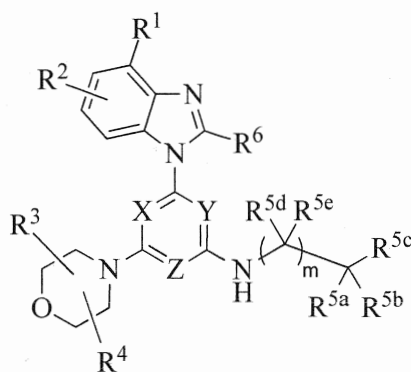


What is claimed is:

1. A compound of Formula I:



(I)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof; wherein:

X, Y, and Z are each independently N or CR^X, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^X is hydrogen or C₁₋₆ alkyl;

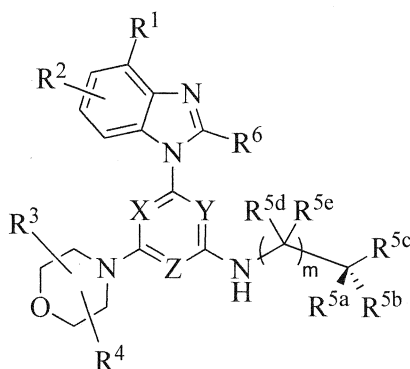
R¹ and R² are each independently (a) hydrogen, cyano, halo, or nitro;

(b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (c) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(NR^{1a})NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)NR^{1b}R^{1c}, -OC(=NR^{1a})NR^{1b}R^{1c}, -OS(O)R^{1a}, -OS(O)₂R^{1a}, -OS(O)NR^{1b}R^{1c}, -OS(O)₂NR^{1b}R^{1c}, -NR^{1b}R^{1c}, -NR^{1a}C(O)R^{1d}, -NR^{1a}C(O)OR^{1d}, -NR^{1a}C(O)NR^{1b}R^{1c}, -NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}, -NR^{1a}S(O)R^{1d}, -NR^{1a}S(O)₂R^{1d}, -NR^{1a}S(O)NR^{1b}R^{1c}, -NR^{1a}S(O)₂NR^{1b}R^{1c}, -SR^{1a}, -S(O)R^{1a}, -S(O)₂R^{1a}, -S(O)NR^{1b}R^{1c}, or -S(O)₂NR^{1b}R^{1c}; wherein each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R^{1b} and R^{1c} together with the N atom to which they are attached form heterocyclyl;

R³ and R⁴ are each independently hydrogen or C₁₋₆ alkyl; or R³ and R⁴ are linked together to form a bond, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, C₂₋₆ alkenylene, or C₂₋₆ heteroalkenylene;

R^{5a} is (a) hydrogen or halo; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (c) -C(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1b}R^{1c}, -C(NR^{1a})NR^{1b}R^{1c}, -OR^{1a}, -OC(O)R^{1a}, -OC(O)OR^{1a}, -OC(O)NR^{1b}R^{1c}, -OC(=NR^{1a})NR^{1b}R^{1c}, -OS(O)R^{1a}, -OS(O)₂R^{1a}, -OS(O)NR^{1b}R^{1c},

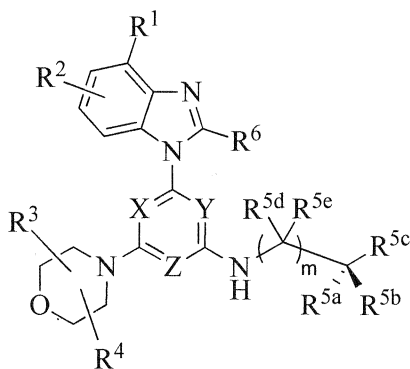
10. The compound of any one of claims 1 to 9, having the structure of Formula Ia:



(Ia)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~
~~prodrug~~ thereof.

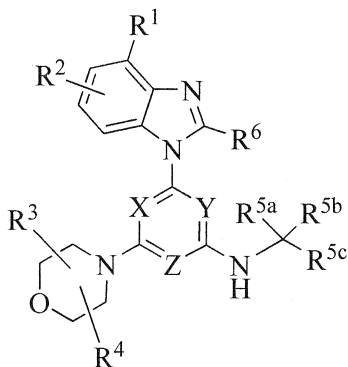
11. The compound of any one of claims 1 to 9, having the structure of Formula Ib:



(Ib)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~
~~prodrug~~ thereof.

12. The compound of any one of claims 1 to 8, having the structure of Formula II:

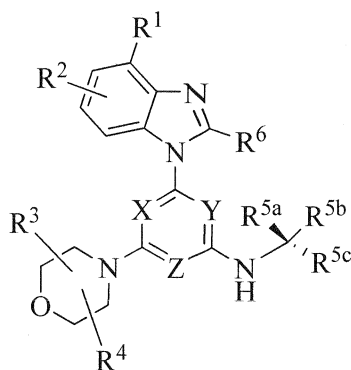


(II),

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~

prodrug thereof.

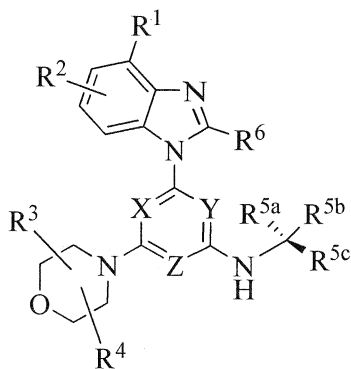
13. The compound of claim 12, having the structure of Formula IIa:



(IIa)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ prodrug thereof.

14. The compound of claim 12, having the structure of Formula IIb:



(IIb)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ prodrug thereof.

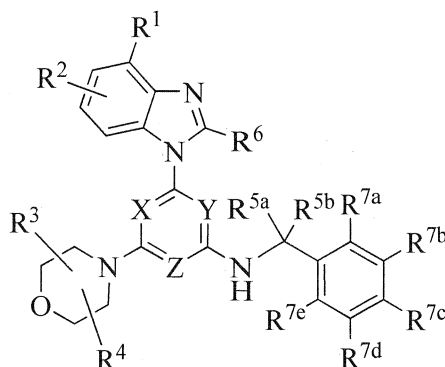
15. The compound of any one of claims 1 to 14, wherein R^{5c} is C₆₋₁₄ aryl, optionally substituted with one or more substituents Q.

16. The compound of claim 15, wherein R^{5c} is phenyl, optionally substituted with one or more substituents Q.

17. The compound of claim 15, wherein R^{5c} is naphthyl, optionally substituted with one or more substituents Q.

18. The compound of any one of claims 1 to 14, wherein R^{5c} is $-(CR^{5f}R^{5g})_n-(C_{6-14})$

29. The compound of any one of claims 1 to 12, having the structure of Formula VII:



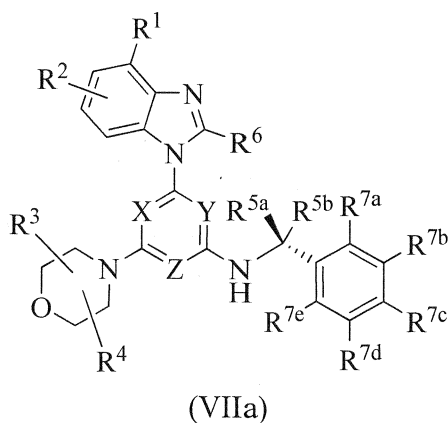
(VII)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof; wherein:

R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} are each independently (a) hydrogen, cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (c) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

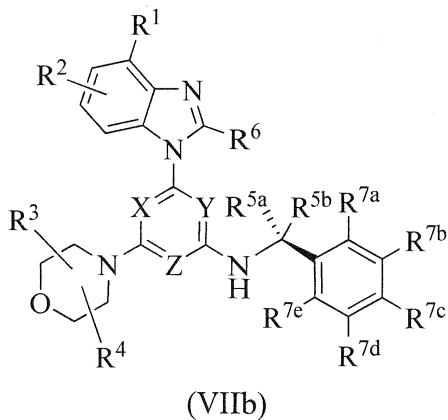
two of R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} that are adjacent to each other form C_{3-10} cycloalkenyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q.

30. The compound of claim 29, having the structure of Formula VIIa:



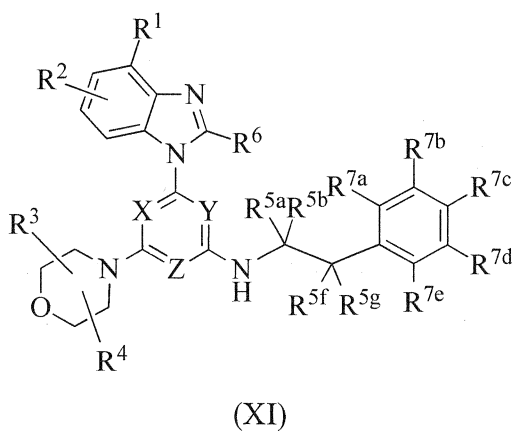
or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ ~~prodrug~~ thereof.

31. The compound of claim 29, having the structure of Formula VIIb:



or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ ~~prodrug~~ thereof.

32. The compound of any one of claims 1 to 12, having the structure of Formula XI:



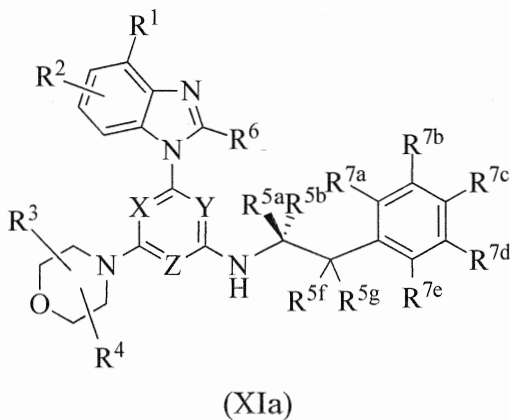
or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an

isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof; wherein:

R^{7a} , R^{7b} , R^{7c} , R^{7d} , and R^{7e} are each independently (a) hydrogen, cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (c) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$; or

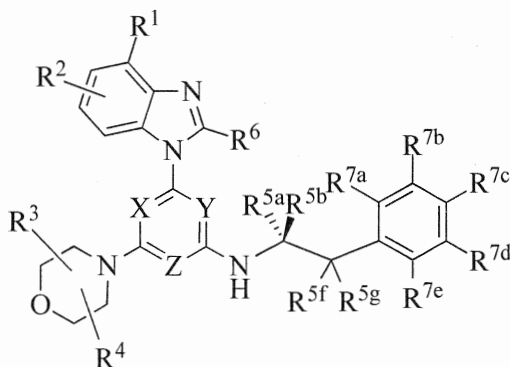
two of R^{7a}, R^{7b}, R^{7c}, R^{7d}, and R^{7e} that are adjacent to each other form C₃₋₁₀ cycloalkenyl, C₆₋₁₄ aryl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q.

33. The compound of claim 32, having the structure of Formula XIa:



or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ prodrug thereof.

34. The compound of claim 32, having the structure of Formula XIb:



(XIb)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof.

35. The compound of any one of claims 32 to 34, wherein R^{7a} is hydrogen, halo, C_{1-6} alkyl optionally substituted with one or more substituents Q, or $-OR^{1a}$.

36. The compound of claim 35, wherein R^{7a} is hydrogen.

37. The compound of claim 35, wherein R^{7a} is (a) cyano, halo, or nitro;
(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or
(c) $-C(O)R^{1a}$, $-C(O)OR^{1a}$, $-C(O)NR^{1b}R^{1c}$, $-C(NR^{1a})NR^{1b}R^{1c}$, $-OR^{1a}$, $-OC(O)R^{1a}$, $-OC(O)OR^{1a}$, $-OC(O)NR^{1b}R^{1c}$, $-OC(=NR^{1a})NR^{1b}R^{1c}$, $-OS(O)R^{1a}$, $-OS(O)_2R^{1a}$, $-OS(O)NR^{1b}R^{1c}$, $-OS(O)_2NR^{1b}R^{1c}$, $-NR^{1b}R^{1c}$, $-NR^{1a}C(O)R^{1d}$, $-NR^{1a}C(O)OR^{1d}$, $-NR^{1a}C(O)NR^{1b}R^{1c}$, $-NR^{1a}C(=NR^{1d})NR^{1b}R^{1c}$, $-NR^{1a}S(O)R^{1d}$, $-NR^{1a}S(O)_2R^{1d}$, $-NR^{1a}S(O)NR^{1b}R^{1c}$, $-NR^{1a}S(O)_2NR^{1b}R^{1c}$, $-SR^{1a}$, $-S(O)R^{1a}$, $-S(O)_2R^{1a}$, $-S(O)NR^{1b}R^{1c}$, or $-S(O)_2NR^{1b}R^{1c}$.

38. The compound of claim 35, wherein R^{7a} is (i) halo; (ii) C_{1-6} alkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more substituents Q; or (iii) $-OR^{1a}$ or $-NR^{1b}R^{1c}$.

39. The compound of any one of claims 32 to 38, wherein R^{7b} is hydrogen, halo, C_{1-6} alkyl optionally substituted with one or more substituents Q, or $-OR^{1a}$.

40. The compound of claim 39, wherein R^{7b} is hydrogen.

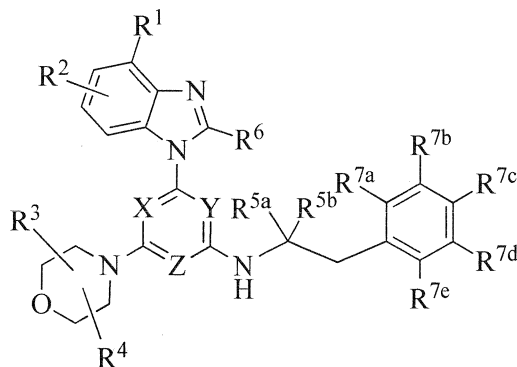
41. The compound of any one of claims 32 to 40, wherein R^{7c} is hydrogen, halo, C_{1-6} alkyl optionally substituted with one or more substituents Q, or $-OR^{1a}$.

42. The compound of claim 41, wherein R^{7c} is hydrogen, halo, or $-OR^{1a}$.

43. The compound of claim 41, wherein R^{7c} is chloro.

44. The compound of claim 41, wherein R^{7c} is $-O-C_{1-6}$ alkyl, optionally substituted with one or more substituents Q.

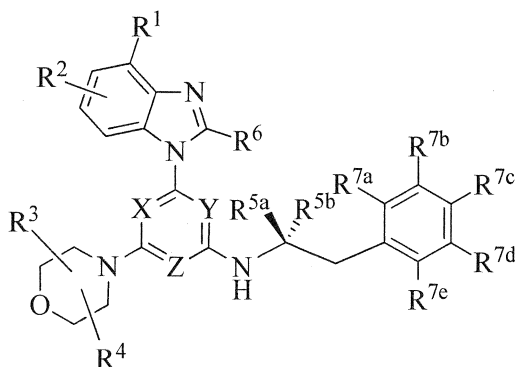
58. The compound of claim 57, wherein R^{5b} is $-C(O)O-C_{1-6}$ alkyl.
59. The compound of claim 57, wherein R^{5b} is $-C(O)OCH_3$.
60. The compound of claim 32, having the structure of Formula XV:



(XV)

or an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof.

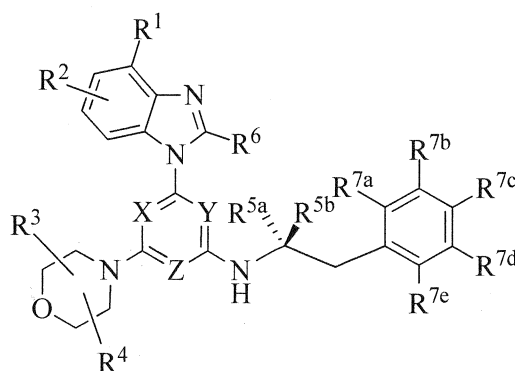
61. The compound of claim 60, having the structure of Formula XVa:



(XVa)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof.

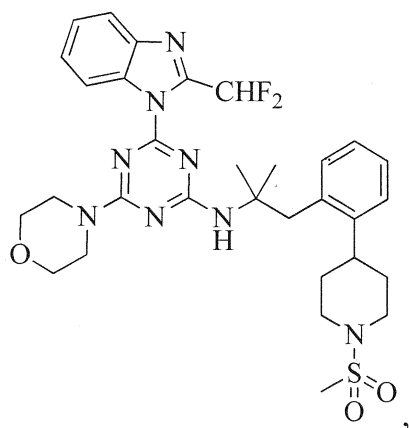
62. The compound of claim 60, having the structure of Formula XVb:



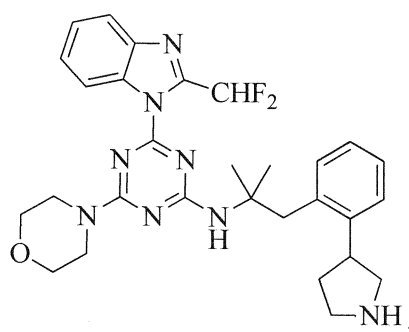
(XVb)

or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or~~ ~~prodrug~~ thereof.

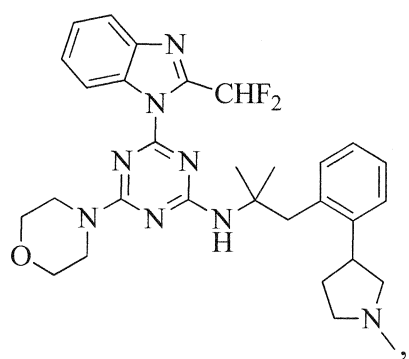
63. The compound of any one of claims 60 to 62, wherein R^{5a} is C_{1-6} alkyl, optionally substituted with one or more substituents Q.
64. The compound of claim 63, wherein R^{5a} is methyl.
65. The compound of any one of claims 60 to 64, wherein R^{5b} is C_{1-6} alkyl, optionally substituted with one or more substituents Q.
66. The compound of claim 65, wherein R^{5b} is methyl.
67. The compound of any one of claims 60 to 66, wherein R^{5a} and R^{5b} are methyl.
68. The compound of any one of claims 60 to 67, wherein R^{7a} is hydrogen, halo, C_{1-6} alkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl, where the alkyl, aryl, heteroaryl, and heterocyclyl are each optionally substituted with one or more substituents Q.
69. The compound of claim 68, wherein R^{7a} is C_{6-14} aryl, optionally substituted with one or more substituents Q.
70. The compound of claim 69, wherein R^{7a} is phenyl, optionally substituted with one or more substituents Q.
71. The compound of claim 69, wherein R^{7a} is phenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 2-methylphenyl, 2-(3-dimethylaminopropyl)phenyl, 2-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-methylphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-methoxyphenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 4-fluoro-3-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, or



A73

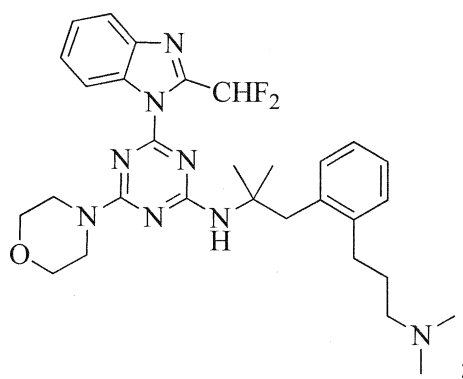


A74



A75

and



A76

and enantiomers, mixtures of enantiomers, mixtures of two or more diastereomers, and isotopic variants thereof; and pharmaceutically acceptable salts, solvates, or hydrates, ~~and~~ ~~prodrugs~~ thereof.

114. A pharmaceutical composition comprising the compound of any one of claims 1 to 113, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or hydrate, ~~or prodrug~~ thereof; and one or more pharmaceutically acceptable excipients.

115. The pharmaceutical composition of claim 114, wherein the composition is formulated for single dose administration.

116. The pharmaceutical composition of claim 114 or 115, wherein the composition is formulated as an oral, parenteral, or intravenous dosage form.

117. The pharmaceutical composition of claim 116, wherein the composition is formulated as an oral dosage form.

118. The pharmaceutical composition of claim 117, wherein the oral dosage form is a tablet or capsule.

119. The pharmaceutical composition of any one of claims 114 to 118, further comprising a second therapeutic agent.

120. Use of a compound of any one of claims 1 to 113 or the pharmaceutical composition of any one of claims 114 to 118 in the manufacture of a medicament for the treatment, prevention, or amelioration of one or more symptoms of a PI3K-mediated disorder, disease, or condition in a subject.

121. The use of claim 120, wherein the PI3K-mediated disorder, disease, or condition is an inflammatory disease or a proliferative disease.

122. The use of claim 120 or 121, wherein the compound or the composition is to be administered in combination with a second therapeutic agent.

123. An *in vitro* method for modulating PI3K enzymatic activity, comprising contacting a PI3K enzyme with the compound of any one of claims 1 to 113 or the pharmaceutical composition of any one of claims 114 to 118.

124. The method of any one of claims 120 to 123, wherein the PI3K is a wild type.

125. The method of any one of claims 120 to 123, wherein the PI3K is a PI3K variant.

126. The method of any one of claims 120 to 125, wherein the PI3K is a Class I PI3K.

127. The method of claim 126, wherein the PI3K is p110 γ .