cell cycle regulation, proliferation, survival, apoptosis and motility and are significant components of the molecular mechanisms of diseases such as cancer, diabetes and immune inflammation (Vivanco et al (2002) Nature Rev. Cancer 2:489; Phillips et al (1998) Cancer 83:41).

[0007] The main PI3-kinase isoform in cancer is the Class I PI3-kinase, p110 α (alpha) (US 5824492; US 5846824; US 6274327). Other isoforms are implicated in cardiovascular and immune-inflammatory disease (Workman P (2004) Biochem Soc Trans 32:393-396; Patel et al (2004) Proceedings of the American Association of Cancer Research (Abstract LB-247) 95th Annual Meeting, March 27-31, Orlando, Florida, USA; Ahmadi K and Waterfield MD (2004) Encyclopedia of Biological Chemistry (Lennarz W J, Lane M D eds) Elsevier/Academic Press).

[0008] The PI3 kinase/Akt/PTEN pathway is an attractive target for cancer drug development since such agents would be expected to inhibit proliferation, reverse the repression of apoptosis and surmount resistance to cytotoxic agents in cancer cells (Garcia-Echeverria et al (2008) Oncogene 27:5511-5526). PI3 kinase inhibitors have been reported (Folkes et al (2008) Jour. Med. Chem. 51:5522-5532; Belvin et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 15, Abstract 4004; Folkes et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 14, Abstract LB-146; Friedman et al, American Association for Cancer Research Annual Meeting 2008, 99th:April 14, Abstract LB-110; Yaguchi et al (2006) Jour. of the Nat. Cancer Inst. 98(8):545-556; US 7173029; US 7037915; US 6608056; US 6608053; US 6838457; US 6770641; US 6653320; US 6403588; US 6703414; WO 97/15658; WO 2006/046031; WO 2006/046035; WO 2006/046040; WO 2007/042806; WO 2007/042810; WO 2004/017950; US 2004/092561; WO 2004/007491; WO 2004/006916; WO 2003/037886; US 2003/149074; WO 2003/035618; WO 2003/034997; US 2003/158212; EP 1417976; US 2004/053946; JP 2001247477; JP 08175990; JP 08176070). including p110 alpha binding activity (US 2008/0207611; US 2008/0039459; US 2008/0076768; US 2008/0269210; US 2008/0242665).

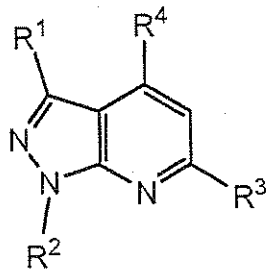
[0009] SUMMARY ~~OF THE INVENTION~~

[0010] The disclosure~~invention~~ relates generally to pyrazolo[3,4-b]pyridine compounds of Formula I with anti-cancer activity, and more specifically with PI3 kinase inhibitory activity. Certain hyperproliferative disorders are characterized by the modulation of PI3 kinase function, for example by mutations or overexpression of the proteins. Accordingly, the

compounds of the disclosure~~invention~~ may be useful in the treatment of hyperproliferative disorders such as cancer or inflammation related disorders such as rheumatoid arthritis. The compounds may inhibit tumor growth in mammals and may be useful for treating human cancer patients.

[0011] The disclosure~~invention~~ also relates to methods of using the pyrazolo[3,4-b]pyridines compounds of Formula I for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

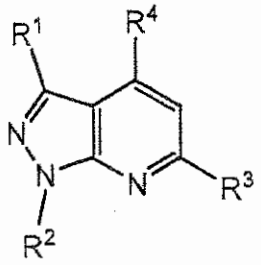
[0012] Formula I compounds include:



I

[0013] and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents R^1, R^2, R^3, R^4 are as defined herein.

[0013a] In one aspect, there is provided a compound selected from Formula I:



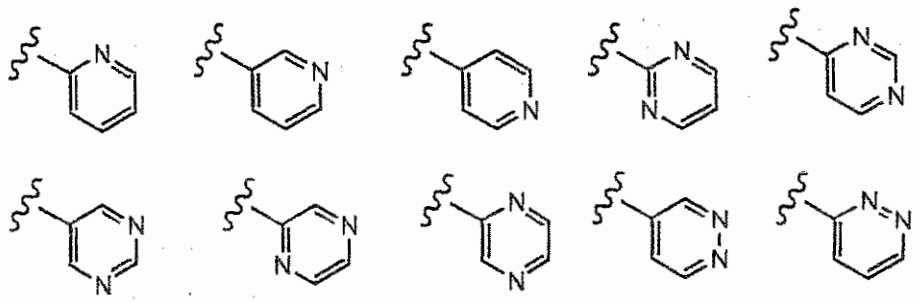
I

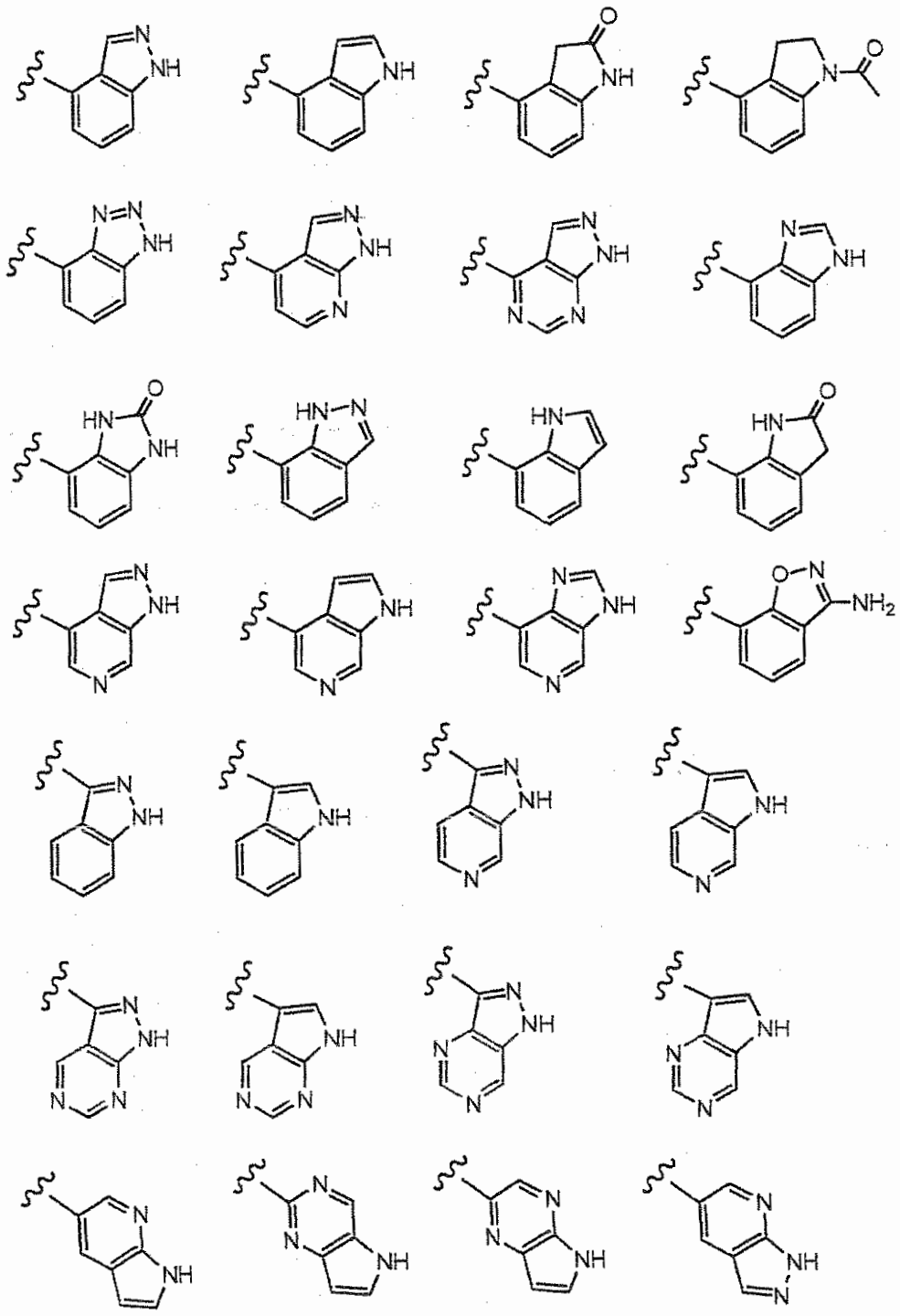
and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

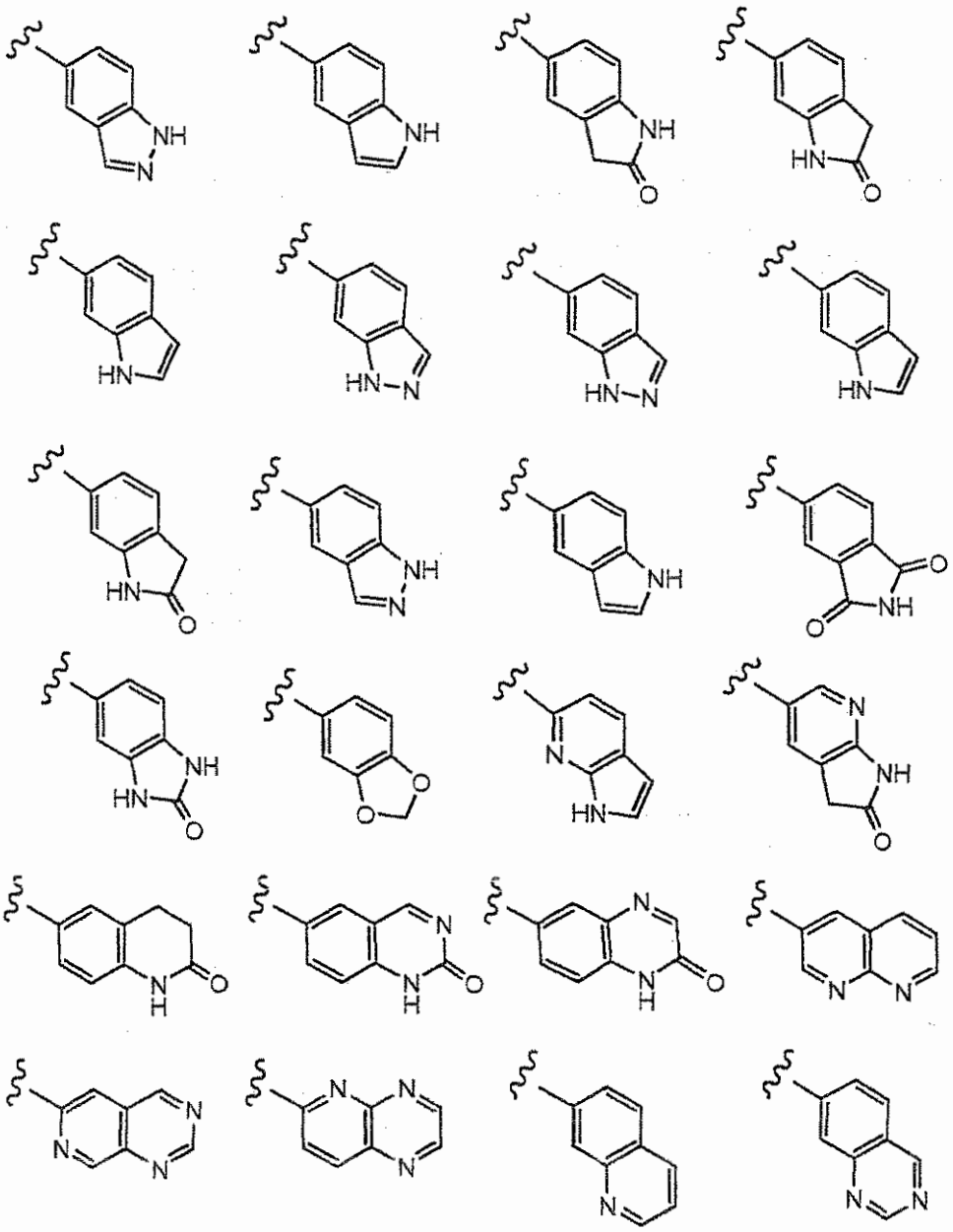
R^1 is selected from H, C_1–C_{12} alkyl, $-C(=O)NR^{10}R^{11}$, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, and C_1–C_{20} heteroaryl where C_1–C_{20} heteroaryl is optionally substituted with one or more groups independently selected from C_1–C_{12} alkyl, C_1–C_{12} alkyl-$NR^{10}R^{11}$, C_1–C_{12} alkyl-OR^{10}, C_6–C_{20} aryl, F, Cl, Br, I, $-CN$, $-CF_3$, $-CO_2H$, $-C(=O)NR^{10}R^{11}$, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{10}$, $-OR^{10}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{10}$;

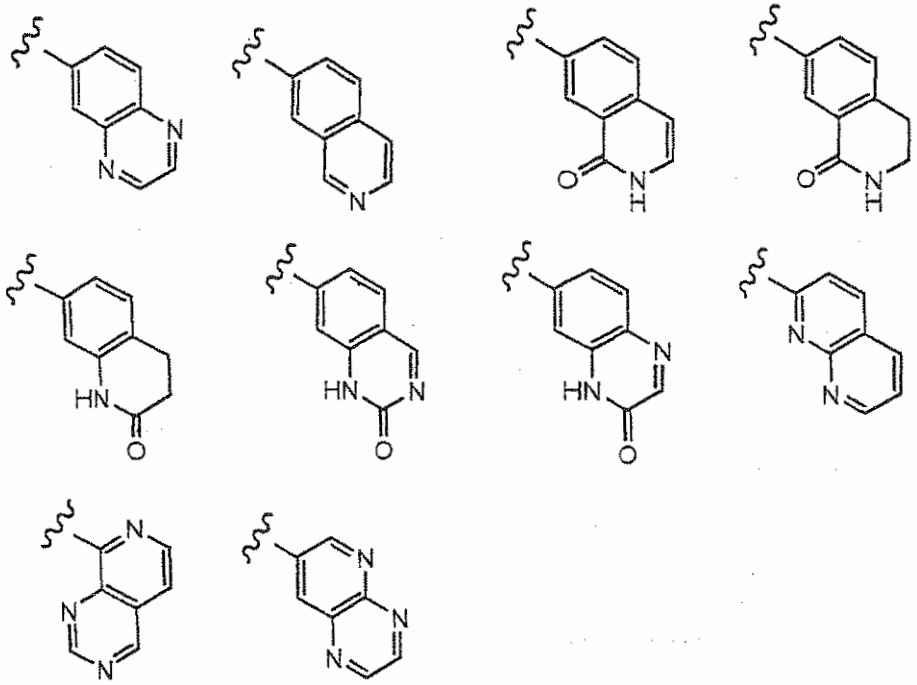
R^2 is C_1–C_{12} alkyl;

R^3 is selected from:









where the wavy line indicates the site of attachment;

optionally substituted with one or more groups independently selected from C_1–C_{12} alkyl, C_6–C_{20} aryl, F, Cl, Br, I, $-CH_3$, $-CN$, $-CF_3$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCOCH_3$, $-OH$, $-OCH_3$, -SH, -NHC(=O)NHCH$_3$, and $-S(O)_2CH_3$;

R^4 is selected from from $-NR^{10}R^{13}$, $-NR^{12}C(=O)R^{10}$, $-NR^{10}(C_1$–C_{12} alkyl)$NR^{10}R^{13}$, $-NR^{10}(C_1$–C_{12} alkyl)OR^{10}, $-NR^{10}(C_1$–C_{12} alkyl)$C(=O)NR^{10}R^{13}$, $-NR^{10}(C_1$–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), $-NR^{10}(C_1$–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), $-NR^{10}(C_1$–C_{12} alkylene)–(C_6–C_{20} aryl), $-NR^{10}(C_1$–C_{12} alkylene)–(C_1–C_{20} heteroaryl), $-OR^{10}$, $-O(C_1$–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), $-O(C_1$–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), $-O(C_1$–C_{12} alkylene)–(C_6–C_{20} aryl), $-O(C_1$–C_{12} alkylene)–(C_1–C_{20} heteroaryl), $-(C_1$–C_{12} alkylene)$NR^{10}R^{13}$, $-(C_1$–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), $-(C_1$–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), $-(C_1$–C_{12} alkylene)–(C_6–C_{20} aryl), $-(C_1$–C_{12} alkylene)–(C_1–C_{20} heteroaryl), $-(C_2$–C_8 alkynylene)$NR^{10}R^{13}$, $-(C_2$–C_8 alkynylene)–(C_3–C_{12} carbocyclyl), $-(C_2$–C_8 alkynylene)–(C_2–C_{20} heterocyclyl), $-(C_2$–C_8 alkynylene)–(C_6–C_{20} aryl), $-(C_2$–C_8 alkynylene)–(C_1–C_{20} heteroaryl), $-(C_1$–C_{12} alkylene)–(C_6–C_{20} arylene)–(C_2–C_{20} heterocyclyl), $-(C_6$–C_{20} aryl)-(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), $-C(=O)NR^{10}R^{11}$, C_1–C_{12} alkyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkylene, alkynyl, alkynylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are

optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_3, –CH_2OH, –CN, –CF_3, –CO_2H, –$COCH_3$, –$CONH_2$, –$CONHCH_3$, –$CON(CH_3)_2$, –NO_2, –NH_2, –$NHCH_3$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –$S(O)_2N(CH_3)_2$, –SCH_3, –CH_2OCH_3, and –$S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, -CN, -CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, -OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –SCH_3, –$S(O)CH_3$, –CH_2OCH_3, –CH_3, and –$S(O)_2CH_3$;

or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring; and

R^{13} is selected from C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –SCH_3, –$S(O)CH_3$, –OCH_2CH_2–$N(CH_3)_2$, and –$S(O)_2CH_3$;

or R^{10} and R^{13} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring.

[0014] Another embodiment~~aspect~~ of the disclosure~~invention~~ provides a pharmaceutical composition comprising a 1,3,4,6-substituted pyrazolo[3,4-*b*]pyridine compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more additional therapeutic agent.

[0014a] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

[0014b] In one aspect, there is provided a process for making a pharmaceutical composition which comprises combining a compound as defined herein with a pharmaceutically acceptable carrier.

[0015] Another embodiment~~aspect~~ of the disclosure~~invention~~ provides methods of inhibiting PI3 kinase activity, comprising contacting a PI3 kinase with an effective inhibitory amount of a compound of Formula I.

[0015a] In one aspect, there is provided a compound as defined herein for use in therapy.

[0016] Another embodimentaspect of the disclosureinvention provides methods of preventing or treating a hyperproliferative disease or disorder modulated by PI3 kinases, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I. Examples of such hyperproliferative disease or disorder include, but are not limited to, cancer.

[0017] Another embodimentaspect of the disclosureinvention provides methods of preventing or treating a hyperproliferative disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, alone or in combination with one or more additional compounds having anti-hyperproliferative properties.

[0017a] In one aspect, there is provided a compound as defined herein for use in a method of treating a hyperproliferative disorder in a mammal, wherein the hyperproliferative disorder is cancer, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

[0017b] In one aspect, there is provided the use of a compound as defined herein in the manufacture of a medicament for the treatment of a hyperproliferative disorder in a mammal, wherein the hyperproliferative disorder is cancer, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

[0018] Another embodimentaspect of the disclosureinvention provides methods of preventing or treating a inflammation disorder, comprising administering to a mammal in need of such treatment an

effective amount of a compound of Formula I, alone or in combination with one or more additional compounds having anti-hyperproliferative properties.

[0019] In a further embodimentaspect the present disclosureinvention provides a method of using a compound of this disclosureinvention to treat a hyperproliferative disease or condition modulated by PI3 kinase in a mammal.

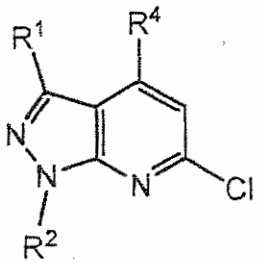
[0020] An additional embodimentaspect of the disclosureinvention is the use of a compound of this disclosureinvention in the preparation of a medicament for the treatment or prevention of a disease or condition modulated by PI3 kinase in a mammal.

[0021] Another embodimentaspect of the disclosureinvention includes kits comprising a compound of Formula I, a container, and optionally a package insert or label indicating a treatment.

[0021a] In one aspect, there is provided a kit for treating a PI3K-mediated condition, comprising: a) a first pharmaceutical composition comprising a compound as defined herein; and b) instructions for use in treating cancer, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

[0022] Another embodimentaspect of the disclosureinvention includes methods of preparing, methods of separating, and methods of purifying compounds of Formula I.

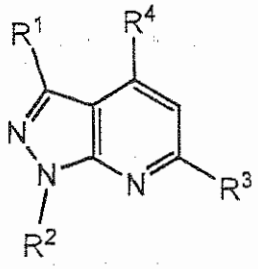
[022a] In one aspect, there is provided a method of making a Formula I compound comprising reacting a Formula II compound:



II

and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, with a boronate compound comprising a monocyclic heteroaryl, a fused bicyclic heterocycle, or a fused bicyclic heteroaryl,

whereby a Formula I compound is formed:



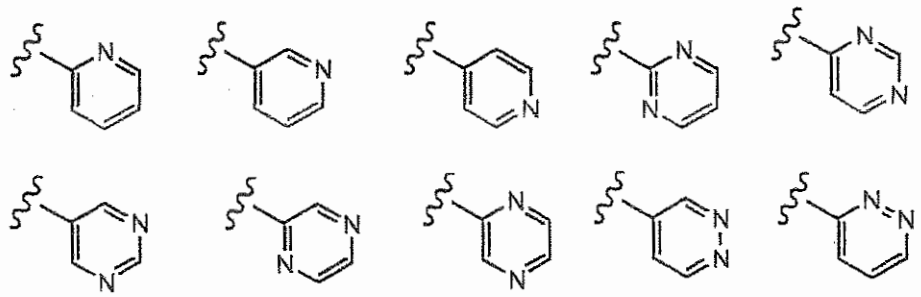
I

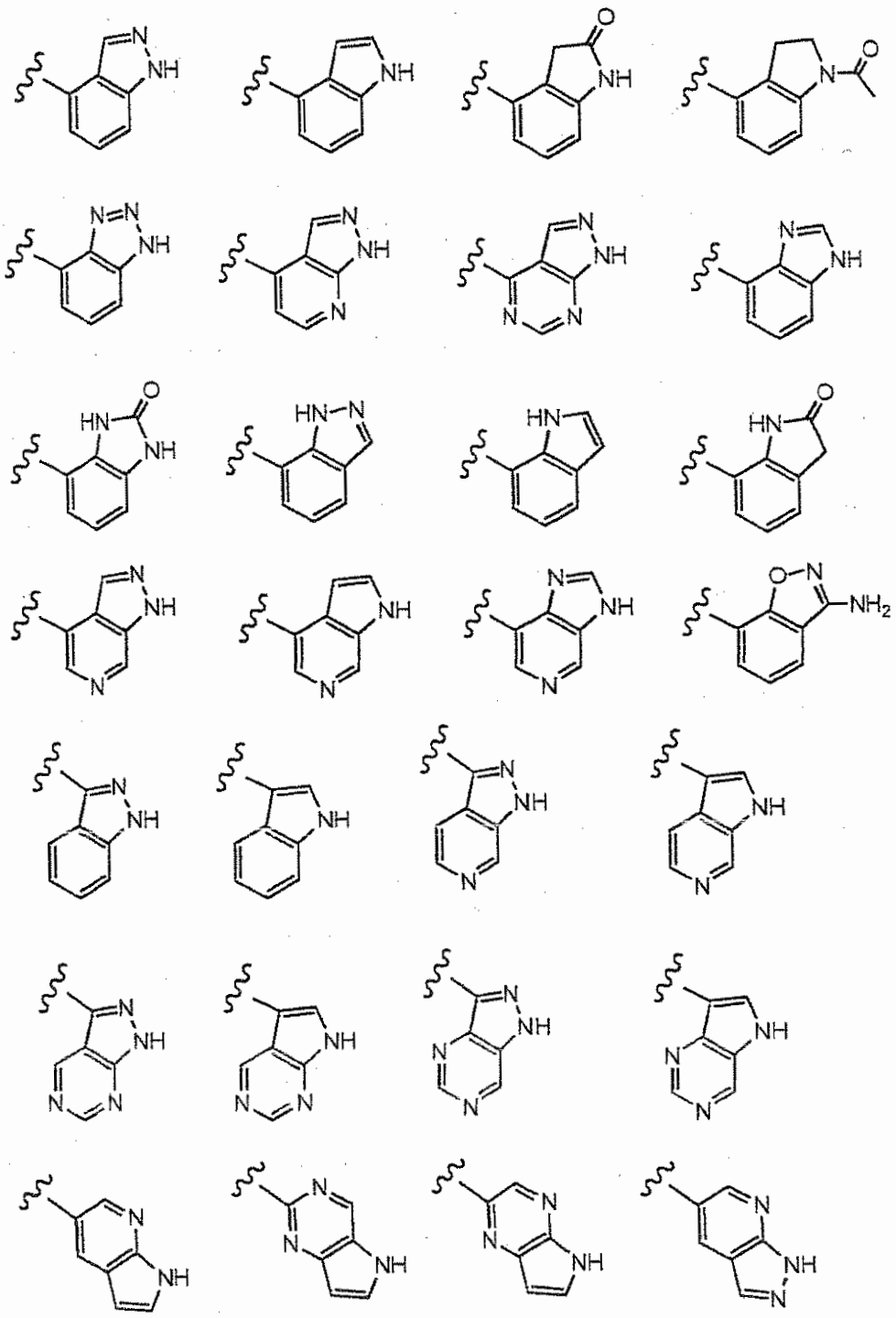
and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

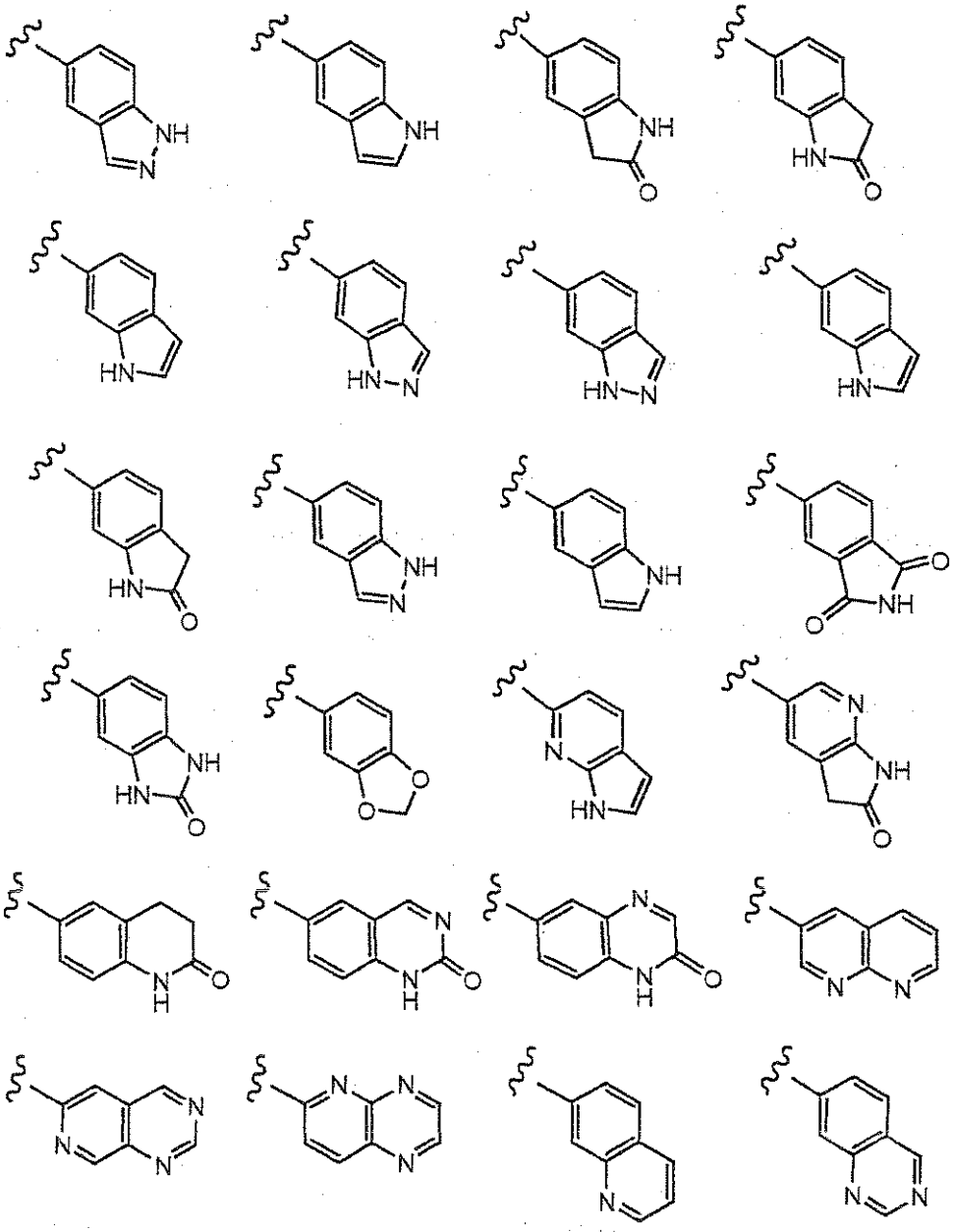
R^1 is selected from H, C_1–C_{12} alkyl, $-C(=O)NR^{10}R^{11}$, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, and C_1–C_{20} heteroaryl where C_1–C_{20} heteroaryl is optionally substituted with one or more groups independently selected from C_1–C_{12} alkyl, C_1–C_{12} alkyl-$NR^{10}R^{11}$, C_1–C_{12} alkyl-OR^{10}, C_6–C_{20} aryl, F, Cl, Br, I, $-CN$, $-CF_3$, $-CO_2H$, $-C(=O)NR^{10}R^{11}$, $-NO_2$, $-NR^{10}R^{11}$, $-NHCOR^{10}$, $-OR^{10}$, $-S(O)_2NR^{10}R^{11}$, and $-S(O)_2R^{10}$;

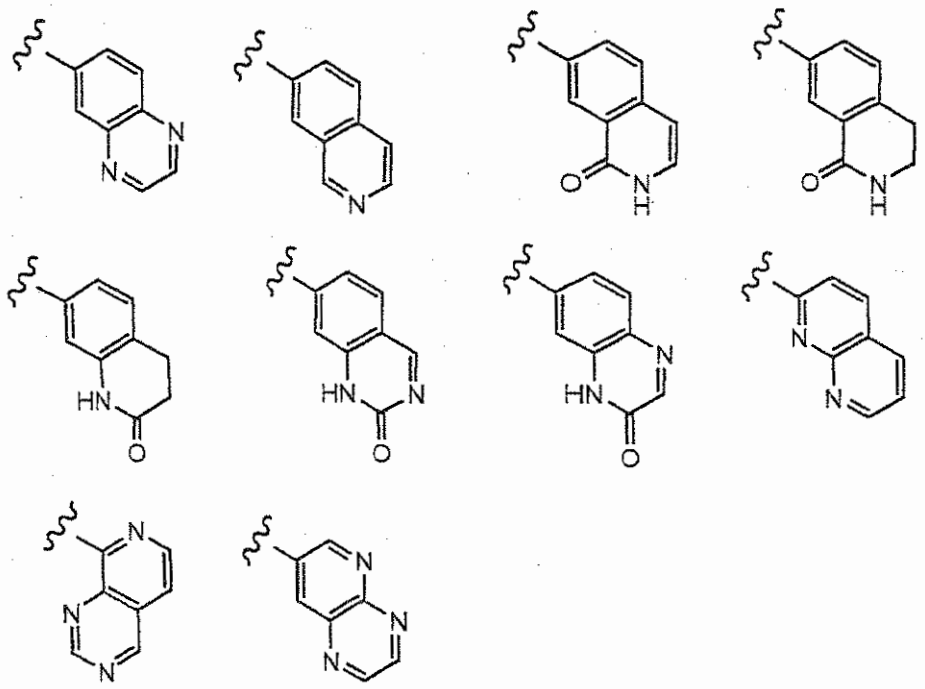
R^2 is C_1–C_{12} alkyl;

R^3 is selected from:









where the wavy line indicates the site of attachment;

optionally substituted with one or more groups independently selected from C_1–C_{12} alkyl, C_6–C_{20} aryl, F, Cl, Br, I, –CH_3, –CN, –CF_3, –CH_2OH, –CO_2H, –$CONH_2$, –$CON(CH_3)_2$, –NO_2, –NH_2, –$NHCH_3$, –$NHCOCH_3$, –OH, –OCH_3, -SH, -NHC(=O)$NHCH_3$, and –$S(O)_2CH_3$;

R^4 is selected from from –$NR^{10}R^{13}$, –$NR^{12}C(=O)R^{10}$, –NR^{10}(C_1–C_{12} alkyl)$NR^{10}R^{13}$, –NR^{10}(C_1–C_{12} alkyl)OR^{10}, -NR^{10}(C_1–C_{12} alkyl)C(=O)$NR^{10}R^{13}$, –NR^{10}(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –NR^{10}(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –NR^{10}(C_1–C_{12} alkylene)–(C_6–C_{20} aryl), –NR^{10}(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –OR^{10}, –O(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –O(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –O(C_1–C_{12} alkylene)–(C_6–C_{20} aryl), –O(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)$NR^{10}R^{13}$, –(C_1–C_{12} alkylene)–(C_3–C_{12} carbocyclyl), –(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), –(C_1–C_{12} alkylene)–(C_6–C_{20} aryl), –(C_1–C_{12} alkylene)–(C_1–C_{20} heteroaryl), –(C_2–C_8 alkynylene)$NR^{10}R^{13}$, –(C_2–C_8 alkynylene)–(C_3–C_{12} carbocyclyl), –(C_2–C_8 alkynylene)–(C_2–C_{20} heterocyclyl), –(C_2–C_8 alkynylene)–(C_6–C_{20} aryl), –(C_2–C_8 alkynylene)–(C_1–C_{20} heteroaryl), –(C_1–C_{12} alkylene)–(C_6–C_{20} arylene)–(C_2–C_{20} heterocyclyl), –(C_6–C_{20} aryl)-(C_1–C_{12} alkylene)–(C_2–C_{20} heterocyclyl), -C(=O)$NR^{10}R^{11}$, C_1–C_{12} alkyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkylene, alkynyl, alkynylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are

optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_3, –CH_2OH, –CN, –CF_3, –CO_2H, –$COCH_3$, –$CONH_2$, –$CONHCH_3$, –$CON(CH_3)_2$, –NO_2, –NH_2, –$NHCH_3$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –$S(O)_2N(CH_3)_2$, –SCH_3, –CH_2OCH_3, and –$S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, -CN, -CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, -OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –SCH_3, –$S(O)CH_3$, –CH_2OCH_3, –CH_3, and –$S(O)_2CH_3$;

or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring; and

R^{13} is selected from C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –SCH_3, –$S(O)CH_3$, –OCH_2CH_2–$N(CH_3)_2$, and –$S(O)_2CH_3$;

or R^{10} and R^{13} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring.

[0023] Another embodimentaspect of the disclosureinvention includes novel intermediates useful for preparing Formula I compounds.

[0024] Additional advantages and novel features of this disclosureinvention shall be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the disclosureinvention. The advantages of the disclosureinvention may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

[0025] DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0026] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.