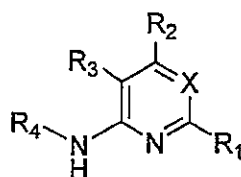


CLAIMS

1. A compound of Formula (I):



(I)

or a form thereof, wherein

R₁ is bicyclic heteroaryl or bicyclic heterocyclyl optionally substituted on a carbon atom ring member with one, two, three or four R₅ substituents, or on a nitrogen atom ring member with an oxygen atom substituent to form an N-oxide, wherein:

bicyclic heteroaryl is selected from the group consisting of 1H-indolyl, azaindolyl, 2H-indazolyl, azaindazolyl, isoindolyl, indoliziny, benzofuranyl, benzothienyl, 1H-benzimidazolyl, benzothiazolyl, benzoxazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl, 9H-purinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, and homologs and regioisomers thereof; and

bicyclic heterocyclyl is selected from the group consisting of dihydro-indolyl, indolinyl, tetrahydro-indolyl, dihydro-indazolyl, tetrahydro-indazolyl, dihydro-isoindolyl, dihydro-benzofuranyl, tetrahydro-benzofuranyl, dihydro-benzothienyl, tetrahydro-benzothienyl, dihydro-benzoimidazolyl, tetrahydro-benzoimidazolyl, dihydro-benzooxazolyl, tetrahydro-benzooxazolyl, dihydro-benzooxazinyl, tetrahydro-benzooxazinyl, benzo[1,3]dioxolyl, benzo[1,4]dioxanyl, benzo[1,4]dioxinyl, 4,5,6,7-tetrahydro-2H-indazolyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, dihydro-purinyl, tetrahydro-purinyl, dihydro-quinolinyl, tetrahydro-quinolinyl, dihydro-

isoquinolinyl, tetrahydro-isoquinolinyl, dihydro-quinazolinyl, tetrahydro-quinazolinyl, dihydro-quinoxaliny, tetrahydro-quinoxaliny and homologs thereof;

X is N or N substituted with an oxygen atom substituent to form an N-oxide;

R₂ is hydrogen, cyano, halo, hydroxyl, nitro, C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl, C₁₋₈alkoxy-amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, hydroxyl-amino, hydroxyl-C₁₋₈alkyl-amino, C₁₋₈alkoxy-C₁₋₈alkyl-amino, C₁₋₈alkyl-thio, C₁₋₈alkyl-carbonyl, C₁₋₈alkyl-carbonyl-amino, amino-carbonyl, C₁₋₈alkyl-amino-carbonyl, (C₁₋₈alkyl)₂-amino-carbonyl, amino-carbonyl-amino, C₁₋₈alkyl-amino-carbonyl-amino, (C₁₋₈alkyl)₂-amino-carbonyl-amino, C₁₋₈alkoxy-carbonyl, C₁₋₈alkoxy-carbonyl-amino, amino-sulfonyl, C₁₋₈alkyl-amino-sulfonyl, (C₁₋₈alkyl)₂-amino-sulfonyl, amino-sulfonyl-amino, C₁₋₈alkyl-amino-sulfonyl-amino, (C₁₋₈alkyl)₂-amino-sulfonyl-amino, P(O)(R₇)₂-amino or heteroaryl, wherein heteroaryl is optionally substituted with one, two, three or four C₁₋₈alkyl substituents;

R₃ is hydrogen, cyano, halo, C₁₋₈alkyl, amino, C₁₋₈alkyl-amino or (C₁₋₈alkyl)₂-amino;

R₄ is phenyl, optionally substituted with one, two, three or four R₆ substituents;

R₅ is independently selected from cyano, halo, hydroxyl, nitro, oxo, C₁₋₈alkyl, cyano-C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, halo-C₁₋₈alkoxy, C₂₋₈alkenyl, C₁₋₈alkoxy-C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy-C₂₋₈alkynyl, carboxyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl-amino, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-thio, C₁₋₈alkyl-carbonyl, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkyl-carbonyl-oxo, C₁₋₈alkyl-carbonyl-oxo-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, C₁₋₈alkoxy-carbonyl-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl-amino, C₁₋₈alkyl-sulfonyl, C₃₋₁₄cycloalkyl, aryl, aryl-C₁₋₈alkyl, aryl-amino, aryl-C₁₋₈alkyl-amino, heteroaryl, heteroaryl-C₁₋₈alkyl or heterocyclyl, wherein C₃₋₁₄cycloalkyl, aryl, heteroaryl or heterocyclyl and the aryl and heteroaryl portions of aryl-C₁₋₈alkyl, aryl-amino, aryl-C₁₋₈alkyl-amino and heteroaryl-C₁₋₈alkyl are each optionally substituted with one, two, three or four halo, C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, hydroxyl-C₁₋₈alkoxy or carboxyl substituents;

R₆ is independently selected from cyano, halo, hydroxyl, nitro, C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl, C₁₋₈alkoxy, halo-C₁₋₈alkoxy, C₂₋₈alkenyl, C₁₋₈alkoxy-C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy-C₂₋₈alkynyl, carboxyl, formyl, formyl-oxy, C₁₋₈alkyl-carbonyl, halo-C₁₋₈alkyl-carbonyl, C₁₋₈alkyl-thio, halo-C₁₋₈alkyl-thio, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, C₁₋₈alkyl-carbonyl, C₁₋₈alkyl-carbonyl-oxy, C₁₋₈alkyl-carbonyl-oxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, halo-C₁₋₈alkoxy-carbonyl, C₁₋₈alkoxy-carbonyl-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl-amino, C₁₋₈alkoxy-carbonyl-amino-C₁₋₈alkyl, amino-carbonyl, C₁₋₈alkyl-amino-carbonyl, (C₁₋₈alkyl)₂-amino-carbonyl, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkyl-carbonyl-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl-amino, hydroxyl-C₁₋₈alkyl-amino, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, imino-C₁₋₈alkyl, hydroxyl-imino-C₁₋₈alkyl, C₁₋₈alkoxy-imino-C₁₋₈alkyl, C₁₋₈alkyl-sulfonyl, halo-C₁₋₈alkyl-sulfonyl, amino-sulfonyl, C₁₋₈alkyl-amino-sulfonyl, (C₁₋₈alkyl)₂-amino-sulfonyl, B(OR₈)₂, C₃₋₁₄cycloalkyl, heterocyclyl aryl or heteroaryl, wherein C₃₋₁₄cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with one, two, three or four halo or C₁₋₈alkyl substituents;

R₇ is independently hydroxyl or (C₁₋₈alkoxy)_n, wherein n represents an integer from 1 to 5; and,

R₈ is independently hydrogen or C₁₋₈alkyl,

wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, chelate, clathrate, polymorph, isotopologue, stereoisomer, racemate, enantiomer, diastereomer or tautomer thereof.

2. The compound of claim 1, wherein R₁ is optionally substituted bicyclic heteroaryl or bicyclic heterocyclyl selected from 1H-indolyl, 2H-indazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-c]pyridinyl, 4,5,6,7-tetrahydro-

3H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

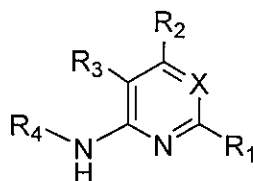
3. The compound of claim 2, wherein R₁ is optionally substituted bicyclic heteroaryl selected from 1H-indolyl, 1H-benzimidazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrazinyl or imidazo[1,2-a]pyrimidinyl.
4. An effective amount of the compound of claim 1 for use in the treatment of cancer mediated by Bmi-1, by inhibiting Bmi-1 function and reducing the level of Bmi-1 in a subject.
5. The compound of claim 4, wherein the treatment initially comprises contacting a cell having elevated Bmi-1 levels from the subject with an amount of the compound, wherein the cell is selected from a cancer cell, tumor cell, cancer stem cell or tumor stem cell, determining an effective amount of the compound that inhibits Bmi-1 function in the cell and subsequently comprises administering the effective amount of the compound to the subject.
6. The compound of claim 5, wherein the effective amount of the compound determined to inhibit Bmi-1 function in the contacted cell reduces Bmi-1 levels in the contacted cell.
7. The compound of claim 6, wherein the effective amount of the compound is in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day.
8. The compound of claim 6, wherein the effective amount of the compound or a form thereof is in a range of from about 0.1 ng to about 3500 mg.
9. The compound of claim 4, wherein the compound is to be administered in combination with one or more additional agents selected from anti-cancer agents, anti-proliferative

agents, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, anti-inflammatory agents, alkylating agents, steroidal and non-steroidal anti-inflammatory agents, pain relievers, leukotriene antagonists, β 2-agonists, anticholinergic agents, hormonal agents, biological agents, tubulin binding agents, glucocorticoids, corticosteroid agents, antibacterial agents, antihistamines, anti-malarial agents, anti-viral agents, antibiotics and the like; and, optionally with radiation therapy.

10. The use of the compound of claim 1 in the manufacture of a medicament to treat a cancer mediated by Bmi-1 in a subject wherein the medicament is formulated to inhibit Bmi-1 function and reduce the level of Bmi-1 in the subject.
11. A pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound of claim 1 in admixture with a pharmaceutically acceptable excipient.

CLAIMS

1. A compound of Formula (I):



(I)

or a form thereof, wherein

R₁ is heteroaryl or heterocyclyl substituted on a carbon atom ring member with one, two, three or four R₅ substituents, or on a nitrogen atom ring member with an oxygen atom substituent to form an N-oxide;

X is N or N substituted with an oxygen atom substituent to form an N-oxide;

R₂ is amino;

R₃ is hydrogen, cyano, halo, C₁₋₈alkyl, amino, C₁₋₈alkyl-amino or (C₁₋₈alkyl)₂-amino;

R₄ is phenyl, optionally substituted with one, two, three or four R₆ substituents;

R₅ is independently selected from cyano, halo, hydroxyl, nitro, oxo, C₁₋₈alkyl, cyano-C₁₋₈alkyl, halo-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkoxy-C₁₋₈alkyl, halo-C₁₋₈alkoxy, C₂₋₈alkenyl, C₁₋₈alkoxy-C₂₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy-C₂₋₈alkynyl, carboxyl, amino, C₁₋₈alkyl-amino, (C₁₋₈alkyl)₂-amino, amino-C₁₋₈alkyl, C₁₋₈alkyl-amino-C₁₋₈alkyl, (C₁₋₈alkyl)₂-amino-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl-amino, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl, hydroxyl-C₁₋₈alkyl-amino-C₁₋₈alkyl-amino, C₁₋₈alkyl-thio, C₁₋₈alkyl-carbonyl, C₁₋₈alkyl-carbonyl-amino, C₁₋₈alkyl-carbonyl-oxy, C₁₋₈alkyl-carbonyl-oxy-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl, C₁₋₈alkoxy-carbonyl-C₁₋₈alkyl, C₁₋₈alkoxy-carbonyl-amino, C₁₋₈alkyl-sulfonyl, C₃₋₁₄cycloalkyl, aryl, aryl-C₁₋₈alkyl, aryl-amino, aryl-C₁₋₈alkyl-amino, heteroaryl, heteroaryl-C₁₋₈alkyl or heterocyclyl, wherein C₃₋₁₄cycloalkyl, aryl, heteroaryl or heterocyclyl and the aryl and heteroaryl portions of aryl-C₁₋₈alkyl, aryl-amino, aryl-C₁₋₈alkyl-amino and heteroaryl-C₁₋₈alkyl are each optionally substituted with one, two, three or four halo, C₁₋₈alkyl, halo-C₁₋₈alkyl,

hydroxyl- C_{1-8} alkyl, C_{1-8} alkoxy, halo- C_{1-8} alkoxy, hydroxyl- C_{1-8} alkoxy or carboxyl substituents;

R_6 is independently selected from cyano, halo, hydroxyl, nitro, C_{1-8} alkyl, halo- C_{1-8} alkyl, hydroxyl- C_{1-8} alkyl, C_{1-8} alkoxy, halo- C_{1-8} alkoxy, C_{2-8} alkenyl, C_{1-8} alkoxy- C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy- C_{2-8} alkynyl, carboxyl, formyl, formyl-oxy, C_{1-8} alkyl-carbonyl, halo- C_{1-8} alkyl-carbonyl, C_{1-8} alkyl-thio, halo- C_{1-8} alkyl-thio, amino, C_{1-8} alkyl-amino, $(C_{1-8}alkyl)_2$ -amino, C_{1-8} alkyl-carbonyl, C_{1-8} alkyl-carbonyl-oxy, C_{1-8} alkyl-carbonyl-oxy- C_{1-8} alkyl, C_{1-8} alkoxy-carbonyl, halo- C_{1-8} alkoxy-carbonyl, C_{1-8} alkoxy-carbonyl- C_{1-8} alkyl, C_{1-8} alkoxy-carbonyl-amino, C_{1-8} alkoxy-carbonyl-amino- C_{1-8} alkyl, amino-carbonyl, C_{1-8} alkyl-amino-carbonyl, $(C_{1-8}alkyl)_2$ -amino-carbonyl, C_{1-8} alkyl-carbonyl-amino, C_{1-8} alkyl-carbonyl-amino- C_{1-8} alkyl, amino- C_{1-8} alkyl, C_{1-8} alkyl-amino- C_{1-8} alkyl, $(C_{1-8}alkyl)_2$ -amino- C_{1-8} alkyl, amino- C_{1-8} alkyl-amino, C_{1-8} alkyl-amino- C_{1-8} alkyl-amino, $(C_{1-8}alkyl)_2$ -amino- C_{1-8} alkyl-amino, hydroxyl- C_{1-8} alkyl-amino, hydroxyl- C_{1-8} alkyl-amino- C_{1-8} alkyl, hydroxyl- C_{1-8} alkyl-amino- C_{1-8} alkyl-amino, imino- C_{1-8} alkyl, hydroxyl-imino- C_{1-8} alkyl, C_{1-8} alkoxy-imino- C_{1-8} alkyl, C_{1-8} alkyl-sulfonyl, halo- C_{1-8} alkyl-sulfonyl, amino-sulfonyl, C_{1-8} alkyl-amino-sulfonyl, $(C_{1-8}alkyl)_2$ -amino-sulfonyl, $B(OR_8)_2$, C_{3-14} cycloalkyl, heterocyclyl aryl or heteroaryl, wherein C_{3-14} cycloalkyl, heterocyclyl, aryl, and heteroaryl are each optionally substituted with one, two, three or four halo or C_{1-8} alkyl substituents;

R_7 is independently hydroxyl or $(C_{1-8}alkoxy)_n$, wherein n represents an integer from 1 to 5; and,

R_8 is independently hydrogen or C_{1-8} alkyl;

wherein the form of the compound is selected from a free acid, free base, salt, ester, hydrate, solvate, racemate, enantiomer, diastereomer or tautomer thereof.

2. The compound of claim 1, wherein R_1 is substituted heteroaryl or heterocyclyl selected from 1H-pyrazolyl, 1H-imidazolyl, 1,2-oxazolyl, pyridinyl, 1H-indolyl, 2H-indazolyl, 4,5,6,7-tetrahydro-2H-indazolyl, 1H-benzimidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-c]pyrimidinyl, imidazo[1,2-a]pyridinyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, 1H-imidazo[4,5-

c]pyridinyl, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridinyl, imidazo[1,2-a]pyrazinyl, imidazo[1,2-a]pyrimidinyl, 7H-purinyl or quinolinyl.

3. The compound of claim 2, wherein R₁ is substituted heteroaryl selected from 1H-pyrazolyl, 1H-indolyl, 1H-benzimidazolyl, pyrazolo[1,5-a]pyridinyl, imidazo[1,2-a]pyridinyl, 1H-imidazo[4,5-b]pyridinyl, imidazo[1,2-a]pyrazinyl or imidazo[1,2-a]pyrimidinyl.
4. An effective amount of the compound of claim 1 for use in the treatment of cancer mediated by Bmi-1, by inhibiting Bmi-1 function and reducing the level of Bmi-1 in a subject.
5. The use of the compound of claim 1 in the manufacture of a medicament to treat a cancer mediated by Bmi-1 in a subject wherein the medicament is formulated to inhibit Bmi-1 function and reduce the level of Bmi-1 in the subject.
6. A pharmaceutical composition for use in treating a cancer mediated by Bmi-1 comprising an effective amount of the compound of claim 1 in admixture with a pharmaceutically acceptable excipient.