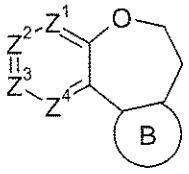
BENZOXAZEPIN PI3K INHIBITOR COMPOUNDS AND METHODS OF USE

The disclosure ~~invention~~ relates generally to compounds with anti-cancer activity and more specifically to compounds which inhibit PI3 kinase activity. The disclosure ~~invention~~ also relates to methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

The present disclosure ~~invention~~ provides benzoxazepin compounds, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3 kinases.

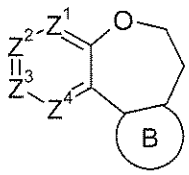
~~In one aspect t~~The present ~~invention~~ disclosure provides compounds of Formula I



I

including stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein: Z^1 is CR^1 or N; Z^2 is CR^2 or N; Z^3 is CR^3 or N; Z^4 is CR^4 or N; and B is a pyrazolyl, imidazolyl, or triazolyl ring fused to the benzoxazepin ring. The various substituents are as defined herein.

More specifically, the present invention provides compounds of Formula I:



I

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

Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

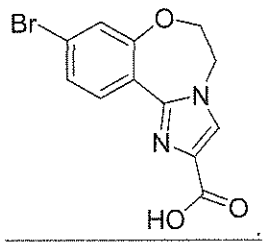
Z^3 is CR^3 or N;

$-C(O)CH_3$, $-C(O)CH(OH)CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, =O (oxo), $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OP(O)(OH)_2$, $-SCH_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2N(CH_3)_2$, $-CH_2S(O)_2NHCH_3$, $-CH_2S(O)_2CH_2CH_3$, $-S(O)_2NHCH_3$, $-S(O)_2CH_2CH_3$, pyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, cyclopropyl, cyclopentyl, oxetanyl, 4-methyl-piperazin-1-yl, and 4-morpholinyl; or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} hetero-cyclyl ring or C_1–C_{20} heteroaryl each of which are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CF_3$, $-CH_2CH_2OH$ and $-C(CH_3)_2OH$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

In one aspect, the present disclosure relates to a compound having the structure:



In another aspect, the present disclosure relates to a process for the preparation of a compound as defined above.

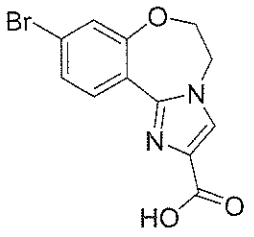
Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit 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.

The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et,

Claims

1. A compound having the structure:



~~2. A pharmaceutical composition comprised of a compound of claim 1 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient, optionally further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.~~

~~3. The use of a compound of claim 1 in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.~~

~~4. A compound of claim 1 for use in the prophylactic or therapeutic treatment of cancer.~~

~~5. A kit for treating a PI3K-mediated condition, comprising (a) a first pharmaceutical composition comprising a compound of claim 1; and (b) instructions for use.~~

62. A process for the preparation of a compound according to ~~any one of~~ claims 1 ~~to 6~~.