AXL INHIBITORS FOR USE IN COMBINATION THERAPY FOR PREVENTING, TREATING OR MANAGING METASTATIC CANCER

FIELD OF THE INVENTION

This invention is directed to combination therapies for the prevention, treatment, or management of metastatic cancer in a patient having cancer or a patient having other proliferative diseases or disorders.

BACKGROUND OF THE INVENTION

All of the protein kinases that have been identified to date in the human genome share a highly conserved catalytic domain of around 300 aa. This domain folds into a bi-lobed structure in which resides ATP-binding and catalytic sites. The complexity of protein kinase regulation allows many potential mechanisms of inhibition including competition with activating ligands, modulation of positive and negative regulators, interference with protein dimerization, and allosteric or competitive inhibition at the substrate or ATP binding sites.

Axl (also known as UFO, ARK, and Tyro7; nucleotide accession numbers NM_021913 and NM_001699; protein accession numbers NP_068713 and NP_001690) is a receptor protein tyrosine kinase (RTK) that comprises a C-terminal extracellular ligand-binding domain and N-terminal cytoplasmic region containing the catalytic domain. The extracellular domain of Axl has a unique structure that juxtaposes immunoglobulin and fibronectin Type III repeats and is reminiscent of the structure of neural cell adhesion molecules. Axl and its two close relatives, Mer /Nyk and Sky (Tyro3 / Rse / Dtk), collectively known as the Tyro3 family of RTK's, all bind and are stimulated to varying degrees by the same ligand, Gas6 (growth arrest specific-6), a ~76kDa secreted protein with significant homology to the coagulation cascade regulator, Protein S. In addition to binding to ligands, the Axl extracellular domain has been shown to undergo homophilic interactions that mediate cell aggregation, suggesting that one important function of Axl may be to mediate cell-cell adhesion.

Axl is predominantly expressed in the vasculature in both endothelial cells (EC's) and vascular smooth muscle cells (VSMC's) and in cells of the myeloid lineage and is also detected in breast epithelial cells, chondrocytes, Sertoli cells and neurons. Several

functions including protection from apoptosis induced by serum starvation, TNF-α or the viral protein E1A, as well as migration and cell differentiation have been ascribed to Axl signaling in cell culture. However, Axl-/- mice exhibit no overt developmental phenotype and the physiological function of Axl *in vivo* is not clearly established in the literature.

Angiogenesis (the formation of new blood vessels) is limited to functions such as wound healing and the female reproductive cycle in healthy adults. This physiological process has been co-opted by tumors, thus securing an adequate blood supply that feeds tumor growth and facilitates metastasis. Deregulated angiogenesis also a feature of many other diseases (for example, psoriasis, rheumatoid arthritis, endometriosis and blindness due to age-related macular degeneration (AMD), retinopathy of prematurity and diabetes) and often contributes to the progression or pathology of the condition.

The overexpression of Axl and/or its ligand has also been reported in a wide variety of solid tumor types including, but not limited to, breast, renal, endometrial, ovarian, thyroid, non-small cell lung carcinoma, and uveal melanoma as well as in myeloid leukemia's. Furthermore, it possesses transforming activity in NIH3T3 and 32D cells. It has been demonstrated that loss of Axl expression in tumor cells blocks the growth of solid human neoplasms in an *in vivo* MDA-MB-231 breast carcinoma xenograft model. Taken together, these data suggest Axl signaling can independently regulate EC angiogenesis and tumor growth and thus represents a novel target class for tumor therapeutic development.

The expression of Axl and Gas6 proteins is upregulated in a variety of other disease states including endometriosis, vascular injury and kidney disease and Axl signaling is functionally implicated in the latter two indications. Axl - Gas6 signaling amplifies platelet responses and is implicated in thrombus formation. Axl may thus potentially represent a therapeutic target for a number of diverse pathological conditions including solid tumors, including, but not limited to, breast, renal, endometrial, ovarian, thyroid, non-small cell lung carcinoma and uveal melanoma; liquid tumors, including but not limited to, leukemias (particularly myeloid leukemias) and lymphomas; endometriosis, vascular disease / injury (including but not limited to restenosis, atherosclerosis and thrombosis), psoriasis; visual impairment due to macular degeneration; diabetic retinopathy and retinopathy of prematurity; kidney disease (including but not limited to glomerulonephritis, diabetic nephropathy and renal transplant rejection), rheumatoid arthritis; osteoporosis, osteoarthritis and cataracts.

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Application No. 20080153815, U.S. Published Patent Application No. 20080188454, U.S. Published Patent Application No. 20080176847, U.S. Published Patent Application No. 20080188455, U.S. Published Patent Application No. 20080182862, U.S. Published Patent Application No. 20080188474, U.S. Published Patent Application No. 20080117789, U.S. Published Patent Application No. 20090111816, PCT Published Patent Application No. WO 2007/0030680, PCT Published Patent Application No. WO 2008/045978, PCT Published Patent Application No. WO 2008/083353, PCT Published Patent Application No. WO 2008/0083357, PCT Published Patent Application No. WO 2008/083367, PCT Published Patent Application No. WO 2008/083354, PCT Published Patent Application No. WO 2008/083356, PCT Published Patent Application No. WO 2008/080134, and PCT Published Patent Application No. WO 2009/054864, the disclosures of which are incorporated in full by reference herein in their entireties, discloses compounds which are useful as Axl inhibitors.

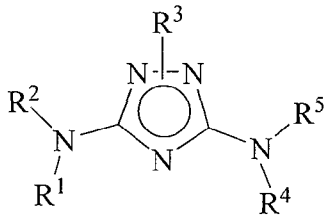
SUMMARY OF THE INVENTION

This invention is directed to combination therapies that provide better therapeutic profiles than current single agent therapies or other combination therapies utilizing Axl inhibitors. Encompassed by the invention are combination therapies, of one or more AXL inhibitors with one or more chemotherapeutic agents, that have at least an additive potency or at least an additive therapeutic effect. Preferably, the invention is directed to combination therapies where the therapeutic efficacy is greater than additive, *e.g.*, a synergy exists between an AXL inhibitor and one or more chemotherapeutic agents when co-administered. Preferably, such combination therapies also reduce or avoid unwanted or adverse effects. In certain embodiments, the combination therapies of the invention provide an improved overall therapy relative to the administration of the therapeutic agents by themselves. In certain embodiments, doses of existing chemotherapeutic agents can be reduced or administered less frequently in using the combination therapies of the invention, thereby increasing patient compliance, improving therapy and reducing unwanted or adverse effects.

Accordingly, this invention is directed to combination therapies designed to prevent, treat or manage cancer, preferably metastatic cancer, in a patient, wherein the combination therapies comprise administering an Axl inhibitor to the patient in need thereof in combination with one or more chemotherapeutic agents. In particular, this

invention provides methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents.

In one embodiment, the Axl inhibitor utilized in the combination therapies of the invention is a compound of formula (I):



(I)

wherein:

R^1, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, aralkyl, $-C(O)R^8$, $-C(O)N(R^6)R^7$, and $-C(=NR^6)N(R^6)R^7$;

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^8$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

or R^2 is a polycyclic heteroaryl containing more than 14 ring atoms as described above and R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally

substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

or R^3 is a polycyclic heteroaryl containing more than 14 ring atoms as described above, and

R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl,

optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkynyl;

each R^9 is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{10} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted

heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl , optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two $R^{12's}$, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain; and

each R^{14} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain;

as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or N-oxide thereof.

In another aspect, this invention provides *in vivo* assays to determine the effectiveness of a compound of formula (I) in combination with one or more chemotherapeutic agents in preventing, treating or managing cancer, preferably metastatic cancer, in a patient.

These and other aspects of the invention will be evident upon reference to the following detailed description. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents is hereby incorporated by reference in its entirety.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows the effect of an Axl inhibitor (*i.e.*, Compound A) on the number of macroscopic lung metastases in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 2 shows the effect of an Axl inhibitor (*i.e.*, Compound A) on the number of medium (≤2mm) macroscopic lung metastases in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 3 shows the effect of an Axl inhibitor (*i.e.*, Compound A) on the number of large (>3mm) macroscopic lung metastases in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 4 shows the effect of an Axl inhibitor (*i.e.*, Compound A) on the number of microscopic liver metastases in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 5 shows the effect of an Axl inhibitor (*i.e.*, Compound A) in combination with a chemotherapeutic agent (*i.e.*, cisplatin) on the volume of the primary tumor in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 6 shows the effect of an Axl inhibitor (*i.e.*, Compound A) in combination with a chemotherapeutic agent (*i.e.*, cisplatin) on the number of micrometastasis in the liver in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 7 shows the effect of an Axl inhibitor (*i.e.*, Compound A) in combination with a chemotherapeutic agent (*i.e.*, cisplatin) on the number of large (>3mm) metastases in the lung in the mouse 4T1 breast tumor model of metastatic cancer.

FIGURE 8 shows the percentage of mice bearing large (>3mm) metastases after treatment with an Axl inhibitor (*i.e.*, Compound A) in combination with a chemotherapeutic agent (*i.e.*, cisplatin) in the mouse 4T1 breast tumor model of metastatic cancer.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Amino" refers to the $-NH_2$ radical.

"Carboxy" refers to the -C(O)OH radical.

"Cyano" refers to the -CN radical.

"Nitro" refers to the $-NO_2$ radical.

"Oxa" refers to the -O- radical.

"Oxo" refers to the =O radical.

"Thioxo" refers to the =S radical.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms and which is attached to the rest of the molecule by a single bond, for example, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. For purposes of this invention, the term "lower alkyl" refers to an alkyl radical having one to six carbon atoms.

"Optionally substituted alkyl" refers to an alkyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, for example, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Optionally substituted alkenyl" refers to an alkenyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one triple bond, optionally containing at least one double bond, having from two to twelve carbon atoms, preferably

one to eight carbon atoms and which is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

"Optionally substituted alkynyl" refers to an alkynyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon in the alkylene chain or through any two carbons within the chain.

"Optionally substituted straight or branched alkylene chain" refers to an alkylene chain, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they

are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, for example, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a double bond or a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Optionally substituted straight or branched alkenylene chain" refers to an alkenylene chain, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Straight or branched alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to twelve carbon atoms, for example, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Optionally substituted straight or branched alkynylene chain" refers to an alkynylene chain, as defined above, which is optionally substituted by one or more

substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkenyl, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^{20}$, $-OC(O)-R^{20}$, $-N(R^{20})_2$, $-C(O)R^{20}$, $-C(O)OR^{20}$, $-C(O)N(R^{20})_2$, $-N(R^{20})C(O)OR^{20}$, $-N(R^{20})C(O)R^{20}$, $-N(R^{20})S(O)_2R^{20}$, $-S(O)_tOR^{20}$ (where t is 1 or 2), $-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-S(O)_2N(R^{20})_2$ where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 14 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical may be a monocyclic, bicyclic, or tricyclic system and which may include spiro ring systems. An aryl radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the aryl radical. For purposes of this invention, an "aryl" radical as defined herein can not contain rings having more than 7 members and cannot contain rings wherein two non-adjacent ring atoms thereof are connected through an atom or a group of atoms (*i.e.,* a bridged ring system). Aryl radicals include, but are not limited to, aryl radicals derived from acenaphthylene, anthracene, azulene, benzene, 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, and phenanthrene.

"Optionally substituted aryl" refers to an aryl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$,

$-R^{21}$-C(O)OR^{20}, $-R^{21}$-C(O)$N(R^{20})_2$, $-R^{21}$-O-R^{22}-C(O)$N(R^{20})_2$, $-R^{21}$-$N(R^{20})$C(O)OR^{20}, $-R^{21}$-$N(R^{20})$C(O)R^{20}, $-R^{21}$-$N(R^{20})S(O)_2R^{20}$, $-R^{21}$-C(=NR^{20})$N(R^{20})_2$, $-R^{21}$-$S(O)_tOR^{20}$ (where t is 1 or 2), $-R^{21}$-$S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}$-$S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^{22} is a straight or branched alkylene or alkenylene chain.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like.

"Optionally substituted aralkyl" refers to an aralkyl radical, as defined above, wherein the alkylene chain of the aralkyl radical is an optionally substituted alkylene chain, as defined above, and each aryl radical of the aralkyl radical is an optionally substituted aryl radical, as defined above.

"Aralkenyl" refers to a radical of the formula $-R_d-R_c$ where R_d is an alkenylene chain as defined above and R_c is one or more aryl radicals as defined above.

"Optionally substituted aralkenyl" refers to an aralkenyl radical, as defined above, wherein the alkenylene chain of the aralkenyl radical is an optionally substituted alkenylene chain, as defined above, and each aryl radical of the aralkenyl radical is an optionally substituted aryl radical, as defined above.

"Aralkynyl" refers to a radical of the formula $-R_eR_c$ where R_e is an alkynylene chain as defined above and R_c is one or more aryl radicals as defined above.

"Optionally substituted aralkynyl" refers to an aralkynyl radical, as defined above, wherein the alkynylene chain of the aralkynyl radical is an optionally substituted alkynylene chain, as defined above, and each aryl radical of the aralkynyl radical is an optionally substituted aryl radical, as defined above.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused, spiro or bridged ring systems, having from three to fifteen carbon atoms, preferably having from

three to ten carbon atoms, more preferably from five to seven carbons and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. For purposes of this invention, a bridged ring system is a system wherein two non-adjacent ring atoms thereof are connected through an atom or a group of atoms, wherein the atom or the group of atoms are the bridging element. An example of a bridged cycloalkyl (monovalent) radical is norbornanyl (also called bicyclo[2.2.1]heptanyl). For purposes of this invention, a non-bridged ring system is a system which does not contain a bridging element, as described above. For purposes of this invention, a fused ring system is a system wherein two adjacent ring atoms thereof are connected through an atom or a group of atoms. An example of a fused cycloalkyl (monovalent) radical is decahydronaphthalenyl (also called decalinyl). For purposes of this invention, a spiro ring system is a system wherein two rings are joined via a single carbon (quaternary) atom. An example of a spiro cycloalkyl (monovalent) radical is spiro[5.5]undecanyl. Monocyclic cycloalkyl radicals do not include spiro, fused or bridged cycloalkyl radicals, but do include for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic radicals include fused, spiro or bridged cycloalkyl radicals, for example, C_{10} radicals such as adamantanyl (bridged) and decalinyl (fused), and C_7 radicals such as bicyclo[3.2.0]heptanyl (fused), norbornanyl and norbornenyl (bridged), as well as substituted polycyclic radicals, for example, substituted C_7 radicals such as 7,7-dimethylbicyclo[2.2.1]heptanyl (bridged), and the like.

"Optionally substituted cycloalkyl" refers to a cycloalkyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where t is 1 or 2),

$-R^{21}-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"Cycloalkylalkyl" refers to a radical of the formula $-R_bR_g$ where R_b is an alkylene chain as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkyl" refers to a cycloalkylalkyl radical, as defined above, wherein the alkylene chain of the cycloalkylalkyl radical is an optionally substituted alkylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkyl radical is an optionally substituted cycloalkyl radical, as defined above.

"Cycloalkylalkenyl" refers to a radical of the formula $-R_dR_g$ where R_d is an alkenylene chain as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkenyl" refers to a cycloalkylalkenyl radical, as defined above, wherein the alkenylene chain of the cycloalkylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkenyl radical is an optionally substituted cycloalkyl radical as defined above.

"Cycloalkylalkynyl" refers to a radical of the formula $-R_eR_g$ where R_e is an alkynylene radical as defined above and R_g is a cycloalkyl radical as defined above.

"Optionally substituted cycloalkylalkynyl" refers to a cycloalkylalkynyl radical, as defined above, wherein the alkynylene chain of the cycloalkylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the cycloalkyl radical of the cycloalkylalkynyl radical is an optionally substituted cycloalkyl radical as defined above.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, for example, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by

one or more halo radicals, as defined above.

"Haloalkynyl" refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring system radical which comprises one to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include spiro or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of a bridged heterocyclyl include, but are not limited to, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.2]octanyl, diazabicyclo[3.2.1]octanyl, diazabicyclo[3.3.1]nonanyl, diazabicyclo[3.2.2]nonanyl and oxazabicyclo[2.2.1]heptanyl. A "bridged *N*-heterocyclyl" is a bridged heterocyclyl containing at least one nitrogen, but which optionally contains up to four additional heteroatoms selected from O, N and S. For purposes of this invention, a non-bridged ring system is a system wherein no two non-adjacent ring atoms thereof are connected through an atom or a group of atoms. Examples of heterocyclyl radicals include, but are not limited to, dioxolanyl, 1,4-diazepanyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, octahydro-1*H*-pyrrolo[3,2-*c*]pyridinyl, octahydro-1*H*-pyrrolo[2,3-*c*]pyridinyl, octahydro-1*H*-pyrrolo[2,3-*b*]pyridinyl, octahydro-1*H*-pyrrolo[3,4-*b*]pyridinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, octahydro-1*H*-pyrido[1,2-*a*]pyrazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, 3,7-diazabicyclo[3.3.1]nonan-3-yl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuranyl, thienyl[1,3]dithianyl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, azetidinyl, octahydropyrrolo[3,4-*c*]pyrrolyl, octahydropyrrolo[3,4-*b*]pyrrolyl, decahydroprazino[1,2-*a*]azepinyl, azepanyl, azabicyclo[3.2.1]octyl, and 2,7-diazaspiro[4.4]nonanyl.

"Optionally substituted heterocyclyl" refers to a heterocyclyl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally

substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where t is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the *N*-heterocyclyl radical to the rest of the molecule may be through a nitrogen atom in the *N*-heterocyclyl radical or through a carbon in the *N*-heterocyclyl radical.

"Optionally substituted *N*-heterocyclyl" refers to an *N*-heterocyclyl, as defined above, which is optionally substituted by one or more substituents as defined above for optionally substituted heterocyclyl.

"Heterocyclylalkyl" refers to a radical of the formula $-R_bR_h$ where R_b is an alkylene chain as defined above and R_h is a heterocyclyl radical as defined above, and when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkyl" refers to a heterocyclylalkyl radical, as defined above, wherein the alkylene chain of the heterocyclylalkyl radical is an optionally substituted alkylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heterocyclylalkenyl" refers to a radical of the formula $-R_dR_h$ where R_d is an alkenylene chain as defined above and R_h is a heterocyclyl radical as defined above, and when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkenylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkenyl" refers to a heterocyclylalkenyl radical, as defined above, wherein the alkenylene chain of the heterocyclylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkenyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heterocyclylalkynyl" refers to a radical of the formula $-R_eR_h$ where R_e is an alkynylene chain as defined above and R_h is a heterocyclyl radical as defined above, and when the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkynylene chain at the nitrogen atom.

"Optionally substituted heterocyclylalkynyl" refers to a heterocyclylalkynyl radical, as defined above, wherein the alkynylene chain of the heterocyclylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the heterocyclyl radical of the heterocyclylalkynyl radical is an optionally substituted heterocyclyl radical, as defined above.

"Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. A heteroaryl radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the heteroaryl radical. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include spiro or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized and the nitrogen atom may be optionally quaternized. For purposes of this invention, the aromatic ring of the heteroaryl radical need not contain a heteroatom, as long as one ring of the heteroaryl radical contains a heteroatom. For example benzo-fused heterocyclyls such as 1,2,3,4-tetrahydroisoquinolin-7-yl are considered a "heteroaryl" for the purposes of this invention. Except for the polycyclic heteroaryls containing more than 14 ring atoms, as defined below, a "heteroaryl" radical as defined herein can not contain rings having more than 7 members and cannot contain rings wherein two non-adjacent members thereof are connected through an atom or a group of atoms (*i.e.*, a

bridged ring system). Examples of heteroaryl radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[*b*][1,4]oxazinyl, benzo[*b*]azepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-*d*]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepinyl, cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl such as 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazinyl, 5,6-dihydrobenzo[*h*]cinnolinyl, 7',8'-dihydro-5'*H*-spiro[[1,3]dioxolane-2,6'-quinoline]-3'-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazinyl, 2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]oxazinyl, 3',4'-dihydrospiro[cyclobutane-1,2'-pyrido[3,2-*b*][1,4]oxazinyl, dihydropyridooxazinyl such as 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazinyl, dihydropyridothiazinyl such as 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-*c*]pyridinyl, furopyrimidinyl, furopyridazinyl, furopyrazinyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, imidazopyridazinyl, imidazopyrazinyl, imidazo[1,2-*a*]pyridinyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolinyl (isoquinolyl), indolizinyl, isoxazolyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 3'-oxo-3',4'-dihydrospiro[cyclobutane-1,2'-pyrido[3,2-*b*][1,4]oxazine]yl, 7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, phenanthridinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-*d*]pyrimidinyl, pyridinyl (pyridyl), pyrido[3,2-d]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl (pyridazyl), pyrrolyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrrolopyrazinyl, 2*H*-pyrido[3,2-*b*][1,4]oxazinonyl, 1*H*-pyrido[2,3-*b*][1,4]oxazinonyl, pyrrolopyridinyl such as 1*H*-pyrrolo[2,3-*b*]pyridinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 2,3,4,5-tetrahydrobenzo[*b*]oxepinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridinyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepinyl,

5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-*c*]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, 1,2,3,4-tetrahydroisoquinolin-7-yl, triazinyl, thieno[2,3-*d*]pyrimidinyl, thienopyrimidinyl (*e.g.*, thieno[3,2-*d*]pyrimidinyl), thieno[2,3-*c*]pyridinyl, thienopyridazinyl, thienopyrazinyl, and thiophenyl (thienyl).

"Optionally substituted heteroaryl" refers to a heteroaryl radical, as defined above, which is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_2R^{20}2$, $-R^{21}-C(=NR^{20})N(R^{20})_2$, $-R^{21}-S(O)_tOR^{20}$ (where t is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}-S(O)_2N(R^{20})_2$, where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the *N*-heteroaryl radical to the rest of the molecule may be through a nitrogen atom in the *N*-heteroaryl radical or through a carbon atom in the *N*-heteroaryl radical.

"Optionally substituted *N*-heteroaryl" refers to an *N*-heteroaryl, as defined above,

which is optionally substituted by one or more substituents as defined above for optionally substituted heteroaryl.

"Polycyclic heteroaryl containing more than 14 ring atoms" refers to a 15- to 20-membered ring system radical comprising hydrogen atoms, one to fourteen carbon atoms, one to eight heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. A "polycyclic heteroaryl containing more than 14 ring atoms" radical is commonly, but not necessarily, attached to the parent molecule via an aromatic ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical. For purposes of this invention, the "polycyclic heteroaryl containing more than 14 ring atoms" radical may be a bicyclic, tricyclic or tetracyclic ring system, which may include fused or spiro ring systems; and the nitrogen, carbon or sulfur atoms in the "polycyclic heteroaryl containing more than 14 ring atoms" radical may be optionally oxidized and the nitrogen atom may also be optionally quaternized. For purposes of this invention, the aromatic ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical need not contain a heteroatom, as long as one ring of the "polycyclic heteroaryl containing more than 14 ring atoms" radical contains a heteroatom. Examples of "polycyclic heteroaryl containing more than 14 ring atoms" radicals include, but are not limited to, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl.

"Optionally substituted polycyclic heteroaryl containing more than 14 ring atoms" is meant to include "polycyclic heteroaryl containing more than 14 ring atoms" radicals, as

defined above, which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{21}-OR^{20}$, $-R^{21}-OC(O)-R^{20}$, $-R^{21}-N(R^{20})_2$, $-R^{21}-C(O)R^{20}$, $-R^{21}-C(O)OR^{20}$, $-R^{21}-C(O)N(R^{20})_2$, $-R^{21}-N(R^{20})C(O)OR^{20}$, $-R^{21}-N(R^{20})C(O)R^{20}$, $-R^{21}-N(R^{20})S(O)_tR^{20}$ (where t is 1 or 2), $-R^{21}-S(O)_tOR^{20}$ (where t is 1 or 2), $-R^{21}-S(O)_pR^{20}$ (where p is 0, 1 or 2), and $-R^{21}-S(O)_tN(R^{20})_2$ (where t is 1 or 2), where each R^{20} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{20}'s, together with the common nitrogen to which they are both attached, may optionally form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl, and each R^{21} is independently a direct bond or a straight or branched alkylene or alkenylene chain.

"Heteroarylalkyl" refers to a radical of the formula $-R_bR_i$ where R_b is an alkylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkyl" refers to a heteroarylalkyl radical, as defined above, wherein the alkylene chain of the heteroarylalkyl radical is an optionally substituted alkylene chain, as defined above, and the heteroaryl radical of the heteroarylalkyl radical is an optionally substituted heteroaryl radical, as defined above.

"Heteroarylalkenyl" refers to a radical of the formula $-R_dR_i$ where R_d is an alkenylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkenylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkenyl" refers to a heteroarylalkenyl radical, as defined above, wherein the alkenylene chain of the heteroarylalkenyl radical is an optionally substituted alkenylene chain, as defined above, and the heteroaryl radical of the heteroarylalkenyl radical is an optionally substituted heteroaryl radical, as defined above.

"Heteroarylalkynyl" refers to a radical of the formula $-R_eR_i$ where R_e is an alkynylene chain as defined above and R_i is a heteroaryl radical as defined above, and when the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl may be attached to the alkynylene chain at the nitrogen atom.

"Optionally substituted heteroarylalkynyl" refers to a heteroarylalkynyl radical, as defined above, wherein the alkynylene chain of the heteroarylalkynyl radical is an optionally substituted alkynylene chain, as defined above, and the heteroaryl radical of the heteroarylalkynyl radical is an optionally substituted heteroaryl radical, as defined above.

"Hydroxyalkyl" refers to an alkyl radical as defined above which is substituted by one or more hydroxy radicals (-OH).

Certain chemical groups named herein may be preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example; C_7-C_{12}alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C_4-C_{12}cycloalkylalkyl describes a cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Patient" means a mammal who has been diagnosed as having cancer and/or metastatic cancer, or who is predisposed to having metastatic cancer due to having cancer.

"Mammal" means any vertebrate of the class *Mammalia*. Humans and domestic animals, such as cats, dogs, swine, cattle, sheep, goats, horses, rabbits, and the like are a particular focus. Preferably, for purposes of this invention, the mammal is a primate (*e.g.*, monkey, baboon, chimpanzee and human), and more preferably, the mammal is a human.

"Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally

substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution. However, when a first functional group is described as "optionally substituted," and in turn, substituents on the first functional group are also "optionally substituted" and so forth, for the purposes of this invention, such iterations for a radical to be optionally substituted are limited to three. Thus, groups described as substituents on the third iteration are not themselves optionally substituted. For example, if an R group herein is defined as being "optionally substituted aryl" (the first iteration) and the optional substituents for the "optionally substituted aryl" include "optionally substituted heteroaryl" (the second iteration) and the optional substituents for the "optionally substituted heteroaryl" include "optionally substituted cycloalkyl" (the third iteration), the optional substituents on the cycloalkyl can not be optionally substituted.

"Pharmaceutically acceptable excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfonic acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic

acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

A "pharmaceutical composition" refers to a formulation of a compound of formula (I) or a formulation of a chemotherapeutic agent described herein and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, for example, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

"Therapeutically effective amount" refers to that amount of the therapeutic agent sufficient to destroy, modify, control or remove mestastatic cancer tissue. A therapeutically effective amount may refer to the amount of therapeutic agents sufficient to delay or minimize the spread of metastatic cancer. A therapeutically effective amount may also refer to the amount of the therapeutic agent that provides a therapeutic benefit in the treatment or management of metastatic cancer. Further, a therapeutically effective amount with respect to an Axl inhibitor of the combination therapies of the invention means that amount of an Axl inhibitor in combination with one or more chemotherapeutic agents that

provides a therapeutic benefit in the treatment or management of metastatic cancer, including the amelioration of symptoms associated with metastatic cancer. Used in connection with an amount of an Axl inhibito, the term can encompass an amount that improves overall therapy, reduces or avoids unwanted effects, or enhances the therapeutic efficacy of or synergizes with the one or more chemotherapeutic agents utilized in the combination therapies of the invention.

"Prophylactically effective amount" refers to that amount of the prophylactic agent sufficient to result in the prevention of metastatic cancer. A prophylactically effective amount may refer to the amount of prophylactic agent sufficient to prevent metastatic cancer in a patient, including, but not limited to, those patients who are predisposed to cancer or previously exposed to carcinogens. A prophylactically effective amount may also refer to the amount of the prophylactic agent that provides a prophylactic benefit in the prevention of metastatic cancer. Further, a prophylactically effective amount with respect to with respect to an Axl inhibitor of the combination therapies of the invention means that amount of an Axl inhibitor in combination with other chemotherapeutic agents, that provides a prophylactic benefit in the prevention of metastatic cancer. Used in connection with an amount of an Axl inhibitor, the term can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of or synergizes with another prophylactic or therapeutic agent.

As used herein, the terms "manage", "managing" and "management" refer to the beneficial effects that a patient derives from a combination therapy of the invention, which does not result in a cure of the metastatic cancer. In certain embodiments, a combination therapy of the invention "manages" metastatic cancer so as to prevent the progression or worsening of the metastatic cancer.

As used herein, the terms "prevent", preventing" and "prevention" refer to the prevention of the spread or onset of metastatic cancer in a patient.

As used herein, the terms "treat", "treating" and "treatment" refer to the eradication, removal, modification or control of metastatic cancer that results from the combination therapy of the invention. In certain embodiments, such terms refer to the minimizing or delay of the spread of metastatic cancer.

The compounds of formula (I), or their pharmaceutically acceptable salts, may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute

stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as HPLC using a chiral column. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

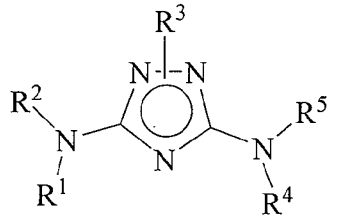
A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

"Atropisomers" are stereoisomers resulting from hindered rotation about single bonds where the barrier to rotation is high enough to allow for the isolation of the conformers (Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds;* Wiley & Sons: New York, 1994; Chapter 14). Atropisomerism is significant because it introduces an element of chirality in the absence of stereogenic atoms. The invention is meant to encompass atropisomers, for example in cases of limited rotation around the single bonds emanating from the core triazole structure, atropisomers are also possible and are also specifically included in the compounds of the invention.

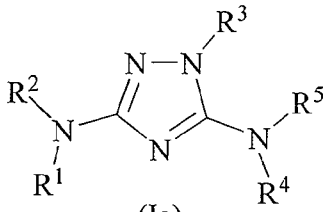
The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system wherein the compounds of formula (I) are named herein as derivatives of the central core structure, *i.e.*, the triazole structure. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. In chemical structure diagrams, all bonds are identified, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

For purposes of this invention, the depiction of the bond attaching the R^3 substituent to the parent triazole moiety in formula (I), as shown below:



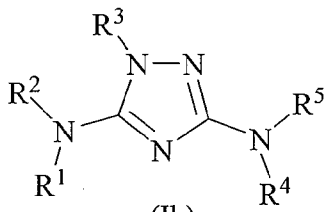
(I)

is intended to include only the two regioisomers shown below, *i.e.*, compounds of formula (Ia) and (Ib):



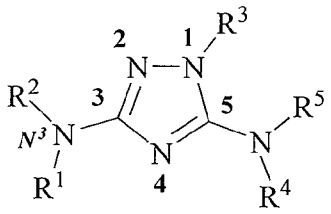
(Ia)

and



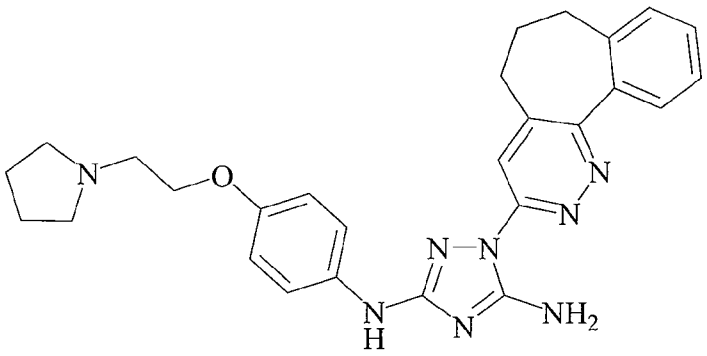
(Ib)

The numbering system of the ring atoms in compounds of formula (Ia) is shown below:



(Ia)

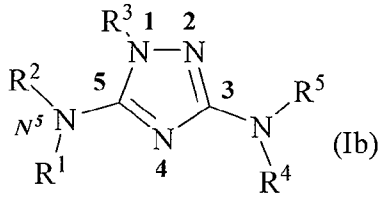
For example, a compound of formula (Ia) wherein R^1, R^4 and R^5 are each hydrogen, R^2 is 4-(2-(pyrrolidin-1-yl)ethoxy)phenyl and R^3 is 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl; *i.e.*, a compound of the following formula:



is named herein as 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

The numbering system of the ring atoms in compounds of formula (Ib) is shown

below:



(Ib)

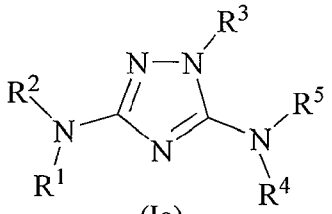
Compounds of formula (Ib) are similarly named herein.

EMBODIMENTS OF THE INVENTION

Of the various aspects of the invention, as set forth herein, certain embodiments are preferred.

In one embodiment of the methods of preventing, treating or managing cancer in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is a compound of formula (I), as set forth above in the Summary of the Invention, as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

Of this embodiment, one preferred embodiment is wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein R^1, R^2, R^3, R^4 and R^5 are as described in the Summary of the Invention for compounds of formula (I), as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above, R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and R^1, R^4, R^5, each R^6, each R^7, each R^8, each R^9, each R^{10}, each R^{11} and R^{12} are as described above for compounds of formula (Ia).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring

atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method wherein the compound of formula (Ia) is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(5',5'-dimethyl-6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above, R^2 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$,

$-R^9$-O-R^{10}-O-R^{10}-OR^8, $-R^9$-O-R^{10}-CN, $-R^9$-O-R^{10}-C(O)OR^8, $-R^9$-O-R^{10}-C(O)N(R^6)R^7, $-R^9$-O-R^{10}-S(O)$_p R^8$ (where p is 0, 1 or 2), $-R^9$-O-R^{10}-N(R^6)R^7, $-R^9$-O-R^{10}-C(NR^{11})N(R^{11})H, $-R^9$-OC(O)-R^8, $-R^9$-N(R^6)R^7, $-R^9$-C(O)R^8, $-R^9$-C(O)OR^8, $-R^9$-C(O)N(R^6)R^7, $-R^9$-N(R^6)C(O)OR^{12}, $-R^9$-N(R^6)C(O)R^8, $-R^9$-N(R^6)S(O)$_t R^8$ (where t is 1 or 2), $-R^9$-S(O)$_t OR^8$ (where t is 1 or 2), $-R^9$-S(O)$_p R^8$ (where p is 0, 1 or 2), and $-R^9$-S(O)$_t$N(R^6)R^7 (where t is 1 or 2); R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}$-OR^{12}, $-R^{13}$-OC(O)-R^{12}, $-R^{13}$-O-R^{14}-N(R^{12})$_2$, $-R^{13}$-N(R^{12})-R^{14}-N(R^{12})$_2$, $-R^{13}$-N(R^{12})$_2$, $-R^{13}$-C(O)R^{12}, $-R^{13}$-C(O)OR^{12}, $-R^{13}$-C(O)N(R^{12})$_2$, $-R^{13}$-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}, $-R^{13}$-C(O)N(R^{12})-R^{14}-OR^{12}, $-R^{13}$-N(R^{12})C(O)OR^{12}, $-R^{13}$-N(R^{12})C(O)R^{12}, $-R^{13}$-N(R^{12})S(O)$_t R^{12}$ (where t is 1 or 2), $-R^{13}$-S(O)$_t OR^{12}$ (where t is 1 or 2), $-R^{13}$-S(O)$_p R^{12}$ (where p is 0, 1 or 2), and $-R^{13}$-S(O)$_t$N(R^{12})$_2$ (where t is 1 or 2); and R^1, R^4, R^5, each R^6, each R^7, each R^8, each R^9, each R^{10}, each R^{11}, each R^{12}, each R^{13} and each R^{14} are as described above for compounds of formula (Ia).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}$-OR^8, $-R^{10}$-CN, $-R^{10}$-NO_2, $-R^{10}$-N(R^8)$_2$, $-R^{10}$-C(O)OR^8 and $-R^{10}$-C(O)N(R^8)$_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally

substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bondand an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two $R^{12's}$, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each hydrogen;

R^2 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-c]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl,

5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[b]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bondand an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl,

optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two $R^{12's}$, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

Another embodiment is a method where, in the compound of formula (Ia) as set forth above:

R^2 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and

R^3 is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, thieno[3,2-*d*]pyrimidinyl and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

Another embodiment is a method wherein the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dimethoxy-quinazolin-4-yl)-N^3-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N^3-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N^3-(5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(2-chloro-7-methylthieno[3,2-*d*]pyrimidin-4-yl)-N^3-(5',5'-dimethyl-6,8,9,10-9tetrahydro-

5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above, R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and R^1, R^4, R^5, each R^6, each R^7, each R^8, each R^9, each R^{10}, each R^{11}, each R^{12}, each R^{13} and each R^{14} are as described above for compounds of formula (I).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two R^{12}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is aryl optionally substituted by one or more substitutents selected from the group

consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is aryl selected from the group consisting of phenyl and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$,

$-R^{13}$-OC(O)-R^{12}, $-R^{13}$-O-R^{14}-N(R^{12})$_2$, $-R^{13}$-N(R^{12})-R^{14}-N(R^{12})$_2$, $-R^{13}$-N(R^{12})$_2$, $-R^{13}$-C(O)R^{12}, $-R^{13}$-C(O)OR^{12}, $-R^{13}$-C(O)N(R^{12})$_2$, $-R^{13}$-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}, $-R^{13}$-C(O)N(R^{12})-R^{14}-OR^{12}, $-R^{13}$-N(R^{12})C(O)OR^{12}, $-R^{13}$-N(R^{12})C(O)R^{12}, $-R^{13}$-N(R^{12})S(O)$_t$$R^{12}$ (where t is 1 or 2), $-R^{13}$-S(O)$_t$OR^{12} (where t is 1 or 2), $-R^{13}$-S(O)$_p$$R^{12}$ (where p is 0, 1 or 2), and $-R^{13}$-S(O)$_t$N(R^{12})$_2$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocyclyl where the optionally substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-a]azepinyl, octahydropyrrolo[3,4-c]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydropyrrolo[3,2-c]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidinyl; each independently optionally substituted by one or two substituents selected from the group consisting of $-R^9$-OR^8, $-R^9$-N(R^6)R^7, $-R^9$-C(O)OR^6, $-R^9$-C(O)N(R^6)R^7, $-R^9$-N(R^6)C(O)R^7, $-R^9$-N(R^6)C(O)OR^7, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-b]pyridin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-c]pyridazine-5,1'-cyclopentane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-c]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and $-R^9$-OR^8.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

N^3-(4-(4-cyclohexanylpiperazin-1-yl)phenyl)-1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-

(pyrrolidin-1-yl)piperidin-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-methyl-3-phenylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-(4-(4-piperidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(indolin-2-on-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(morpholin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-cyclopentyl-2-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-(pyrrolidin-1-yl)piperidin-1-yl)-3-cyanophenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-(diethylamino)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(diethylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9-methoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperdin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-10-fluorobenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperdin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-10-fluorobenzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(cyclohexyl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9-methoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(cyclohexyl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(4-methylpiperidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-dimethylaminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-chloro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-trifluoromethyl-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9,10-dimethoxybenzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9,10, 11-trimethoxybenzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(5-methyloctahydropyrrolo[3,4-c]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-pyrrolidin-1-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-pyrrolidin-1-yl-azepan-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-N-methylpiperidin-4-yl-piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-N^3-(3-fluoro-4-(4-(pyrrolidinyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(5-propyloctahydropyrrolo[3,4-c]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(decahydropyrazino[1,2-a]azepin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(5-cyclopentyloctahydropyrrolo[3,4-c]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-(pyrrolidin-1-yl)-8-azabicyclo[3.2.1]oct-8-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-yl-azepan-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(4-isopropylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(1-methyloctahydropyrrolo[3,4-b]pyrrol-5-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(N-methylcyclopentylamino)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(dipropylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(1-propyloctahydro-1H-pyrrolo[3,2-c]pyridine-5-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-N^3-(3-fluoro-4-(4-(N-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(tert-butyloxycarbonylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-aminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(5-cyclohexyloctahydropyrrolo[3,4-*c*]pyrrolyl)piperidin-1-yl)phenyl) -1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(methylpiperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-methyl-4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-cyclopentylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-N-

methylpiperidin-4-ylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(N-isopropylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-pyrrolidin-1-ylazetidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-methyl-4-(4-(N-methylpiperazin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-((S)-3-(pyrrolidin-1-ylmethyl)pyrrolidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidinylmethyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-((4a*R*,8a*S*)-decahydroisoquinolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(octahydro-1*H*-pyrido[1,2-a]pyrazin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-(4-(3-pyrrolidin-1-yl)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(5-methyloctahydropyrrolo[3,4-c]pyrrolyl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(octahydropyrrolo[3,4-c]pyrrolyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-9-chloro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-9-chloro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(N-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-iodophenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(spiro[chromeno[4,3-c]pyridazine-5,1'-cyclopentane]-3-yl)-N^3-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(spiro[chromeno[4,3-c]pyridazine-5,1'-cyclopentane]-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-

1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(3-(3*R*)-dimethylaminopyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl)-N^3-(3-methyl-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-c]pyridazin-2-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-N^3-(3-fluoro-4-(4-cyclohexylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-N^3-(4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(1-bicyclo[2.2.1]heptan-2-yl)-piperidin-4-ylphenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(1-cyclopropylmethylpiperidin-4-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-cyclopropylmethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)- N^3-(4-(1-bicyclo[2.2.1]heptan-2-yl)-piperidin-4-ylphenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(4-phenyl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine, and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of halo, alkyl, heterocyclylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)N(R^{12})_2$, and $-R^{13}-N(R^{12})C(O)R^{12}$;

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-c]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and $-R^9-OR^8$.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-(cyclopentyl)piperazin-1-ylcarbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((2-pyrrolidin-1-ylethyl)aminocarbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxyphenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((2-(dimethylamino)ethyl)aminocarbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((2-(methoxy)ethyl)aminocarbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((2-(pyrrolidin-1-yl)ethyl)aminocarbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-chloro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-10-fluorobenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-9-methoxybenzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-

(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(2-(N-methylcyclopentylamino)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(N-methylpiperidin-4-yl-N-methylamino)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl)-N^3-(4-((N-butyl-N-acetoamino)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-(4-methylpiperazin-1-yl)piperidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-(piperidin-1-yl)piperidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(piperidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(pyrrolidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(3-dimethylaminopyrrolidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(3-diethylaminopyrrolidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-pyrrolidin-1-ylpiperidin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-methylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-isopropylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(4-cyclopentylpiperazin-1-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(morpholin-4-ylprop-1-enyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(1-methylpiperidin-3-yl-oxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set

forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocyclyl where the optionally substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-a]azepinyl, octahydropyrrolo[3,4-c]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydropyrrolo[3,2-c]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidinyl; each independently optionally substituted by one or two substituents selected from the group consisting of $-R^9-OR^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)R^7$, $-R^9-N(R^6)C(O)OR^7$, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl; and

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and $-R^9-OR^8$.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-N^3-(4-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-N^3-(3-fluoro-4-(4-(diethylamino)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-N^3-(4-(N-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-N^3-(3-fluoro-4-(4-cyclohexylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-N^3-(4-(4-(2S)-bicyclo[2.2.1]heptan-2-yl)-piperazinylphenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of halo, alkyl, heterocyclylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)N(R^{12})_2$, and $-R^{13}-N(R^{12})C(O)R^{12}$; and

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and $-R^9-OR^8$.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl)-N^3-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl)-N^3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of alkyl, halo, haloalkyl, cyano, and optionally substituted heterocyclyl where the optionally substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, decahydropyrazino[1,2-a]azepinyl, octahydropyrrolo[3,4-c]pyrrolyl, azabicyclo[3.2.1]octyl, octahydropyrrolo[3,4-b]pyrrolyl, octahydropyrrolo[3,2-c]pyridinyl, 2,7-diazaspiro[4.4]nonanyl and azetidinyl; each independently optionally substituted by one or two substituents selected from the group consisting of $-R^9-OR^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)OR^6$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)R^7$, $-R^9-N(R^6)C(O)OR^7$, alkyl, halo, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl; and

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, and 6,7-dihydro-5*H*-

benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, halo and -R^9-OR^8.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N^3-(4-(N-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-cyclohexylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-((Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-N^3-(4-(4-N-methylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-((Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-N^3-(3-fluoro-4-(4-diethylaminopiperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-N^3-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidinylmethyl)piperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-((4a*R*,8a*S*)-decahydroisoquinolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(octahydro-1*H*-pyrido[1,2-a]pyrazin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of halo, alkyl, heterocyclylalkenyl, -R^{13}-OR^{12}, -R^{13}-O-R^{14}-$N(R^{12})_2$, -R^{13}-$N(R^{12})$-R^{14}-$N(R^{12})_2$, -R^{13}-$N(R^{12})_2$, -R^{13}-$C(O)R^{12}$, -R^{13}-$C(O)N(R^{12})_2$, and -R^{13}-$N(R^{12})C(O)R^{12}$; and

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-

c]pyridazin-3-yl, (*Z*)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, and 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-((*Z*)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl)-N^3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is phenyl optionally substituted by a substitutent selected from the group consisting of optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R^3 is selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-yl and 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2)

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl,

alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and

R^{12} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((5-fluoroindolin-2-on-3-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((4-pyrrolidin-1-ylpiperidinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((4-cyclopentylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-((4-isopropylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(isoindolin-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-

[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and each R^6, each R^7, each R^8, each R^9, each R^{12}, each R^{13} and each R^{14} are as described above for compounds of formula (Ia).

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((bicyclo[2.2.1]heptan-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((bicyclo[2.2.1]heptan-2-yl)(methyl)amino) 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-azetidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-diethylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-cyclopentylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(2-(*S*)-methyloxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(2-(*S*)-carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(8-diethylaminoethyl-9hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(3-(*S*)-fluoropyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(2-(*S*)-methylpyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(3-(*R*)-hydroxypyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(2-(*R*)-methylpyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(3-(*S*)-hydroxypyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(3-(*R*)-fluoropyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-cyclohexylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-cyclopropylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-methylpiperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(tetrahydrofuran-2-ylmethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-cyclobutylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(cyclopropylmethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(2-(diethylamino)ethyl)methylamino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-pyrrolidin-1-ylpiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(piperidin-1-ylmethyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(2-(dimethylamino)ethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(carboxymethyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(acetamido)-6,7,8,9-

tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*s*)-7-

(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-

1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-carboxyphenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3-bromophenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-

benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is heteroaryl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$,

$-R^{13}$-C(O)N(R^{12})-R^{14}-OR^{12}, $-R^{13}$-N(R^{12})C(O)OR^{12}, $-R^{13}$-N(R^{12})C(O)R^{12}, $-R^{13}$-N(R^{12})S(O)$_t$$R^{12}$ (where t is 1 or 2), $-R^{13}$-S(O)$_t$OR^{12} (where t is 1 or 2), $-R^{13}$-S(O)$_p$$R^{12}$ (where p is 0, 1 or 2), and $-R^{13}$-S(O)$_t$N(R^{12})$_2$ (where t is 1 or 2);

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9$-OR^8, $-R^9$-O-R^{10}-OR^8, $-R^9$-O-R^{10}-O-R^{10}-OR^8, $-R^9$-O-R^{10}-CN, $-R^9$-O-R^{10}-C(O)OR^8, $-R^9$-O-R^{10}-C(O)N(R^6)R^7, $-R^9$-O-R^{10}-S(O)$_p$$R^8$ (where p is 0, 1 or 2), $-R^9$-O-R^{10}-N(R^6)R^7, $-R^9$-O-R^{10}-C(NR^{11})N(R^{11})H, $-R^9$-OC(O)-R^8, $-R^9$-N(R^6)R^7, $-R^9$-C(O)R^8, $-R^9$-C(O)OR^8, $-R^9$-C(O)N(R^6)R^7, $-R^9$-N(R^6)C(O)OR^{12}, $-R^9$-N(R^6)C(O)R^8, $-R^9$-N(R^6)S(O)$_t$$R^8$ (where t is 1 or 2), $-R^9$-S(O)$_t$OR^8 (where t is 1 or 2), $-R^9$-S(O)$_p$$R^8$ (where p is 0, 1 or 2), and $-R^9$-S(O)$_t$N(R^6)R^7 (where t is 1 or 2); and each R^6, each R^7, each R^8, each R^9, each R^{12}, each R^{13} and each R^{14} are as described above for compounds of formula (Ia); and

each R^6, each R^7, each R^8, each R^9, each R^{10}, each R^{11}, each R^{12}, each R^{13} and each R^{14} are as described above for compounds of formula (Ia).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally

substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^2 is selected from the group consisting of pyridinyl and pyrimidinyl, each optionally

substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-(bicyclo[2.2.1]heptan-2-yl)piperazin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-cyclopentyl-1,4-diazepan-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(6-aminopyridin-3-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-aminophenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-cyanophenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(

benzo[d][1,3]dioxole-6-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-methylsulfonamidylphenyl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(2-diethylaminomethyl)pyrrolidin-1-ylpyridin-3-yl) -1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-diethylaminopyrrolidin-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-(4-(N-methylpiperazin-4-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-(pyrrolidin-1-yl)piperidin-1-yl)-5-methylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-piperidin-1-yl-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-(bicyclo[2.2.1]heptan-2-yl)-1,4-diazepan-1-yl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-(4-(pyrrolidin-1-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-piperidin-1-yl)-propanylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-(4-(piperidin-1-yl)piperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(3-(4-dimethylaminopiperidin-1-yl)-(E)-propenyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidin-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(4-(piperidin-1-ylmethyl)piperidin-1-yl)pyrimidin-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-((4-piperidin-1-ylpiperidin-1-yl)carbonyl)pyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(4-

cyclopropylmethylpiperazin-1-yl)pyridine-5-yl)-1*H*-1,2,4-triazole-3,5-diamine; and 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(3-(*S*)-methyl-4-cyclopropylmethylpiperazin-1-yl)pyridine-5-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ia) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is selected from the group consisting of 4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl,

6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-c]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ia), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4,5-dihydro-1*H*-benzo[b]azepin-2(3*H*)-on-8-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(dimethylaminomethyl)-1*H*-benzo[d]imidazol-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-cyclopentyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-d]azepin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(4-methylpiperazin-1-yl)carbonyl-5,6,7,8-tetrahydroquinolin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine, compound #31, 1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2,3,4,5-tetrahydrobenzo[b]oxepin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3,4-dihydro-2*H*-

benzo[b][1,4]dioxepin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-N^3-(2-(pyrrolidin-1-ylmethyl)benzo[d]oxazol-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(4-(2-dimethylaminoethyl)-(3,4-dihydro-2*H*-benzo[b][1,4]oxazin-7-yl))–1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl)-N^3-(4-(2-dimethylaminoethyl)-(3,4-dihydro-2*H*-benzo[b][1,4]oxazin-7-yl))-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^3-(2-(1-(4-(2-(dimethylamino)ethyl)piperazin-1-yl)oxomethyl)benzo[b]thiophen-5-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-cyclopentyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl) -1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3 (2-cyclopentyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-(pyrrolidin-1-yl)-5,6,7,8-tetrahydroquinolin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(6-cyclopentyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

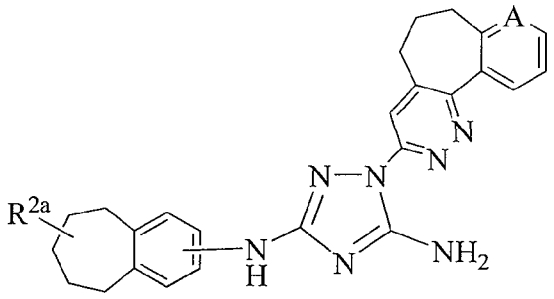
1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((S)-7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[b]pyridine-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(2-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where the compound of formula (Ia), as set forth above, is a compound of formual (Ia1):



(Ia1)

;

wherein:

A is =C(H)- or =N-;

each R^{2a} is independently selected from the group consisting of $-N(R^{12a})_2$ and $-N(R^{12a})C(O)R^{12a}$,

or R^{2a} is an *N*-heterocyclyl optionally substituted by one or more substituents selected from the group consisting of halo and $-R^{21}-C(O)OR^{20}$,

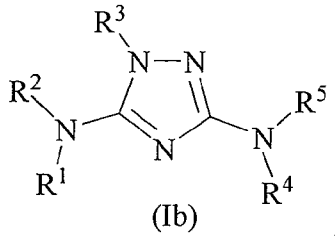
each R^{12a} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R^{20} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; and

R^{21} is independently selected from the group consisting of a direct bond or an optionally substituted straight or branched alkylene chain;

as an isolated stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

Of the embodiment of utilizing a compound of formula (I), as set forth above in the Summary of the Invention, in the methods of the invention, another embodiment is wherein the compound of formula (I) is a compound of formula (Ib):



(Ib)

,

wherein R^1, R^2, R^3, R^4 and R^5 are as described above in the Summary of the Invention for compounds of formula (I), as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or *N*-oxide thereof.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above, R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2); and R^1, R^4, R^5, each R^6, each R^7, each R^8, each R^9, each R^{10}, each R^{11} and R^{12} are as described above in the Summary of the Invention.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^1, R^4 and R^5 are each hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain; and

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-c]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2)

Another embodiment is the method where the compound of formula (Ib), as set forth above, is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'[1,3]dioxolane]-3-yl)-1H-1,2,4-triazole-3,5-

diamine.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

each R^9 is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain;

each R^{10} is an optionally substituted straight or branched alkylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl, or two R^{12}'s, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond and an optionally substituted straight or branched alkylene chain; and

each R^{14} is an optionally substituted straight or branched alkylene chain.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^2 is aryl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo,

thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is aryl selected from the group consisting of phenyl and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted

cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[b]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where, in the compound of formula (Ib) as set

forth above:

R^2 is phenyl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ib), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(4-(indolin-2-on-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(4-(morpholin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(7-methyl-6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl)-N^5-(4-(N-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-((5-fluoroindolin-2-on-3-yl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-((4-pyrrolidin-1-ylpiperidinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-((4-cyclopentylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-((4-

isopropylpiperazinyl)methyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(4-N-methylpiperid-4-ylpiperazinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(3-pyrrolidin-1-ylazetidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-methyl-4-(4-(N-methylpiperazin-4-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl)-N^5-(4-(4-pyrrolidin-1-ylpiperidinyl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-(4-(3-pyrrolidin-1-yl)pyrrolidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(3-fluoro-4-(4-cyclopropylmethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is 6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-*c*]pyridazin-3-yl, (Z)-dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ib), as set forth above, is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-((bicyclo[2.2.1]heptan-2-yl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(*S*)-pyrrolidin-1-yl-

6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^1, R^4 and R^5 are each independently hydrogen;

R^2 is heteroaryl optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

Another embodiment is the method where, in the compound of formula (Ib) as set forth above:

R^2 is heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl,

4,5-dihydro-1*H*-benzo[*b*]azepin-2(3*H*)-on-8-yl, benzo[*d*]imidazolyl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*d*]azepin-3-yl, 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepin-3-yl, 5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 1,2,3,4-tetrahydroisoquinolin-7-yl, 2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl, benzo[*d*]oxazol-5-yl, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-7-yl, benzo[*b*]thiophenyl, and 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-3-yl, each optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2); and

R^3 is a polycyclic heteroaryl containing more than 14 ring atoms selected from the group consisting of 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidin-4-yl, 6,7-dihydro-5*H*-benzo[2,3]azepino[4,5-c]pyridazin-3-yl, (Z)-dibenzo[b,f][1,4]thiazepin-11-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[4,5-*c*]pyridazin-2-yl, 6,7-dihydro-5*H*-benzo[2,3]oxepino[4,5-*c*]pyridazin-3-yl, spiro[chromeno[4,3-*c*]pyridazine-5,1'-cyclopentane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 5,6,8,9-tetrahydrospiro[benzo[7]annulene-7,2'-[1,3]dioxolane]-3-yl, 5,7,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-6,2'-[1,3]dioxolane]-3-yl, 6,7-dihydro-5*H*-benzo[2,3]thiepino[4,5-*c*]pyridazin-3-yl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-yl, 5,6,8,9-tetrahydrospiro[cyclohepta[*b*]pyridine-7,2'-[1,3]dioxolane]-3-yl, 6,8,9,10-tetrahydro-5*H*-spiro[cycloocta[*b*]pyridine-7,2'-

[1,3]dioxane]-3-yl and 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridin-2-yl, each optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^{12}$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2).

Another embodiment is the method where the compound of formula (Ib), as set forth above, is selected from the group consisting of:

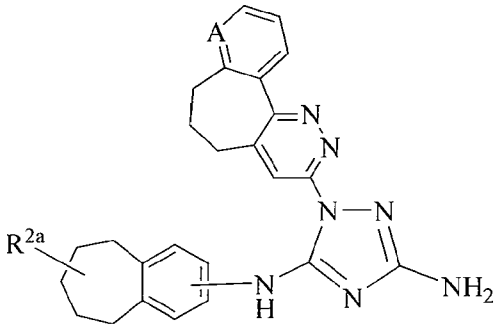
1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(6-(4-(pyrrolidin-1-yl)piperidin-1-yl)-5-methylpyridin-3-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(4-(3,5-dimethylpiperazin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(2-(1-methylpiperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Another embodiment is the method where the compound of formula (Ib), as set forth above, is a compound of formual (Ib1):



(Ib1)

;

wherein:

A is =C(H)- or =N-;

each R^{2a} is independently selected from the group consisting of $-N(R^{12a})_2$ and $-N(R^{12a})C(O)R^{12a}$,

or R^{2a} is an *N*-heterocyclyl optionally substituted by one or more substituents selected from

the group consisting of halo and $-R^{21}-C(O)OR^{20}$,

each R^{12a} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

R^{20} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; and

R^{21} is independently selected from the group consisting of a direct bond or an optionally substituted straight or branched alkylene chain;

as an isolated stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

In one embodiment of the methods of preventing, treating or managing cancer in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents is selected from the group consisting of antimetabolites, alkylating agents, coordination compounds, platinum complexes, DNA cross-linking compounds, inhibitors of transcription enzymes, tyrosine kinase inhibitors, protein kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, vinca alkyloids, taxanes, antitumor antibiotics, hormones, aromatase inhibitors, enzymes, growth factor receptors antibodies, cytokines, cell surface markers antibodies, HDAC inhibitors, HSP 90 inhibitors, BCL-2 inhibitors, mTOR inhibitors, proteasome inhibitors and monoclonal antibodies.

In another embodiment of methods of preventing, treating or managing cancer in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents are independently selected from the group consisting of mechlorothamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine, temozolomide, busulfan, carmustine, lomustine, methotrexate, fluorouracil, capecitabine,

cytarabine, gemcitabine, cytosine arabinoside, mecaptopurine, fludarabine, cladribine, thioguanine, azathioprine, vinblastine, vincristine, paclitaxel, docetaxel, colchicine, actinomycin D, daunorubicin, bleomycin,L-asparaginase, cisplatin, carboplatin, oxaliplatin, prednisone, dexamethasone, amino glutethimide, formestane, anastrozole, hydroxyprogesterone caproate, medroxyprogesterone, tamoxifen, amsacrine, mitoxantrone, topotecan, irinotecan, camptothecin, axtinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sunitinib, vandetanib, vatalanib, anti-Her2 antibodies, interferon-α, interferon-γ, interleukin-2, GM-CSF, anti-CTLA-4 antibodies, rituximab, anti-CD33 antibodies, MGCD0103, vorinostat, 17-AAG, thalidomide, lenalidomide, rapamycin, CCI-779, sorafenib, doxorubicine, gemcitabine, melphalan, bortezomib, NPI052, gemtuzumab, alemtuzumab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, bevacizumab, rituximab, and anti-TRAIL death receptor antibodies.

In another embodiment of methods of preventing, treating or managing cancer in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents are independently selected from the group consisting of paclitaxel, cyclophosphamide, 5-fluorouracil, cisplatin, carboplatin, methotrexate and imitanib.

Preferably, one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is a compound of formula (I) selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-

(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(S)-pyrrolidin-1-yl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-

yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*s*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-

diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-carboxyphenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3-bromophenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-

1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

and the one or more chemotherapeutic agents is selected from the group consisting of paclitaxel, cyclophosphamide, 5-fluorouracil, cisplatin, carboplatin, methotrexate and imitanib.

Preferably, one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in

combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, another embodiment of the methods of preventing, treating or managing

cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, is the method wherein the Axl inhibitor is 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(S)-pyrrolidin-1-yl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

Preferably, in one embodiment, in any of the above embodiments of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents is cisplatin.

Preferably, in another embodiment, in any of the above embodiments of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents is paclitaxel.

Preferably, in another embodiment, in any of the above embodiments of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents is imitanib.

In one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the method prevents metastatic cancer.

In another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective

amount of one or more chemotherapeutic agents, the method treats metastatic cancer.

In another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the method manages metastatic cancer.

In one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is administered to the patient, preferably a human, in an amount of between about 1 mg/kg and about 100 mg/kg twice a day, preferably between about 5 mg/kg and about 80 mg/kg twice a day, even more preferably between about 5 mg/kg and about 25 mg/kg twice a day, and the chemotherapeutic agent is administered to the mammal in an amount of between about 1.0 mg/kg and about 10.0 mg/kg once a week, preferably between about 1.0 mg/kg and about 5 mg/kg once a week, even more preferably between about 1.0 mg/kg and 2.0 mg/kg once a week.

In one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is administered to the patient, preferably a human, at the same time that the one or more chemotherapeutic agent is administered to the patient.

In one embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is administered to the patient, preferably a human, concurrently with the administration of the one or more chemotherapeutic agent is administered to the patient.

In another embodiment of the methods of preventing, treating or managing cancer,

preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is administered to the patient, preferably a human, prior to the administration of the one or more chemotherapeutic agent is administered to the patient.

In another embodiment of the methods of preventing, treating or managing cancer, preferably metastatic cancer, in a patient comprising administering to the patient in need thereof a therapeutically or prophylactically effective amount of an Axl inhibitor in combination with the administration of a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents, the Axl inhibitor is administered to the patient, preferably a human, sequentially to the administration of the one or more chemotherapeutic agent is administered to the patient.

Specific embodiments of the invention are described in more detail in the following sections.

UTILITY AND TESTING OF THE COMBINATION THERAPIES OF THE INVENTION

In the combination therapies of the invention, an Axl inhibitor, preferably a compound of formula (I), as set forth in the Summary of the Invention, is used as an active ingredient in combination with one or more chemotherapeutic agents in the prevention, treatment or management of one or more cancers, preferably metastatic cancers. Preferably, such combination therapies of the present invention will exert greater than additive effects, *i.e.*, synergistic effects, as the mechanisms of action employed for the Axl inhibitor and the one or more chemotherapeutic agents may be different and each may act independently of one another. Accordingly, as used herein "combination therapy" refers to the administration of an Axl inhibitor, preferably a compound of formula (I) as set forth above in the Summary of the Invention, in combination with the administration of one or more chemotherapeutic agents for the prevention, treatment and management of one or more cancers, preferably metastatic cancer. Unless the context makes clear otherwise, "combination therapy" may include simultaneous or sequential administration of the Axl inhibitor and the one or more chemotherapeutic agents, in any order, such as administering the Axl inhibitor at the same time as the administration of the one or more

chemotherapeutic agents, before the administration of the one or more chemotherapeutic agents or after the administration of the one or more chemotherapeutic agents. Unless the context makes clear otherwise, "combination therapy" may include the administration of dosage forms of an Axl inhibitor combined with the dosage forms of one or more chemotherapeutic agents. Unless the context makes clear otherwise, "combination therapy" may include different routes of administration for the Axl inhibitor and for the one or more chemotherapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

The oncogenic receptor tyrosine kinase, Axl, was recently identified, using a retroviral-based functional genetic screening protocol, as a regulator of haptotactic migration, which is a key event in angiogenesis. Inhibition of Axl by RNAi-mediated silencing blocked endothelial cell migration, proliferation and *in vitro* tube formation. These observations, which were disclosed at the American Association Cancer Research General Meeting, April 16-20, 2005, Anaheim, California, and The 7th Annual Symposium on Anti-Angiogenic Agents, February 10-13, 2005, San Diego, California; (*Requirement for The Receptor Tyrosine Kinase Axl in Angiogenesis and Tumor Growth*, Holland, S.J. Powell, M.J., Franci, C., Chan, E., Friera, A.M., Atchison, R., Xu, W., McLaughlin, J., Swift,S.E., Pali, E., Yam, G., Wong, S., Xu, X., Hu, Y., Lasaga, J., Shen, M., Yu, S., Daniel, R., Hitoshi, Y., Bogenberger, J., Nor, J.E., Payan, D.G and Lorens, J.B), were substantiated by an *in vivo* study which demonstrated that stable, shRNAi-mediated Axl knockdown impaired formation of functional human blood vessels in a mouse model of human angiogenesis. These observations were published in a peer reviewed journal (Holland SJ, Powell MJ, Franci C, Chan EW, Friera AM, Atchison RE, McLaughlin J, Swift SE, Pali ES, Yam G, Wong S, Lasaga J, Shen MR, Yu S, Xu W, Hitoshi Y, Bogenberger J, Nor JE, Payan DG, Lorens JB. "Multiple roles for the receptor tyrosine kinase axl in tumor formation", *Cancer Res.* (2005) Vol. 65, pp 9294-303. These observations are also disclosed in U.S. Published Patent Application 2005/0118604 and European Patent Application 1 563 094, the disclosures of which are incorporated in full by reference. Axl signaling, therefore, impacts multiple functions required for neovascularization *in vitro*, and regulates angiogenesis *in vivo*. Regulation of these pro-angiogenic processes required the catalytic activity of Axl. Thus, Axl-mediated angiogenic stimulation would be amenable to modulation by a small molecule inhibitor of Axl catalytic activity.

Accordingly, Axl inhibitors contemplated for use in the combination therapies of the invention are disclosed in U.S. Published Patent Application No. 20070213375, U.S. Published Patent Application No. 20080153815, U.S. Published Patent Application No. 20080188454, U.S. Published Patent Application No. 20080176847, U.S. Published Patent Application No. 20080188455, U.S. Published Patent Application No. 20080182862, U.S. Published Patent Application No. 20080188474, U.S. Published Patent Application No. 20080117789, U.S. Published Patent Application No. 20090111816, PCT Published Patent Application No. WO 2007/0030680, PCT Published Patent Application No. WO 2008/045978, PCT Published Patent Application No. WO 2008/083353, PCT Published Patent Application No. WO 2008/0083357, PCT Published Patent Application No. WO 2008/083367, PCT Published Patent Application No. WO 2008/083354, PCT Published Patent Application No. WO 2008/083356, PCT Published Patent Application No. WO 2008/080134, and PCT Published Patent Application No. WO 2009/054864, the disclosures of which are incorporated in full by reference herein in their entireties. The Axl inhibitors disclosed in PCT Published Patent Application No. WO 2008/083367 are particularly preferred for use in the combination therapies of the invention.

The compounds of formula (I), as set forth above in the Summary of the Invention, are small molecule inhibitors of Axl catalytic activity, and are therefore useful in treating diseases and conditions which are associated with Axl catalytic activity, including those diseases and conditions which are characterized by angiogenesis and/or cell proliferation. In particular, the compounds of formula (I) are useful in treating diseases and conditions which are alleviated by the modulation of Axl activity. Diseases and condtions which are alleviated by the "modulation of Axl activity" includes diseases and conditions which are alleviated by a decrease in Axl activity and diseases and conditions which are alleviated by an increase in Axl activity. Preferably such diseases and conditions are alleviated by a decrease in Axl activity (*i.e.*, inhibition of Axl activity). Diseases and conditions which are alleviated by the modulation of Axl activity include, but are not limited to, solid cancer tumors, including, but not limited to, breast, renal, endometrial, ovarian, thyroid, and non-small cell lung carcinoma, melanoma, prostate carcinoma, sarcoma, gastric cancer and uveal melanoma; liquid tumors, including but not limited to, leukemias (particularly myeloid leukemias) and lymphomas; endometriosis, vascular disease / injury (including but not limited to restenosis, atherosclerosis and thrombosis), psoriasis; visual impairment due to macular degeneration; diabetic retinopathy and retinopathy of prematurity; kidney

disease (including but not limited to glomerulonephritis, diabetic nephropathy and renal transplant rejection), rheumatoid arthritis; osteoarthritis, osteoporosis and cataracts.

In addition to the foregoing, the compounds of formula (I) are useful in treating diseases and conditions which are affected by the following biological processes: Invasion, migration, metastasis, or drug resistance as manifested in cancer; stem cell biology as manifested in cancer; invasion, migration, adhesion, or angiogenesis as manifested in endometriosis; vascular remodeling as manifested in cardiovascular disease, hypertension or vascular injury; bone homeostatasis as manifested in osteoporosis or osteoarthritis; viral infection as manifested, for example, in ebola virus infection; or differentiation as manifested in obesity. The compounds of formula (I) may also be used to modulate inflammatory processes by treating sepsis, acting as vaccine adjuvants, and/or potentiating the immune response in immuno-compromised patients.

In a preferred embodiment, the compounds of formula (I) are useful in preventing, treating and managing cancers, preferably metastatic cancers.

The chemotherapeutic agents utilized in the combination therapies of the invention may be general cytotoxic agents or may target a specific cellular molecule. Preferably, the chemotherapeutic agents utilized in the combination therapies of the invention are useful in the prevention, treatment and management of one or more cancers, preferably metastatic cancers. Various classes of chemotherapeutic agents for the treatment of cancer include, among others, antimetabolites, agents that react with DNA (*e.g.*, alkylating agents, coordination compounds, platinum complexes, DNA cross-linking compounds, etc.), inhibitors of transcription enzymes, tyrosine kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, antimitotic agents (*e.g.*, vinca alkyloids and taxanes), antitumor antibiotics, hormones, and enzymes. Exemplary DNA cross-linking drugs and alkylating agents include, by way of example and not limitation, mechlorothamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine, temozolomide, alkyl sulfonates (*e.g.*, busulfan), carmustine and lomustine. Exemplary antimetabolites include, by way of example and not limitation, folate antagonists, *e.g.*, methotrexate; pyrimidine antagonists, *e.g.*, fluorouracil, capecitabine, cytarabine, gemcitabine and cytosine arabinoside; and purine analogs, *e.g.*, mecaptopurine, fludarabine, cladribine, thioguanine and azathioprine. Exemplary taxanes and vinca alkyloids include, by way of example and not limitation, vinblastine, vincristine, paclitaxel, docetaxel and colchicine. Exemplary

antitumor antibiotics include, by way of example and not limitation, actinomycin D, daunorubicin, and bleomycin. An exemplary enzyme effective as an anti-neoplastic agent is L-asparaginase. Exemplary platinum complexes and coordination compounds include, by way of example and not limitation, cisplatin (*cis*-diamminedichloridoplatinum(II) (CDDP)), carboplatin and oxaliplatin. Exemplary hormones and hormone-related compounds include, by way of example and not limitation, adrenocorticosteroids, *e.g.*, prednisone and dexamethasone; aromatase inhibitors, *e.g.*, amino glutethimide, formestane, and anastrozole; progestin compounds, *e.g.*, hydroxyprogesterone caproate and medroxyprogesterone; and anti-estrogen compounds, *e.g.*, tamoxifen. Exemplary topoisomerase inhibitors include, by way of example and not limitation, amsacrine (m-AMSA), mitoxantrone, topotecan, irinotecan, and camptothecin. Exemplary tyrosine kinase inhibitors include, by way of example and not limitation, axtinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sunitinib, vandetanib and vatalanib. Various derivative anti-neoplastic agents that combine more than one anticancer activity may also be used in the combination therapies of the invention. For instance, NSC290205 is a combination therapy compound incorporating d-lactam derivative of androsterone and an alkylating agent based on *N,N*-bis(2-chloroethyl)aniline (Trafalis *et al.*, 2005, *Br. J. Haematol.* 128(3):343-50).

Other chemotherapeutics useful in the combination therapies of the invention include, by way of example and not limitation, antibodies directed against growth factor receptors (*e.g.*, anti-Her2); cytokines such as interferon-α and interferon-γ, interleukin-2, and GM-CSF; and antibodies for cell surface markers (*e.g.*, anti-CTLA-4. anti-CD20 (rituximab); anti-CD33). When antibodies against cell surface markers are used, a chemotherapeutic agent can be conjugated to it for specific targeting to the tumor cell. Suitable conjugates include radioactive compounds (*e.g.*, radioactive metal bound to an antibody conjugated chelator), cytotoxic compounds, and drug activating enzymes (*e.g.*, allinase, peptidases, esterases, catalytic antibodies, etc.) (see, *e.g.*, Arditti *et al.*, 2005, *Mol. Cancer Therap.* 4(2):325-331, and U.S. Patent No. 6,258,360, the disclosures of which are both incorporated herein in full by reference).

Additional chemotherapeutic agents useful in the combination therapies of the invention include, but are not limited to, HDAC inhibitors (*e.g.*, MGCD0103 and vorinostat), HSP 90 inhibitors (*e.g.*, 17-AAG), BCL-2 inhibitors, thalidomide, lenalidomide, mTOR inhibitors (*e.g.*, rapamycin, CCI-779), sorafenib, doxorubicine,

gemcitabine, dexamethasone, melphalan, proteasome inhibitors (*e.g.*, bortezomib, NPI052), monoclonal antibodies (*e.g.*, gemtuzumab, alemtuzumab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, bevacizumab, rituximab and anti-TRAIL death receptor antibodies), and the like.

These and other chemotherapeutic agents useful in treating cancer are described in the "Commonly Used Antineoplastic Drugs", *The Merck Manuals Online Medical Library For HealthCare Professionals* at www.mercksource.com and *Goodman and Gilmans The Pharmacological Basis of Therapeutics*, 10th Edition, Hardman, J.G. and Limbird, L.E. eds., pg. 1381-1287, McGraw Hill, (1996), the disclosures of which both of which are incorporated by reference herein.

In some embodiments, a compound of formula (I), or a pharmaceutically acceptable salt thereof, can be used in the combination therapies of the invention with a second kinase inhibitor that targets an oncogenic kinase different from Axl. Examples include inhibitors of kinases associated with cell proliferative disorders such as, but not limited to the inhibitors of the kinases, Aurora-A, AKT, CDK1/cyclinB, CDK2/cyclinA, CDK3/cyclinE, CDK5/p35, CDK6/cyclinD3, CDK7/cyclinH/MAT1, CHK1, CHK2, EGFR, c-RAF, RAS, cSRC, Yes, Fyn, Lck, Fes, Lyn, Bmx, FGFR3, GSK3α., GSK3β, P13, IGF-1R, MAPK2, MAPKAP-K2, JNK, MEK1, p70S6K, PAK2, PDGFRα, PDGFRβ, PDK1, PKA, PKCε, PKC, PKD2, VEGF, PRAK, PRK2, RET, ROCK-II, Rsk1, Rsk2, Rsk3, and SGK.

In some embodiments, the second kinase inhibitor is an inhibitor of Abl kinase. For example, chronic myelogenous leukemia is a myeloid neoplasm characterized by malignant proliferation of leukemic stem cells in the bone marrow. The majority of chronic myelogenous leukemia is associated with a cytogenetic abnormality defined by a reciprocal translocation t(9;22)(q34;q11). This chromosomal aberration results in generation of a BCR/ABL fusion protein with activated kinase activity. Inhibitors of the fusion protein kinase activity are effective in treating chronic myelogenous leukemia although resistant forms may develop upon continued treatment. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination of Abl kinase inhibitors may lessen the chances of resistant cells by targeting a cellular process different than that targeted by the kinase inhibitor alone. An exemplary Abl kinase inhibitor is 2-phenylaminopyrimidine, also known as imatinib mesylate and GLEEVEC®. Thus, in some embodiments, a compound of formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with the Abl kinase inhibitor 2-phenylaminopyrimidine and its

derivatives. In other embodiments, the Abl kinase inhibitor may be pyridol[2-3-d]pyrimidine and its derivatives, which was originally identified as inhibitors of Src kinase. In yet further embodiments, the Abl kinase inhibitor is tyrphostins and its derivatives (*e.g.*, adaphostin) which affects the association of the kinase with its substrates. Other Abl kinase inhibitors useful in the combination therapies of the present invention will be apparent to the skilled artisan.

In one embodiment of the combination therapies of the invention, the Axl inhibitor utilized therein works by the same mechanism as the one or more chemotherapeutic agents utilized therein. In another embodiment of the combination therapies of the invention, the Axl inhibitor utilized therein works by a different mechanism than the one or more chemotherapeutic agents utilized therein.

The combination therapies of the invention are useful in preventing, treating or managing one or more cancers, preferably metastatic cancers. When a cancer spreads (metastasizes) from its original site (primary tumor) to another area of the body, it is termed "metastatic cancer". Virtually all cancers have the potential to spread this way. Consequently, the combination therapies of the invention are useful in preventing, treating or managing metastatic cancer wherein the primary tumor is one or more of the following cancers: Leukemias such as but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome, chronic leukemias such as but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, hairy cell leukemia; polycythemia vera; lymphomas such as but not limited to Hodgkin's disease, non-Hodgkin's disease; multiple myelomas such as but not limited to smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma and extramedullary plasmacytoma; Waldenstrom's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone and connective tissue sarcomas such as but not limited to bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, synovial sarcoma; brain tumors such as but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma,

nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, primary brain lymphoma; breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; adrenal cancer such as but not limited to pheochromocytom and adrenocortical carcinoma; thyroid cancer such as but not limited to papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancer such as but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers such as but limited to Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipius; eye cancers such as but not limited to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; vaginal cancers such as squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancer such as squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; cervical cancers such as but not limited to, squamous cell carcinoma, and adenocarcinoma; uterine cancers such as but not limited to endometrial carcinoma and uterine sarcoma; ovarian cancers such as but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; esophageal cancers such as but not limited to, squamous cancer, adenocarcinoma, adenoid cyctic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; stomach cancers such as but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; rectal cancers; liver cancers such as but not limited to hepatocellular carcinoma and hepatoblastoma, gallbladder cancers such as adenocarcinoma; cholangiocarcinomas such as but not limited to pappillary, nodular, and diffuse; lung cancers such as non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; testicular cancers such as but not limited to germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, choriocarcinoma (yolk-sac tumor), prostate cancers such as but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; genital cancers such as penile cancer; oral cancers such as but not limited to squamous cell carcinoma; basal cancers;

salivary gland cancers such as but not limited to adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers such as but not limited to squamous cell cancer, and verrucous; skin cancers such as but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acral lentiginous melanoma; kidney cancers such as but not limited to renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/or uterer); Wilms' tumor; bladder cancers such as but not limited to transitional cell carcinoma, squamous cell cancer, adenocarcinoma, carcinosarcoma. In addition, cancers include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinomas.

Whether metastases develop from a primary tumor depends on the complex interaction of many tumor cell factors, including the type of primary tumor, the degree of maturity (differentiation) of the primary tumor cells, the location of the primary tumor and how long the primary tumor has been present, as well as other incompletely understood factors.

The treatment of metastatic cancer depends on where the primary tumor is located. When breast cancer spreads to the lungs, for example, it remains a breast cancer and the treatment is determined by the metastatic cancer origin within the breast, not by the fact that it is now in the lung. About 5 percent of the time, metastatic cancer is discovered but the primary tumor cannot be identified. The treatment of these metastatic cancers is dictated by their location rather than their origin. Metastatic cancers are named by the tissue of the original tumor (if known). For example, a breast cancer that has spread to the brain is called metastatic breast cancer to the brain.

Metastases spread in three ways: by local extension from the tumor to the surrounding tissues, through the bloodstream to distant sites or through the lymphatic system to neighboring or distant lymph nodes. Each kind of cancer may have a typical route of spread.

Tissues which are particularly susceptible to metastatic cancer are the brain, liver, bone and lung, although all tissues of the body may be affected. Any cancer may spread to the brain, although the most common to do so are lung and breast cancer. The most

common cancer to metastasize to the liver is colon or other gastrointestinal cancer. The most common cancers to spread to the bones are prostate, lung and breast cancer. Metastases to the lung are common for many types of cancer.

In a preferred embodiment of the invention, the specific property of metastasis is targeted using the combination therapies described herein. In some embodiments, an Axl inhibitor, preferably a compound of formula (I) as set forth above in the Summary of the Invention, in combination with one or more chemotherapeutic agents, can be used to treat metastasis arising from a primiary tumor in various tissues of the body, including, but not limited to, primary tumors of the bone, breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract (*e.g.*, bladder), eye, liver, skin, head, neck, thyroid, parathyroid, and metastatic forms thereof. In one embodiment, the metastasis to be treated by the combination therapies of the invention is lung and/or liver metastasis arising from a primary tumor of the breast.

The combination therapies of the invention are also useful in treating certain celluar proliferative disorders. Such disorders include, but are not limited to, the following:

a) proliferative disorders of the breast, which include, but are not limited to, invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma, lobular carcinoma *in situ* and metastatic breast cancer;

b) proliferative disorders of the skin, which include, but are not limited to, basal cell carcinoma, squamous cell carcinoma, malignant melanoma and Karposi's sarcoma;

c) proliferative disorders of the respiratory tract, which include, but are not limited to, small cell and non-small cell lung carcinoma, bronchial adema, pleuropulmonary blastoma and malignant mesothelioma;

d) proliferative disorders of the brain, which include, but are not limited to, brain stem and hyptothalamic glioma, cerebellar and cerebral astrocytoma, medullablastoma, ependymal tumors, oligodendroglial, meningiomas and neuroectodermal and pineal tumors;

e) proliferative disorders of the male reproductive organs, which include, but are not limited to, prostate cancer, testicular cancer and penile cancer;

f) proliferative disorders of the female reproductive organs, which include, but are not limited to, uterine cancer (endometrial), cervical, ovarian, vaginal, vulval cancers, uterine sarcoma and ovarian germ cell tumor;

g) proliferative disorders of the digestive tract, which include, but are not limited to, anal, colon, colorectal, esophageal, gallbladder, stomach (gastric), pancreatic cancer, pancreatic cancer- Islet cell, rectal, small-intestine and salivary gland cancers;

h) proliferative disorders of the liver, which include, but are not limited to, hepatocellular carcinoma, cholangiocarcinoma, mixed hepatocellular cholangiocarcinoma, primary liver cancer and metastatic liver cancer;

i) proliferative disorders of the eye, which include, but are not limited to, intraocular melanoma, retinoblastoma, and rhabdomyosarcoma;

j) proliferative disorders of the head and neck, which include, but are not limited to, laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancers, and lip and oral cancer, squamous neck cancer, metastatic paranasal sinus cancer;

k) proliferative disorders of lymphocytic cells, which include, but are not limited to, various T cell and B cell lymphomas, non-Hodgkins lymphoma, cutaneous T cell lymphoma, Hodgkins disease, and lymphoma of the central nervous system;

l) leukemias, which include, but are not limited to, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia,

m) proliferative disorders of the thyroid, which include, but are not limited to, thyroid cancer, thymoma, malignant thymoma, medullary thyroid carcinomas, papillary thyroid carcinomas, multiple endocrine neoplasia type 2A (MEN2A), pheochromocytoma, parathyroid adenomas, multiple endocrine neoplasia type 2B (MEN2B), familial medullary thyroid carcinoma (FMTC) and carcinoids;

n) proliferative disorders of the urinary tract, which include, but are not limited to, bladder cancer;

o) sarcomas, which include, but are not limited to, sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma;

p) proliferative disorders of the kidneys, which include, but are not limited to, renal cell carcinoma, clear cell carcinoma of the kidney; and renal cell adenocarcinoma;

q) precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia), B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone B-cell lymphoma, hairy cell leukemia, plasma cell myeloma/plasmacytoma, extranodal marginal zone B-cell lymphoma of MALT type, nodal marginal zone B-cell

lymphoma, follicular lymphoma, mantle-cell lymphoma, diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, primary effusion lymphoma and Burkitt's lymphoma/Burkitt cell leukemia

(r) precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia), T-cell prolymphocytic leukemia, T-cell granular lymphocytic leukemia, aggressive NK-cell leukemia, adult T-cell lymphoma/leukemia (HTLV-1), extranodal NK/T-cell lymphoma, nasal type, enteropathy-type T-cell lymphoma, hepatosplenic gamma-delta T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, mycosis fungoides/Sezary syndrome, anaplastic large-cell lymphoma, T/null cell, primary cutaneous type, peripheral T-cell lymphoma, not otherwise characterized, angioimmunoblastic T-cell lymphoma, anaplastic large-cell lymphoma, T/null cell, and primary systemic type;

(s) nodular lymphocyte-predominant Hodgkin's lymphoma, nodular sclerosis Hodgkin's lymphoma (grades 1 and 2), lymphocyte-rich classical Hodgkin's lymphoma, mixed cellularity Hodgkin's lymphoma, and lymphocyte depletion Hodgkin's lymphoma;

(t) myelogenous leukemia (*e.g.*, Philadelphia chromosome positive (t(9;22)(qq34;q11)), multiple myeloma, chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukemia, atypical chronic myelogenous leukemia, juvenile myelomonocytic leukemia, refractory anemia with ringed sideroblasts and without ringed sideroblasts, refractory cytopenia (myelodysplastic syndrome) with multilineage dysplasia, refractory anemia (myelodysplastic syndrome) with excess blasts, 5q-syndrome, and myelodysplastic syndrome with t(9;12)(q22;p12);

(u) AML with t(8;21)(q22;q22), AML1(CBF-alpha)/ETO, acute promyelocytic leukemia (AML with t(15;17)(q22;q11-12) and variants, PML/RAR-alpha), AML with abnormal bone marrow eosinophils (inv(16)(p13q22) or t(16;16)(p13;q11), CBFb/MYH11X), and AML with 11q23 (MLL) abnormalities, AML minimally differentiated, AML without maturation, AML with maturation, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroid leukemia, acute megakaryocytic leukemia, acute basophilic leukemia, and acute panmyelosis with myelofibrosis.

It is to be understood that the descriptions of proliferative disorders is not limited to the conditions described above, but encompasses other disorders characterized by uncontrolled growth and malignancy. It is further understood that proliferative disorders

include various metastatic forms of the primary tumor and cancer types described herein. The combination therapies of the invention may be tested for effectiveness against these disorders, particularly various metastatic forms of the primary tumor, and a therapeutically effective regimen established. Effectiveness, as further described below, includes reduction or remission of the metastatic tumors, decreases in the rate of cell proliferation, or cytostatic or cytotoxic effect on metastatic cancer cell growth.

The antiproliferative effect of a combination therapy of the invention may be assessed by administering the active ingredients of the combination therapy to a cultured tumor cell line. In the context of an *in vitro* assay, administration of an active ingredient may be simply achieved by contacting the cells in culture with the active ingredient in amounts effective to inhibit cell proliferation. Alternatively, the antiproliferative effect of a combination therapy of the invention may be assessed by administering the active ingredients of the combination therapy to an animal in an approved *in vivo* model for cell proliferation.

Examples of tumor cell lines derived from human tumors and available for use in the *in vivo* studies include, but are not limited to, leukemia cell lines (*e.g.*, CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226, SR, P388 and P388/ADR); non-small cell lung cancer cell lines (*e.g.*, A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522 and LXFL 529); small cell lung cancer cell lines (*e.g.*,DMS 114 and SHP-77); colon cancer cell lines (*e.g.*, COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, SW-620, DLD-1 and KM20L2); central nervous system (CNS) cancer cell lines (*e.g.*, SF-268, SF-295, SF-539, SNB-19, SNB-75, U251, SNB-78 and XF 498); melanoma cell lines (*e.g.*, LOX I MVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62, RPMI-7951 and M19-MEL); ovarian cancer cell lines (*e.g.*, IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8 and SK-OV-3); renal cancer cell lines (*e.g.*, 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, UO-31, RXF-631 and SN12K1); prostate cancer cell lines (*e.g.*, PC-3 and DU-145); breast cancer cell lines (*e.g.*, MCF7, NCI/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, BT-549, T-47D and MDA-MB-468); and thyroid cancer cell lines (*e.g.*, SK-N-SH).

The combination therapies of the invention can be tested for the treatment of leukemias and lymphomas by testing the combination therapy in the xenograft in SCID mouse model using human Axl-expresing cancer cell lines including, but not limited to,

HeLa, MDA-MB-231, SK-OV-3, OVCAR-8, DU145, H1299, ACHN, A498 and Caki-1. In addition, the combination therapy may be tested for its use in treating leukemias in the xenograft in SCID or nu/nu mouse model using human Axl-expressing AML and CML leukemia cell lines.

The combination therapies of the invention may be tested for efficacy in preventing, treating or managing metastatic cancers in known animal models of metastatic cancer, such as the Mouse 4T1 Breast Tumor Model (see Pulaski, B.A. *et al.*, *Current Protocols in Immunology* (2000), 20.2.1-20.2.16), the disclosure of which is incorporated herein in full in its entirety, or variations thereof.

PHARMACEUTICAL COMPOSITIONS, DOSAGES AND ADMINISTRATION OF THE COMBINATION THERAPIES OF THE INVENTION

Pharmaceutical compositions of Axl inhibitors and other chemotherapeutic agents used in the combination therapies of the invention are known or can be prepared according to methods known to one skilled in the art. For example, methods of preparing and formulating pharmaceutical compositions of the Axl inhibitors of formula (I), as set forth above in the Summary of the invention, are disclosed in PCT Published Patent Application No. 2008/083367, which is incorporated in full herein in its entirety, as well as methods of administration.

In general, the amount of an Axl inhibitor, preferably a compound of formula (I), as set forth in the Summary of the Invention, or the amount of one or more chemotherapeutic agents which will be effective in the treatment, prevention or management of metastatic cancer in the combination therapies of the invention can be determined by standard research techniques. For example, the dosage amount of each active ingredient in a combination therapy of the invention which will be effective in the treatment, prevention or management of metastatic cancer can be determined by administering the combination therapy to an animal model such as the ones described herein or by one known to one skilled in the art. In addition, *in vivo* assays may optionally be employed to help identify optimal dosage ranges of each active ingredient in a combination therapy of the invention.

Selection of the preferred prophylactically or therapeutically effective dose of an active ingredient used in the combination therapies of the invention can be determined (*e.g.*, by clinical trials) by a skilled artisan based upon the consideration of several factors, including the activity of the specific compound employed; the metabolic stability and

length of action of the compound; the age, body weight, general health, sex, and diet of the patient; the mode and time of administration; the rate of excretion; the drug combination; and the severity of the metastatic cancer.

The precise dose of either the Axl inhibitor or the one or more chemotherapeutic agents used in the combination therapies of the invention will also depend on the route of administration and the seriousness of the metastatic cancer and should be decided according to the judgment of the medical practitioner and each patient's circumstances. Effective doses may be extropolated from dose-respose curves derived from in vitro or animal model test systems.

For example, a therapeutically effective daily dose for an Axl inhibitor, *i.e.*, a compound of formula (I), as set forth above in the Summary of the Invention, is (for a 70 kg mammal) from about 0.001 mg/kg (*i.e.*, 0.07 mg) to about 100 mg/kg (*i.e.*, 7.0 gm); preferaby a therapeutically effective dose is (for a 70 kg mammal) from about 0.01 mg/kg (*i.e.*, 0.7 mg) to about 50 mg/kg (*i.e.*, 3.5 gm); more preferably a therapeutically effective dose is (for a 70 kg mammal) from about 1 mg/kg (*i.e.*, 70 mg) to about 25 mg/kg (*i.e.*, 1.75 gm).

Dosages, routes of administration and recommended usage of the chemotherapeutic agents used in the combination therapies of the invention are known in the art and often described in such literature as the *Physician's Desk Reference* (current edition). In addition, typical doses of certain known chemotherapeutic agents are provided in U.S. Patent 7,351,729, the relevant section of which is incorporated in full by reference herein.

Preferably, the invention provides for any method of administering lower doses of the one or more chemotherapeutic agents used in the combination therapies of the invention than previously known to be effective for the prevention, treatment and management of metastatic cancer. Even more preferably, lower doses of the one or more chemotherapeutic agents are administered in the combination therapies of the invention with lower doses of the Axl inhibitor.

In the combination therapies of the invention, an Axl inhibitor is administered simultaneously with, prior to, or after administration of one or more other chemotherapeutic agents, as described herein, by the same route of administration or by different routes. Such combination therapy includes administration of a single pharmaceutical dosage formulation which contains an Axl inhibitor and one or more additional chemotherapeutic agents, as well as administration of the Axl inhibitor and each

chemotherapeutic agent in its own separate pharmaceutical dosage formulation. For example, the Axl inhibitor and the other one or more chemotherapeutic agents can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, the Axl inhibitor and the one or more chemotherapeutic agents can be administered to the patient at essentially the same time, *i.e.,* concurrently, or at separately staggered times, *i.e.,* sequentially. All such combinations of administration are encompassed by the combination therapies of the invention.

In certain embodiments of the combination therapies of the invention, the Axl inhibitor is administered to a patient, preferably a human, concurrently with one or more chemotherapeutic agents useful for the treatment of cancer. The term "concurrently" is not limited to the administration of the active ingredients (*i.e.*, the Axl inhibitor and the one or more chemotherapeutic agents) at exactly the same time, but rather it is meant that the Axl inhibitor and the other chemotherapeutic agent are administered to a patient in a sequence and within a time interval such that the Axl inhibitor can act together with the other chemotherapeutic agent to provide an increased benefit than if they were administered otherwise. For example, each active ingredient of the combination therapies of the invention may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each active ingredient can be administered separately, in any appropriate form and by any suitable route. In various embodiments, the active ingredients are administered less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In preferred embodiments, two or more active ingredients are administered within the same patient visit.

In other embodiments, the active ingredients are administered at about 2 to 4 days apart, at about 4 to 6 days apart, at about 1 week part, at about 1 to 2 weeks apart, or more than 2 weeks apart. In preferred embodiments, the active ingredients are administered in a

time frame where both active ingredients are still prophylactically and therapeutically active. One skilled in the art would be able to determine such a time frame by determining the half life of the administered active ingredients.

In certain embodiments, the active ingredients of the invention are cyclically administered to a patient. Cycling therapy involves the administration of a first active ingredient, such as the Axl inhibitor, for a period of time, followed by the administration of the second and/or third active ingredient for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In certain embodiments, the active ingredients are administered in a cycle of less than about 3 weeks, about once every two weeks, about once every 10 days or about once every week. One cycle can comprise the administration of an active ingredient by infusion over about 90 minutes every cycle, about 1 hour every cycle, about 45 minutes every cycle. Each cycle can comprise at least 1 week of rest, at least 2 weeks of rest, at least 3 weeks of rest. The number of cycles administered is from about 1 to about 12 cycles, more typically from about 2 to about 10 cycles, and more typically from about 2 to about 8 cycles.

In yet other embodiments, the active ingredients of the combination therapies of the invention are administered in metronomic dosing regimens, either by continuous infusion or frequent administration without extended rest periods. Such metronomic administration can involve dosing at constant intervals without rest periods. Typically the chemotherapeutic agents, in particular cytotoxic agents, are used at lower doses. Such dosing regimens encompass the chronic daily administration of relatively low doses for extended periods of time. In one embodiment, the use of lower doses of the chemotherapeutic agent can minimize toxic side effects and eliminate rest periods. In certain embodiments, the active ingredients are administered by chronic low-dose or continuous infusion ranging from about 24 hours to about 2 days, to about 1 week, to about 2 weeks, to about 3 weeks to about 1 month to about 2 months, to about 3 months, to about 4 months, to about 5 months, to about 6 months. The scheduling of such dose regimens can be optimalized by the skilled oncologist.

In other embodiments, the active ingredients are administered concurrently to a patient such that doses of the chemotherapeutic agent are administered separately yet within a time interval such that the Axl inhibitor can work together with the

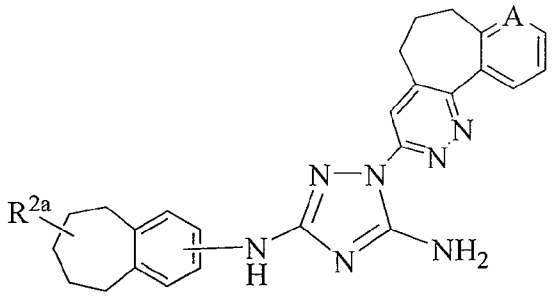
chemotherapeutic agent. For example, the chemotherapeutic agent may be administered one time per week and the Axl inhibitor may be administered every day. In other words, the dosing regimens for the active ingredients are carried out concurrently even if the active ingredients are not administered simultaneously or within the same patient visit.

In a preferred embodiment, the Axl inhibitor is administered every day to the patient and the one or more chemotherapeutic agent is administered once a week.

PREPARATION OF THE COMPOUNDS OF FORMULA (I)

Compounds of formula (I) utilized in the combination therapies of the invention can be made using organic synthesis techniques known to those skilled in the art, as well as by the methods described in PCT Published Patent Application No. 2008/083367, which is incorporated herein by reference in its entirety. Specific examples of the compounds of formula (I) can be found in this publication.

Alternatively, certain compounds of formula (I), as set forth above in the Summary of the Invention, can be made by the methods disclosed herein. In particular, the following Reaction Schemes illustrate methods to make compounds of formula (I) having the following formula (Ia1):



(Ia1)

;

wherein:

A is =C(H)- or =N-;

each R^{2a} is independently selected from the group consisting of $-N(R^{12a})_2$ and $-N(R^{12a})C(O)R^{12a}$,

or R^{2a} is an *N*-heterocyclyl optionally substituted by one or more substituents selected from the group consisting of halo and $-R^{21}-C(O)OR^{20}$,

each R^{12a} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally

substituted heteroarylalkyl;

R^{20} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl; and

R^{21} is independently selected from the group consisting of a direct bond or an optionally substituted straight or branched alkylene chain;

as an isolated stereoisomer or mixture thereof, or a pharmaceutically acceptable salt thereof.

It is understood that one of ordinary skill in the art would be able to make the compounds of formula (Ia1) by methods simliar to the methods described herein or by methods known to one of ordinary skill in the art. It is also understood that one of ordinary skill in the art would be able to make in a similar manner as described below other compounds of formula (Ia1) and the compounds of formula (Ib1), as set forth above in the Embodiments section, not specifically illustrated below by using the appropriate starting components and modifying the parameters of the synthesis as needed.

It is also understood that in the following Reaction Schemes and throughout this description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

It will also be appreciated by those skilled in the art that in the processes described below the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include benzyl, *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R" (where R" is alkyl, aryl or arylalkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acids include alkyl, aryl or arylalkyl esters.

Protecting groups may be added or removed in accordance with standard techniques, which are known to one of ordinary skill in the art and as described herein.

The use of protecting groups is described in detail in Greene, T.W. and P.G.M. Wuts, *Greene's Protective Groups in Organic Synthesis* (1999), 3rd Ed., Wiley. As one of

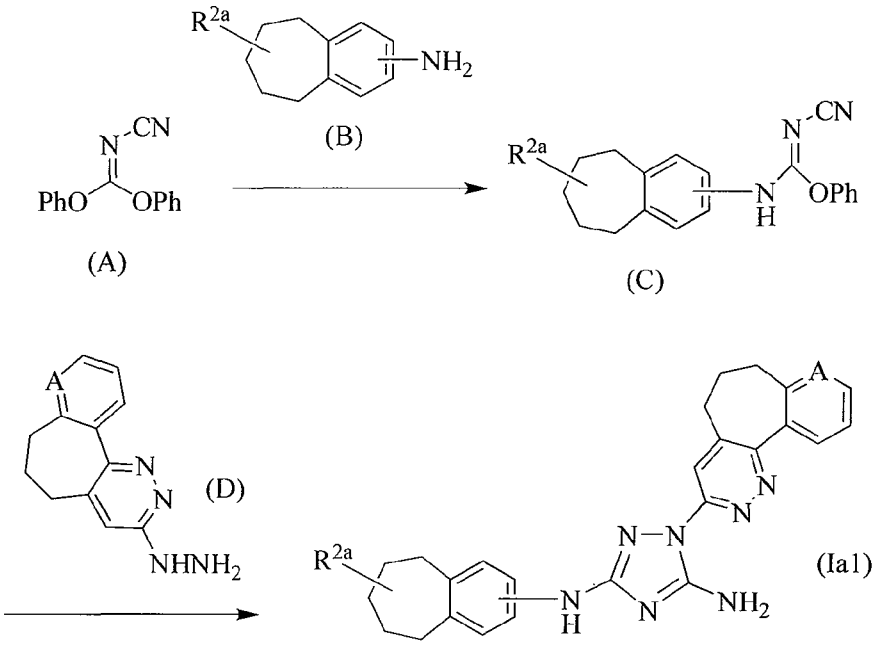
skill in the art would appreciate, the protecting group may also be a polymer resin such as, but not limited to, a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of this invention may not possess pharmacological activity as such, they may be administered to a mammal and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs".

In general, starting components may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described in this invention. ^{1}H NMR spectra were recorded in $CDCl_3$, DMSO-d_6, CD_3OD, Acetone-d_6 with trimethylsilane (TMS) as internal reference using Gemini 300 MHz instrument. Reagents and solvents were purchased from commercial sources and used without further purification. Flash column chromatography was conducted using silica gel (230-400 mesh) under a positive pressure of nitrogen. Waters LCMS instruments were used for recording LCMS spectra for purity and mass determinations. Deionized water was used to dilute the reactions and wash the products. Brine used was prepared by dissolving sodium chloride into deionized water to saturation point.

Compounds of formula (Ia1), as described above, are generally prepared as illustrated below in Reaction Scheme 1 where A and R^{2a} are as described above for the compounds of formula (Ia1) and Ph is a phenyl group:

REACTION SCHEME 1



Compounds of formula (A), formula (B) and formula (D) are commercially available or can be prepared by methods known to one skilled in the art or by methods disclosed herein.

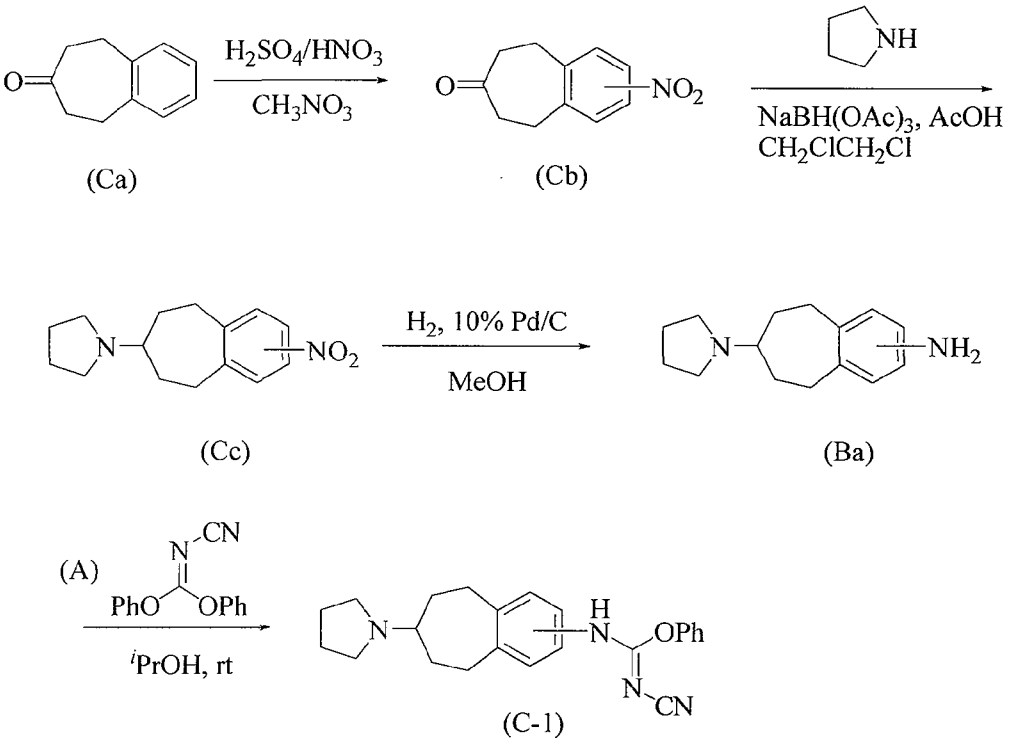
In general, compounds of formula (Ia1) are prepared, as set forth by Reaction Scheme 1, by first treating diphenyl cyanocarbonimidate (A) (where the phenyl groups therein may be replaced with other suitable groups or suitably substituted groups known to one skilled in the art) (1.1 equiv) with an equivalent amount of an aniline of formula (B) in an polar solvent, including, but not limited to, isopropyl alcohol, at ambient temperatures overnight. The diarylisourea product of formula (C) generally precipitates and isolation can be accomplished via filtration, washing with an appropriate solvent, and drying. Hydrazine hydrate of formula (D) (2 equivalents) is added to a slurry of the compound of formula (C) in an alcohol or other appropriate solvent. Generally, the ring formation reaction occurs at ambient temperature and the product triazole of formula (Ia1) can be isolated by standard isolation techniques.

Compounds of formula (Ib1), as set forth above in the Embodiments section, can be prepared using the synthetic route outlined in Reaction Scheme 1 in varying amounts depending on the steric and electronic nature of the starting materials as well as the particular reaction conditions employed. In some instances, compounds of formula (Ib1) are isolated as minor isomers along with compounds of formula (Ia1) as major isomers,

e.g., during column chromatography as described herein.

Compounds of formula (C-1) are compounds of formula (C), as set forth above in Reaction Scheme 1, where R^{2a} is pyrrolidin-1-yl. They can be prepared according to the method described below in relation to Reaction Scheme 2:

REACTION SCHEME 2



Compounds of formula (Ca) and formula (A) are commercially available or can be prepared according to methods described herein or known to one skilled in the art. Compounds of formula (Ba) are compounds of formula (B), as set forth above in Reaction Scheme 1.

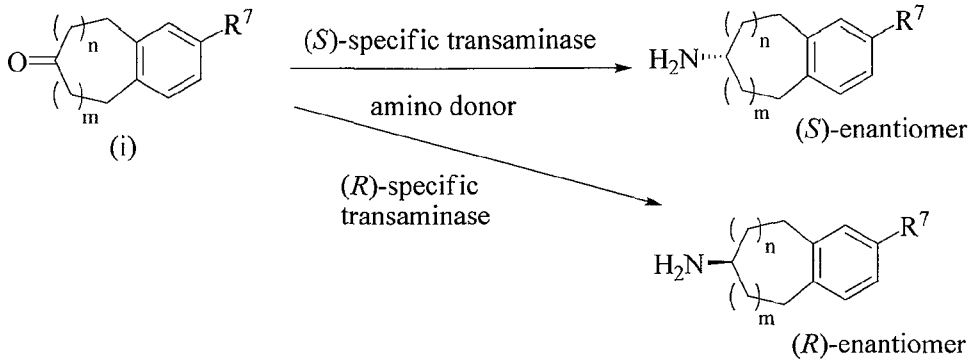
In general, compounds of formula (C-1) are prepared, for example, as set forth above in Reaction Scheme 2, by nitration of the benzo[7]annulene of formula (Ca) to form the nitro compound of formula (Cb). Reductive amination of the keto group in the ketone of formula (Cb) yields the pyrrolidine-substituted compound of formula (Cc). Reduction of the nitro group of the pyrrolidine-substituted compound of formula (Cc), for example, by catalytic hydrogenation, gives the aniline of formula (Ba). Reaction of the aniline of formula (Ba) with diphenyl cyanocarbonimidate of formula (A) yields the compound of formula (C-1). Compounds of formula (C-1) are enantiomeric. The enantiomers of

compound (C-1), and similar compounds of the invention, can be isolated, for example, by chiral phase HPLC.

Stereoselective amination of certain cyclic ketones, such as the compounds of formula (Cb) as set forth above, can be very challenging or impossible. Accordingly, the following describes one method of making compounds of formula (Ia1) and (Ib1) using transaminases to produce enantiomerically pure primary amines from cyclic ketones, particularly from cyclic ketones fused to a substituted aromatic ring.

Transaminases (also known as amino transferases) are enzymes that catalyze a transamination reaction between an amino-donor molecule (such as an amine or amino acid) and an amino-acceptor molecule (such as a ketone or an α-keto acid). Specifically, enzymatic transamination involves removing the amino group from the amino-donor molecule (leaving behind a carbonyl group) and transferring the amino group to the amino-acceptor molecule (or α-keto acid) by converting the ketone moiety therein to an amine (or an amino acid). A description of transaminases and their use in stereo-selective synthesis can be found in "Transminations. Enzyme Catalysis in Organic Synthesis (2nd Edition) (2002)", by J. David Rozzell and Andreas S. Bommarius, pp. 873-893, which is incorporated in full by reference herein.

Transaminases are particularly suitable for the enzymatic synthesis of chiral amines from the corresponding ketone precursors. Commercially available transaminases can be used to achieve a chiral enzymatic amination of a desired starting material in the preparation of the compounds of the invention. In particular, a ketone of the following formula (i) where n and m are the same and are 0, 1 or 2 and R is nitro, halo or $-C(O)OR^{12a}$ (where R^{12a} is as described above for the compounds of formula (Ia1)) can be converted under suitable conditions to the corresponding (*S*)-enantiomer and (*R*)-enantiomer wherein the carbon to which the amino group is attached is either in the (*S*) or the (*R*) configuration, respectively, by utilizing a (*S*)-specific tranasminase and an amino donor molecule, such as L-alanine, or a (*R*)-specific transaminase and an amino donor molecule, such as L-alanine, as shown below:

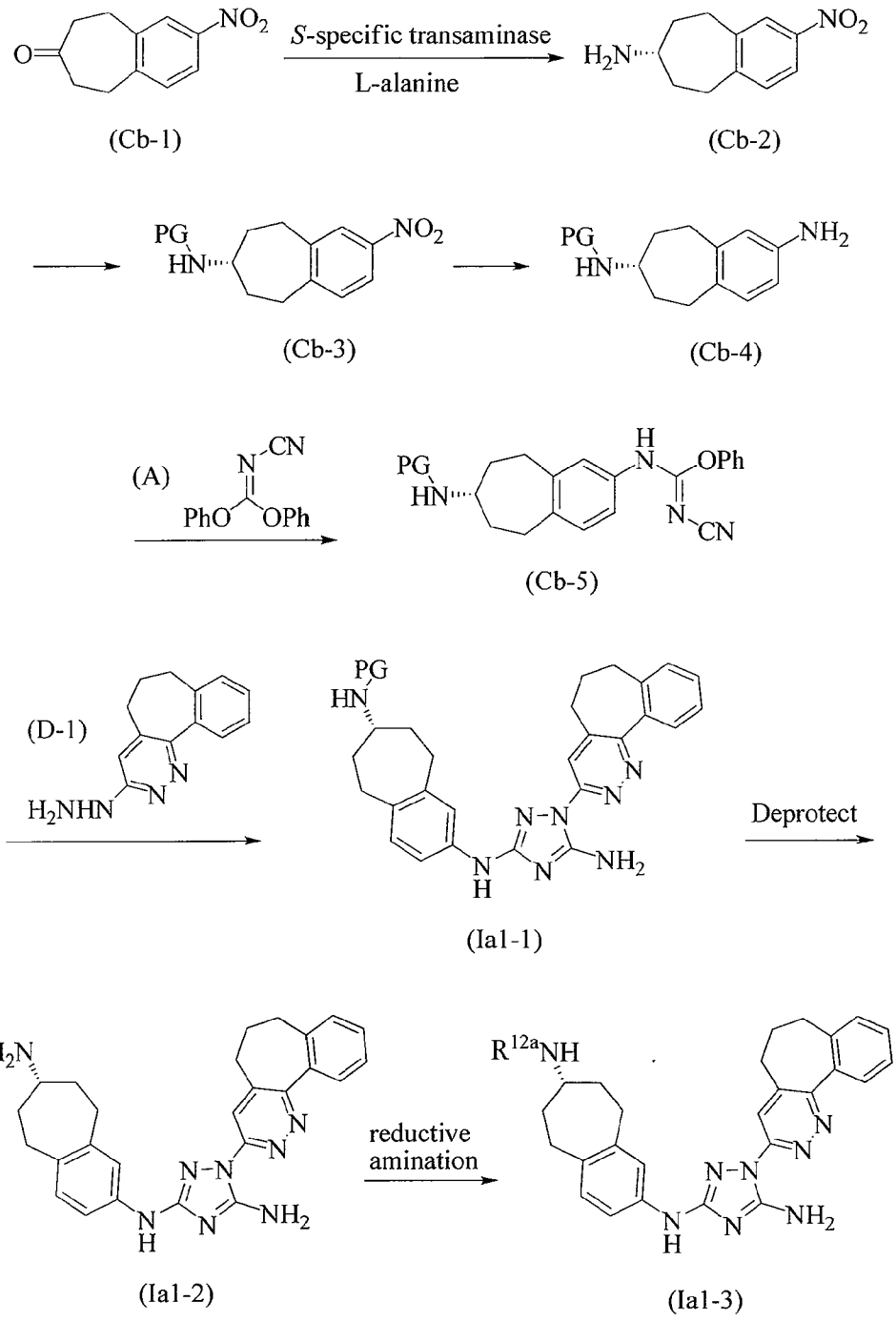


One of ordinary skill in the art would appreciate that the amino group on the (*S*)-enantiomer and the (*R*)-enantiomer can be further functionalized by standard procedures known to one skilled in the art. For example, treatment of the above (*S*)-enantiomer with 1,4-dibromobutane under the appropriate alkylation conditions will result in the amino group being converted to a 1-pyrrolidinyl group without racemization of the chiral center. Alternatively, treatment of the above (*S*)-enantiomer with an appropriate acylating agent with result in the amino group being acylated accordingly, and so forth.

Utilizing the appropriate transaminase to convert the cyclic ketone of formula (i) into the appropriate enantiomer, the appropriate enantiomer can be isolated in greater than 80% ee and preferably greater than 90% ee.

The following Reaction 3, where the compound of formula (Cb-1) is a compound of formula (i) as described above and PG represents a nitrogen protecting group, illustrates a method of preparing a chiral compound of formula (Ia1) utilizing a transaminase as described above:

REACTION SCHEME 3



Compounds of formula (Cb-1) are commercially available, or can be prepared by methods known to one skilled in the art. Compounds of formula (D-1) can be prepared according to methods known to one skilled in the art or by methods disclosed herein. The (*S*)-specific transaminase is commercially available from Codexis. Preferably the (*S*)-specific transaminase is ATA-103 from Codexis.

In general, compounds of formula (Ia1-1) are prepared by the method disclosed above in Reaction Scheme 3 by first converting the ketone of formula (Cb-1) into the chiral compound of formula (Cb-2) wherein the amino group from an amino donor molecule, preferably L-alanine, is transferred to the ketone of formula (Cb-1) through an enzymatic transamination reaction under suitable conditions. In particular, the ketone of formula (Cb-1) is treated with a excess molar amount of an amino donor molecule in the the presence of a catalytic amount of a transaminase, preferably a (*S*)-specific transaminase, and a stoichiometric or excess stoichiometric amount of a pyruvate reductase mixture that reduces (deactivates) the 2-keto acid side product, thereby driving the reaction into the desired direction. Preferably the pyruvate reductase mixture is PRM-102 from Codexix. The reaction is conducted at ambient temperature, at a pH of between about 7.5 and about 8.0, and for a period of time of between about 24 hours and about 6 days, preferably for about 4 days. The chiral compound of formula (Cb-2) is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

Alternatively, the transamination reaction can be driven to completion by coupling the reaction to a second reaction that consumes the 2-keto acid by-product in an essentially irreversible step, as described in more detail in "Transminations. Enzyme Catalysis in Organic Synthesis (2nd Edition) (2002)", by J. David Rozzell and Andreas S. Bommarius, pp. 873-893.

The amino group of the chiral compound of formula (Cb-2) is then protected by standard nitrogen protecting procedures to yield the compound of formula (Cb-3), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art. The compound of formula (Cb-3) is then treated to standard reducing conditions, such as treatment with H_2/Pd, to produce the corresponding aniline compound of formula (Cb-4), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art. The compound of formula (Cb-4) is then treated with diphenyl cyanocarbonimidate of formula (A) to produce the compound of formula (Cb-5), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

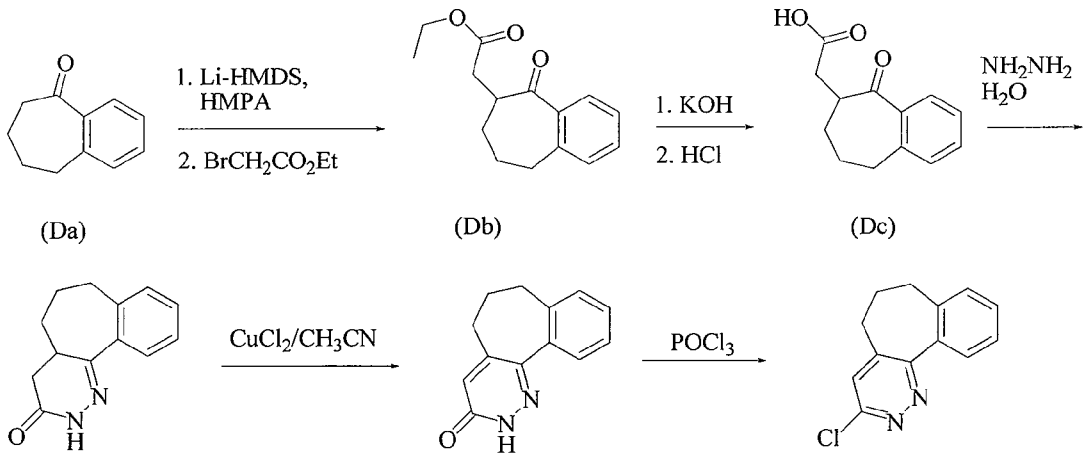
The compound of (Cb-5) is then treated with a compound of formula (D-1) in the presence of an aprotic solvent, preferably toluene, at a temperature of between about 80 °C and about 100 °C for a period of time of between about 12 hours and about 36 hours, preferably for about 24 hours, to yield a compound of formula (Ia1-1), which is isolated

from the reaction mixture by standard isolation techniques known to one skilled in the art. Compound of formula (Ia1-1) is a compound of formula (Ia1), as set forth above.

The protecting group on the compound of formula (Ia1-1) can be removed under standard deprotecting conditions known to one skilled in the art, such as acid hydrolysis, to produce a compound of formula (Ia1-2), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art. The compound of formula (Ia1-2) can be further treated with the appropriate aldehyde or ketone under standard reductive amination conditions to yield a compound of formula (Ia1-3), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

Compounds of formula (D-1) utilized in Reaction Scheme 3 above are compounds of formula (D), as shown above in Reaction Scheme 1, where A is =C(H)-. Compounds of formula (D-1) can be prepared according to the method disclosed below in Reaction Scheme 4:

REACTION SCHEME 4



Compounds of formula (Da) are commercially available or can be prepared by methods known to one skilled in the art or by methods disclosed herein.

In general, compounds of formula (D-1) are prepared, as set forth above in Reaction Scheme 3, by first dissolving the compound of formula (Da) (1.0 equiv) in an anhydrous aprotic polar solvent or mixture of such solvents, for example, tetrahydrofuran with hexamethylphosphoramide (HMPA) (1.2 equiv). The resulting solution is stirred at ambient temperature for about 10 minutes and then cooled to a temperature of between

about -10 °C and about 5 °C, preferably at 0 °C. A strong base, lithium bis(trimethylsilyl)amide (Li-HMDS) (1.1 equiv), is then added dropwise to the stirred mixture over a period of time of between about 20 minutes and 40 minutes, preferably over 30 minutes, while maintaining the temperature of the resulting mixture at between about -10 °C and about 5 °C, preferably at 0 °C. Ethyl bromoacetate (2.5 equiv) is then added to the resulting anion of (Da) and the resulting mixture is stirred for additional period of time of between about 5 minutes and 15 minutes, preferably for about about 10 minutes, and then allowed to warm to ambient temperature and stirred at ambient temperature for a period of time of between about 30 minutes and 3 hours, preferably for about 2 hours. The compound of formula (Db) is then isolated from the reaction mixture by standard isolation techniques known to one skilled in the art, such as solvent evaporation and purification by flash column chromatography.

The compound of formula (Db) is then treated under basic hydrolysis conditions to form the compound of formula (Dc), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

The compound of formula (Dc) (1.0 equiv) is then treated with hydrazine hydrate (1.25 equiv) in the presence of a polar protic solvent, such as ethanol, to yield the compound of formula (Dd), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

A mixture of the compound of formula (Dd) (1.0 equiv) and anhydrous copper(II) chloride (2.0 equiv) is then refluxed in acetonitrile to yield the unsaturated compound of formula (De), which is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

A mixture of the compound of formula (De) and phosphoryl chloride, is refluxed for a period of time of between about 1 hour and 3 hours, preferably for about 2 hours to aromatize and chlorinate the ring containing the N-N linkage. After cooling to ambient temperature, the compound of formula (Df) is isolated from the reaction mixture by standard isolation techniques known to one skilled in the art.

A mixture of the compound of formula (Df) (1.0 equiv) and anhydrous hydrazine (19.8 equiv) in a protic solvent, such as ethanol, is refluxed for a period time of between about 4 hours and 24 hours, preferably for about 16 hours. After cooling to ambient temperature, water is added to the mixture and the compound of formula (D-1) is then isolated from the reaction mixture by standard isolation techniques known to one skilled in

the art.

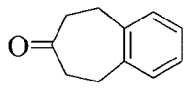
All compounds of the invention which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid by methods known to one of ordinary skill in the art. Salts of the compounds of the invention can be converted to their free base or acid form by standard techniques known to one skilled in the art.

The following specific Synthetic Preparations (for intermediates) and Synthetic Examples (for compounds of formula (Ia1) and (Ib1)) are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

SYNTHETIC PREPARATION 1

Synthesis of 7-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene

A compound of formula (Ca)



A. Sodium methoxide (9.4 g, 174.2 mmol) was added to a 250 mL of flask with dry methanol (100 mL) at 0 °C. After the solid was dissolved, the resulting solution was warmed to ambient temperature and was added to a solution of dimethyl acetone-1,3-dicarboxylate (15.2 g, 87.1 mmol) and o-xylylene dibromide, also known as 1,2-bis(bromomethyl)benzene, (20 g, 75.7 mmol) in 100 mL of dry THF at 0 °C dropwise within 30 min. After the addition, the reaction mixture was warmed to ambient temperature and stirred overnight. The volatiles were evaporated, the residue was poured into 40 mL of 10% HCl solution and extracted with ethyl acetate (EtOAc) (200 mL x 2). The combined extracts were washed with water, saturated $NaHCO_3$ solution and brine. After evaporation, the residual oil was used for next step directly.

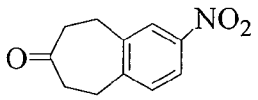
B. The crude dimethyl 7-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6,8-dicarboxylate was dissolved in 200 mL of ethanol (EtOH) and then 100 mL of 2 N KOH. The resulting mixture was refluxed at 85 °C for 17 h. After cooling to ambient temperature, the volatiles were evaporated. To the residue was added 120 mL of 2N HCl at 0 °C, the crude product was extracted by EtOAc (200 mL x 2). The combined extracts were washed with brine. After being dried ($MgSO_4$), filtered, and concentrated, the residue was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:1) to afford

6.6 g (57%) of 7-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene as a white solid: mp 40-41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (m, 4H), 2.94-2.90 (m, 4H), 2.63-2.60 (m, 4H); LC-MS: 161 $(M+H)^+$.

SYNTHETIC PREPARATION 2

Synthesis of 2-nitro-8,9-dihydro-5H-benzo[7]annulene-7(6*H*)-one

A compound of formula (Cb)

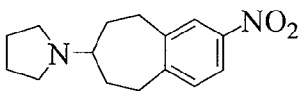


To a solution of cold (0 °C) concentrated sulfuric acid (15 mL) was added 70% nitric acid (15 mL) dropwise over 30 min. The addition was controlled to maintain the internal reaction temperature below 5 °C. After the addition, the resulting solution was transferred into an addition funnel and was added dropwise to a solution of 7-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene (14 g, 87.5 mmol) in nitromethane (80 mL) at 0 °C over a period of 40 min. After the addition, the reaction mixture was stirred at 0 °C for 2 h. Then ice water (~ 80 mL) was added to the reaction mixture, and the mixture was stirred for additional 30 min. Then the mixture was transferred to a separatory funnel where the layers were separated. The aqueous layer was extracted with ethyl acetate (3 X 80 mL). The combined layers were washed with cold water, sat. $NaHCO_3$ solution and brine. After being dried ($MgSO_4$), filtered, and concentrated, the residue was purified by flash column chromatography on silica gel (hexanes/EtOAc = 3:1 to 2:1) to afford the mixture of nitro regioisomers (~15 g), which was then purified by recrystallization from MTBE (*tert*-butyl methyl ether, 180 mL) to yield 7.3 g of 2-nitro-8,9-dihydro-5H-benzo[7]annulene-7(6*H*)-one (40% yield) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10-8.06 (m, 2H), 7.40-7.37 (m, 1H), 3.04-3.00 (m, 4H), 2.67-2.65 (m, 4H); LC-MS: 206 $(M+H)^+$.

SYNTHETIC PREPARATION 3

Synthesis of 1-(2-nitro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-7-yl)pyrrolidine

A compound of formula (Cc)



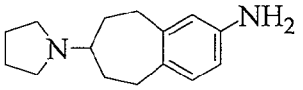
Pyrrolidine (0.85 g, 12 mmol) and 2-nitro-7-oxo-6,7,8,9-tetrahydro-5*H*-

benzo[7]annulene (2.05 g, 10 mmol) were mixed in 1,2-dchloroethane (35 mL) and then treated with $NaBH(OAc)_3$ (3.18 g, 15 mmol) and AcOH (0.60 g, 10 mmol). The mixture was stirred at ambient temperature under a N_2 atmosphere overnight. The reaction mixture was quenched with saturated $NaHCO_3$, and the product was extracted with EtOAc (3 x 30 mL). The organic layers were combined and dried over $NaSO_4$. The solvent was evaporated and the residue was purified by flash column chromatography eluting with CH_2Cl_2/DMA = 1/1 (DMA = CH_2Cl_2/MeOH/30% NH_3 = 80/19/1) to afford 1-(2-nitro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-7-yl)pyrrolidine, a yellow oil (2.2 g, 85%); MS (m/e): 261 ($M+H^+$).

SYNTHETIC PREPARATION 4

Synthesis of 1-(2-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-7-yl)pyrrolidine

A compound of formula (Ba)

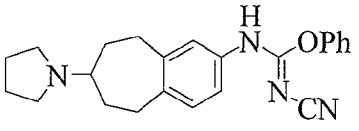


A mixture of 1-(2-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulene-7-yl)pyrrolidine (2.0 g; 7.69 mmol) and 10% palladium on carbon (0.2 g, ~50% water) in methanol (150 mL) was shaken under hydrogen (40 psi) for 1 h. After this time the reaction mixture was filtered through diatomaceous earth and the filtrate was concentrated under reduced pressure to afford 1-(2-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-7-yl)pyrrolidine as an oil (quantitative yield); MS (m/e): 231 ($M+H^+$).

SYNTHETIC PREPARATION 5

Synthesis of Phenyl N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate

A compound of formula (C-1)



A mixture of 1-(2-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-7-yl)pyrrolidine (1.7 g; 7.39 mmo) and diphenyl cyanocarboimidate (1.76 g, 7.39 mmol) in 20 mL of *iso*propanol was stirred at ambient temperature overnight. The solid was filtered, washed with *iso*propanol and ether and dried to give phenyl N'-cyano-N-(7-(pyrrolidin-1-yl)-

6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate, as a white solid (2.2 g, 80%). MS (m/e): 375 ($M+H^+$).

SYNTHETIC PREPARATION 6

Isolation of Phenyl (*S*)-N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate and Phenyl (*R*)-N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate

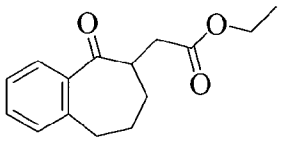
Enantiomers of the Compound of formula (C-1)

Phenyl N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate (0.43 g, racemic) was eluted on a chiral column chromatography mobile phase; ethanol/MeOH/triethyl amine = 1/1/0.2% to afford phenyl (*S*)-N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate and phenyl (*R*)-N'-cyano-N-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate: Chiral column: Chiralcel OJ, 21.2 x 250 mm. 10μM; packing material: cellulose tris-(4-methylbenzoate) coated on 10 μm silica gel substrate. Flow rate 9.9mL/min, sample solubility 30mg/mL in methanol. Single enantiomers were isolated in 170 mg and 190 mg quantities, respectively. Absolute configuration of each enantiomer was not determined at this time.

SYNTHETIC PREPARATION 7

Synthesis of ethyl 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetate

Compound of formula (Db)



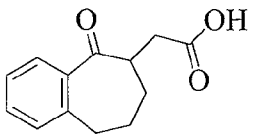
To a mixture of 1-benzosuberone (5.0 g, 31.2 mmol, Aldrich) in dry tetrahydrofuran (THF) (20 mL) was added hexamethylphosphoramide (6.5 mL, 37.5 mmol) (99%, Aldrich). The resulting mixture was stirred at ambient temperature for 10 min and then cooled to 0 °C with a ice-water bath, 1.0 M solution of lithium bis(trimethylsilyl)-amide in THF (32.7 mL, 32.7 mmol) was added dropwise in 30 min. After the addition, the reaction mixture was stirred at 0 °C for 30 min. Ethyl bromoacetate (8.7 mL, 78.1 mmol) was then added. After stirring for a further 10 min, the reaction mixture was warmed to ambient temperature and stirred for 2 h. Solvent was evaporated, the residue was diluted with ethyl

acetate (EtOAc) (300 mL), and washed with water and brine. After being dried ($MgSO_4$), filtered, and concentrated, the residue was purified by flash column chromatography eluting with hexanes-ethyl acetate 6:1 → 4:1) to afford 6.6 g of the compound of formula (Db), ethyl 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetate, as an orange oil (84%), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69-7.21 (m, 4H), 4.22-4.05 (m, 2H), 3.40-3.30 (m, 1H), 3.12-2.92 (m, 3H), 2.52-2.43 (m, 1H), 2.20-1.58 (m, 4H), 1.28-1.21 (m, 3H); LC-MS: purity: 91.8%; MS (m/e): 247 (MH^+).

SYNTHETIC PREPARATION 8

Synthesis of 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetic acid

Compound of formula (Dc)

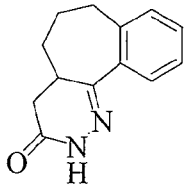


The compound of formula (Db), ethyl 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetate, (6.6 g, 26.8 mmol) was dissolved in ethanol (EtOH) (30 mL), then 10% potassium hydroxide (KOH) aqueous solution (37.5 mL, 67 mmol) was added and the resulting mixture was refluxed for 2 h. After cooling to ambient temperature, the EtOH was removed by evaporation. The residue was extracted with EtOAc twice (15 mL x 2). The aqueous layer was then transferred into a flask and cooled with an ice-water bath, con. HCl was added dropwise to adjust pH to about 2.0. EtOAc (60 mL) was then added, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine. After being dried ($MgSO_4$), filtered, and concentrated, the compound of formula (Dc), 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetic acid, was obtained as an orange oil (5.7 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71-7.68 (m, 1H), 7.41-7.20 (m, 3H), 3.37-3.31 (m, 1H), 3.12-2.91 (m, 3H), 2.57-2.49 (m, 1H), 2.15-1.90 (m, 2H), 1.75-1.62 (m, 2H); LC-MS: purity: 100%; MS (m/e) : 219 (MH^+).

SYNTHETIC PREPARATION 9

Synthesis of 4a,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta[*c*]pyridazin-3(4H)-one

Compound of formula (Dd)



A. A mixture of the compound of formula (Dc), 2-(5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-yl)acetic acid, (5.7 g, 26.1 mmol) and hydrazine hydrate (1.6 mL, 32.7 mmol) in 20 mL of ethanol was refluxed for 2 h, cooled and filtered (washed with small amount of EtOH) to give the compound of formula (Dd), 4a,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta[*c*]pyridazin-3(4*H*)-one, as a white solid (4.7 g, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (bs, 1H), 7.53-7.14 (m, 4H), 2.98-2.75 (m, 3H), 2.58 (dd, *J* = 15.3, 16.8 Hz, 1H), 2.31 (dd, *J* = 12.0, 16.8 Hz, 1H), 1.96-1.59 (m, 4H); LC-MS: purity: 100%; MS (m/e) : 215 (MH^+).

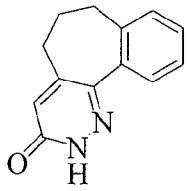
B. Alternatively, a mixture of benzosuberone (10.6 g, 66.2 mmol), glyoxylic acid monohydrate (6.08 g, 66.2 mmol), sodium hydroxide (10.6 g, 265 mmol), ethanol (40 mL) and water (100 mL) were stirred overnight at ambient temperature, and then heated under reflux for 1 h. The mixture was cooled, then diluted with water and extracted twice with dichloromethane (subsequently discarded). The aqueous layer was then acidified with 10% aqueous hydrochloric acid. Ice was added for cooling. The mixture was then filtered to give a pale yellow solid, 10.5 g (after air drying). The crude solid was then heated at 100 °C for 1 h with a mixture of acetic acid (60 mL), water (30 mL) and zinc dust (6 g). The reaction mixture was cooled to ambient temperature and filtered. The filtrate was extracted with ethyl acetate. The organic layer was washed three times with saturated sodium chloride solution, then dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was heated with ethanol (25 mL) and hydrazine monohydrate (10 mL) under reflux for 3 h. The solvent was removed under vacuum and the residue was crystallized from benzene/ethanol, 1/1, to give 4a,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta[*c*]pyridazin-3(4H)-one as a white solid, 2.31 g; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.66 (s, 1H), 7.52 (d, 1H), 7.24-7.50 (m, 2H), 7.16 (d, 2H), 2.75-3.00 (m, 3H), 2.56 (dd, 1H), 2.31 (dd, 1H), 1.60-1.90 (m, 4H) ppm; MS (ES) 215 (M+H). This procedure followed that reported by V. Peesapati and S.C. Venkata, *Indian J. Chem.*, 41B,

839 (2002).

SYNTHETIC PREPARATION 10

Synthesis of 6,7-dihydro-2*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3(5*H*)-one

Compound of formula (De)



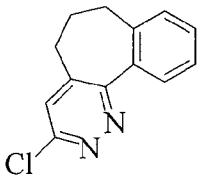
A. A mixture of the compound of formula (Dd), 4a,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta[*c*]pyridazin-3(4*H*)-one (4.7 g, 22 mmol) and anhydrous copper(II) chloride (6 g, 44 mmol) was refluxed in acetonitrile (45 mL) for 2 hours. After cooling to ambient temperature, the mixture was poured into ice-water (200 g) and the solid obtained was washed with 10% HCl solution twice (about 20 mLx2) and cold water twice (about 20 mLx2). After freeze-drying, the compound of formula (De), 6,7-dihydro-2*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3(5H)-one (4.2 g, 90%) was obtained as a white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.80 (bs, 1H), 7.53-7.21 (m, 4H), 6.77 (s, 1H), 2.66 (t, J = 6.9 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.14 (quant, J = 6.9 Hz, 2H); LC-MS: purity: 100%; MS (m/e) : 213 (MH^+).

B. Alternatively, a solution of 4a,5,6,7-tetrahydro-2*H*-benzo[6,7]cyclohepta[c]pyridazin-3(4*H*)-one (2.31 g, 10.74 mmol), sodium m-nitrobenzenesulfonate (2.48 g, 11 mmol), sodium hydroxide (1.86 g, 46.5 mmol) in water (80 mL) was heated under reflux for 1.5 h. The solution was cooled to ambient temperature, and then acidified with concentrated hydrochloric acid. The solid which precipitated was filtered off, washed with water and crystallized from ethanol to give 6,7-dihydro-2*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3(5*H*)-one as tan crystals, 1.46 g; ^{1}H NMR (DMSO-d_6, 300 MHz) 13.04 (s, 1H), 7.25-7.45 (m, 4H), 6.78 (s, 1H), 2.49 (m, 2H), 2.35 (m, 2H), 2.04 (m, 2H) ppm; MS (ES) 213 (M+H).

SYNTHETIC PREPARATION 11

Synthesis of 3-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine

Compound of formula (Df)



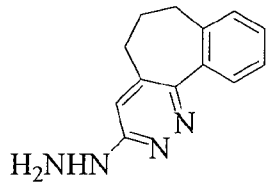
A. A mixture of the compound of formula (De), 6,7-dihydro-2*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3(5*H*)-one (4.0 g, 19.3 mmol) and $POCl_3$ (20 mL) was refluxed for 2 h. After cooling to ambient temperature, the volatiles were evaporated. The residue was poured into a mixture of ice water and sodium bicarbonate, CH_2Cl_2 (200 mL) was added to dissolve the solid. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 one more time. The combined organic layers were washed with brine. After being dried ($MgSO_4$), filtered, and concentrated, the compound of formula (Df), 3-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine was obtained as a yellow solid (4.3 g, 99%), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (m, 1H), 7.45-7.24 (m, 4H), 2.59-2.51 (m, 4H), 2.27 (quant, J = 6.9 Hz, 2H); LC-MS: purity: 100%; MS (m/e): 231 (MH^+).

B. Alternatively, 6,7-dihydro-2*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3(5*H*)-one was heated with 20 mL of phosphorus (III) oxychloride at 100 °C for 4.75 h. The solvent was removed under vacuum. The residue was treated with ice and saturated sodium bicarbonate solution. The solid which formed was filtered off, washed well with water and air-dried to yield the corresponding 3-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine (1.6 g); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.82 (m, 1H), 7.44 (m, 2H), 7.39 (s, 1H), 7.27 (m, 1H), 2.55 (m, 4H), 2.32 (m, 2H) ppm; MS (ES) 231/233 (M+H).

SYNTHETIC PREPARATION 12

Synthesis of 3-hydrazino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine

Compound of formula (D-1)



A. A mixture of the compound of formula (Df), 3-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine, (4.3 g, 18.6 mmol) and anhydrous hydrazine (11.7 mL, 370 mmol) in 45 mL of ethanol was refluxed for 16 h. After cooling to ambient temperature, 5 mL of water was added and the volatiles were then evaporated. To the solid residue was added cold water (about 80 mL). After sonication for 10 min, the resulting solid was collected by filtration and washed with cold water three times. After freeze-drying, the compound of formula (D-1), 3-hydrazino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine, (4.14 g, 98%) was obtained as a slight yellow solid, ^{1}H NMR (300 MHz, CD_3OD) δ: 7.59 (m, 1H), 7.39-7.26 (m, 3H), 7.04 (s, 1H), 2.54 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 6.9 Hz, 2H), 2.18 (quant, J = 6.9 Hz, 2H); LC-MS: purity: 100%; MS (m/e) : 227 (MH^+).

B. Alternatively, 3-chloro-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine (1.6 g) was heated with anhydrous hydrazine (4 mL) in ethanol (50 mL) at 100 °C for 4.75 h. The solvent was removed under vacuum. The residue was partitioned between chloroform and 1M saturated aqueous potassium carbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 3-hydrazino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine as a brown solid; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.74 (m, 1H), 7.30 (m, 2H), 7.17 (m, 1H), 6.92 (s, 1H), 2.49 (m, 2H), 2.39 (m, 2H), 2.12 (m, 2H) ppm; MS (ES) 227 (M+H).

SYNTHETIC PREPARATION 13

Synthesis of Phenyl *N'*-cyano-*N*-(7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate (Cb-5)

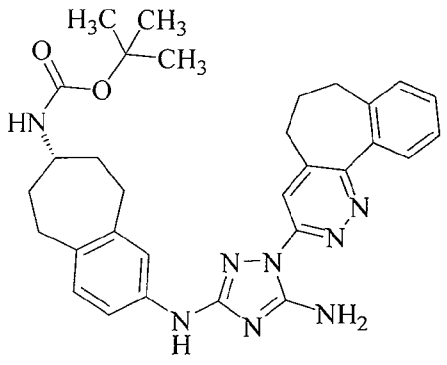
Finely ground 2-Nitro-8,9-dihydro-5H-benzo[7]annulen-7(6*H*)-one(8.00 g, 39.0 mmol) and L-alanine (34.7 g, 390 mmol) were added to the reaction buffer (1000 mL,

Codexis/BioCatalytics). The mixture was stirred vigorously for about 20 min in order to obtain a uniform suspension (bright-yellow in color). The pyruvate reductase mix (40.0 g, PRM-102, Codexis/BioCatalytics) and the transaminase (0.85 g, ~10.6 wt %, ATA-103) were added. The pH of the reaction mixture was ~7. Stirring was continued at a slow pace; the pH was checked once a day and, if necessary, adjusted to pH 7.0-7.5 using 1M NaOH. During the course of the reaction the color of the mixture changed to a yellow-orange color. After 6 days HPLC analysis showed 99% conversion. The reaction was worked up by adding sat. $NaHCO_3$ solution (200 mL) and $CHCl_3$ (600 mL). This mixture was stirred vigorously to ensure complete transfer of the product into the organic phase. After stirring overnight two layers had formed and the organic layer contained large amounts of a gel-like solid. The organic layer was separated and filtered through a large glass frit (medium) to remove the gel-like solid. The aqueous phase was extracted three times with DCM. The combined organic layers were filtered through $MgSO_4$ and the solvents were evaporated to give the desired amine, (7*S*)-2-nitro-7-amino-7,8,9-trihydro-5*H*-benzo[7]annulene (7.27 g, 91%, dark-red oil).

The single enantiomer was then BOC-protected, the nitro group reduced by treatment with H_2/Pd and the primary aniline treated with diphenyl cyanocarboimidate (slight excess) in 20 mL of *iso*propanol with stirring at ambient temperature overnight. The solid was filtered, washed with *iso*propanol and ether and dried to give phenyl (7*S*)-*N'*-cyano-*N*-(7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate, as a white solid in high yield (from the single enantiomer via transamination).

SYNTHETIC EXAMPLE 1

Synthesis of 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine



Phenyl *N'*-cyano-*N*-(7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)carbamimidate (2.00 g, 4.75 mmol) and 3-hydrazino-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazine (1.08 g, 4.75 mmol) were mixed in dry toluene (40 ml). The suspension was heated to 90 °C and stirred for 24 h. The clear solution was allowed to cool to ambient temperature and the toluene was evaporated using a rotavapor. The crude product was then checked by HPLC and TLC. Column chromatography on silica gel using $CHCl_3$ and 5% NH_3 (2M in MeOH) afforded some clean fractions of product which gave 367 mg (14%) of the desired product, 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine. The impure fractions were further purified by reverse phase HPLC to yield another 515 mg (20%) of the desired product, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H, NH), 7.92 (s, 1H), 7.86 (s, 2H), 7.69 (m, 1H), 7.43 (m, 3H), 7.34 (m, 1H), 7.23 (m, 1H), 6.96 (d, 1H), 6.83 (d, 1H), 3.49 (m, 1H), 2.72-2.39 (m, 8H), 2.22 (m, 2H), 2.07 (s, 1H), 1.92 (m, 2H), 1.38 (s, 9H), 1.17 (m, 2H) ppm; trifluoroacetic acid salt MS (ES) 553.24 (M+H), 551.42 (M-H).

SYNTHETIC EXAMPLE 2

The following compounds of the invention were prepared according to the methods similar to those described herein:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.07 (s, 1H), 7.93 (s, 1H), 7.90-7.65 (m, 3H), 7.47-7.31 (m, 3H), 7.24 (s, 1H), 7.00 (d, 1H), 3.89-3.80 (m, 1H), 2.71-2.50 (m, 8H), 2.30-2.19 (m, 2H), 1.96-1.88 (m, 2H), 1.80 (s, 3H), 1.37-1.19 (m, 2H) ppm; MS (ES) 495.21 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR ($CDCl_3$, 300 MHz) 8.90-8.78 (m, 1H), 8.48 (bs, 2H), 7.93 (s, 1H), 7.80-7.78 (m, 1H), 7.47-7.41 (m, 2H), 7.38-7.30 (m, 3H), 7.05-7.00 (m, 1H), 3.82 (s, 3H), 3.80-3.64 (m, 2H), 2.94-2.81 (m, 3H), 2.79-2.71 (m, 4H), 2.70-2.67 (m, 3H), 2.38-2.43 (m, 4H), 2.38-2.29 (m, 3H), 1.80-1.60 (m, 2H) ppm; MS (ES) 565.29 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4,4-

difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.60 (s, 1H), 9.11 (s, 1H), 7.92 (s, 1H), 7.85 (s, 1H), 7.71-7.68 (m, 1H), 7.51-7.45 (m, 2H), 7.39-7.33 (m, 2H), 7.08 (d, 1H), 3.67 (t, 1H), 3.52 (d, 2H), 3.18 (bs, 2H), 2.84-2.52 (m, 6H), 2.37-2.22 (m, 8H), 1.58-1.41 (m, 3H) ppm; MS (ES) 557.23 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.62 (s, 1H), 9.11 (s, 1H), 7.92 (s, 1H), 7.81 (s, 1H), 7.78-7.71 (m, 1H), 7.45-7.41 (m, 2H), 7.38-7.32 (m, 1H), 7.04 (d, 1H), 4.37 (d, 1H), 4.11 (d, 1H), 3.78 (s, 2H), 3.59 (t, 1H), 2.81-2.74 (m, 4H), 2.65-2.57 (m, 7H), 2.31-2.21 (m, 3H), 1.59-1.40 (m, 2H) ppm; MS (ES) 539.21 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.55 (s, 1H), 9.18 (s, 1H), 7.94 (s, 1H), 7.72-7.68 (m, 1H), 7.47-7.40 (m, 2H), 7.38-7.31 (m, 2H), 7.05 (d, 1H), 5.05-4.70 (bs, 3H), 4.55 (q, 1H), 3.64 (t, 1H), 3.52-3.48 (m, 1H), 3.31-3.25 (m, 1H), 2.80-2.70 (m, 3H), 2.62-2.52 (m, 3H), 2.39-2.20 (m, 5H), 2.09-1.78 (m, 4H), 1.49-1.38 (m, 3H) ppm; MS (ES) 551.27 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.11 (s, 1H), 8.97-8.90 (m, 1H), 7.94 (s, 1H), 7.85 (s, 1H), 7.71-7.68 (m, 1H), 7.50-7.40 (m, 2H), 7.38-7.30 (m, 2H), 7.05 (d, 1H), 4.09 (q, 2H), 3.55 (t, 1H), 3.38 (d, 1H), 3.10 (q, 1H), 2.85-2.57 (m, 5H), 2.52-2.42 (m, 6H), 2.29-2.18 (m, 3H), 2.06 (d, 2H), 1.77-1.70 (m, 2H), 1.54-1.36 (m, 3H), 1.29 (t, 3H) ppm; MS (ES) 593.28 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.90 (bs, 1H), 9.10 (s, 1H), 7.96 (s, 2H), 7.74-7.69 (m, 1H), 7.50-7.41 (m, 2H), 7.37-7.40 (m, 1H), 7.05 (d, 1H), 4.40-3.83 (m, 5H), 3.53-3.44 (m, 1H), 3.36 (d, 1H), 3.12-2.98 (m, 1H), 2.83-2.71 (m, 2H), 2.62-2.59 (m, 1H), 2.57-2.43 (m, 7H), 2.41-2.36 (m, 1H), 2.29-2.20 (m, 1H), 2.02-1.91 (m, 2H), 1.50-1.38 (m, 1H) ppm; MS (ES) 565.26 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.42 (s, 1H), 9.10 (s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.73-7.68 (m, 1H), 7.48-7.41 (m, 2H), 7.39-7.33 (m, 2H), 7.05 (d, 1H), 4.10 (bs, 3H), 3.57 (t, 1H), 2.78 (s, 3H), 2.68-2.45 (m, 9H), 2.3.4-2.22 (m, 3H). 1.55-1.39 (m, 2H) ppm; MS (ES) 525.22 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H-NMR (DMSO-d6, 300 MHz) 9.21 (s, 1H), 9.12 (s, 1H), 7.93 (s, 1H), 7.87 (s, 1H), 7.73-7.69 (m, 1H), 7.49-7.41 (m, 3H), 7.38-7.32 (m, 2H), 7.06 (d, 1H), 4.11 (q, 2H), 3.54-3.29 (m, 5H), 3.13-2.97 (m, 4H), 2.80-2.70 (m, 8H), 2.60 (t, 2H), 2.37-2.22 (m, 4H), 1.53-1.39 (m, 2H), 1.26 (t, 3H) ppm; MS (ES) 608.31 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 580.25 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 507.24 (M+H), 505.33 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 507.25 (M+H), 505.28 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 553.31 (M+H), 551.47 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, formic acid salt ^{1}H NMR (DMSO-d_6, 300 MHz) 9.11 (s, 1H, NH), 7.93 (s, 1H), 7.65 (m, 3H), 7.72 (d, 1H), 7.47 (m, 2H), 7.38 (s, 1H), 7.27 (s, 1H), 7.03 (d, 1H), 3.32 (s, 1H), 2.71 (m, 4H), 2.65-2.45 (m, 4H), 2.21 (m, 4H), 1.29 (m, 2H) ppm; MS (ES) 553.65 (M+H), 551.37 (M-H); free base MS (ES) 453.65 (M+H), 451.39 (M-H); trifluoroacetic acid salt MS (ES) 453.14 (M+H), 451.23 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*s*)-7-

(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.12 (s, 1H, NH), 7.95 (s, 1H), 7.82 (s, 2H, NH_2), 7.71 (m, 1H), 7.45 (m, 3H), 7.31 (m, 2H), 7.05 (d, 2H), 3.75 (t, 1H), 2.96 (m, 4H), 2.73 (m, 4H), 2.65-2.42 (m, 4H), 2.23 (m, 4H), 1.31 (m, 2 H), 1.08 (s br, 2H), 0.61 (d, 4H), 0.29 (d, 4H) ppm; MS (ES) 561.30 (M+H), 559.42 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.13 (s, 1H), 8.25 (s br, 2H), 7.81-8.00 (m, 3H), 7.66-7.76 (m, 1H), 7.41-7.53 (m, 3H), 7.27-7.39 (m, 2H), 6.97-7.11 (m, 1H), 3.19-3.47 (m, 1H), 2.66-2.86 (m, 6H), 2.43-2.65 (m, 7H), 2.14-2.37 (m, 4H), 1.82-1.99 (m, 1H), 1.20-1.47 (m, 2H), 0.93 (d, J = 6.6 Hz, 6H) ppm; MS (ES) 509.23 (M+H), 507.36 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.06-9.18 (m, 1H), 8.19-8.40 (m, 2H), 7.76-7.99 (m, 3H), 7.23-7.54 (m, 5H), 7.03 (d, 1H), 3.20-3.44 (m, 1H), 2.83-3.00 (m, 2H), 2.66-2.82 (m, 4H), 2.51-2.66 (m, 4H), 2.11-2.34 (m, 4H), 1.46-1.73 (m, 2H), 1.19-1.44 (m, 2H), 0.91 (s, 3H) ppm; MS (ES) 495.24 (M+H), 493.38 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.12 (s, 1H), 8.67-8.85 (m, 1H), 7.77-8.02 (m, 3H), 7.65-7.76 (m, 1H), 7.25-7.56 (m, 5H), 7.05 (d, J = 8.3 Hz, 1H), 3.47-3.70 (m, 1H), 2.99-3.18 (m, 2H), 2.83-2.98 (m, 2H), 2.66-2.83 (m, 4H), 2.50-2.66 (m, 5H), 2.10-2.34 (m, 4H), 1.34-1.78 (m, 6H), 0.88 (t, J = 7.2 Hz, 5H) ppm; MS (ES) 537.30 (M+H), 535.49 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.10 (s, 1H), 7.94 (s, 1H), 7.83 (s br, 2H), 7.67-7.75 (m, 1H), 7.41-7.53 (m, 3H), 7.29-7.41 (m, 2H), 7.05 (d, 1H), 3.52-3.68 (m, 2H), 2.93-3.27 (m, 4H), 2.66-2.85 (m, 4H), 2.50-2.65 (m, 4H), 2.11-2.31 (m, 5H), 1.33-1.60 (m, 2H), 1.09-1.29 (m, 7H) ppm; MS (ES) 509.23 (M+H), 507.35 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 535.30 (M+H), 533.46 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 521.28 (M+H), 519.28 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 563.30 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.09 (s, 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.84 (s, 2H), 7.63-7.77 (m, 1H), 7.40-7.52 (m, 2H), 7.36 (s br, 1H), 7.28 (s, 1H), 7.01 (d, 1H), 3.16-3.35 (m, 2H), 3.10-3.16 (m, 1H), 2.65-2.80 (m, 4H), 2.56-2.65 (m, 2H), 2.07-2.33 (m, 5H), 1.19-1.40 (m, 2H), 1.16 (d, J = 6.3 Hz, 6H) ppm; MS (ES) 495.26 (M+H), 493.37 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 536.18 (M);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 549.28 (M+H), 547.29 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 645.43 (M+H), 643.51 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.12 (s, 1H), 8.86 (s br, 2H), 7.66-7.99 (m, 3H), 7.26-7.53 (m, 4H), 7.17 (d, 2H), 7.04 (d, 1H), 4.43 (s br, 2H), 3.21-3.36 (m, 2H), 2.65-2.86 (m, 7H), 2.13-2.39 (m, 4H), 1.17-1.50 (m, 2H) ppm; MS (ES) 583.15 (M+H), 581.28 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-carboxyphenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-

1,2,4-triazole-3,5-diamine, MS (ES) 587.26 (M+H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3-bromophenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.09 (s, 1H), 8.01 (s, 1H), 7.67-7.96 (m, 6H), 7.27-7.50 (m, 5H), 7.03 (d, 1H), 6.50 (s, 1H), 4.12 (s br, 1H), 3.05-3.20 (m, 3H), 2.65-2.79 (m, 4H), 2.55-2.64 (m, 2H), 2.15-2.37 (m, 4H), 1.17-1.46 (m, 3H) ppm; MS (ES) 623.00 (M+H), 619.06 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.06 (s, 1H), 8.25 (s br, 2H), 7.81-8.01 (m, 3H), 7.65-7.78 (m, 2H), 7.25-7.51 (m, 2H), 6.97-7.08 (m, 1H), 4.86-5.00 (m, 1H), 3.99-4.08 (m, 1H), 2.66-2.85 (m, 2H), 2.52-2.65 (m, 4H), 2.15-2.36 (m, 5H), 1.87-2.12 (m, 5H), 1.12-1.48 (m, 3H) ppm; MS (ES) 481.10 (M+H), 479.13 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 507.15 (M+H), 505.24 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 523.16 (M+H), 521.27 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.05 (s, 1H), 8.29 (s, 1H), 7.93 (s, 1H), 7.85 (s br, 2H), 7.61-7.75 (m, 1H), 7.32-7.49 (m, 3H), 7.28 (s, 1H), 6.99 (d, 1H), 2.82-2.96 (m, 1H), 2.65-2.78 (m, 3H), 2.56-2.65 (m, 2H), 2.36-2.54 (m, 5H), 2.17-2.33 (m, 2H), 1.99-2.16 (m, 2H), 1.15-1.42 (m, 2H), 0.88 (s, 9H) ppm; MS (ES) 523.16 (M+H), 521.26 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 617.28 (M+H), 615.31 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.07 (s, 1H), 8.34 (s,

1H), 7.94 (s, 1H), 7.84 (s br, 2H), 7.66-7.75 (m, 1H), 7.33-7.53 (m, 3H), 7.28 (s, 1H), 7.00 (d, 1H), 2.87-3.13 (m, 1H), 2.40-2.84 (m, 10H), 1.92-2.33 (m, 5H), 1.63-1.80 (m, 2H), 1.39-1.63 (m, 4H), 1.05-1.38 (m, 4H) ppm; MS (ES) 535.18 (M+H), 533.16 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 665.26 (M+H), 663.40 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.03 (s, 1H), 8.32 (s, 1H), 7.92 (s, 1H), 7.83 (s br, 2H), 7.63-7.75 (m, 1H), 7.32-7.55 (m, 3H), 7.27 (s, 1H), 6.99 (d, 1H), 6.08-6.21 (m, 1H), 5.89-6.01 (m, 1H), 2.83-3.03 (m, 2H), 2.65-2.82 (m, 4H), 2.54-2.65 (m, 4H), 2.29-2.44 (m, 4H), 1.93-2.33 (m, 6H), 1.81 (t, 1H), 1.14-1.37 (m, 4H), 0.39-0.60 (m, 1H) ppm; MS (ES) 559.17 (M+H), 557.39 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.08 (s, 1H), 8.34 (s, 1H), 7.93 (s, 1H), 7.86 (s br, 2H), 7.67-7.74 (m, 1H), 7.40-7.51 (m, 3H), 7.33-7.39 (m, 1H), 7.29 (s br, 1H), 7.01 (d, J = 8.3 Hz, 1H), 3.08 (s br, 1H), 2.52-2.87 (m, 10H), 2.07-2.33 (m, 4H), 1.52-1.68 (m, 1H), 1.35-1.48 (m, 2H), 1.17-1.34 (m, 2H), 0.87 (d, J = 6.3 Hz, 6H) ppm; MS (ES) 523.20 (M+H), 521.27 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.01 (s, 1H), 7.91 (s, 1H), 7.83 (s br, 2H), 7.67-7.74 (m, 1H), 7.39-7.49 (m, 3H), 7.33-7.39 (m, 1H), 7.25-7.31 (m, 1H), 6.99 (d, J = 8.3 Hz, 1H), 2.52-2.75 (m, 9H), 2.16-2.38 (m, 7H), 1.86-2.04 (m, 2H), 1.49-1.62 (m, 2H), 1.11-1.28 (m, 5H), 0.83 (d, J = 6.6 Hz, 12H) ppm; MS (ES) 593.28 (M+H), 591.33 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): ^{1}H NMR (DMSO-d_6) d: 9.04 (s, 1H),

8.28 (s, 1H), 7.93 (s, 1H), 7.84 (s br, 2H), 7.66-7.75 (m, 1H), 7.40-7.50 (m, 3H), 7.32-7.40 (m, 1H), 7.29 (s, 1H), 7.01 (d, J = 8.3 Hz, 1H), 2.96-3.11 (m, 1H), 2.44-2.82 (m, 13H), 2.06-2.30 (m, 4H), 1.17-1.51 (m, 6H), 0.82 (t, J = 7.3 Hz, 6H) ppm; MS (ES) 537.20 (M+H), 535.27 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 507.16 (M+H), 505.11 (M-H);

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 562.16 (M);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, MS (ES) 554.10 (M+H), 552.22 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz): 9.23 (s, 1H), 8.54-8.69 (m, 1H), 8.10 (d, 1H), 7.98 (s, 1H), 7.87 (s br, 2H), 7.31-7.56 (m, 3H), 6.97 (t, 1H), 3.38-3.43 (m, 3H), 2.53-2.80 (m, 6H), 2.18-2.41 (m, 5H), 1.97-2.15 (m, 2H), 1.84-1.97 (m, 3H), 1.42-1.76 (m, 4H) ppm; MS (ES) 541.63 (M+H), 539.45 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H), 8.59 (d, 1H), 8.21 (s, 1H), 8.06 (d, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 7.62-7.43 (m, 2H), 7.26 (s, 1H), 6.95 (d, 1H) 2.92 (m, 1H), 2.68-2.42 (m, 4H), 2.44 (s, 2H), 2.29 (m, 2H), 2.05 (m, 2H), 1.29 (m, 2H), 1.01 (m, 4H) ppm; MS (ES) 454.37 (M+H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.03 (s, 1H), 8.53 (d, 1 H), 8.25 (s, 1H), 8.11 (d, 1H), 7.95 (s, 1H), 7.88 (s, 1H), 7.51-7.39 (m, 2H), 7.26 (s, 1H), 7.08 (d, 1H), 2.92 (m, 1H), 2.72-2.48 (m, 8H), 2.40 (s, 2H), 2.31 (m, 2H), 2.02 (m, 2H), 1.25 (m, 2H), 1.06 (m, 4H) ppm; MS (ES) 482.08 (M+H), 480.23 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-

3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.05 (s, 1 H), 8.58 (d, 1 H), 8.22 (s, 1H), 8.09 (d, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.56-7.38 (m, 2H), 7.28 (s, 1H), 7.03 (d, 1H), 2.98 (m, 1H), 2.79-2.52 (m, 12H), 2.49 (s, 2H), 2.33 (m, 2H), 2.04 (m, 2H), 1.27 (m, 2H), 1.03 (m, 4H) ppm; MS (ES) 510.57 (M+H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H), 8.58 (d, 1H), 8.18 (s, 1H), 8.08 (d, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.60-7.40 (m, 2H), 7.28 (s, 1H), 6.99 (d, 1H), 2.86-2.56 (m, 10H), 2.41-2.24 (m, 6H), 1.99 (m, 2H), 1.50-1.09 (m, 5H), 0.82 (t, 6H) ppm; MS (ES) 538.15 (M+H), 536.25 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.05 (s, 1H), 8.60 (d, 1H), 8.21 (s, 1H), 8.09 (d, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.55-7.39 (m, 2H), 7.26 (s, 1H), 7.00 (d, 1H), 3.10 (t, 2H), 2.77-2.54 (m, 8H), 2.45-2.22 (m, 6H), 2.01 (m, 4H), 1.30-1.09 (m, 2H), 0.84 (m, 2H), 0.43 (d, 3H), 0.10 (d, 2H) ppm; MS (ES) 562.16 (M+H), 560.39 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H), 8.59 (d, 1H), 8.21 (s, 1H), 8.06 (d, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 7.62-7.43 (m, 2H), 7.26 (s, 1H), 6.95 (d, 1H), 2.83-2.59 (m, 6H), 2.51-2.31 (m, 6H), 2.01 (m, 2H), 1.66-1.38 (m, 5H), 1.24 (m, 6H), 0.88 (d, 6H), 0.83 (d, 6H) ppm; MS (ES) 594.21 (M+H); 592.25 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H), 8.59 (d, 1H), 8.29 (s, 1H), 8.10 (d, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.55-7.39 (m, 2H), 7.24 (s, 1H), 6.99 (d, 1H), 2.93-2.53 (m, 8H), 2.31 (m, 4H), 2.11 (m, 2H), 1.96 (m, 2H), 1.80 (m, 2H), 1.62 (m, 2H), 1.32-1.10 (m, 2H) ppm; MS (ES) 508.05 (M+H), 506.13 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-

triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.06 (s, 1H), 8.60 (d, 1H), 8.31 (s, 1H), 8.10 (d, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 7.54-7.39 (m, 2H), 7.27 (s, 1H), 6.97 (d, 1H), 2.89-2.58 (m, 8H), 2.52 (m, 2H), 2.36 (m, 2H), 2.09 (m, 2H), 1.87 (m, 2H), 1.70 (m, 2H), 1.56 (m, 2H), 1.36-1.01 (m, 6H) ppm; MS (ES) 536.12 (M+H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.04 (s, 1H), 8.57 (d, 1H), 8.32 (s, 1H), 8.09 (d, 1H), 7.94 (s, 1H), 7.84 (s, 1H), 7.57-7.38 (m, 2H), 7.22 (s, 1H), 6.96 (d, 1H), 3.18-3.32 (m, 2H), 3.16-3.12 (m, 1H), 2.80-2.64 (m, 4H), 2.66-2.56 (m, 2H), 2.35-2.07 (m, 5H), 1.41-1.08 (m, 2H), 1.15 (d, J = 6.3 Hz, 6H) ppm; MS (ES) 496.09 (M+H), 494.12 (M-H);

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.05 (s, 1H), 8.61 (d, 1H), 8.21 (s, 1H), 8.11 (d, 1H), 7.96 (s, 1H), 7.84 (s, 1H), 7.57-7.39 (m, 2H), 7.29 (s, 1H), 6.96 (d, 1H), 3.36 (m, 2H) 2.81-2.52 (m, 8H), 2.45-2.21 (m, 6H), 2.01 (m, 2H), 1.87-1.44 (m, 4H), 1.29 (m, 2H) ppm; MS (ES) 522.12 (M+H), 520.31 (M-H); and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, ^{1}H NMR (DMSO-d_6, 300 MHz) 9.06 (s, 1H), 8.60 (d, 1H), 8.27 (s, 1H), 8.07 (d, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.59-7.43 (m, 2H), 7.20 (s, 1H), 7.01 (d, 1H), 3.28 (m, 2H), 2.95-2.63 (m, 8H), 2.19 (m, 5H), 1.75 (m, 2H), 1.41-1.11 (m, 2H), 0.95 (t, 3H) ppm; MS (ES) 510.09 (M+H), 508.38 (M-H).

BIOLOGICAL EXAMPLES

The following biological examples are provided by way of illustration, not limitation. In the following biological examples, 1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine, which is a compound of formula (I), as set forth above in the Summary of the Invention, and which is designated in the following examples and Figures 1-8 as "Compound A" or "Cpd A" or "Cmpd A", was

assayed for its ability to prevent, treat or manage metastatic cancer, either alone or in combination with another chemotherapeutic agent.

BIOLOGICAL EXAMPLE 1

Efficacy of Compound A in Preventing Lung and Liver Metastasis of a Primary Tumor in Breast Tissue

Using a variation of the mouse 4T1 breast tumor model, as described in *Current Protocols in Immunology* (2000), 20.2.1-20.2.16, Compound A was assayed to determine its ability to prevent, treat or manage metastatic cancer in BALB/c mice.

Formulations

Vehicle: 0.5% HPMC / 0.1% Tween.

Compound A: Preformulated dosing solutions in vehicle for 25 mg/kg, 40 mg/kg and 75 mg/kg for oral administration.

Cisplatin (Reference Control): Diluted in sterile saline for 1.2 mg/kg, 2.4 mg/kg and 75 mg/kg for intravenous administration.

Zometa: Diluted in sterile saline as per clinical formulation for subcutaneous administration.

Protocol

Eighty-eight BALB/c mice were inoculated with $5x10^5$ 4T1 tumor cells (ATCC) orthotopically into the third mammary fat pad. On Day 0 of the study (2 days post-inoculation), 80 mice were randomized into 8 groups (10 mice per group). Dose administration began on Day 0 and continued for 21 days (3 weeks). Compound A was administered twice a day, Cisplatin was administered once a week, and Zometa was administered three times weekly. Tumor measurements were performed three times per week, starting when tumors were palpable (approximately 3x3 mm). Body weight measurements were taken three times per week at the same time each day. Tumor and body weight measurements for all mice were measured prior to dose administration.

On Day 21 of the treatment, mice were euthanized and the lungs exposed and the numbers of surface lung metastases were counted. The size of each metastasis was measured using a caliper in one dimension and categorized as follows:

Small: Less than 2mm

Medium: Greater or equal to 2mm

Large: Greater or equal to 3mm

The lungs and livers from all mice were excised and placed in PLP fixative and stained for micrometastasis quantification.

Results

The results of this assay with respect to the effect of Compound A on the total number of macroscopic lung metastases are shown in FIGURE 1.

The results of this assay with respect to the effect of Compound A on the number of medium lung metastases are shown in FIGURE 2. The difference between the effect of Compound A at 45 mg/kg and the vehicle was significant ($p < 0.05$, Mann-Whitney Test). The difference between the effect of cisplatin at 4 mg/kg and the vehicle was significant ($p<0.001$, Mann-Whitney Test).

The results of this assay with respect to the effect of Compound A on the number of large lung metastases are shown in FIGURE 3. The difference between the effect of Compound A at 25 mg/kg and the vehicle was significant ($p < 0.05$, Mann-Whitney Test). The difference between the effect of Cisplatin at 1.2 mg/kg and 2.4 mg/kg and the vehicle was significant ($p<0.05$, Mann-Whitney Test).

The results of this assay with respect to the effect of Compound A on the incidence of liver micrometastases are shown in FIGURE 4. The difference between the effect of Compound A at 25 mg/kg, 45 mg/kg and 75 mg/kg and the vehicle was significant ($p < 0.05$, Mann-Whitney Test). The difference between the effect of Cisplatin at 2.4 mg/kg and 4 mg/kg and the effect of Cisplatin at 1.2 mg/kg was significant ($p< 0.05$, Mann-Whitney Test). The difference between the effect of Compound A at 45 mg/kg and 75 mg/kg and the effect of Compound A at 25 mg/kg was significant ($p<0.05$, Mann-Whitney Test). The difference between the effect of Zometa at 0.1 mg/kg and the vehicle was significant ($p<0.05$, Mann-Whitney Test).

BIOLOGICAL EXAMPLE 2

Efficacy of Compound A in combination with Cisplatin in Preventing Lung and Liver Metastasis of a Primary Tumor in Breast Tissue

Using a variation of the mouse 4T1 breast tumor model, as described in *Current Protocols in Immunology* (2000), 20.2.1-20.2.16, Compound A in combination with Cisplatin was assayed to determine the efficacy of the combination therapy to prevent, treat or manage metastatic cancer in BALB/c mice.

Formulations

Vehicle: 0.5% HPMC / 0.1% Tween.

Compound A: Preformulated dosing solutions in vehicle for 7 mg/kg and 21 mg/kg for oral administration.

Cisplatin: Diluted in sterile saline for 1.2 mg/kg (suboptimal clinical formulation) for intravenous administration.

Protocol

Sixty-six BALB/c mice were inoculated with $5x10^5$ 4T1 tumor cells (ATCC) orthotopically into the third mammary fat pad. On Day 0 of the study (2 days post-inoculation), 60 mice were randomized into 6 groups (10 mice per group). Dose administration began on Day 0 and continued for 21 days (3 weeks). Compound A was administered twice a day, Cisplatin was administered once a week, and Zometa was administered three times weekly. Tumor measurements were performed three times per week, starting when tumors were palpable (approximately 3x3mm). Body weight measurements were taken three times per week at the same time each day. Tumor and body weight measurements for all mice were measured prior to dose administration.

On Day 21 of the treatment, mice were euthanized and the lungs exposed and the number of surface lung metastases were counted. The size of each metastasis was measured using a caliper in one dimension and categorized as follows:

Small: Less than 2mm

Medium: Greater or equal to 2mm

Large: Greater or equal to 3mm

The lungs and livers from all mice were excised and placed in PLP fixative and stained for micrometastasis quantification.

Results

The results of this assay with respect to the effect of the combination therapy of Compound A and Cisplatin on the size of the primary tumor is shown in FIGURE 5.

The results of this assay with respect to the effect of the combination therapy of Compound A and Cisplatin on the incidence of liver micrometastases is shown in FIGURE 6. The difference between the effect of both combination therapies (Compound A at 7 mg/kg or 21 mg/kg and Cisplatin at 1.2 mg/kg) and the effect of the vehicle alone or the active ingredients (Cisplatin or Compound A) alone was significant ($p < 0.05$, Mann-Whitney Test).

The results of this assay with respect to the effect of the combination therapy of Compound A and Cisplatin on reducing the number of large lung metastases is shown in FIGURE 7. The difference between the effect of Compound A at 21 mg/kg and 7 mg/kg and vehicle was significant ($p<0.01$, Mann-Whitney Test). The difference between the effect of Cisplatin at 1.2 mg/kg and vehicle was significant ($p<0.05$, Mann-Whitney Test).

The results of this assay with respect to the effect of the combination therapy of Compound A and Cisplatin on reducing the incidence of large lung metastases is shown in FIGURE 8. The difference between the effect of both combination therapies (Compound A at 7 mg/kg or 21 mg/kg and Cisplatin at 1.2 mg/kg) and the effect of the vehicle alone was significant ($p < 0.05$, Mann-Whitney Test).

* * * * *

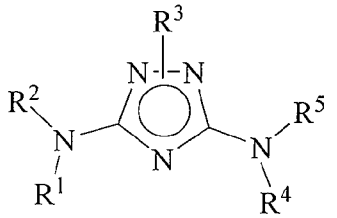
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entireties.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

WHAT IS CLAIMED IS:

1. A method for preventing, treating or managing cancer in a patient in need thereof, wherein the method comprises comprises administering to the patent a therapeutically or prophylactically effective amount of an Axl inhibitor and a therapeutically or prophylactically effective amount of one or more chemotherapeutic agents.

2. The method of Claim 1 wherein the Axl inhibitor is a compound of formula (I):



(I)

wherein:

R^1, R^4 and R^5 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, aralkyl, $-C(O)R^8$, $-C(O)N(R^6)R^7$, and $-C(=NR^6)N(R^6)R^7$;

R^2 and R^3 are each independently a polycyclic heteroaryl containing more than 14 ring atoms optionally substituted by one or more substituents selected from the group consisting of oxo, thioxo, cyano, nitro, halo, haloalkyl, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, $-R^9-OR^8$, $-R^9-O-R^{10}-OR^8$, $-R^9-O-R^{10}-O-R^{10}-OR^8$, $-R^9-O-R^{10}-CN$, $-R^9-O-R^{10}-C(O)OR^8$, $-R^9-O-R^{10}-C(O)N(R^6)R^7$, $-R^9-O-R^{10}-S(O)_pR^8$ (where p is 0, 1 or 2), $-R^9-O-R^{10}-N(R^6)R^7$, $-R^9-O-R^{10}-C(NR^{11})N(R^{11})H$, $-R^9-OC(O)-R^8$, $-R^9-N(R^6)R^7$, $-R^9-C(O)R^8$, $-R^9-C(O)OR^8$, $-R^9-C(O)N(R^6)R^7$, $-R^9-N(R^6)C(O)OR^8$, $-R^9-N(R^6)C(O)R^8$, $-R^9-N(R^6)S(O)_tR^8$ (where t is 1 or 2), $-R^9-S(O)_tOR^8$ (where t is 1 or 2), $-R^9-S(O)_pR^8$ (where p is 0, 1 or 2), and $-R^9-S(O)_tN(R^6)R^7$ (where t is 1 or 2);

or R^2 is a polycyclic heteroaryl containing more than 14 ring atoms as described above and R^3 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more

substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

or R^3 is a polycyclic heteroaryl containing more than 14 ring atoms as described above, and

R^2 is selected from the group consisting of aryl and heteroaryl, where the aryl and the heteroaryl are each independently optionally substituted by one or more substitutents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{13}-OR^{12}$, $-R^{13}-OC(O)-R^{12}$, $-R^{13}-O-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})-R^{14}-N(R^{12})_2$, $-R^{13}-N(R^{12})_2$, $-R^{13}-C(O)R^{12}$, $-R^{13}-C(O)OR^{12}$, $-R^{13}-C(O)N(R^{12})_2$, $-R^{13}-C(O)N(R^{12})-R^{14}-N(R^{12})R^{13}$, $-R^{13}-C(O)N(R^{12})-R^{14}-OR^{12}$, $-R^{13}-N(R^{12})C(O)OR^{12}$, $-R^{13}-N(R^{12})C(O)R^{12}$, $-R^{13}-N(R^{12})S(O)_tR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_tOR^{12}$ (where t is 1 or 2), $-R^{13}-S(O)_pR^{12}$ (where p is 0, 1 or 2), and $-R^{13}-S(O)_tN(R^{12})_2$ (where t is 1 or 2);

each R^6 and R^7 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, hydroxyalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, optionally substituted heteroarylalkynyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or any R^6 and R^7, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heteroaryl or an optionally substituted *N*-heterocyclyl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkylalkenyl, optionally substituted cycloalkylalkynyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heterocyclylalkenyl, optionally substituted heterocyclylalkynyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkynyl;

each R^9 is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{10} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain, an optionally substituted straight or branched alkenylene chain and an optionally substituted straight or branched alkynylene chain;

each R^{11} is independently selected from the group consisting of hydrogen, alkyl, cyano, nitro and $-OR^8$;

each R^{12} is independently selected from the group consisting of hydrogen, alkyl, alkenyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl , optionally substituted heteroarylalkyl, $-R^{10}-OR^8$, $-R^{10}-CN$, $-R^{10}-NO_2$, $-R^{10}-N(R^8)_2$, $-R^{10}-C(O)OR^8$ and $-R^{10}-C(O)N(R^8)_2$, or two $R^{12's}$, together with the common nitrogen to which they are both attached, form an optionally substituted *N*-heterocyclyl or an optionally substituted *N*-heteroaryl;

each R^{13} is independently selected from the group consisting of a direct bond, an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain; and

each R^{14} is independently selected from the group consisting of an optionally substituted straight or branched alkylene chain and an optionally substituted straight or branched alkenylene chain;

as an isolated stereoisomer or mixture thereof or as a tautomer or mixture thereof, or a pharmaceutically acceptable salt or N-oxide thereof.

3. The method of Claim 2 wherein the compound of formula (I) is selected from the group consisting of:

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*S*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7-(*R*)-pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(3-fluoro-4-(4-(pyrrolidin-1-yl)piperidin-1-yl)phenyl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-(7-(*S*)-pyrrolidin-1-yl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-

triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(acetamido)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(methoxycarbonyl)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4,4-difluoropiperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((methoxycarbonylmethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((2*R*)-2-(carboxy)pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonyl)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxy)piperidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-((carboxymethyl)(methyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(4-(carboxymethyl)piperazin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-(7-(pyrrolidin-1-yl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-1-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-

tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*s*)-7-(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-methylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((propyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((1-cyclopentylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-propylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3,3-dimethylbut-2-yl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclohexylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((5-chlorothien-2-yl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2-carboxyphenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((3-bromophenyl)methyl)amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-pentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((2,2-dimethylpropyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((cyclopentylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((bicyclo[2.2.1]hept-2-en-5-ylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(3-methylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-ethylbutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(but-2-enylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(butyl(but-2-enyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^5-((7*S*)-7-(*t*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(diethylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(dipropylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-

(di(cyclopropylmethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(di(3-methylbutyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclobutylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclohexylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-((methylethyl)amino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine;

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(cyclopentylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine; and

1-(6,7-dihydro-5*H*-pyrido[2',3':6,7]cyclohepta[1,2-*c*]pyridazin-3-yl)-N^3-((7*S*)-7-(2-butylamino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-2-yl)-1*H*-1,2,4-triazole-3,5-diamine.

4. The method of any one of Claims 1 to 3 wherein the one or more chemotherapeutic agents is selected from the group consisting of antimetabolites, alkylating agents, coordination compounds, platinum complexes, DNA cross-linking compounds, inhibitors of transcription enzymes, tyrosine kinase inhibitors, protein kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, vinca alkyloids, taxanes, antitumor antibiotics, hormones, aromatase inhibitors, enzymes, growth factor receptors antibodies, cytokines, cell surface markers antibodies, HDAC inhibitors, HSP 90 inhibitors, BCL-2 inhibitors, mTOR inhibitors, proteasome inhibitors and monoclonal antibodies.

5. The method of Claim 4 wherein the one or more chemotherapeutic agents is selected from the group consisting of mechlorothamine, cyclophosphamide, ifosfamide,

melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine, temozolomide, busulfan, carmustine, lomustine, methotrexate, fluorouracil, capecitabine, cytarabine, gemcitabine, cytosine arabinoside, mecaptopurine, fludarabine, cladribine, thioguanine, azathioprine, vinblastine, vincristine, paclitaxel, docetaxel, colchicine, actinomycin D, daunorubicin, bleomycin,L-asparaginase, cisplatin, carboplatin, oxaliplatin, prednisone, dexamethasone, amino glutethimide, formestane, anastrozole, hydroxyprogesterone caproate, medroxyprogesterone, tamoxifen, amsacrine, mitoxantrone, topotecan, irinotecan, camptothecin, axtinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sunitinib, vandetanib, vatalanib, anti-Her2 antibodies, interferon-α, interferon-γ, interleukin-2, GM-CSF, anti-CTLA-4 antibodies, rituximab, anti-CD33 antibodies, MGCD0103, vorinostat, 17-AAG, thalidomide, lenalidomide, rapamycin, CCI-779, sorafenib, doxorubicine, gemcitabine, melphalan, bortezomib, NPI052, gemtuzumab, alemtuzumab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, bevacizumab, rituximab, and anti-TRAIL death receptor antibodies.

6. The method of any one of Claims 1 to 5 wherein the Axl inhibitor and the one or more chemotherapeutic agents are administered concurrently.

7. The method of any one of Claims 1 to 5 wherein the Axl inhibitor and the one or more chemotherapeutic agents are administered sequentially.

8. The method of any one of Claims 1 to 7 wherein the cancer is metastatic cancer.