Akt pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol. Cell. Biol.* 17:1595-1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997).
- 25 Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns(3,4,5)-P₃), which in turn binds to, and promotes the activation of, the serine/threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt mutants abolish survival-promoting
- 30 activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt by upstream kinases. In addition, introduction of constitutively active PI3K or Akt mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).
- 35 Three members of the Akt subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/PKB α , Akt2/PKB β , and Akt3/PKB γ (hereinafter

referred to as "Akt1", "Akt2" and "Akt3"), respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akts are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt. The current model of Akt activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

10 Phosphorylation of Akt1 occurs on two regulatory sites, Thr³⁰⁸ in the catalytic domain activation loop and on Ser⁴⁷³ near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2 and Akt3. The upstream kinase, which phosphorylates Akt at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

20 Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheng *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheng *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani *et al. J. Biol. Chem.* 274:21528-21532 (1999)).

25 The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P₃, is a negative regulator of the PI3K/Akt pathway (Li *et al. Science* 275:1943-1947 (1997), Stambolic *et al. Cell* 95:29-39 (1998), Sun *et al. Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw *et al. Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li *et al. supra*, Gulberg *et al. Cancer Research* 57:3660-3663 (1997), Risinger *et al. Cancer Research* 57:4736-4738 (1997)).

30 These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

35 Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to

indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PtdIns(3,4,5)-P₃, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

5 Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

10 Akt. It is an object of the instant invention to provide novel compounds that are inhibitors of

It is also an object of the present invention to provide pharmaceutical compositions that comprise the novel compounds that are inhibitors of Akt.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt activity.

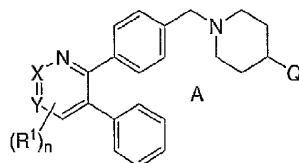
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SUMMARY OF THE INVENTION

The instant invention provides for compounds which comprise substituted pyridazines and pyrimidines that inhibit Akt activity. In particular, the compounds disclosed selectively inhibit one or two of the Akt isoforms. The invention also provides for compositions comprising such inhibitory 20 compounds and methods of inhibiting Akt activity by administering the compound to a patient in need of treatment of cancer.

DETAILED DESCRIPTION OF THE INVENTION

25 The compounds of the instant invention are useful in the inhibition of the activity of the serine/threonine kinase Akt. In a first embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula A:



wherein:

X is N and Y is CH or X is CH and Y is N;

30

Q is: heterocyclyl, which is optionally substituted with 1-3 R_Z;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; n is 0, 1 or 2; r is 0 or 1; s is 0 or 1;

R¹ is independently selected from: (C=O)_aO_bC₁-C₁₀ alkyl, (C=O)_aO_baryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, (C=O)_aO_b heterocyclyl, (C=O)_aO_bC₃-C₈ cycloalkyl, CO₂H, halo, CN, OH, O_bC₁-C₆ perfluoroalkyl, O_a(C=O)_bNR²R³, NR^c(C=O)_bNR²R³, S(O)_mR^a, S(O)₂NR²R³, NR^cS(O)_mR^a, CHO, NO₂, NR^c(C=O)O_bR^a, O(C=O)O_bC₁-C₁₀ alkyl, O(C=O)O_bC₃-C₈ cycloalkyl, O(C=O)O_baryl, C₁-C₆alkyl(C=NR^b)N(R^b)₂; O(C=O)O_b-heterocycle, and O_a-P=O(OH)₂, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R²;

R² and R³ are independently selected from: H, (C=O)O_bR^a, C₁-C₁₀ alkyl, aryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, heterocyclyl, C₃-C₈ cycloalkyl, SO₂R^a, (C=O)NR^b₂, OH, and O_a-P=O(OH)₂, said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R², or R² and R³ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 4-7 members in each ring and optionally containing, in addition to the nitrogen, one or more additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R²;

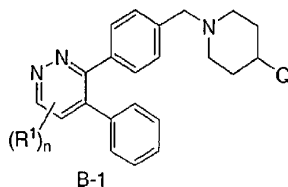
R² is selected from: (C=O)_rO_s(C₁-C₁₀)alkyl, O_r(C₁-C₃)perfluoroalkyl, (C₀-C₆)alkylene-S(O)_mR^a, oxo, OH, halo, CN, (C=O)_rO_s(C₂-C₁₀)alkenyl, (C=O)_rO_s(C₂-C₁₀)alkynyl, (C=O)_rO_s(C₃-C₆)cycloalkyl, (C=O)_rO_s(C₀-C₆)alkylene-aryl, (C=O)_rO_s(C₀-C₆)alkylene-heterocyclyl, (C=O)_rO_s(C₀-C₆)alkylene-N(R^b)₂, C(O)R^a, (C₀-C₆)alkylene-CO₂R^a, C(O)H, (C₀-C₆)alkylene-CO₂H, C(O)N(R^b)₂, S(O)_mR^a, S(O)₂N(R^b)₂ NR^c(C=O)O_bR^a, O(C=O)O_bC₁-C₁₀ alkyl, O(C=O)O_bC₃-C₈ cycloalkyl, O(C=O)O_baryl, O(C=O)O_b-heterocycle, and O_a-P=O(OH)₂, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, (C₁-C₆)alkoxy, halogen, CO₂H, CN, O(C=O)C₁-C₆ alkyl, oxo, N(R^b)₂ and O_a-P=O(OH)₂;

R^a is: substituted or unsubstituted (C₁-C₆)alkyl, substituted or unsubstituted (C₂-C₆)alkenyl, substituted or unsubstituted (C₂-C₆)alkynyl, substituted or unsubstituted (C₃-C₆)cycloalkyl, substituted or unsubstituted aryl, (C₁-C₆)perfluoroalkyl, 2,2,2-trifluoroethyl, or substituted or unsubstituted heterocyclyl;

R^b is independently: H, (C₁-C₆)alkyl, substituted or unsubstituted aryl, substituted or unsubstituted benzyl, substituted or unsubstituted heterocyclyl, (C₃-C₆)cycloalkyl, (C=O)OC₁-C₆ alkyl, (C=O)C₁-C₆ alkyl or S(O)₂R^a; and

R^c is selected from: H, C₁-C₁₀ alkyl, aryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, heterocyclyl, C₃-C₈ cycloalkyl, and C₁-C₆ perfluoroalkyl, said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R²; or a pharmaceutically acceptable salt or a stereoisomer thereof.

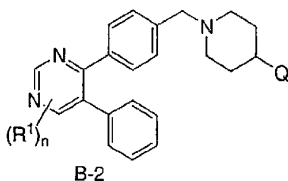
In a second embodiment of the instant invention is a compound illustrated by Formula B-1:



wherein:

- Q is: heterocyclyl, which is optionally substituted with one to three R²;
 R¹ is selected from: NH₂; halogen; OH; CN; phenyl; heterocyclyl; (C=O)_rO_s(C₀-C₆)alkyl; (C₀-C₆)alkyl-NR^aR^b; and O_a-P=O(OH)₂; wherein R^a and R^b are independently H or (C₁-C₆)alkyl and wherein said alkyl and heterocyclyl are optionally substituted with OH, oxo, O_a-P=O(OH)₂ and O(C₁-C₆)alkyl; and all other substituents and variables are as defined in the first embodiment; or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a third embodiment of the instant invention is a compound illustrated by Formula B-2:



wherein:

- all substituents and variables are as defined in the second embodiment; or a pharmaceutically acceptable salt or a stereoisomer thereof.

Specific compounds of the instant invention include:

- N,N*-dimethyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)]piperidin-1-yl)methyl)phenyl)pyridazin-3-amine (1-5);
N-methyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)]piperidin-1-yl)methyl)phenyl)pyridazin-3-amine (1-6);
 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)]piperidin-1-yl)methyl)phenyl)pyridazin-3-yl]morpholine (1-7);

- tert-butyl 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]piperazine-1-carboxylate (**1-8**);
 4-phenyl-6-piperazin-1-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (**1-9**);
- 5 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine (**1-10**);
 4-[5-phcnyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1-oxide (**1-11**);
 10 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1,1-dioxide (**1-12**);
 3-methoxy-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (**2-3**);
 5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-ol (**2-4**);
 4-phenyl-6-pyridin-3-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (**3-4**);
- 15 5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine (**4-4**); and
 5-phenyl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidin-2-amine (**4-5**); or a pharmaceutically acceptable salt or a stereoisomer thereof.
- 20 Specific TFA salts of the compounds of the instant invention include:
 N-methyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-amine (**1-6**);
 3-methoxy-5-phcnyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (**2-3**); and
- 25 5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine (**4-4**); or a stereoisomer thereof.
- In a further embodiment, a specific compound of the instant invention is:
 N,N-dimethyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-amine (**1-5**); and
- 30 5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine (**4-4**); or a pharmaceutically acceptable salt or a stereoisomer thereof.
- In another embodiment, compounds of the instant invention include:
 N,N-dimethyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-amine (**1-5**);

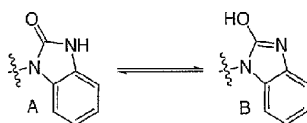
- N-methyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-amine (1-6);
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]morpholine (1-7);
- 5 tert-butyl 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]piperazine-1-carboxylate (1-8);
- 4-phenyl-6-piperazin-1-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (1-9);
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine (1-10);
- 10 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1-oxide (1-11);
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1,1-dioxide (1-12);
- 15 3-methoxy-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (2-3);
- 5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-ol (2-4);
- 4-phenyl-6-pyridin-3-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (3-4);
- 20 5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine (4-4);
- 5-phenyl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidin-2-amine (4-5);
- 1-[4-[5-phenyl-2-(pyridine-3-ylamino)pyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-6);
- 25 1-[4-[2-(5-amino-1,3,4-thiadiazol-2-yl)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-7);
- 1-methyl-4-(2-([5-phenyl-4-(4-([4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidin-2-yl]amino)ethyl)piperazine (5-8);
- 30 1-[4-(2-amino-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-9);
- 1-[4-[2-(methylthio)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-10);
- 1-[4-[2-(4-acetyl)piperazin-1-yl]-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-11);

- 1-[4-(2-([1-(ethoxycarbonyl)piperidin-4-yl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-12**);
- 1-methyl-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (**5-13**);
- 5 1-(2-hydroxyethyl)-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (**5-14**);
- 1-[2-(dimethylamino)ethyl]-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (**5-15**);
- 1-(4-{5-phenyl-2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-16**);
- 10 2-[[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]amino]pyridine (**5-17**);
- 2-[5-[1-(4-{2-[methyl(pyridin-2-yl)amino]-5-phenylpyrimidin-4-yl}benzyl)piperidin-4-yl]-4h-1,2,4-triazol-3-yl]pyridine (**5-18**);
- 15 1-[4-[2-(dimethylamino)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-19**);
- 1-(4-{2-[2-(dimethylamino)ethyl](methylamino)-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-20**);
- 1-[4-(2-([3-(dimethylammonio)propyl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-21**);
- 20 1-[4-(2-([2-(dimethylammonio)ethyl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-22**); and
- 1-(4-{2-([3-(dimethylammonio)propyl](methylamino)-5-phenylpyrimidin-4-yl)benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-23**);
- 25 or a pharmaceutically acceptable salt or a stereoisomer thereof.
- In another embodiment, specific TFA salts of the compounds of the instant invention include:
- N-methyl-5-phenyl-6-(4-{[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-amine (**1-6**);
- 30 3-methoxy-5-phenyl-6-(4-{[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazine (**2-3**);
- 5-phenyl-2-pyridin-2-yl-4-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidine (**4-4**);
- 1-[4-[5-phenyl-2-(pyridine-3-ylamino)pyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (**5-6**);
- 35

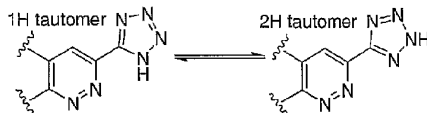
- 1-{4-[2-(5-amino-1,3,4-thiadiazol-2-yl)-5-phenylpyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-7);
- 1-methyl-4-(2-{[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]amino}ethyl)piperzine (5-8);
- 5 1-[4-(2-amino-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-9);
- 1-(4-[2-(methylthio)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-10);
- 1-(4-[2-(4-acetylpiperazin-1-yl)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-11);
- 10 1-[4-(2-{[1-(ethoxycarbonyl)piperidin-4-yl]amino}-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-12);
- 1-methyl-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (5-13);
- 1-(2-hydroxyethyl)-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (5-14);
- 15 1-[2-(dimethylamino)ethyl]-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine (5-15);
- 1-(4-{5-phenyl-2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-16);
- 20 2-{[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]amino}pyridine (5-17);
- 2-{5-[1-(4-[2-[methyl(pyridin-2-yl)amino]-5-phenylpyrimidin-4-yl]benzyl)piperidin-4-yl]-4h-1,2,4-triazol-3-yl}pyridine (5-18);
- 1-(4-[2-(dimethylamino)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-19);
- 25 1-(4-{2-[2-(dimethylamino)ethyl](methyl)amino]-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-20);
- 1-(4-(2-{[3-(dimethylammonio)propyl]amino}-5-phenylpyrimidin-4-yl)benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-21);
- 30 1-(4-(2-{[2-(dimethylammonio)ethyl]amino}-5-phenylpyrimidin-4-yl)benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-22); and
- 1-(4-{2-[3-(dimethylammonio)propyl](methyl)amino]-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine (5-23);
- or a stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention.

In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example, any claim to compound A below is understood to include tautomeric structure B, and vice versa, as well as mixtures thereof. The two tautomeric forms of the benzimidazolonyl moiety are also within the scope of the instant invention.



Tetrazoles exist as a mixture of 1H/2H tautomers. The tautomeric forms of the tetrazol moiety are also within the scope of the instant invention.



When any variable (e.g. R¹, R², etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is polycyclic, it is intended that the bond be attached to any of the suitable carbon atoms on the proximal ring only.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one

substituent” and in such cases an embodiment will have from zero to four substituents, and another embodiment will have from zero to three substituents.

As used herein, “alkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₁₀, as in
5 “C₁-C₁₀ alkyl” is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, “C₁-C₁₀ alkyl” specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term “cycloalkyl” means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, “cycloalkyl” includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-
10 cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

“Alkoxy” represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. “Alkoxy” therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term “alkenyl” refers to a non-aromatic
15 hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, “C₂-C₆ alkenyl” means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may
20 contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term “alkynyl” refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, “C₂-C₆ alkynyl” means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The
25 straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C₀-C₆)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH₂Ph, -CH₂CH₂Ph, -CH(CH₃)CH₂CH(CH₃)Ph, and so on.

As used herein, “aryl” is intended to mean any stable monocyclic or bicyclic carbon ring
30 of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up
35 to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms

selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxaliny, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinolinc. As with
 5 the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. Such heteroaryl moieties for substituent Q include but are not limited to: 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-
 10 isoquinolinyl and 4-isoquinolinyl.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of
 15 "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl,
 20 pyrazolopyrimidinyl, pyridyl, pyrimidyl, pyrrolyl, quiazoliny, quinolyl, quinoxaliny, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, 1,4-dioxanyl, hexahydroazepiny, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl,
 25 dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

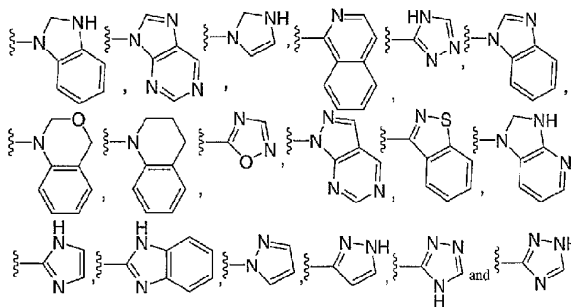
30 As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

As used herein, unless otherwise specifically defined, substituted alkyl, substituted cycloalkyl, substituted aryl, substituted heteroaryl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 4 substituents (and in another
 35 embodiment 1 to 3 substituents) in addition to the point of attachment to the rest of the compound. Such

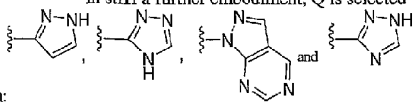
substituents are selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, (aryl)O-, -OH, O=P(OH)₂, (C₁-C₆ alkyl)S(O)_m, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, (C₁-C₆ alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C₁-C₂₀ alkyl. For example, a (C₁-C₆)alkyl may be substituted with one, two, three or four (in another embodiment one, two or three) substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: -(C=O)CH₂CH(OH)CH₃, -(C=O)OH, -CH₂(OH)CH₂CH(O), and so on.

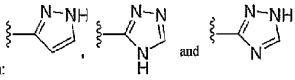
- 10 In another embodiment, n is 0 or 1.
 In a further embodiment, n is 1.
 In another embodiment, R^a is H, (C₁-C₆)alkyl or phenyl.
 In another embodiment, R^b is independently H, (C₁-C₆)alkyl, (C=O)O(C₁-C₆)alkyl, (C=O)(C₁-C₆)alkyl or S(O)₂R^a.
- 15 In an embodiment, Q is selected from 2-azepinone, benzimidazolyl, benzimidazolonyl, 2-diazapinone, imidazolyl, 2-imidazolidinone, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinone, 2-pyrimidinone, 2-pyrrolidinone, quinolinyl, tetrazolyl, tetrahydrofuryl, tetrahydroisoquinolinyl, thienyl, pyrazolopyrimidinyl, pyrazolyl, thiazolyl, oxadiazolyl and triazolyl, optionally substituted with 1-3 R^Z.

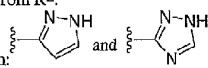
20 In a further embodiment, Q is selected from:



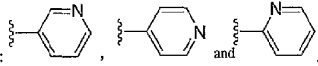
which are optionally substituted with one to three substituents selected from R^Z.

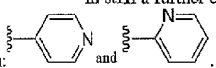
In still a further embodiment, Q is selected from: , which are optionally substituted with one substituent selected from R^Z.

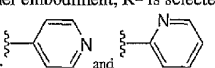
In a further embodiment, Q is selected from: , which are optionally substituted with one substituent selected from R^Z.


In yet a further embodiment, Q is selected from: , which are optionally substituted with one substituent selected from R^Z.

In another embodiment, R^Z is selected from: (C₁-C₆)alkyl, phenyl, heterocyclyl, N(R^b)₂, (C=O)_aO_bC₁-C₆alkyl, (C=O)NR²R³, halogen, OH, O_a-P=O(OH)₂, and oxo.

In a further embodiment, R^Z is selected from: (C₁-C₆)alkyl, phenyl, heterocyclyl, N(R^b)₂, (C=O)_aO_bC₁-C₆alkyl, (C=O)NR²R³, halogen, OH, O_a-P=O(OH)₂, and oxo, wherein said heterocyclyl is selected from: .

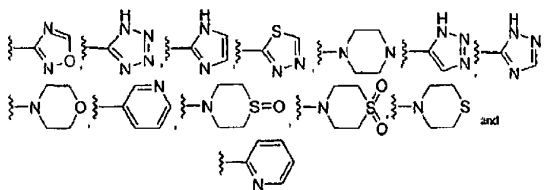
In still a further embodiment, when R^Z is heterocyclyl, said heterocyclyl is selected from: .

In yet a further embodiment, R^Z is selected from: NH₂ and heterocyclyl, said heterocyclyl is selected from: .

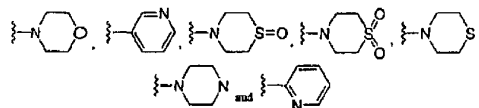
In yet a further embodiment, R^Z is: .

In another embodiment, R¹ is selected from: OH; heterocyclyl; and NR^aR^b; wherein R^a and R^b are independently H or (C₁-C₆)alkyl and wherein said heterocyclyl is optionally substituted with oxo and (C=O)_tO_s(C₁-C₆)alkyl.

In another embodiment, when R¹ is heterocyclyl, said heterocyclyl is selected from:



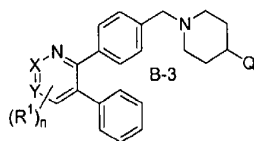
In a further embodiment, when R¹ is heterocyclyl, said heterocyclyl is selected from:



In another embodiment, R² and R³ are independently selected from H, (C₁-C₆)alkyl and aryl, optionally substituted with one to two substituents selected from R^Z, or R² and R³ together with the nitrogen to which they are attached form a monocyclic or bicyclic heterocycle, optionally substituted with one to two substituents selected from R^Z.

In a further embodiment, R² and R³ are independently selected from H or (C₁-C₆)alkyl, optionally substituted with one to two substituents selected from R^Z, or R² and R³ together with the nitrogen to which they are attached form a monocyclic or bicyclic heterocycle, optionally substituted with one to two substituents selected from R^Z.

In a fourth embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula B-3:



wherein:

X is N and Y is CH or X is CH and Y is N;

Q is selected from: , which are optionally substituted with 1-3 R⁶;

a is 0 or 1; b is 0 or 1; m is 0, 1, or 2; n is 0, 1 or 2

R¹ is independently selected from: H, (C=O)_aO_bC₁-C₁₀ alkyl, (C=O)_aO_b aryl, (C=O)_aO_bC₂-C₁₀ alkenyl, (C=O)_aO_bC₂-C₁₀ alkynyl, CO₂H, halo, OH, O_bC₁-C₆ perfluoroalkyl, (C=O)_aNR⁷R⁸, CN, (C=O)_aO_bC₃-C₈ cycloalkyl, S(O)_mNR⁷R⁸, S(O)_m-(C₁-C₁₀)alkyl and (C=O)_aO_bheterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R⁶;

R⁶ is independently: (C=O)_aO_bC₁-C₁₀ alkyl, (C=O)_aO_baryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, (C=O)_aO_b heterocyclyl, CO₂H, halo, CN, OH, O_bC₁-C₆ perfluoroalkyl, O_a(C=O)_bNR⁷R⁸, oxo, CHO, (N=O)R⁷R⁸, S(O)_mNR⁷R⁸, S(O)_m-(C₁-C₁₀)alkyl or (C=O)_aO_bC₃-C₈ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^{6a};

R^{6a} is independently selected from: (C=O)_aO_b(C₁-C₁₀)alkyl, O_a(C₁-C₃)perfluoroalkyl, (C₀-C₆)alkylene-S(O)_mR^a, oxo, OH, halo, CN, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₆)cycloalkyl, (C₀-C₆)alkylene-aryl, (C₀-C₆)alkylene-heterocyclyl, (C₀-C₆)alkylene-N(R^b)₂, C(O)R^a, (C₀-C₆)alkylene-CO₂R^a, C(O)H, and (C₀-C₆)alkylene-CO₂H, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b, OH, (C₁-C₆)alkoxy, halogen, CO₂H, CN, O(C=O)C₁-C₆ alkyl, oxo, and N(R^b)₂;

R⁷ and R⁸ are independently selected from: H, (C=O)O_bC₁-C₁₀ alkyl, (C=O)O_bC₃-C₈ cycloalkyl, (C=O)O_baryl, (C=O)O_bheterocyclyl, C₁-C₁₀ alkyl, aryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, heterocyclyl, C₃-C₈ cycloalkyl, SO₂R^a, and (C=O)NR^b₂, said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^{6a}, or R⁷ and R⁸ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a};

R^a is independently: (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, or heterocyclyl; and

R^b is independently: H, (C₁-C₆)alkyl, aryl, heterocyclyl, (C₃-C₆)cycloalkyl (C=O)OC₁-C₆ alkyl, (C=O)C₁-C₆ alkyl or S(O)₂R^a;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a fifth embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula A-3:

wherein:

Q is: (C₃-C₆)cycloalkyl, aryl or heterocyclyl, which is optionally substituted with 1-3

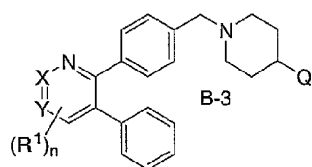
R⁶;

and all other substituents and variables are as defined in the fourth embodiment;

5

or a pharmaceutically acceptable salt or a stereoisomer thereof.

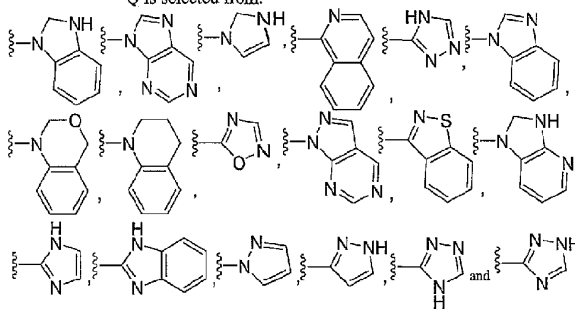
In a sixth embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula B-3:



wherein:

10

Q is selected from:



which is optionally

substituted with 1-3 R⁶;

n is 0, 1 or 2;

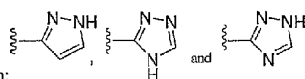
and all other substituents and variables are as defined in the fifth embodiment;

15

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a seventh embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula B-3:

wherein:



Q is selected from:

, which are optionally

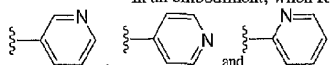
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substituted with 1-3 R⁶;

and all other substituents and variables are as defined in the sixth embodiment;
or a pharmaceutically acceptable salt or a stereoisomer thereof.

In an embodiment, when R⁶ is attached to Q; R⁶ is independently selected from: (C₁-C₆)alkyl, phenyl, heterocyclyl, N(R^b)₂, (C=O)_aO_bC₁-C₆alkyl, (C=O)NR²R³, halogen, OH, O_a-P=O(OH)₂, and oxo.

In an embodiment, when R⁶ is attached to Q; R⁶ is independently selected from:



Included in the instant invention is the free form of compounds of Formula A, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the isolated specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the isolated salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula A. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic (TFA) and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

UTILITY

The compounds of the instant invention are inhibitors of the activity of Akt and are thus useful in the treatment of cancer, in particular cancers associated with irregularities in the activity of Akt and downstream cellular targets of Akt. Such cancers include, but are not limited to, ovarian, pancreatic, breast and prostate cancer, as well as cancers (including glioblastoma) where the tumor suppressor PTEN is mutated (Cheng *et al.*, *Proc. Natl. Acad. Sci.* (1992) 89:9267-9271; Cheng *et al.*, *Proc. Natl. Acad. Sci.* (1996) 93:3636-3641; Bellacosa *et al.*, *Int. J. Cancer* (1995) 64:280-285; Nakatani *et al.*, *J. Biol. Chem.* (1999) 274:21528-21532; Graff, *Expert. Opin. Ther. Targets* (2002) 6(1):103-113; and Yamada and Araki, *J. Cell Science.* (2001) 114:2375-2382; Mischel and Cloughesy, *Brain Pathol.* (2003) 13(1):52-61).

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac; sarcoma

(angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-theca cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Akt signaling regulates multiple critical steps in angiogenesis. Shiojima and Walsh, *Circ. Res.* (2002) 90:1243-1250. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. *Cancer Research*, 55:4575-4580, 1995 and Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi et al., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); bladder carcinomas (A.J. Dickinson et al., *Br. J. Urol.*, 1994, 74:762-766); colon carcinomas (L.M. Ellis et al., *Surgery*, 1996, 120(5):871-878); and oral cavity tumors (J.K. Williams et al., *Am. J. Surg.*, 1994, 168:373-380). Other cancers include, advanced tumors, hairy cell leukemia, melanoma, advanced head and neck, metastatic renal cell, non-Hodgkin's lymphoma, metastatic breast, breast adenocarcinoma, advanced melanoma, pancreatic, gastric, glioblastoma, lung, ovarian, non-small cell lung, prostate, small cell lung, renal cell carcinoma, various solid tumors, multiple myeloma, metastatic prostate, malignant glioma, renal cancer, lymphoma, refractory metastatic disease, refractory multiple myeloma, cervical cancer, Kaposi's sarcoma, recurrent anaplastic glioma, and metastatic colon cancer (Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). Thus, the Akt inhibitors disclosed in the instant application, are also useful in the treatment of these angiogenesis related cancers.

Tumors which have undergone neovascularization show an increased potential for metastasis. In fact, angiogenesis is essential for tumor growth and metastasis. (S.P. Cunningham, et al., *Can. Research*, 61: 3206-3211 (2001)). The Akt inhibitors disclosed in the present application are therefore also useful to prevent or decrease tumor cell metastasis.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 June 2000). The undesirable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Further included within the scope of the invention is a method of treating or preventing a non-malignant disease in which angiogenesis is implicated, including but not limited to: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis, psoriasis, obesity and Alzheimer's disease (Dredge et al., *Expert Opin. Biol.*

Ther. (2002) 2(8):953-966). In another embodiment, a method of treating or preventing a disease in which angiogenesis is implicated includes: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis and psoriasis.

Further included within the scope of the invention is a method of treating
5 hyperproliferative disorders such as restenosis, inflammation, autoimmune diseases and allergy/asthma.

Further included within the scope of the invention is a method of treating
hyperinsulinism.

The compounds of the invention are also useful in preparing a medicament that is useful
in treating the diseases described above, in particular cancer.

10 In an embodiment of the invention, the instant compound is a selective inhibitor whose
inhibitory efficacy is dependent on the PH domain. In this embodiment, the compound exhibits a
decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt proteins
lacking the PH domain.

In a further embodiment, the instant compound is selected from the group of a selective
15 inhibitor of Akt1, a selective inhibitor of Akt2 and a selective inhibitor of both Akt1 and Akt2.

In another embodiment, the instant compound is selected from the group of a selective
inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3 and a selective inhibitor of
two of the three Akt isoforms.

In another embodiment, the instant compound is a selective inhibitor of all three Akt
20 isoforms, but is not an inhibitor of one, two or all of such Akt isoforms that have been modified to delete
the PH domain, the hinge region or both the PH domain and the hinge region.

The present invention is further directed to a method of inhibiting Akt activity which
comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant
compound.

25 The compounds of this invention may be administered to mammals, including humans,
either alone or, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a
pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be
administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal,
subcutaneous, rectal and topical routes of administration.

30 The pharmaceutical compositions containing the active ingredient may be in a form
suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible
powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for
oral use may be prepared according to any method known to the art for the manufacture of
pharmaceutical compositions and such compositions may contain one or more agents selected from the
35 group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to

provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, 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, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth 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 butylated hydroxyanisole or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture 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, for example
5 sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-
10 occurring phosphatides, for example soy bean lecithin, and 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, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

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

The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then
20 introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant
25 compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile
30 injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or

suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula A may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable
5 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. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the
10 compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in
15 the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a composition according to this invention is administered into a human subject,
20 the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In an embodiment, a suitable amount of an inhibitor of Akt is administered to a mammal
25 undergoing treatment for cancer. Administration occurs in an amount of inhibitor of between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, or between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day. Another therapeutic dosage that comprises the instant composition includes from about 0.01 mg to about 1000 mg of inhibitor of Akt. In another embodiment, the dosage comprises from about 1 mg to about 1000 mg of inhibitor of Akt.

The instant compounds are also useful in combination with known therapeutic agents
30 and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition
35 (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art

would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)-phenyl]-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinases, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, anti-metabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic/cytostatic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosylate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profirmycin, 5 cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis- μ -(hexane-1,6-diamine)- μ -(diamine-platinum(II))bis[diamine(chloro)platinum(II)]tetra-chloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxy-10-hydroxycarminomycin, 10 annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032), Raf kinase inhibitors (such as Bay43-9006) and mTOR inhibitors (such as Wyeth's CCI-779).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and MLN-15 341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'- α -orvinalcalkoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflumine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrzolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, 30 (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-35

carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768 and WO 01/98278, and pending U.S. Ser. Nos. 60/338,779 (filed December 6, 2001) (corresponding to WO 03/049,527), 60/338,344 (filed December 6, 2001) (corresponding to WO 03/049,679), 60/338,383 (filed December 6, 2001) (corresponding to WO 03/050,064), 60/338,380 (filed December 6, 2001) (corresponding to WO 03/050,122), 60/338,379 (filed December 6, 2001) (corresponding to WO 03/049,678) and 60/344,453 (filed November 7, 2001) (corresponding to WO 03/039,460). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be

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used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see
5 U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893,

5,489,691 and 5,342,952) and cerivastatin (also known as ri-vastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08 542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloproteinase) inhibitors, integrin blockers, interferon- α , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Ophthalmol.*, Vol. 108, p.573 (1990);

- Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin. Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Int. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).
- Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).
- "Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystauroripin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.
- "Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).
- As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an IC₅₀ for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.
- The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ for COX-2 over IC₅₀ for COX-1 evaluated by cell or microsomal assays.

Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, U.S. Patent 5,861,419, U.S. Patent 6,001,843, U.S. Patent 6,020,343, U.S. Patent 5,409,944, U.S. Patent 5,436,265, U.S. Patent 5,536,752, U.S. Patent 5,550,142, U.S. Patent 5,604,260, U.S. Patent 5,698,584, U.S. Patent 5,710,140, WO 94/15932, U.S. Patent 5,344,991, U.S. Patent 5,134,142, U.S. Patent 5,380,738, U.S. Patent 5,393,790, U.S. Patent 5,466,823, U.S. Patent 5,633,272 and U.S. Patent 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CMI01, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[ircaino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidene]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-

dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD 121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed
5 compounds with PPAR- γ (i.e., PPAR-gamma) agonists and PPAR- δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malignancies. PPAR- γ and PPAR- δ are the nuclear peroxisome proliferator-activated receptors γ and δ . The expression of PPAR- γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121;
10 *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR- γ agonists have been shown to inhibit the angiogenic response to VEGF *in vitro*; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthalmol.* 2001; 119:709-717). Examples of PPAR- γ agonists and PPAR γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011,
15 troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856) (corresponding to WO 01/060,807), and 2(R)-7-(3-(2-
20 chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 (corresponding to WO 02/026,729) and 60/244,697 (corresponding to WO 02/026,729)).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an
25 overview of genetic strategies to treating cancer see Hall *et al* (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe *et al* (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a
30 uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination
35 with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated

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with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valsopodar).

5 A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with

other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT₃ receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S. Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or chlorabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT₃ receptor antagonist and a corticosteroid is disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-

bis(trifluoromethyl)phenoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

5 A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous erythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

10 A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- γ agonists, PPAR- δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

25 As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

35 The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by

killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula A in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR- γ agonists, PPAR- δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula A in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of Formula A in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula A and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR- γ agonist, a PPAR- δ agonist, an inhibitor of cell proliferation and survival signaling, and an agent that interferes with a cell cycle checkpoint.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and in the Examples that follow are: AEBSF (p-aminoethylbenzenesulfonyl fluoride); BSA (bovine serum albumin); BuLi (n-Butyl lithium); CDCl₃ (chloroform-d); CuI (copper iodide); CuSO₄ (copper sulfate); DCE (dichloroethane); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DMF (N,N-dimethylformamide); DMSO (dimethyl sulfoxide); DTT (dithiothreitol); EDTA (ethylene-diamine-tetra-acetic acid); EGTA (ethylene-glycol-tetra-acetic acid); EtOAc (ethyl acetate); EtOH (ethanol); HOAc (acetic acid); HPLC (high-performance liquid chromatography); HRMS (high resolution mass spectrum); LCMS (liquid chromatograph-mass spectrometer); LHMDs (lithium bis(trimethylsilyl)amide); LRMS (low resolution mass spectrum); MeOH (methanol); MP-B(CN)H₃ (Macroporous cyanoborohydride); NaHCO₃ (sodium bicarbonate); Na₂SO₄ (sodium sulfate); Na(OAc)₃BH (sodium triacetoxyborohydride); NH₄OAc (ammonium acetate); NBS (N-bromosuccinamide); NMR (nuclear magnetic resonance); PBS (phosphate buffered saline); PCR (polymerase chain reaction); Pd(dppf) ([1,1'-bis(diphenylphosphino)ferrocene]palladium); Pd(Ph₃)₄ (palladium(0) tetrakis-triphenylphosphine); POCl₃ (phosphorous oxychloride); PS-DIEA (polystyrene diisopropylethylamine); TBAF (tetrabutylammonium fluoride); THF (tetrahydrofuran); TFA (trifluoroacetic acid); and TMSCH₂N₂ (trimethylsilyldiazomethane).


The compounds of this invention may be prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the Reaction Schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are optionally allowed under the definitions of Formula A hereinabove.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the Reaction Schemes I-III, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures.

SYNOPSIS OF REACTION SCHEMES

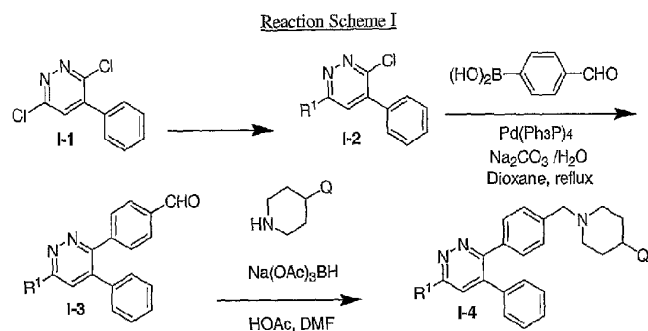
Reaction Scheme I illustrates the preparation of the pyridazine compounds of the instant invention, starting with 4-phenyl-3,6-dichloropyridazine 1-1. This material can be reacted with a nucleophile to give 1-2. When the nucleophile is an amine, heating under microwave conditions is preferred and when the nucleophile is an alcohol, the metal alkoxide is used. In addition, a (hetero)aryl group can be introduced under Suzuki coupling conditions. In all cases the substitution occurs predominately at the less hindered 6-position. Intermediate 1-2 can be subjected to a standard Suzuki

coupling with (4-formylphenyl) boronic acid to afford I-3. This material can then undergo reductive

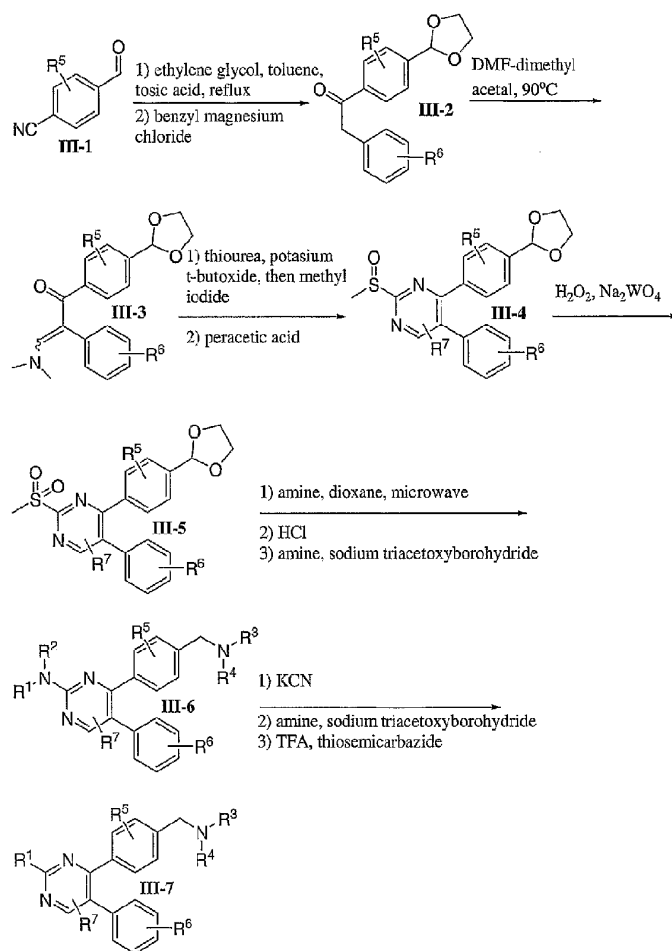
amination with a diverse array of amines, for example,  and a borohydride to provide I-4.

Reaction Scheme II illustrates the synthesis of the pyrimidine compounds of the instant invention, starting with methyl (2*Z*)-3-methoxy-3-phenylacrylate II-1. Condensation of II-1 with amidine or guanidines provides II-2, which reacts with POCl₃ to afford pyrimidine II-3. Suzuki coupling of II-3 with (4-formylphenyl)boronic acid produces the aldehyde II-4. Reductive amination with suitably substituted amines generates amines II-5.

Reaction Scheme III illustrates the preparation of the 4-(5-phenylpyrimidin-4-yl)benzyl compounds. Synthesis starts with a commercially available carboxaldehyde (III-1), which is converted to the corresponding acetal and then treated with a Grignard reagent to produce ketone (III-2). Ketone (III-2) is then formylated using a formyl group donor such as dimethylformamide-dimethyl acetal to produce enamine (III-3). The enamine can then be converted to the thiopyrimidine by the treatment with thiourea and a base such as potassium-butoxide, sodium methoxide or sodium hydroxide in a solvent such as methanol or ethanol. The thiopyrimidine is then alkylated in situ using an alkylating reagent such as methyl iodide or benzyl bromide to produce the alkylthiopyrimidine (III-4). Oxidation to the sulfone can be easily achieved by those skilled in the art. One possible method is a two step procedure using peracetic acid to produce the sulfoxide and then hydrogen peroxide and catalytic sodium tungstenate to provide sulfone (III-5). Sulfone (III-5) is a versatile intermediate and can be treated with a variety of amines in dioxane with or without a base such as sodium bis(trimethylsilyl)amide in solvents including, but not limited to dioxane or THF with or without heating in a microwave. The acetal is then removed under acidic conditions and the liberated aldehyde can be converted to the amine using reductive amination conditions to produce (III-6). Alternatively, sulfone (III-5) can be treated with potassium cyanide in DMSO with or without heating. The acetal could then be removed under acidic conditions and treatment of the aldehyde with an amine under reductive conditions produces the corresponding alkylated product. Finally, treatment with thiosemicarbazide in TFA produces aminothiazole (III-7).



Reaction Scheme III



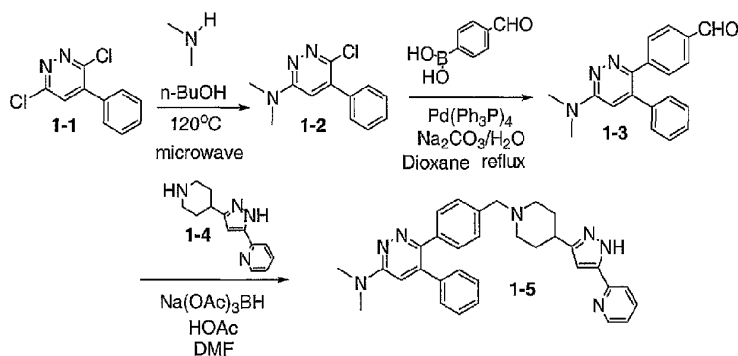
EXAMPLES

Examples provided are intended to assist in a further understanding of the invention.

5 Particular materials employed, species and conditions are intended to be further illustrative of the

invention and not limitative of the reasonable scope thereof. The reagents utilized in synthesizing the compounds depicted in the following Tables are either commercially available or are readily prepared by one of ordinary skill in the art.

SCHEME 1



5

N,N-dimethyl-5-phenyl-6-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenylpyridazin-3-amine (1-5)

4-Phenyl-3,6-dichloropyridazine (1-1; 226 mg, 1.0 mmol) (prepared as described in U.S. Pat. No. 6,444,666) was added to a mixture of diisopropylethylamine (0.16 mL, 1 mmol) and 2M dimethylamine/methanol (1.0 mL, 2.0 mmol) in n-butanol (1 mL), sealed in a reaction tube and heated in a microwave for two 15 min. cycles. The reaction mixture was evaporated to remove solvents and the residue was dissolved in ethyl acetate, washed with sat'd. aqueous Na_2CO_3 , the solvent dried over anhydrous Na_2SO_4 , and solution filtered and evaporated to give a mixture of two isomeric products, the predominant product being the desired product. This residue was triturated with diethyl ether/ hexane to give N,N-dimethyl 6-chloro-5-phenylpyridazin-3-amine (1-2) as a crystalline solid (132 mg). Additional material could be obtained by chromatographic separation of the mother liquors on silica gel by gradient elution with ethyl acetate/ hexane. $^1\text{H NMR}(\text{CDCl}_3)$: δ 7.48 (5H, s), 6.73 (1H, s), 3.20 (6 H, s); m/e (m+1): 234.2

N,N-dimethyl 6-chloro-5-phenylpyridazin-3-amine (1-2; 120 mg, 0.51 mmol) was dissolved in dry dioxane (3 mL) and 4-formylphenyl boronic acid (136 mg, 0.91 mmol). 2 M aqueous Na_2CO_3 (0.75 mL) and palladium(0) tetrakis-triphenylphosphine (66 mg, 0.058 mmol) were then added. This mixture was degassed, the vessel sealed and heated at 110 °C for 24 hours. The cooled reaction was diluted with water and the product extracted into ethyl acetate, the extract dried over anhydrous Na_2SO_4 , filtered and evaporated. The product was purified by chromatography on silica gel and elution with a 25-

- 40 -

65% ethyl acetate/ hexane gradient to give 4-[6-(Dimethylamino)-4-phenylpyridazin-3-yl]benzaldehyde (**1-3**). NMR(CDC₁₃): δ 9.98 (1H, s), 7.74 (2H, d, J=8 Hz), 7.54 (2H, d, J=8 Hz), 7.35 (3H, m), 7.19 (2H, d, J= 8 Hz), 6.76 (1H, s), 3.29 (6H, s); m/e (m + 1): 304.2

4-[6-(Dimethylamino)-4-phenylpyridazin-3-yl]benzaldehyde (**1-3**: 76 mg, 0.25 mmol)
5 was dissolved in dry dimethylformamide (2 mL). Then 2-(3-piperidin-4-yl-1H-pyrazol-5-yl)pyridine (**1-4** [see synthesis below]; 62 mg, 0.27 mmol) and acetic acid (0.06 mL, 1.0 mmol) were added. After stirring for 15 min., sodium triacetoxyborohydride (120 mg, 0.58 mmol) was added and the reaction mixture was stirred at ambient temperature for 12 hours. This reaction mixture was partially evaporated and the residue chromatographed on a silica gel column eluting with a 0-7% methanol/ ethyl acetate (sat'd with
10 NH₄OH). N,N-dimethyl-5-phenyl-6-(4-[[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl]phenyl)pyridazin-3-amine (**1-5**) was obtained as a white solid upon trituration with diethyl ether/ hexane. NMR(CDC₁₃): δ 8.57 (1H, d, J=4.5 Hz), 7.68-7.73 (2H, m), 7.28-7.35 (6H, m), 7.20 (4H, br d, J=7 Hz), 6.74 (1H, s), 6.60 (1H, s), 3.35 (2H, s), 3.26 (6H, s), 2.96 (2H, d, J=11 Hz), 2.72 (1H, m), 2.10 (2H, br t, J=11 Hz), 1.97 (2H, br d, J=12 Hz), 1.81 (2H, br q, J= 11 Hz); m/e (m +1): 516.3.

15 2-(3-Piperidin-4-yl-1H-pyrazol-5-yl)pyridine (1-4)

tert-Butyl 4-acetylpiperidine-1-carboxylate (described in U.S. Pat. No. 5,952,341, 4.00 g, 17.6 mmol) was dissolved in 40 ml of anhydrous THF under N₂. NaH (60% suspension, 0.93 g, 38.7 mmol) was added followed by the addition of ethyl pyridine-2-carboxylate (2.38 ml, 17.6 mmol). The reaction was heated to 60°C. After 2h anhydrous DMF (20 ml) was added and heating was continued for
20 2h. The reaction was allowed to cool to ambient temperature and was quenched with saturated aqueous NH₄Cl. The mixture was extracted 3x with DCM and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting oil consisting primarily of *tert*-butyl 4-(3-oxo-3-pyridin-2-ylpropanoyl)piperidine-1-carboxylate was used without purification.

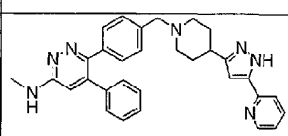
Unpurified *tert*-butyl 4-(3-oxo-3-pyridin-2-ylpropanoyl)piperidine-1-carboxylate (2.00 g,
25 6.02 mmol) was dissolved in 20 ml of EtOH and hydrazine hydrate (0.321 ml, 6.62 mmol) was added and the reaction was warmed to 80°C. After 15h the reaction was concentrated in vacuo and the residue was purified by flash column chromatography (dissolve in DCM, elute with 98:2 to 95:5 DCM/MeOH). *tert*-Butyl 4-(3-pyridin-2-yl-1H-pyrazol-5-yl)piperidine-1-carboxylate was obtained as a yellow oil. 1H
NMR(CDC₁₃): δ 8.60 (m, 1H), 7.73 (dt, J = 1.7, 7.6 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.22 (m, 1H), 6.57
30 (s, 1H), 4.18 (bs, 2H), 2.89 (m, 4H), 2.00 (d, J = 12.5 Hz, 2H), 1.67 (m, 2H), 1.48 (s, 9H). m/z (m +1): 329.2

tert-Butyl 4-(3-pyridin-2-yl-1H-pyrazol-5-yl)piperidine-1-carboxylate (1.46 g, 4.45 mmol) was dissolved in 15 ml DCM. Trifluoroacetic acid (5 ml) was added gradually and the resulting solution was stirred at ambient temperature for 3h and was then concentrated in vacuo. The residue was
35 dissolved in 4:1 MeOH/water and treated with MP-carbonate resin (5g, 2.55 mmol/g). After stirring

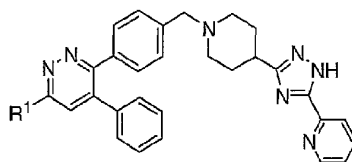
overnight the reaction was filtered and the filtrate was concentrated in vacuo to provide 1.1 g of 2-(3-piperidin-4-yl-1H-pyrazol-5-yl)pyridine (1-4) as a tan solid. δ 8.56 (d, J = 3.9 Hz, 1H), 7.84 (m, 2H), 7.21 (m, 1H), 6.65 (s, 1H), 3.22 (m, 3H), 2.87 (m, 2H), 2.03 (d, J = 12.8 Hz, 2H), 1.71 (d, J = 10.3 Hz, 2H). m/z (m+1): 229.3.

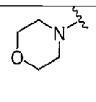
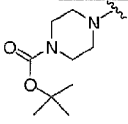

- 5 The following compounds in Tables 1a and 1b were prepared by the procedures described in Scheme 1 substituting the appropriate amines at the first and last steps and where necessary oxidation of the morpholine ring or removal of a Boc protecting group.

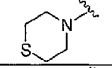
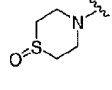
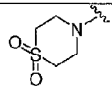
Table 1a

Cmpd No.	Structure	Nomenclature	MS M+1
1-6		N-methyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-amine	502.2

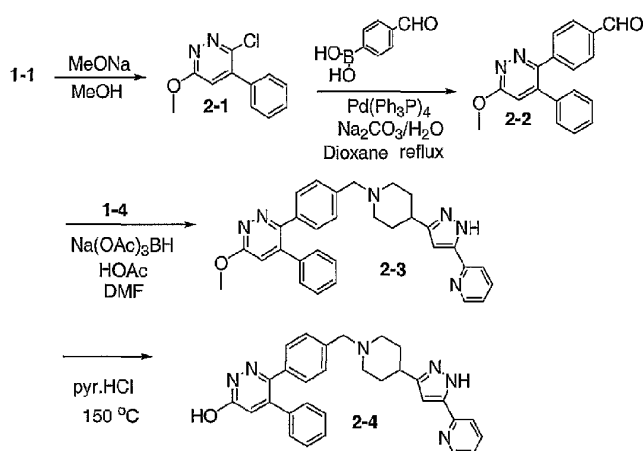
10 Table 1b



Cmpd No.	Structure R1	Nomenclature	MS M+1
1-7		4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]morpholine	559.3
1-8		tert-butyl 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]piperazine-1-carboxylate	658.6
1-9		4-phenyl-6-piperazin-1-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine	558.1

1-10		4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine	575.4
1-11		4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1-oxide	591.3
1-12		4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl]thiomorpholine-1,1-dioxide	607.3

SCHEME 2



3-methoxy-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine
 5 (2-3) and 5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazin-3-yl
 (2-4)

A commercial solution of 25 wt % sodium methoxide in methanol (0.49 mL, 2.0 mmol) was added drop wise to an ice-cooled solution of 4-phenyl-3,6-dichloropyridazine (1-1; 448 mg, 2.0 mmol) in dry methanol (10 mL). This solution was gradually warmed to room temperature over three
 10 hours. The solvent was evaporated and the residue dissolved in methylene chloride, washed with aq. NaHCO₃, the organic layer dried over anhydrous Na₂SO₄, filtered and evaporated to give a 2:1 mixture of isomeric products. Upon chromatography on silica gel and elution with 15% ethyl acetate/hexane, the

desired and major isomer was isolated. Trituration of this material with diethyl ether/ hexane afforded 3-chloro-6-methoxy-4-phenylpyridazine as a white solid (2-1). NMR(CDC_l₃): δ7.49 (5H, br s), 6.96 (1H, s), 4.17 (3H, s).

3-Chloro-6-methoxy-4-phenylpyridazine (2-1; 179 mg, 0.81 mmol) was dissolved in dry dioxane (4 mL) and 4-formylphenyl boronic acid (165 mg, 1.1 mmol), 2 M aqueous Na₂CO₃ (1.2 mL) and palladium(0) tetrakis-triphenylphosphine (108 mg, 0.09 mmol) were added. This mixture was degassed, the vessel sealed and heated at 110 °C for 24 hours. The cooled reaction was diluted with water and the product extracted into ethyl acetate, the extract dried over anhydrous Na₂SO₄, filtered and evaporated. This residue was chromatographed on silica gel and eluted with a 25-45% ethyl acetate/hexane gradient to 4-(6-methoxy-4-phenylpyridazin-3-yl)benzaldehyde (2-2) as a viscous oil. NMR(CDC_l₃): δ10.0 (1H, s), 7.79 (2H, d, J=8 Hz), 7.54 (2H, d, J=8 Hz), 7.31-7.37 (3H, m), 7.15 (2H, d, J= 8 Hz), 7.03 (1H, s), 4.24 (3H, s).

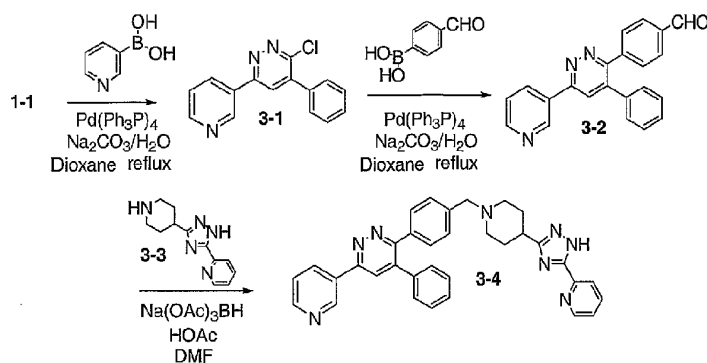
4-(6-Methoxy-4-phenylpyridazin-3-yl)benzaldehyde (2-2; 80 mg, 0.27 mmol) was dissolved in dry dimethylformamide (2 mL) and 2-(3-piperidin-4-yl-1H-pyrazol-5-yl)pyridine (1-4; 99 mg, 0.43 mmol) and acetic acid (0.14 mL, 2.3 mmol) were added. After stirring for 15 min., sodium triacetoxyborohydride (116 mg, 0.54 mmol) was added and the reaction mixture was stirred at ambient temperature for 12 hours. This reaction mixture was partially evaporated and the residue chromatographed on a silica gel column eluting with a 0-5% methanol/ ethyl acetate sat'd with NH₄OH. 3-methoxy-5-phenyl-6-(4-[[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl]phenyl)pyridazine (2-3) was obtained as a nearly pure viscous oil. NMR(CDC_l₃): δ8.60 (1H, d, J=5 Hz), 7.69-7.72 (2H, m), 7.23-7.35 (6H, m), 7.17 (2H, br d, J=7 Hz), 6.98 (1H, s), 6.61 (1H, s), 4.22 (3H, s), 3.52 (2H, s), 2.95 (2H, d, J=1.2 Hz), 2.72 (1H, m), 2.10 (2H, br t, J=11 Hz), 1.97 (2H, br d, J=12 Hz), 1.81 (2H, br q, J= 11).

This material was re-chromatographed on a HPLC by reversed-phase elution with 95 to 5% water/CH₃CN(0.1%TFA) to obtain pure title compound (2-3) as a TFA salt. The pure fractions were combined, the solvents evaporated and the residue chased with toluene to remove traces of water. Upon stirring this residue in diethyl ether, the product slowly precipitated as a white solid (60 mg). m/e(m+1): 503.2

A mixture of 3-methoxy-5-phenyl-6-(4-[[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl]phenyl)pyridazine (2-3) TFA (36.8 mg, 0.059 mmol) and pyridine hydrochloride (591 mg, 5.1 mmol) was heated at 150 °C for 5 min. This solid was dissolved in water, the solution made basic with NaHCO₃, and the product extracted into methylene chloride/ methanol (5%). This solution was dried, filtered and the solvents evaporated. This residue was digested in acetonitrile to give 5-phenyl-6-(4-[[4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl]phenyl)pyridazin-3-ol (2-4) as a tan solid freebase. NMR(CDC_l₃/CD₃OD): δ8.66 (1H, br d, J=4.5 Hz), 8.40 (1H, br d, J=7Hz), 8.29 (1H, br m), 7.67 (2H, br m), 7.55 (2H, d, J=7.5 Hz), 7.42 (1H, s), 7.35 (1H, t, J=7.5 Hz), 7.11 -7.30 (4H, m), 7.08

(2H, d, J=9 Hz), 6.98 (1H, s), 4.21 (2H, s), 3.47 (2H, d, J=10 Hz), 3.26 (1H, m), 3.00 (2H, m), 2.43 (2H, br d, J=11 Hz), 2.13 (2H, m); m/e(m+1): 489.2.

SCHEME 3



- 5 4-phenyl-6-pyridin-3-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (3-4)

4-Phenyl-3,6-dichloropyridazine (1-1; 113 mg, 0.5 mmol) was dissolved in dry dioxane (2 mL). Then pyridine-3-boronic acid (99 mg, 0.8 mmol), 2 M aqueous Na₂CO₃ (0.75 mL) and palladium(0) tetrakis-triphenylphosphine (60 mg, 0.04 mmol) were added. This mixture was degassed, the vessel sealed and heated at 110 °C for 9 hours. The cooled reaction was diluted with water and the product mixture extracted into ethyl acetate, the extract dried over anhydrous Na₂SO₄, filtered and evaporated. The product was purified by chromatography on silica gel and elution with a 20-70% ethyl acetate/ hexane gradient to give 3-chloro-4-phenyl-6-pyridin-3-ylpyridazine (3-1). NMR(CDCl₃): 89.26 (1H, s), 8.78 (1H, d, J=4.6 Hz), 8.51 (1H, d, J=8 Hz), 7.86 (1H, s), 7.55- 7.58 (5H, m), 7.51 (1H, dd, J=8Hz, J=4.5Hz); m/e(m+1): 268.1.

4-(4-Phenyl-6-pyridin-3-ylpyridazin-3-yl)benzaldehyde (3-2), was prepared according to the procedure described in Scheme 1, except 3-chloro-4-phenyl-6-pyridin-3-ylpyridazine (3-1) is substituted for N,N-dimethyl 6-chloro-5-phenylpyridazin-3-amine (1-2). NMR(CDCl₃): 10.06 (1H, s), 9.36 (1H, s), 8.78 (1H, d, J=4.6 Hz), 8.60 (1H, d, J=11.7Hz), 7.95 (1H, s), 7.85 (2H, d, J=8Hz), 7.69 (2H, d, J=8Hz), 7.52 (1H, m), 7.38-7.44 (3H, m), 7.28 (2H, d, J= 4.6 Hz); m/e(m+1): 338.2

4-Phenyl-6-pyridin-3-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyridazine (3-4) was prepared according to the procedure described in Scheme 1, except 4-(4-phenyl-6-pyridin-3-ylpyridazin-3-yl)benzaldehyde (3-2) is substituted for 4-[6-

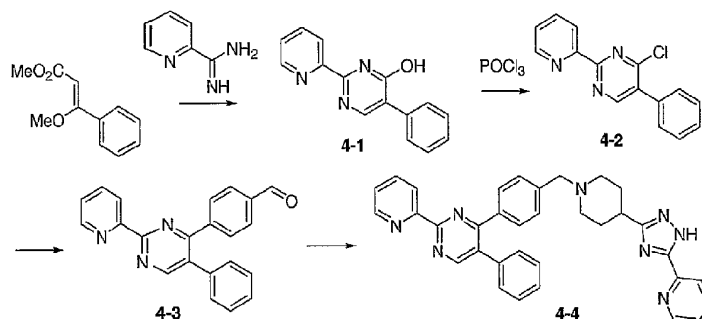
(dimethylamino)-4-phenylpyridazin-3-yl]benzaldehyde (**1-3**) and 2-(3-piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyridine (**3-3**; see synthesis below) for 2-(3-piperidin-4-yl-1*H*-pyazol-5-yl)pyridine (**1-4**).
 NMR(CDCl₃): δ9.34 (1H, s), 8.76 (1H, d, J=4 Hz), 8.64 (1H, d, J=4.3 Hz), 8.58 (1H, d, J=8Hz), 8.14 (1H, d, J=7.8Hz), 7.88 (1H, s), 7.83 (1H, t, J=7.8Hz), 7.44-7.53 (3H, m), 7.30-7.42 (5H, m), 3.57 (2H, s),
 5 2.98 (2H, br s), 2.87 (1H, m), 2.06-2.22 (4H, m), 2.00 (2H, m); m/e(m+1): 551.5
2-(3-Piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyridine (3-3)

Carbonyl diimidazole (3.57 g, 22 mmol) was added to a solution of 1-*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid (4.59 g, 20 mmol) in methylene chloride (50 mL) and stirred for two hours until gas evolution ceased. Then hydrazine (0.8 mL, ~26 mmol) was added to the
 10 reaction and the reaction was stirred at room temperature for another two hours. The reaction was diluted with more methylene chloride and washed with sat'd aqueous NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered and the solvent evaporated to give a viscous residue. Trituration with diethyl ether afforded *tert*-butyl 4-(hydrazinocarbonyl)-piperidine-1-carboxylate as an off-white solid.
 NMR(CDCl₃): δ6.77 (1H, br s), 4.15 (2H, br s), 3.90 (2H, v br s), 2.75 (2H, b s), 2.22 (1H, m), 1.78 (2H,
 15 br d, J=11.9 Hz), 1.66 (2H, br q, J=12.2 Hz, J=27.5 Hz), 1.47 (9H, s).

This material (2.43g, 10 mmol) was dissolved in anhydrous 2-ethoxyethanol (20 mL) and 2-cyanopyridine (1.14 g, 11 mmol) was added to the solution. After 25 wt. % sodium methoxide/methanol (1.1 mL, ~5 mmol) was added the mixture was heated to 130 °C for 16 hours. The cooled reaction was neutralized with acetic acid and partitioned between ethyl acetate and aq.
 20 NaHCO₃. The organic layer was dried over Na₂SO₄, the salts removed by filtration and the solvent evaporated under vacuum. This residue was triturated with diethyl ether to give *tert*-butyl 4-(5-pyridin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate as a white solid. NMR(CDCl₃): δ8.70 (1H, d, J=3.9Hz), 8.19 (1H, d, J=7.9Hz), 7.87 (1H, d t, J=1.7Hz, J=8Hz), 7.40 (1H, m), 4.20 (2H, br s), 3.03 (1H, m), 2.95 (2H, br s), 2.09 (2H, br d, J=12 Hz), 1.86 (2H, br q, J= 4.2Hz), 1.49 (9H, s); m/e (m+1): 330.2

This material (2.68 g, 8.14 mmol) was suspended in 4 N HCl/dioxane. The stoppered reaction mixture was stirred at room temperature for 16 hours and then diluted with diethyl ether. The solids were isolated by filtration and the hydroscopic solid was digested in acetonitrile. This solid was isolated by filtration and partially dissolved in hot methanol. Upon cooling and addition of some ethyl ether to the mixture 2-(3-piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyridine (**3-3**) was obtained as the
 30 dihydrochloride salt. NMR(DMSO-d₆): δ9.10 (1H, br s), 8.92 (1H, br s), 8.73 (1H, d, J=4.9Hz), 8.10-8.20 (2H, m), 7.64 (1H, t, J=5.7 Hz), 3.33 (2H, br d, J=12.7 Hz), 3.16 (1H, m), 3.05 (2H, br q, J=11.9 Hz, J=21.8 Hz), 2.18 (2H, br d, J=11.5 Hz), 1.99 (2H, br q, j=11.0 Hz, J=22.2 Hz); m/c(m+1): 230.3.

SCHEME 4



5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine (4-4)

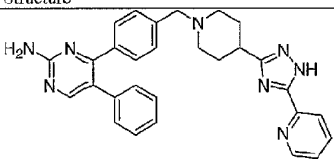
- 5 Methyl (2Z)-3-methoxy-3-phenylacrylate (*J. Chem. Soc. Perkin Trans. 2*, 1988, 227-234, 1.00 g, 5.20 mmol), 2-pyridine-2-carboximidamide hydrochloride (0.983 g, 6.24 mmol) and sodium hydroxide (0.250 g, 6.24 mmol) were stirred in 10 ml EtOH and heated to reflux. After 1h the reaction was cooled and concentrated in vacuo. The resulting residue was diluted with water, extracted 3x w/ EtOAc. The combined extracts was dried over Na₂SO₄, filtered and concentrated. Purification by flash
- 10 column chromatography (suspend material on silica, elute with 98:2 DCM/MeOH) afforded an impure yellow solid. The solid was triturated with ether, filtered, and washed with ether. This afforded 5-phenyl-2-pyridin-2-ylpyrimidin-4-ol (4-1) as a white solid. ¹H NMR(CDCl₃): δ 11.22 (bs, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.45 (d, J = 4.8 Hz, 1H), 8.24 (s, 1H), 7.93 (dt, J = 1.7, 7.6 Hz, 1H), 7.77 (d, J = 7.1 Hz, 2H), 7.50 (ddd, J = 1.1, 4.6, 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H).
- 15 5-Phenyl-2-pyridin-2-ylpyrimidin-4-ol (4-1; 206 mg, 0.826 mmol) was stirred in 4 ml of anhydrous MeCN. Phosphorous oxychloride (0.077 ml, 0.83 mmol) was added and the resulting mixture was heated to reflux. After 1h the reaction was cooled and concentrated in vacuo and quenched with half-saturated aqueous NaHCO₃. The mixture was extracted 3x with DCM. The combined organic
- 20 phases was dried over Na₂SO₄, filtered and concentrated to provide 4-chloro-5-phenyl-2-pyridin-2-ylpyrimidine (4-2). ¹H NMR(CDCl₃): δ 8.88 (s, 1H), 8.84 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 7.90 (dt, J = 1.5, 7.6 Hz, 1H), 7.53 (m, 5H), 7.46 (dd, J = 4.9, 7.1 Hz, 1H).
- 25 4-Chloro-5-phenyl-2-pyridin-2-ylpyrimidine (4-2; 0.15 g, 0.56 mmol), (4-formylphenyl)boronic acid (0.126 g, 0.840 mmol), bis (tri-*t*-butylphosphine)palladium(0) (0.014 g, 0.028 mmol) and anhydrous K₂F (0.107g, 1.85 mmol) were stirred in 2 ml anhydrous dioxane under N₂. The reaction was heated to reflux. After 15 min an additional sample of bis(tri-*t*-

butylphosphine)palladium(0) (0.014 g, 0.028 mmol) was added and the reaction was heated at reflux overnight. The reaction was cooled and diluted with water. The mixture was extracted 3x with DCM. The combined organic phases was dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (dissolved sample in DCM, eluted with 98:2 DCM/EA) and provided an impure sample of 4-(5-phenyl-2-pyridin-2-ylpyrimidin-4-yl)benzaldehyde (**4-3**) that was used directly in the next transformation.

4-(5-Phenyl-2-pyridin-2-ylpyrimidin-4-yl)benzaldehyde (**4-3**; 0.011 g, 0.035 mmol), sodium triacetoxyborohydride (0.010 g, 0.049 mmol) and 2-(3-piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyridine hydrochloride (0.022 g, 0.082 mmol) were stirred in 0.5 ml of anhydrous DMF. Triethylamine (0.014 ml, 0.098 mmol) and acetic acid (0.007 ml, 0.13 mmol) were added and the reaction was stirred at ambient temperature for 6h. The reaction was quenched by the addition of 3 drops of water and the resulting solution was purified by reverse phase preparative chromatography. This afforded 5-phenyl-2-pyridin-2-yl-4-([4-(5-pyridin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenylpyrimidine (**4-4**) as a trifluoroacetic acid salt. ¹H NMR(CDCl₃): δ 9.12 (s, 1H), 9.09 (d, 1H), 8.94 (d, 1H), 8.72 (d, 2H), 8.20 (m, 1H), 8.15 (m, 2H), 7.98 (s, 1H), 7.75 (d, 2H), 7.58 (m, 3H), 7.43 (m, 2H), 7.36 (m, 2H), 4.40 (s, 2H), 3.62 (m, 2H), 3.25 (m, 2H), 2.42 (m, 2H), 2.12 (m, 2H). m/z (m +1): 551.2

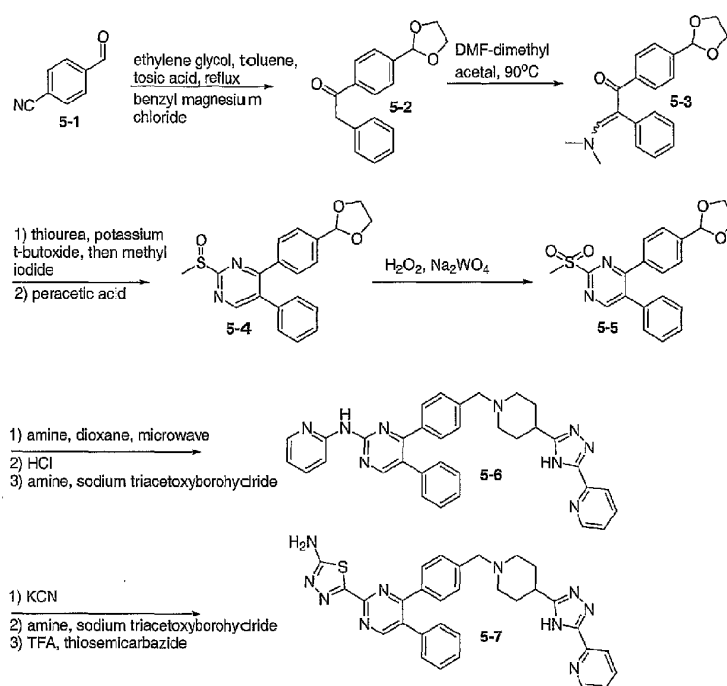
The following compound in Table 2 was made in an analogous manner.

Table 2

Cmpd. No.	Structure	Nomenclature	MS M+1
4-5		5-phenyl-4-([4-(5-pyridin-2-yl-1 <i>H</i> -1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenylpyrimidin-2-amine	488.2

20

SCHEME 5



5

1-(4-{5-phenyl-2-(pyridine-3-ylamino)pyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-6) and 1-(4-{2-(5-amino-1,3,4-thiadiazol-2-yl)-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine (5-7)

10

To a solution of 4-cyanobenzaldehyde (5-1) (20.0 g, 152.5 mmol) and ethylene glycol (25.5 mL, 457.5 mmol) in toluene (250 mL) was added *p*-toluenesulfonic acid (300 mg). The flask was equipped with a Dean-Stark trap and the mixture heated to reflux. After 5 hours, the mixture was concentrated. The residue was taken up in ethyl acetate and washed with saturated NaHCO₃, H₂O (2x), and brine. The organic layer was dried (MgSO₄), filtered, and concentrated to give 4-(1,3-dioxolan-2-yl)benzylidenebenzylbenzene as a clear oil which solidified under vacuum: ¹H-NMR (500 MHz, CDCl₃) δ 7.67 (d, J = 8.06 Hz, 2 H), 7.59 (d, J = 8.30 Hz, 2 H), 5.85 (s, 1 H), 4.13-4.05 (m, 4 H).

To a solution of 4-(1,3-dioxolan-2-yl)benzotrile (26.9 g, 154 mmol) in anhydrous THF (300 mL) was added benzylmagnesium chloride (100 mL, 2.0 M solution in THF, 200 mmol) slowly with internal temperature -30°C. After 1 hr the mixture was warmed to room temperature. After 4 hours, the mixture was recooled to

5 warmed to room temperature and extracted with ethyl acetate (3x). The combined organic layers were dried with sodium sulfate, filtered, and concentrated. Flash column (10%-40% ethyl acetate/hexanes) gave the acetal-ketone (5-2) as a pale yellow solid: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 8.02 (d, $J = 8.30$ Hz, 2 H), 7.57 (d, $J = 8.30$ Hz, 2 H), 7.38-7.24 (m, 5 H), 5.86 (s, 1 H), 4.29 (s, 2 H), 4.28-4.09 (m, 4 H).

A flask containing acetal-ketone (5-2) (6.7 g, 25 mol), dimethylformamide-
10 dimethylacetal (10 g) and dimethylformamide (2g) was fitted with an air cooled condenser and placed in an oil bath at 100°C to stir for 4.5 hours at which time LCMS indicated that only a trace of starting material remained. The mixture was then cooled to 40°C and isopropyl alcohol (10 ml) was added and allowed to continue stirring. When the mixture reached room temperature, diethyl ether (30 ml) was added and the stirring was continued as the mixture was cooled to 0°C . The yellowish crystals of
15 eneaminone (5-3) were filtered off to give 5.37 g of product consisted of a mixture of double bond isomers: LCMS, m/e 324.16 ($\text{M}+\text{H}^+$).

To a mixture of eneaminone (5-3) (3.23 g, 10 mmol), thiourea (912 mg, 12 mmol) and ethanol (40 ml) was added potassium tert-butoxide (1400 mg, 12.5 mmol). The mixture was heated to reflux with stirring for 1 hour at which time LCMS indicated that all the starting material had been
20 consumed. The reaction was diluted with dichloromethane (50 ml) and cooled to 0°C . Methyl iodide (0.934 ml, 15 mmol) was added at such a rate as to maintain an internal temperature $<4^{\circ}\text{C}$. The reaction mixture was allowed to stir for 30 minutes during which time a white precipitate forms. The volatiles were removed with a rotary evaporator and the residue was taken up in ethyl acetate, washed with water, dried with sodium sulfate and concentrated with a rotary evaporator. The resulting residue was triturated
25 with dichloromethane, diethyl ether and hexanes to yield 3.1 g of a pale yellow solid. The mother liquors could be purified by flash chromatography to yield another 257 mg of product: LCMS, m/e 351.06 ($\text{M}+\text{H}^+$). A solution of sulfide (3.034 g, 8.6 mmol) in dichloromethane (30 ml) was cooled in an ice bath with stirring. Peracetic acid (2.7 g of 32% in acetic acid diluted with 10 ml dichloromethane) was added drop-wise at such a rate as to maintain the temperature below 5°C . Stirring was continued for 2 hours at
30 which time LCMS indicated that all the starting material had been consumed. The reaction was quenched with saturated sodium sulfite, washed with saturated sodium bicarbonate, dried with sodium sulfate and concentrated with a rotary evaporator to give the sulfoxide (5-4) as a white solid: $^1\text{H-NMR}$ (500MHz, CDCl_3) δ 8.86 (s, 1H), 7.52-7.50 (m, 2H), 7.41-7.38 (m, 5H), 7.25-7.23 (m, 2H), 5.79 (s, 1H), 4.11-4.01 (m, 4H), 3.04 (s, 3H), LCMS, m/e 367.56 ($\text{M}+\text{H}^+$).

A solution of sulfoxide (5-4) (3.1 g, 8.7 mmol) in ethyl acetate (20 ml) was cooled to 0°C with rapid stirring. Sodium tungstenate (696 mg, 2.1 mmol) and hydrogen peroxide (20 ml, 169 mmol) were added and the mixture was allowed to slowly warm to room temperature with stirring. The reaction was stirred overnight at which time LCMS indicated that all the sulfoxide had been oxidized to the sulfone. The solution was carefully quenched with saturated sodium sulfite, dried with sodium sulfate and concentrated with a rotary evaporator to give the sulfone (5-5) as a white solid: ¹H-NMR (500MHz, CDCl₃) δ 8.88 (s, 1H), 7.56-7.54 (m, 2H), 7.45-7.42 (m, 5H), 7.27-7.25 (m, 2H), 5.82 (s, 1H), 4.14-4.04 (m, 4H), 3.46 (s, 3H), LCMS, m/e 383.44 (M+H⁺).

To a solution of sulfone (5-5) (177 mg, 0.48 mmol) and 2-amino-pyridine (64 mg, 0.68 mmol) in THF (4.5 ml) was added sodium bis(trimethylsilyl)amide (0.360 ml, 0.72 mmol, 2 M in THF). LCMS indicates reaction is done after a few minutes. LCMS m/e 397.69 (M+H⁺). Concentrated HCl (0.5 ml) was then added to the reaction mixture and stirred at room temperature for a few minutes. LCMS indicated that the reaction was complete. LCMS m/e 353.51 (M+H⁺). The volatiles were removed on a rotary evaporator, made alkaline with 50% sodium hydroxide and extracted with ethyl acetate (X2). Separately, a solution of the triazole-amine trifluoroacetate salt in dichloromethane (2ml) and methanol (2ml) was neutralized with Hunig's base (2ml) and then added to the organic fraction. The mixture was concentrated using a rotary evaporator and diluted with dichloromethane (10 ml). The mixture was stirred for 15 minutes at room temperature and then sodium triacetoxyborohydride (405 mg, 1.92 mol) was added. Stirring was continued for an additional 18 hours. The reaction mixture was diluted with sodium hydroxide (50%, 10 ml) and extracted twice with ethyl acetate, dried with sodium sulfate and concentrated on a rotary evaporator. The residue was purified by preparative reverse phase HPLC to give the product (5-6) as an amorphous solid: ¹H-NMR δ (500 MHz, CD₃OD) 8.80 (s, 1H), 8.75 (br, 1H), 8.43-8.32 (m, 4H), 7.82 (m, 1H), 7.65-7.58 (m, 3H), 7.54-7.52 (m, 2H), 7.45-7.42 (m, 1H), 7.40-7.38 (m, 3H), 7.28 (m, 2H), 4.40 (s, 2H), 3.64-3.45 (m, 3H), 3.24-3.22 (m, 2H), 2.41-2.38 (m, 2H), 2.17-2.15 (m, 2H), LCMS m/e 566.70 (M+H⁺).

A solution of sulfone (5-5) (250mg, 0.654mmol) and potassium cyanide (64mg, 0.983mmol) in DMSO (5mL) was stirred at rt for 1h. The reaction was diluted with ethyl acetate (50mL) and washed with water (3x25mL), and brine (2.5mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography (0-35% ethyl acetate/hexanes) to yield 4-[4-(1,3-dioxolan-2-yl)phenyl]-5-phenylpyrimidine-2-carbonitrile as a white solid. ¹H NMR (CDCl₃) δ 8.78 (s, 1H), 7.50 (m, 2H), 7.40 (m, 5H), 7.22 (m, 2H), 5.79 (s, 1H), 4.07 (m, 4H); MS (EI) m/z 330 (M+1).

A solution of 4-[4-(1,3-dioxolan-2-yl)phenyl]-5-phenylpyrimidine-2-carbonitrile (165mg, 0.501mmol) in THF (7mL) and 6N HCl (4mL) was stirred at rt for 1h. The reaction mixture was neutralized with sodium hydroxide and diluted with ethyl acetate (50mL). The solution was washed with

water (2x25mL) and dried over magnesium sulfate. Hunig's base (1mL) was added to the solution and it was then added to a solution of 4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidinium trifluoroacetate (206mg, 0.600mmol) in dichloromethane (5mL) and Hunig's base (1mL). The reaction mixture was concentrated under reduced pressure and diluted with dichloromethane (10mL). Sodium triacetoxycoborohydride (320mg, 1.509mmol) was added and stirred over night. The reaction mixture was basified with sodium hydroxide, extracted with ethyl acetate (50mL) and purified on reverse phase HPLC to yield 5-phenyl-4-(4-([4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine-2-carbonitrile as a solid. MS (EI) m/z 499 (M+1).

A solution of 5-phenyl-4-(4-([4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidine-2-carbonitrile (100mg, 0.163mmol) and hydrazinecarbothioamide (23mg, 0.252mmol) in trifluoroacetic acid (2.5mL) was heated at 75°C for 15min. Trifluoroacetic acid was removed under reduced pressure and the crude material was purified on reverse phase HPLC to yield the desired product (5-7) (75 mg, 67%). ¹H-NMR (500 MHz, CD₃OD) δ 8.88 (s, 1H), 8.75 (br s, 1H), 8.35 (m, 2H), 7.28-7.80 (m, 10H), 4.40 (s, 2H), 3.23-3.65 (m, 3H), 2.41-2.17 (m, 4H); MS (EI) m/z 573 (M+1).

The following compounds in Table 3 were made in an analogous manner.

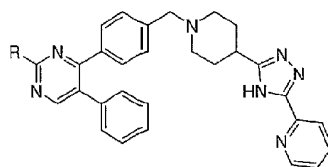
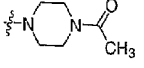
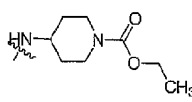
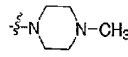
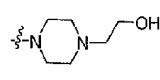
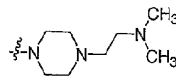
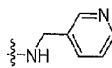

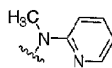

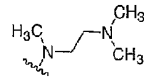
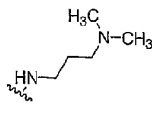
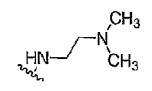
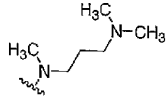


Table 3

Cmpd. No.	R	Nomenclature	MS M+1
5-8		1-methyl-4-(2-([5-phenyl-4-(4-([4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidin-2-yl]amino)ethyl)piperazine	614.8
5-9		1-[4-(2-amino-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine	488.6
5-10		1-[4-[2-(methylthio)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine	519.7

5-11		1-[4-[2-(4-acetylpiperazin-1-yl)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-1,4h-1,2,4-triazol-3-yl)piperidine	599.7
5-12		1-[4-(2-{[1-(ethoxycarbonyl)piperidin-4-yl]amino}-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	643.8
5-13		1-methyl-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidinium-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine	571.7
5-14		1-(2-hydroxyethyl)-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine	601.8
5-15		1-[2-(dimethylamino)ethyl]-4-[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]piperazine	628.8
5-16		1-(4-{5-phenyl-2-[(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	579.7
5-17		2-{[5-phenyl-4-(4-{[4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-yl]amino}pyridine	565.7
5-18		2-[5-[1-(4-{2-[methyl(pyridin-2-yl)amino]-5-phenylpyrimidin-4-yl}benzyl)piperidin-4-yl]-4h-1,2,4-triazol-3-yl]pyridine	579.7
5-19		1-[4-[2-(dimethylamino)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	516.7
5-20		1-(4-[2-[[2-(dimethylamino)ethyl](methyl)amino]-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	573.8

5-21		1-[4-(2-[[3-(dimethylammonio)propyl]amino]-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	573.8
5-22		1-[4-(2-[[2-(dimethylammonio)ethyl]amino]-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	559.7
5-23		1-(4-{2-[[3-(dimethylammonio)propyl](methyl)amino]-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine	587.8

EXAMPLE 1

Cloning of the human Akt isoforms and ΔPH-Akt1

- The pS2neo vector (deposited in the ATCC on April 3, 2001 as ATCC PTA-3253) was prepared as follows: The pRmHA3 vector (prepared as described in *Nucl. Acid Res.* 16:1043-1061 (1988)) was cut with BglII and a 2734 bp fragment was isolated. The pUChsneo vector (prepared as described in *EMBO J.* 4:167-171 (1985)) was also cut with BglII and a 4029 bp band was isolated. These two isolated fragments were ligated together to generate a vector termed pS2neo-1. This plasmid contains a polylinker between a metallothionein promoter and an alcohol dehydrogenase poly A addition site. It also has a neo resistance gene driven by a heat shock promoter. The pS2neo-1 vector was cut with Psp5II and BsiWI. Two complementary oligonucleotides were synthesized and then annealed (CTGCGGCCGC (SEQ.ID.NO.: 1) and GTACGCGCCCGCAG (SEQ.ID.NO.: 2)). The cut pS2neo-1 and the annealed oligonucleotides were ligated together to generate a second vector, pS2neo. Added in this conversion was a NotI site to aid in the linearization prior to transfection into S2 cells.
- Human Akt1 gene was amplified by PCR (Clontech) out of a human spleen cDNA (Clontech) using the 5' primer: 5'CGCGAATTCAGATCTACCATGAGCGACGTGGCTATTGTG 3' (SEQ.ID.NO.: 3), and the 3' primer: 5'CGCTCTAGAGGATCCTCAGGCCGTGCTGTGGC3' (SEQ.ID.NO.: 4). The 5' primer included an EcoRI and BglII site. The 3' primer included an XbaI and BamHI site for cloning purposes. The resultant PCR product was subcloned into pGEM3Z (Promega) as an EcoRI / Xba I fragment. For expression / purification purposes, a middle T tag was added to the 5' end of the full length Akt1 gene using the PCR primer: 5'GTACGATGCTGAACGATATCTTCG 3' (SEQ.ID.NO.: 5). The resulting

PCR product encompassed a 5' KpnI site and a 3' BamHI site which were used to subclone the fragment in frame with a biotin tag containing insect cell expression vector, pS2neo.

For the expression of a pleckstrin homology domain (PH) deleted (Δ aa 4-129, which includes deletion of a portion of the Akt1 hinge region) version of Akt1, PCR deletion mutagenesis was done using the full length Akt1 gene in the pS2neo vector as template. The PCR was carried out in 2 steps using overlapping internal primers (5' GAATACATGCCGATGGAAAGCGACGGGGCTGAAGAGATGGAGGTG 3' (SEQ.ID.NO.: 6), and 5' CCCCTCCATCTCTCAGCCCCGTGCTTCCATCGGCATG TATTC 3' (SEQ.ID.NO.: 7)) which encompassed the deletion and 5' and 3' flanking primers which encompassed the KpnI site and middle T tag on the 5' end. The final PCR product was digested with KpnI and SmaI and ligated into the pS2neo full length Akt1 KpnI / Sma I cut vector, effectively replacing the 5' end of the clone with the deleted version.

Human Akt3 gene was amplified by PCR of adult brain cDNA (Clontech) using the amino terminal oligo primer:

5' GAATTCAGATCTACCATGAGCGATGTTACCATTGTG 3' (SEQ.ID.NO.: 8); and the carboxy terminal oligo primer :

5' TCTAGATCTTATTCTCGTCCACTTGCAGAG 3' (SEQ.ID.NO.: 9).

These primers included a 5' EcoRI / BglII site and a 3' XbaI / BglII site for cloning purposes. The resultant PCR product was cloned into the EcoRI and XbaI sites of pGEM4Z (Promega). For expression / purification purposes, a middle T tag was added to the 5' end of the full length Akt3 clone using the PCR primer: 5' GGTACCATGGAATACATGCCGATGGAAAGCGATGTTACCATTGTGAAG 3' (SEQ.ID.NO.: 10). The resultant PCR product encompassed a 5' KpnI site which allowed in frame cloning with the biotin tag containing insect cell expression vector, pS2neo.

Human Akt2 gene was amplified by PCR from human thymus cDNA (Clontech) using the amino terminal oligo primer:

5' AAGCTTAGATCTACCATGAATGAGGTGTCTGTC 3' (SEQ.ID.NO.: 11); and the carboxy terminal oligo primer: 5' GAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.NO.: 12).

These primers included a 5' HindIII / BglII site and a 3' EcoRI / BamHI site for cloning purposes. The resultant PCR product was subcloned into the HindIII / EcoRI sites of pGem3Z (Promega). For expression / purification purposes, a middle T tag was added to the 5' end of the full length Akt2 using the PCR primer: 5' GGTACCATGGAATACATGCCGATGGAAAATGAGGTGTCTGTCATCAAAG 3' (SEQ.ID.NO.: 13). The resultant PCR product was subcloned into the pS2neo vector as described above.

EXAMPLE 2

35 Expression of human Akt isoforms and APH-Akt1

The DNA containing the cloned Akt1, Akt2, Akt3 and ΔPH-Akt1 genes in the pS2neo expression vector was purified and used to transfect *Drosophila* S2 cells (ATCC) by the calcium phosphate method. Pools of antibiotic (G418, 500 μg/ml) resistant cells were selected. Cells were expanded to a 1.0 L volume (~7.0 x 10⁶ / ml), biotin and CuSO₄ were added to a final concentration of 50 μM and 50 mM respectively. Cells were grown for 72 h at 27°C and harvested by centrifugation. The cell paste was frozen at -70°C until needed.

EXAMPLE 3

Purification of human Akt isoforms and ΔPH-Akt1

Cell paste from one liter of S2 cells, described in Example 2, was lysed by sonication with 50 mls 1% CHAPS in buffer A: (50 mM Tris pH 7.4, 1 mM EDTA, 1 mM EGTA, 0.2 mM AEBBSF, 10 μg/ml benzamidine, 5 μg/ml of leupeptin, aprotinin and pepstatin each, 10% glycerol and 1 mM DTT). The soluble fraction was purified on a Protein G Sepharose fast flow (Pharmacia) column loaded with 9mg/ml anti-middle T monoclonal antibody and eluted with 75 μM EYMPME (SEQ.ID.NO.: 14) peptide in buffer A containing 25% glycerol. Akt containing fractions were pooled and the protein purity evaluated by SDS-PAGE. The purified protein was quantitated using a standard Bradford protocol. Purified protein was flash frozen on liquid nitrogen and stored at -70°C.

Akt and Akt pleckstrin homology domain deletions purified from S2 cells required activation. Akt and Akt pleckstrin homology domain deletions was activated (Alessi et al. *Current Biology* 7:261-269) in a reaction containing 10 nM PDK1 (Upstate Biotechnology, Inc.), lipid vesicles (10 μM phosphatidylinositol-3,4,5-trisphosphate – Metreya, Inc, 100 μM phosphatidylcholine and 100 μM phosphatidylserine – Avanti Polar lipids, Inc.) and activation buffer (50 mM Tris pH7.4, 1.0 mM DTT, 0.1 mM EGTA, 1.0 μM Microcystin-LR, 0.1 mM ATP, 10 mM MgCl₂, 333 μg/ml BSA and 0.1mM EDTA). The reaction was incubated at 22°C for 4 hours. Aliquots were flash frozen in liquid nitrogen.

EXAMPLE 4

Akt Kinase Assays

Activated Akt isoforms and pleckstrin homology domain deletion constructs were assayed utilizing a GSK-derived biotinylated peptide substrate. The extent of peptide phosphorylation was determined by Homogeneous Time Resolved Fluorescence (HTRF) using a lanthanide chelate(Lance)-coupled monoclonal antibody specific for the phosphopeptide in combination with a streptavidin-linked allophycocyanin (SA-APC) fluorophore which will bind to the biotin moiety on the peptide. When the Lance and APC are in proximity (i.e. bound to the same phosphopeptide molecule), a non-radiative energy transfer takes place from the Lance to the APC, followed by emission of light from APC at 665 nm.

Materials required for the assay:

- A. Activated Akt isozyme or pleckstrin homology domain deleted construct.
- B. Akt peptide substrate: GSK3 α (S21) Peptide no.3928 biotin-GGRARTSSFAEPG (SEQ.ID.NO.:15), Macromolecular Resources.
- C. Lance labeled anti-phospho GSK3 α monoclonal antibody (Cell Signaling Technology, clone # 27).
- D. SA-APC (Prozyme catalog no. PJ25S lot no. 896067).
- E. Microfluor[®]B U Bottom Microtiter Plates (Dynex Technologies, Catalog no. 7205).
- F. Discovery[®] HTRF Microplate Analyzer, Packard Instrument Company.
- G. 100 X Protease Inhibitor Cocktail (PIC): 1 mg/ml benzamidine, 0.5 mg/ml pepstatin, 0.5 mg/ml leupeptin, 0.5 mg/ml aprotinin.
- H. 10X Assay Buffer: 500 mM HEPES, pH 7.5, 1% PEG, mM EDTA, 1 mM EGTA, 1% BSA, 20 mM β -Glycerol phosphate.
- I. Quench Buffer: 50 mM HEPES pH 7.3, 16.6 mM EDTA, 0.1% BSA, 0.1% Triton X-100, 0.17 nM Lance labeled monoclonal antibody clone # 27, 0.0067 mg/ml SA-APC
- J. ATP/MgCl₂ working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 125 mM KCl, 5% Glycerol, 25 mM MgCl₂, 375 μ M ATP
- K. Enzyme working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, active Akt. The final enzyme concentrations were selected so that the assay was in a linear response range.
- L. Peptide working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, 2 μ M GSK3 biotinylated peptide # 3928
- The reaction is assembled by adding 16 μ l of the ATP/MgCl₂ working solution to the appropriate wells of a 96-well microtiter plate. Inhibitor or vehicle (1.0 μ l) is added followed by 10 μ l of peptide working solution. The reaction is started by adding 13 μ l of the enzyme working solution and mixing. The reaction is allowed to proceed for 50 min and then stopped by the addition of 60 μ l HTRF quench buffer. The stopped reactions were incubated at room temperature for at least 30 min and then read on the Discovery instrument.
- PKA assay:
- Each individual PKA assay consists of the following components:
- A. 5X PKA assay buffer (200 mM Tris pH7.5, 100 mM MgCl₂, 5mM β -mercaptoethanol, 0.5 mM EDTA)
- B. 50 μ M stock of Kemptide (Sigma) diluted in water
- C. ³³P-ATP prepared by diluting 1.0 μ l ³³P-ATP [10 mCi/ml] into 200 μ l of a 50 μ M stock of unlabeled ATP
- D. 10 μ l of a 70 nM stock of PKA catalytic subunit (UBI catalog # 14-114) diluted in 0.5 mg/ml BSA

E. PKA/Kemptide working solution: equal volumes of 5X PKA assay buffer, Kemptide solution and PKA catalytic subunit.

The reaction is assembled in a 96 deep-well assay plate. The inhibitor or vehicle (10 μ l) is added to 10 μ l of the 35 P-ATP solution. The reaction is initiated by adding 30 μ l of the PKA/Kemptide working solution to each well. The reactions were mixed and incubated at room temperature for 20 min. The reactions were stopped by adding 50 μ l of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing.

The enzyme reaction product (phosphorylated Kemptide) was collected on p81 phosphocellulose 96 well filter plates (Millipore). To prepare the plate, each well of a p81 filter plate was filled with 75 mM phosphoric acid. The wells were emptied through the filter by applying a vacuum to the bottom of the plate. Phosphoric acid (75 mM, 170 μ l) was added to each well. A 30 μ l aliquot from each stopped PKA reaction was added to corresponding wells on the filter plate containing the phosphoric acid. The peptide was trapped on the filter following the application of a vacuum and the filters were washed 5 times with 75 mM phosphoric acid. After the final wash, the filters were allowed to air dry. Scintillation fluid (30 μ l) was added to each well and the filters counted on a TopCount (Packard).

PKC assay:

Each PKC assay consists of the following components:

- A. 10X PKC co-activation buffer: 2.5 mM EGTA, 4mM CaCl₂
- 20 B. 5X PKC activation buffer: 1.6 mg/ml phosphatidylserine, 0.16 mg/ml diacylglycerol, 100 mM Tris pH 7.5, 50 mM MgCl₂, 5 mM β -mercaptoethanol
- C. 33 P-ATP prepared by diluting 1.0 μ l 33 P-ATP [10 mCi/ml] into 100 μ l of a 100 μ M stock of unlabeled ATP
- D. Myelin basic protein (350 μ g/ml, UBI) diluted in water
- 25 E. PKC (50 ng/ml, UBI catalog # 14-115) diluted into 0.5 mg/ml BSA
- F. PKC/Myelin Basic Protein working solution: Prepared by mixing 5 volumes each of PKC co-activation buffer and Myelin Basic protein with 10 volumes each of PKC activation buffer and PKC.

The assays were assembled in 96 deep-well assay plates. Inhibitor or vehicle (10 μ l) was added to 5.0 μ l of 33 P-ATP. Reactions were initiated with the addition of the PKC/Myelin Basic Protein working solution and mixing. Reactions were incubated at 30 $^{\circ}$ C for 20 min. The reactions were stopped by adding 50 μ l of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing. Phosphorylated Myelin Basic Protein was collected on PVDF membranes in 96 well filter plates and quantitated by scintillation counting.

Specific compounds of the instant invention were tested in the assay described above and were found to have IC₅₀ of ≤ 50 μ M against one or more of Akt1, Akt2 and Akt3.

EXAMPLE 5

Cell based Assays to Determine Inhibition of Akt

5 Cells (for example LnCaP or a PTEN^{+/+} tumor cell line with activated Akt) were plated in 100 mM dishes. When the cells were approximately 70 to 80% confluent, the cells were refed with 5 ml of fresh media and the test compound added in solution. Controls included untreated cells, vehicle treated cells and cells treated with either LY294002 (Sigma) or wortmanin (Sigma) at 20 μ M or 200 nM, respectively. The cells were incubated for 2, 4 or 6 hrs and the media removed. The cells were washed
10 with PBS, scraped and transferred to a centrifuge tube. They were pelleted and washed again with PBS. Finally, the cell pellet was resuspended in lysis buffer (20 mM Tris pH8, 140 mM NaCl, 2 mM EDTA, 1% Triton, 1 mM Na Pyrophosphate, 10 mM β -Glycerol Phosphate, 10 mM NaF, 0.5 mM NaVO₄, 1 μ M Microcystine, and 1x Protease Inhibitor Cocktail), placed on ice for 15 minutes and gently vortexed to lyse the cells. The lysate was spun in a Beckman tabletop ultra centrifuge at 100,000 x g at 4°C for 20
15 min. The supernatant protein was quantitated by a standard Bradford protocol (BioRad) and stored at -70° C until needed.

Proteins were immunoprecipitated (IP) from cleared lysates as follows: For Akt1, lysates are mixed with Santa Cruz sc-7126 (D-17) in NETN (100 mM NaCl, 20 mM Tris pH 8.0, 1 mM EDTA, 0.5% NP-40) and Protein A/G Agarose (Santa Cruz sc-2003) was added. For Akt2, lysates were mixed
20 in NETN with anti-Akt-2 agarose (Upstate Biotechnology #16-174) and for Akt3, lysates were mixed in NETN with anti-Akt3 agarose (Upstate Biotechnology #16-175). The IPs were incubated overnight at 4° C, washed and separated by SDS-PAGE.

Western blots were used to analyze total Akt, pThr308 Akt1, pSer473 Akt1, and corresponding phosphorylation sites on Akt2 and Akt3, and downstream targets of Akt using specific
25 anti bodies (Cell Signaling Technology): Anti-Total Akt (cat. no. 9272), Anti-Phospho Akt Serine 473 (cat. no. 9271), and Anti-Phospho Akt Threonine 308 (cat. no. 9275). After incubating with the appropriate primary antibody diluted in PBS + 0.5% non-fat dry milk (NFDm) at 4 °C overnight, blots were washed, incubated with Horseradish peroxidase (HRP)-tagged secondary antibody in PBS + 0.5% NFDm for 1 hour at room temperature. Proteins were detected with ECL Reagents
30 (Amersham/Pharmacia Biotech RPN2134).

EXAMPLE 6

Heregulin Stimulated Akt Activation

MCF7 cells (a human breast cancer line that is PTEN^{+/+}) were plated at 1x10⁶ cells per 100 mM plate. When the cells were 70 – 80% confluent, they were refed with 5 ml of serum free media
35 and incubated overnight. The following morning, compound was added and the cells were incubated for

1 – 2 hrs, after which time heregulin was added (to induce the activation of Akt) for 30 minutes and the cells were analyzed as described above.

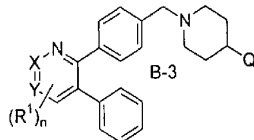
EXAMPLE 7

Inhibition Of Tumor Growth

- 5 In vivo efficacy of an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art.
- Human tumor cell lines which exhibit a deregulation of the PI3K pathway (such as LnCaP, PC3, C33a, OVCAR-3, MDA-MB-468 or the like) are injected subcutaneously into the left flank of 6-10 week old female nude mice (Harlan) on day 0. The mice are randomly assigned to a vehicle,
- 10 compound or combination treatment group. Daily subcutaneous administration begins on day 1 and continues for the duration of the experiment. Alternatively, the inhibitor test compound may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.2 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 4 to 5.5 weeks after the cells were injected. The
- 15 average weight of the tumors in each treatment group for each cell line is calculated.

The claims defining the invention are as follows:

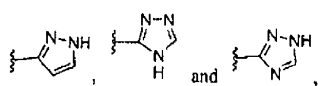
1. A compound of the Formula B-3:



5

wherein:

X is N and Y is CH or X is CH and Y is N;

Q is selected from: , which are optionally substituted with 1-3 R⁶;

a is 0 or 1; b is 0 or 1; m is 0, 1, or 2; n is 0, 1 or 2

R¹ is independently selected from: H, (C=O)_aO_bC₁-C₁₀ alkyl, (C=O)_aO_b aryl, (C=O)_aO_bC₂-C₁₀ alkenyl, (C=O)_aO_bC₂-C₁₀ alkynyl, CO₂H, halo, OH, O_bC₁-C₆ perfluoroalkyl, (C=O)_aNR⁷R⁸, CN, (C=O)_aO_bC₃-C₈ cycloalkyl, S(O)_mNR⁷R⁸, S(O)_m-(C₁-C₁₀)alkyl and (C=O)_aO_bheterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from R⁶;

R⁶ is independently: (C=O)_aO_bC₁-C₁₀ alkyl, (C=O)_aO_baryl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, (C=O)_aO_b heterocyclyl, CO₂H, halo, CN, OH, O_bC₁-C₆ perfluoroalkyl, O_a(C=O)_bNR⁷R⁸, oxo, CHO, (N=O)R⁷R⁸, S(O)_mNR⁷R⁸, S(O)_m-(C₁-C₁₀)alkyl or (C=O)_aO_bC₃-C₈ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from R^{6a};

R^{6a} is independently selected from: $(C=O)_nO_b(C_1-C_{10})$ alkyl, $O_n(C_1-C_3)$ perfluoroalkyl, (C_0-C_6) alkylene- $S(O)_mR^a$, oxo, OH, halo, CN, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, (C_3-C_6) cycloalkyl, (C_0-C_6) alkylene-aryl, (C_0-C_6) alkylene-heterocyclyl, (C_0-C_6) alkylene- $N(R^b)_2$, $C(O)R^a$, (C_0-C_6) alkylene- CO_2R^a , $C(O)H$, and (C_0-C_6) alkylene- CO_2H , said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from R^b , OH, (C_1-C_6) alkoxy, halogen, CO_2H , CN, $O(C=O)C_1-C_6$ alkyl, oxo, and $N(R^b)_2$;

R^7 and R^8 are independently selected from: H, $(C=O)O_bC_1-C_{10}$ alkyl, $(C=O)O_bC_3-C_8$ cycloalkyl, $(C=O)O_b$ aryl, $(C=O)O_b$ heterocyclyl, C_1-C_{10} alkyl, aryl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, heterocyclyl, C_3-C_8 cycloalkyl, SO_2R^a , and $(C=O)NR^b_2$, said alkyl, cycloalkyl, aryl, heterocyclyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from R^{6a} , or R^7 and R^8 can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 5-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocyclic or bicyclic heterocycle optionally substituted with one or more substituents selected from R^{6a} ;

R^a is independently: (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, aryl, or heterocyclyl; and

R^b is independently: H, (C_1-C_6) alkyl, aryl, heterocyclyl, (C_3-C_6) cycloalkyl, $(C=O)OC_1-C_6$ alkyl, $(C=O)C_1-C_6$ alkyl or $S(O)_2R^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

2. A compound which is selected from:

- N,N-dimethyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-amine;
- 10 N-methyl-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-amine;
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-yl)morpholine;
- tert-butyl 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-yl)piperazine-1-carboxylate;
- 15 4-phenyl-6-piperazin-1-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazine;
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-yl]thiomorpholine;
- 20 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-yl]thiomorpholine-1-oxide;
- 4-[5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-yl]thiomorpholine-1,1-dioxide;
- 3-methoxy-5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazine;
- 25 5-phenyl-6-(4-([4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazin-3-ol;
- 4-phenyl-6-pyridin-3-yl-3-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyridazine;
- 5-phenyl-2-pyridin-2-yl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidine;
- 30 5-phenyl-4-(4-([4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)pyrimidin-2-amine;
- 1-[4-[5-phenyl-2-(pyridine-3-ylamino)pyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine;
- 1-[4-[2-(5-amino-1,3,4-thiadiazol-2-yl)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine;

- 1-methyl-4-(2-([5-phenyl-4-(4-([4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl)methyl]phenyl)pyrimidin-2-yl]amino)ethyl)piperazine;
- 1-[4-(2-amino-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-[4-(2-(methylthio)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-[4-(2-(4-acetyl)piperazin-1-yl)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-[4-(2-([1-(ethoxycarbonyl)piperidin-4-yl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-methyl-4-[5-phenyl-4-(4-([4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl]phenyl)pyrimidin-2-yl]piperazine;
- 1-(2-hydroxyethyl)-4-[5-phenyl-4-(4-([4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl]phenyl)pyrimidin-2-yl]piperazine;
- 1-(2-(dimethylamino)ethyl)-4-[5-phenyl-4-(4-([4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl]phenyl)pyrimidin-2-yl]piperazine;
- 1-(4-[5-phenyl-2-[(pyridin-3-yl)methyl]amino]pyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 2-([5-phenyl-4-(4-([4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl]methyl)phenyl)pyrimidin-2-yl]amino)pyridine;
- 2-[5-[1-(4-[2-[methyl(pyridin-2-yl)amino]-5-phenylpyrimidin-4-yl)benzyl]piperidin-4-yl]-4h-1,2,4-triazol-3-yl]pyridine;
- 1-[4-[2-(dimethylamino)-5-phenylpyrimidin-4-yl]benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-(4-[2-([2-(dimethylamino)ethyl](methyl)amino)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-[4-(2-([3-(dimethylammonio)propyl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-[4-(2-([2-(dimethylammonio)ethyl]amino)-5-phenylpyrimidin-4-yl)benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine; and
- 1-(4-[2-([3-(dimethylammonio)propyl](methyl)amino)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

3. The TFA salt of a compound which is selected from:

- N-methyl-5-phenyl-6-(4-({4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl)methyl}phenyl)pyridazin-3-amine;
- 3-methoxy-5-phenyl-6-(4-({4-(5-pyridin-2-yl-1H-pyrazol-3-yl)piperidin-1-yl)methyl}phenyl)pyridazine;
- 5-phenyl-2-pyridin-2-yl-4-(4-({4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidine;
- 1-4-[5-phenyl-2-(pyridine-3-ylamino)pyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine;
- 1-4-[2-(5-amino-1,3,4-thiadiazol-2-yl)-5-phenylpyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidine;
- 1-methyl-4-(2-({5-phenyl-4-(4-({4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidin-2-yl}amino)ethyl)piperazine;
- 1-4-(2-amino-5-phenylpyrimidin-4-yl)benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-4-[2-(methylthio)-5-phenylpyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-4-[2-(4-acetyl)piperazin-1-yl)-5-phenylpyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-4-(2-([1-(ethoxycarbonyl)piperidin-4-yl]amino)-5-phenylpyrimidin-4-yl)benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-methyl-4-[5-phenyl-4-(4-({4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidin-2-yl]piperazine;
- 1-(2-hydroxyethyl)-4-[5-phenyl-4-(4-({4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidin-2-yl]piperazine;
- 1-[2-(dimethylamino)ethyl]-4-[5-phenyl-4-(4-({4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidin-2-yl]piperazine;
- 1-(4-[5-phenyl-2-((pyridin-3-ylmethyl)amino)pyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 2-({5-phenyl-4-(4-({4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidin-1-yl)methyl}phenyl)pyrimidin-2-yl}amino)pyridine;
- 2-{5-[1-(4-[2-[methyl(pyridin-2-yl)amino]-5-phenylpyrimidin-4-yl]benzyl)piperidin-4-yl]-4h-1,2,4-triazol-3-yl]pyridine};
- 1-4-[2-(dimethylamino)-5-phenylpyrimidin-4-yl]benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-(4-[2-([2-(dimethylamino)ethyl](methyl)amino)-5-phenylpyrimidin-4-yl]benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;
- 1-4-(2-([3-(dimethylammonio)propyl]amino)-5-phenylpyrimidin-4-yl)benzyl}-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;

1-[4-(2-{{2-(dimethylammonio)ethyl}amino)-5-phenylpyrimidin-4-yl}benzyl]-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine; and

1-(4-{2-[[3-(dimethylammonio)propyl](methyl)amino]-5-phenylpyrimidin-4-yl}benzyl)-4-(5-pyridin-2-yl-4h-1,2,4-triazol-3-yl)piperidine;

5 or a stereoisomer thereof.

4. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1 or 2 or a pharmaceutically acceptable salt or a stereoisomer thereof.

5. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a TFA salt of Claim 3 or a stereoisomer thereof.

6. The use of a compound according to Claim 1 or 2, or a pharmaceutically acceptable salt or a stereoisomer thereof, for the preparation of a medicament useful in the treatment or prevention of cancer in a mammal in need of such treatment.

7. The use of a TFA salt according to Claim 3, or a stereoisomer thereof, for the preparation of a medicament useful in the treatment or prevention of cancer in a mammal in need of such treatment.

8. A pharmaceutical composition made by combining a compound of Claim 1 or 2, or a pharmaceutically acceptable salt or a stereoisomer thereof, and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition made by combining the TFA salt of Claim 3 and a pharmaceutically acceptable carrier.

10. A method of treating cancer in a mammal comprising administering to said mammal in need thereof a pharmaceutically effective amount of a compound of Claim 1 or 2, or a pharmaceutically acceptable salt or a stereoisomer thereof.

11. A method of treating cancer in a mammal comprising administering to said mammal in need thereof a pharmaceutically effective amount of a TFA salt of Claim 3 or a stereoisomer thereof.

Dated 27 October, 2010

Merck Sharp & Dohme Corp.

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 Chua, Peter C.
 Cosford, Nicholas D.P.
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