3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-fluoro-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide; and

N-(4-fluoro-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide,

or a pharmaceutically acceptable salt thereof.

[0008] A second example of the disclosure relates to a method of treating a c-Kit-mediated disease or disorder. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0008a] In yet another aspect, the present disclosure refers to use of the compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a c-Kit-mediated disease or disorder, wherein said cKit-mediated disease or disorder is selected from cell proliferative disorder, a fibrotic disorder, a metabolic disorder, multiple sclerosis, asthma, an allergic reaction, inflammatory arthritis, or mastocytosis.

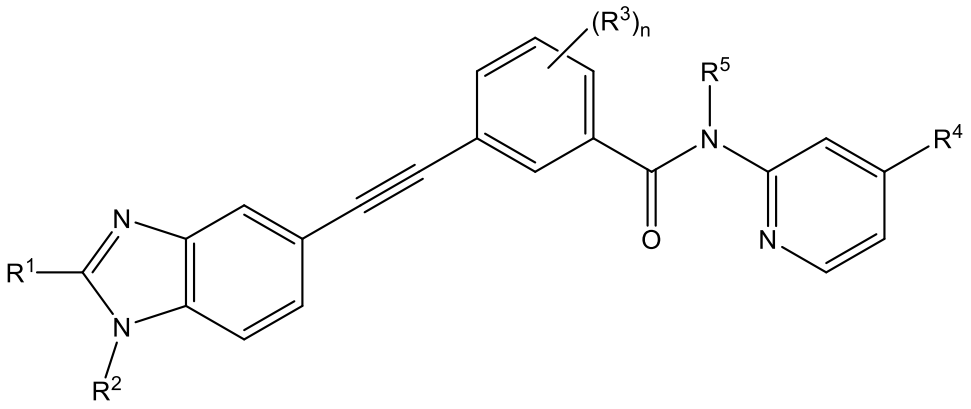
[0009] Another example of the disclosure relates to a method of preventing a c-Kit-mediated disease or disorder. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

[0010] Another example of the disclosure relates to a method of inhibiting c-Kit. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

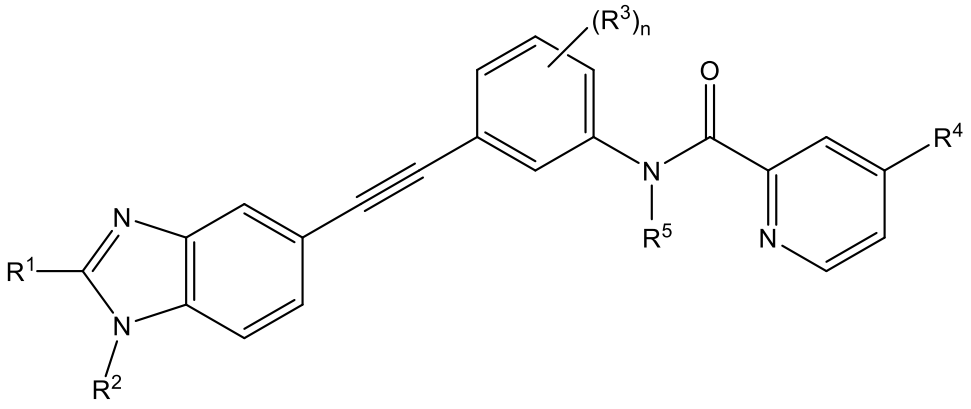
[0011] Another example of the disclosure relates to a method of treating a disease or disorder associated with inhibiting c-Kit. The method comprises administering to a patient in

Claims

1. A compound of formulae (Ii) or (Ij):



(Ii), or



(Ij),

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is H, (C_1-C_6) alkylamino, or (C_1-C_6) dialkylamino;

R^2 is H, (C_1-C_6) alkyl, -$(C(R^{6a})_2)_p$-(C_3-C_7) cycloalkyl, -$(C(R^{6a})_2)_p$-heterocycloalkyl wherein the heterocycloalkyl comprises a 4- to 7-membered ring and 1 to 3 heteroatoms selected from N, O, and S , -$(C(R^{6a})_2)_p$-(C_6-C_{10}) aryl, or -$(C(R^{6a})_2)_p$-heteroaryl wherein the heteroaryl comprises a 5- or 6-membered ring and 1 to 3 heteroatoms selected from N, O, and S, wherein the alkyl is optionally substituted with one or more R^7, wherein the cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is optionally substituted with one or more R^9;

each R^3 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, or OH;

each R^4 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, halogen, -OH, CN, (C_3-C_7) cycloalkyl, -($C(R^{6b})_2)_q$-NH_2, -($C(R^{6b})_2)_q$-(C_1-C_6) alkylamino, -($C(R^{6b})_2)_q$-(C_1-C_6) dialkylamino, -($C(R^{6b})_2)_q$-heterocycloalkyl wherein the heterocycloalkyl comprises a 4- to 7-membered ring and 1 to 3 heteroatoms selected from N, O, and S , or -($C(R^{6b})_2)_q$-heteroaryl wherein the heteroaryl comprises a 5- or 6-membered ring and 1 to 3 heteroatoms selected from N, O, and S, and wherein the heterocycloalkyl or heteroaryl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -NH_2, (C_1-C_6) alkylamino, and (C_1-C_6) dialkylamino;

R^5 is H, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl;

each R^{6a} and R^{6b} is independently H or (C_1-C_6) alkyl;

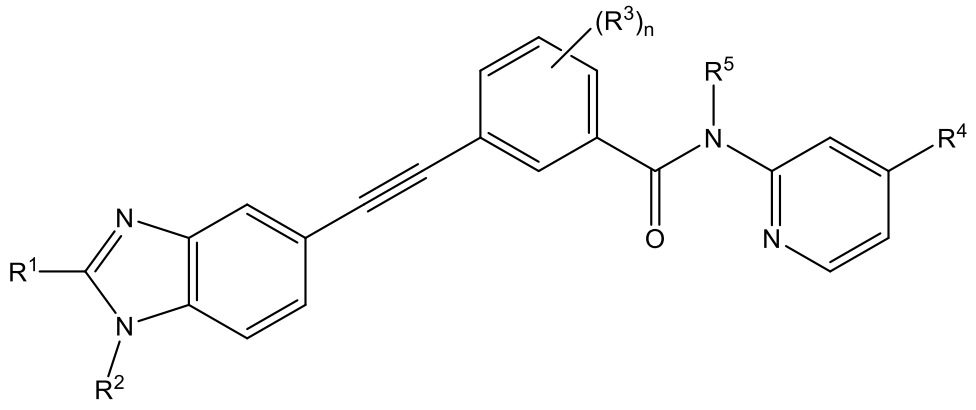
R^7 is (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, -OH, -NH_2, (C_1-C_6) alkylamino, (C_1-C_6) dialkylamino, or -C(O)N(R^8)$_2$;

each R^8 is independently H, (C_1-C_6) alkyl, or (C_1-C_6) haloalkyl;

each R^9 is independently at each occurrence (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, -C(O)H, -C(O)(C_1-C_6) alkyl, or 5- to 7-membered heterocycloalkyl ring comprising 1 to 3 heteroatoms selected from N, O and S, wherein the heterocycloalkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkyl, -C(O)H, or -C(O)(C_1-C_6) alkyl, and wherein the alkyl is optionally substituted with one or more substituents each independently selected from (C_1-C_6) alkoxy, -OH, (C_1-C_6) haloalkoxy, -NH_2,
(C_1-C_6) alkylamino, or (C_1-C_6) dialkylamino; and

each n, p, and q is independently 0, 1 or 2.

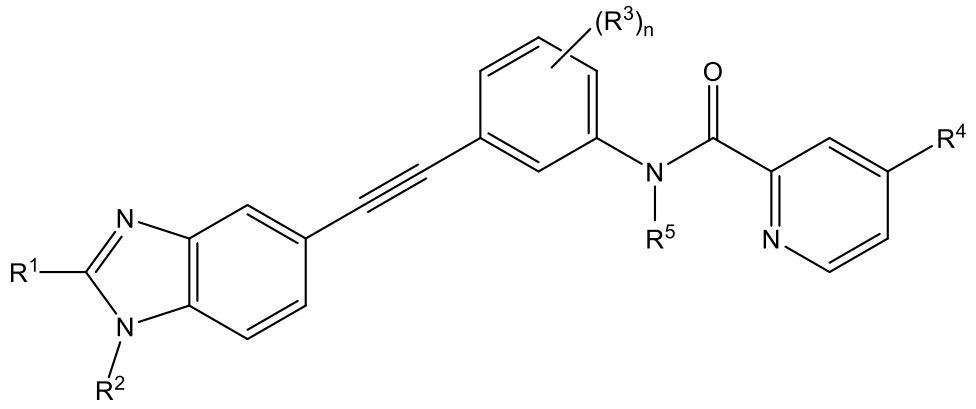
2. The compound of claim 1, having a structure according to Formula (Ii):



(Ii),

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, having a structure according to Formula (Ij),



(Ij),

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, wherein R^5 is H.

5. The compound of any one of claims 1 to 4, wherein R^4 is (C_1-C_6) haloalkyl.

6. The compound of any one of claims 1 to 5, wherein R^4 is CF_3.

7. The compound of any one of claims 1 to 6, wherein n is 1, R^3 is methyl, R^1 is H, and R^2 is H; CH_3; CH_2CH_3; $-(CH_2)_2N(CH_3)_2$; $-(CH_2)_3N(CH_3)_2$; $-CH_2C(O)NH(CH_3)$; $-(CH_2)_2$morpholinyl;$-(CH_2)_2OCH_3$; piperidinyl substituted with methyl; phenyl optionally substituted with 4-methylpiperzine; $-CH_2$-pyridinyl;cyclopropyl; triazolyl substituted with methyl; or imidazolyl substituted with methyl or N-methyl piperidinyl.

8. The compound of any one of claims 1 to 6, wherein n is 1 and R^3 is methyl, R^2 is pyrazolyl optionally substituted with methyl;
$-(CH_2)_2OH$; $-(CH_2)_2OCH_3$; $-(CH_2)_2N(CH_3)_2$; $-(CH_2)_2N(CH_2CH_3)_2$; morpholinyl; or piperidinyl optionally substituted with methyl or –C(O)H.

9. The compound of any one of claims 1 to 6, wherein n is 0 or 1 and R^3 is F, R^2 is pyrazolyl optionally substituted with methyl.

10. A compound selected from the group consisting of:
4-methyl-3-((1-(2-(methylamino)-2-oxoethyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;
3-((1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(2-(dimethylamino)ethyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(2-morpholinoethyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(3-(dimethylamino)propyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-ethyl-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-methyl-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((2-amino-1H-benzo[d]imidazol-6-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-methyl-1H-benzo[d]imidazol-6-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(pyridin-3-ylmethyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-cyclopropyl-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(3-(4-methylpiperazin-1-yl)phenyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(4-(4-methylpiperazin-1-yl)phenyl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

N-(4-methyl-3-((1-methyl-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide;

4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-methylpiperidin-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-phenyl-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-methyl-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)benzamide;

4-methyl-3-((1-(1-methyl-1H-imidazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(1-(1-formylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

N-(3-cyclopropylphenyl)-4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)benzamide;

4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide;

4-methyl-3-((1-methyl-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide;

3-((1-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-methyl-3-((1-(1-(1-methylpiperidin-4-yl)-1H-imidazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

3-((1-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

N-(4-methyl-3-((1-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide

N-(4-cyano-3-(trifluoromethyl)phenyl)-4-methyl-3-((1-(1-methyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)benzamide;

N-(3-((1-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((1-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((1-(1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((1-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((1-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(3-((1-(1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-4-methylphenyl)-4-(trifluoromethyl)picolinamide;

N-(4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

N-(4-methyl-3-((1-methyl-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

N-(4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)benzamide;

N-(4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)benzamide;

N-(4-methyl-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(morpholinomethyl)-3-(trifluoromethyl)benzamide;

N-(3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide;

3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide;

4-fluoro-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide; and

N-(4-fluoro-3-((1-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-5-yl)ethynyl)phenyl)-4-(trifluoromethyl)picolinamide,

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

12. Use of the compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a c-Kit-mediated disease or disorder,

wherein said cKit-mediated disease or disorder is selected from cell proliferative disorder, a fibrotic disorder, a metabolic disorder, multiple sclerosis, asthma, an allergic reaction, inflammatory arthritis, or mastocytosis.

13. The use of claim 12, wherein said cell proliferative disorder is cancer, optionally wherein

said cancer is selected from the group consisting of leukemia, mast cell tumor, small cell lung cancer, testicular cancer, cancer of the gastrointestinal tract, cancer of the central nervous system, cancer of the female genital tract, sarcoma of neuroectodermal origin, and Schwann cell neoplasia associated with neurofibromatosis; or

said cancer is selected from the group consisting of small cell lung carcinoma, acute myeloid leukemia (AML), neuroblastoma, malignant melanomas, colorectal cancer, systemic mastocytosis (SM), and gastrointestinal stromal tumors (GISTs).

14. The use of claim 12, wherein said cKit-mediated disease or disorder is multiple sclerosis, asthma, an allergic reaction, inflammatory arthritis, or mastocytosis.