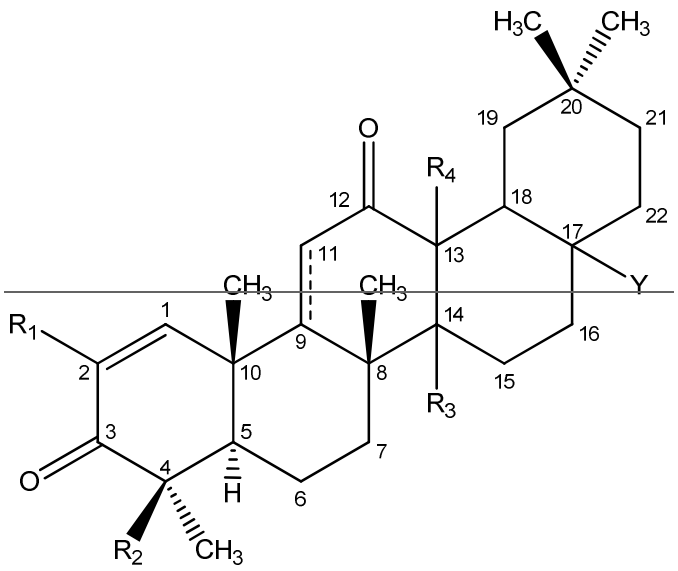
CLAIMS

1. ~~A method of treating or preventing endothelial dysfunction in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount~~ Use of a compound of the formula:



~~(I)~~,

~~wherein:~~

~~R1 is –CN, halo, –CF3, or –C(O)Ra, wherein Ra is –OH, alkoxy(C1-4), –NH2, alkylamino(C1-4), or –NH–S(O)2–alkyl(C1-4);~~

~~R2 is hydrogen or methyl;~~

~~R3 and R4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group Rc; and~~

~~Y is:~~

~~–H, –OH, –SH, –CN, –F, –CF3, –NH2 or =NCO;~~

~~alkyl(C≤8), alkenyl(C≤8), alkynyl(C≤8), aryl(C≤12), aralkyl(C≤12), heteroaryl(C≤8), heterocycloalkyl(C≤12), alkoxy(C≤8), aryloxy(C≤12), acyloxy(C≤8), alkylamino(C≤8), dialkylamino(C≤8), alkenylamino(C≤8), arylamino(C≤8),~~

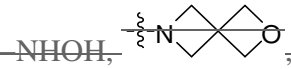
aralkylamino(C≤8), alkylthio(C≤8), acylthio(C≤8), alkylsulfonyl-amino(C≤8), or substituted versions of any of these groups;

–alkanediyl(C≤8)–Rb, –alkenediyl(C≤8)–Rb, or a substituted version of any of these groups, wherein Rb is:

hydrogen, hydroxy, halo, amino or thio; or

heteroaryl(C≤8), alkoxy(C≤8), alkenyloxy(C≤8), aryloxy(C≤8), aralkoxy(C≤8), heteroaryloxy(C≤8), acyloxy(C≤8), alkylamino(C≤8), dialkylamino(C≤8), alkenylamino(C≤8), arylamino(C≤8), aralkylamino(C≤8), heteroarylamino(C≤8), alkylsulfonylamino(C≤8), amido(C≤8), –OC(O)NH–alkyl(C≤8), –OC(O)CH2NHC(O)O–t-butyl, –OCH2–alkylthio(C≤8), or a substituted version of any of these groups;

–(CH2)mC(O)Rc, wherein m is 0–6 and Rc is:

hydrogen, hydroxy, halo, amino, –NHOH, , or thio; or

alkyl(C≤8), alkenyl(C≤8), alkynyl(C≤8), aryl(C≤8), aralkyl(C≤8), heteroaryl(C≤8), heterocycloalkyl(C≤8), alkoxy(C≤8), alkenyloxy(C≤8), aryloxy(C≤8), aralkoxy(C≤8), heteroaryloxy(C≤8), acyloxy(C≤8), alkylamino(C≤8), dialkylamino(C≤8), arylamino(C≤8), alkyl-sulfonylamino(C≤8), amido(C≤8), –NH–alkoxy(C≤8), –NH–heterocycloalkyl(C≤8), –NHC(NOH)–alkyl(C≤8), –NH–amido(C≤8), or a substituted version of any of these groups;

Rc and R3, taken together, are –O– or –NRd–, wherein Rd is hydrogen or alkyl(C≤4); or

Rc and R4, taken together, are –O– or –NRd–, wherein Rd is hydrogen or alkyl(C≤4); or

–NHC(O)Re, wherein Re is:

~~hydrogen, hydroxy, amino; or~~

~~alkyl(C≤8), alkenyl(C≤8), alkynyl(C≤8), aryl(C≤8), aralkyl(C≤8), heteroaryl(C≤8), heterocycloalkyl(C≤8), alkoxy(C≤8), aryloxy(C≤8), aralkoxy(C≤8), heteroaryloxy(C≤8), acyloxy(C≤8), alkylamino(C≤8), dialkylamino(C≤8), arylamino(C≤8), or a substituted version of any of these groups;~~

or a pharmaceutically acceptable salt or tautomer thereof, in the manufacture of a medicament for treating or preventing chronic kidney disease (CKD) or acute renal injury in a patient in need thereof, wherein the medicament comprises a pharmaceutically effective amount of the compound, and

wherein the patient has been identified as not having at least one of the following characteristics:

(a) a history of left-sided myocardial disease;

(b) an elevated B-type natriuretic peptide (BNP) level; and

(c) an elevated albumin/creatinine ratio (ACR)~~;~~ ~~and~~

~~(d) chronic kidney disease (CKD).~~

~~2. The method of claim 1, wherein the patient has pulmonary arterial hypertension or exhibits one or more symptoms of pulmonary arterial hypertension.~~

2~~3~~. The ~~method~~ use of ~~either~~ claim 1 ~~or 2~~, wherein the patient has been identified as not having at least two of the characteristics.

3~~4~~. The ~~method~~ use of either claim 1 or 2, wherein the patient has been identified as not having ~~at least~~all ~~-~~three of the characteristics.

~~5. The method of either claim 1 or 2, wherein the patient has been identified as not having all four of the characteristics.~~

~~6. The method according to any one of claims 1-5, wherein the pressure in the pulmonary artery of the patient has been measured or will be measured.~~

~~7. The method of claim 6, wherein the pressure in the pulmonary artery of the patient has been measured prior to administering the compound and will be measured after administering the compound.~~

~~8~~4. The ~~method~~ use according to any one ~~according to any one~~ of claims 1-3 ~~-4 and 6-7~~, wherein the patient does not have a history of left-sided myocardial disease.

~~9. The method according to any one of claims 1-4 and 6-7, wherein the patient has a history of left-sided myocardial disease.~~

~~10. The method according to any one of claims 1-7, wherein the patient does not have a history of heart failure.~~

~~11. The method according to any one of claims 1-4 and 6-7, wherein the patient has a history of heart failure.~~

~~12. The method of claim 11, wherein the heart failure is left-sided.~~

~~13. The method of claim 11, wherein the heart failure is right-sided.~~

~~14~~5. The ~~method~~ use according to any one of claims 1-~~11~~4, wherein the patient does not have an elevated BNP level.

~~15. The method according to any one of claims 1-4 and 6-11, wherein the patient has an elevated BNP level.~~

~~16~~6. The ~~method~~ use according to any one of claims ~~15~~1-5, wherein the ~~elevated~~ patient does not have a BNP level ~~is~~ greater than 200 pg/mL.

~~17~~7. The ~~method~~ use according to any one of claims 1-~~16~~6, wherein the patient does not have an elevated ACR.

~~18. The method according to any one of claims 1-4 and 6-16, wherein the patient has an elevated ACR.~~

~~19~~8. The ~~method~~ use according to any one of claim~~s~~ ~~18~~1-7, wherein the ~~elevated~~ patient does not have an ACR ~~is~~ greater than 300 mg/g.

~~20~~9. The ~~method~~ use according to any one of claims 1-~~8~~19, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 45 mL/min/1.73 m^2.

~~21~~10. The ~~method~~ use according to any one of claims 1-~~8~~20, wherein the patient's eGFR is greater than or equal to ~~60~~ 20 mL/min/1.73 m^2.

~~22. The method according to any one of claims 1-19, wherein the patient's eGFR is less than 60 mL/min/1.73 m^2.~~

~~23. The method according to any one of claims 1-22, wherein the patient is less than 75 years old.~~

~~24. The method of claim 23, wherein the patient is less than 70 years old.~~

~~25. The method of claim 24, wherein the patient is less than 65 years old.~~

~~26. The method of claim 25, wherein the patient is less than 60 years old.~~

~~27. The method of claim 26, wherein the patient is less than 55 years old.~~

~~28~~11. The ~~method~~ use according to any one of claims 1-~~27~~10, wherein the patient has been identified as having chronic obstructive pulmonary disease (COPD).

~~29~~12. The ~~method~~ use according to any one of claims 1-~~27~~10, wherein the patient has been identified as not having COPD.

~~30. The method according to any one of claims 1-27, wherein the patient is a smoker.~~

~~31. The method according to any one of claims 1-27, wherein the patient is not a smoker.~~

~~32. The method according to any one of claims 1-31, wherein the patient suffers from renal disease.~~

~~33. The method according to any one of claims 1-31, wherein the patient does not suffer from renal disease.~~

~~34. The method according to any one of claims 1-31, wherein the patient has elevated levels of at least one biomarker associated with renal disease.~~

~~35. The method according to any one of claims 1-31, wherein the patient does not have elevated levels of a biomarker associated with renal disease.~~

~~36. The method of either one of claims 34 and 35, wherein the biomarker is serum creatinine.~~

~~37. The method of either one of claims 34 and 35, wherein the biomarker is cystatin C.~~

~~38. The method of either one of claims 34 and 35, wherein the biomarker is uric acid.~~

~~39. The method according to any one of claims 1-31, wherein the patient does not have elevated levels of any biomarker associated with renal disease.~~

~~40. The method according to any one of claims 1-39, wherein the patient has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.~~

~~41. The method according to any one of claims 1-39, wherein the patient does not have CKD.~~

~~42. The method according to any one of claims 1-39, wherein the patient does not exhibit any symptoms of CKD.~~

~~43. The method according to any one of claims 1-4 and 6-39, wherein the patient has been identified as having CKD.~~

~~44. The method according to any one of claims 1-39, wherein the patient has been identified as not having CKD.~~

~~45~~13. The ~~method~~ use according to any one of claims 1-~~39~~12, wherein the patient does not have stage 4 CKD.

~~46~~14. The ~~method~~ use of claim ~~45~~13, wherein the patient does not have stage 3 or stage 4 CKD.

~~47~~15. The ~~method~~ use of claim ~~46~~14, wherein the patient does not have stage 2, stage 3, or stage 4 CKD.

~~48. The method according to any one of claims 1-47, wherein the level of a marker of CKD in the patient has been measured or will be measured.~~

~~49. The method of claim 48, wherein the marker is the level of serum creatinine.~~

~~50. The method of claim 49, wherein the level of serum creatinine in the blood of the patient has been measured or will be measured.~~

~~51. The method of claim 50, wherein the administering reduces the level of serum creatinine in the patient.~~

~~52~~16. The ~~method~~ use according to any one of claims 1-~~51~~15, wherein the patient has been identified as having cancer.

~~53~~17. The ~~method~~ use according to any one of claims 1-~~51~~15, wherein the patient has been identified as not having cancer.

~~54~~18. The ~~method~~ use according to any one of claims 1-~~51~~17, wherein the patient has been identified as having type 2 diabetes.

~~55~~19. The ~~method~~ use according to any one of claims 1-~~51~~17, wherein the patient has been identified as not having type 2 diabetes.

~~56. The method according to any one of claims 1-51, wherein the patient has been identified as having cardiovascular disease.~~

~~57. The method of claim 56, wherein the patient has been identified as having or at risk of having atherosclerosis, restenosis, pulmonary hypertension, pulmonary arterial hypertension, or thrombosis.~~

~~58. The method of claim 57, wherein the patient has been identified as having or at risk of having atherosclerosis.~~

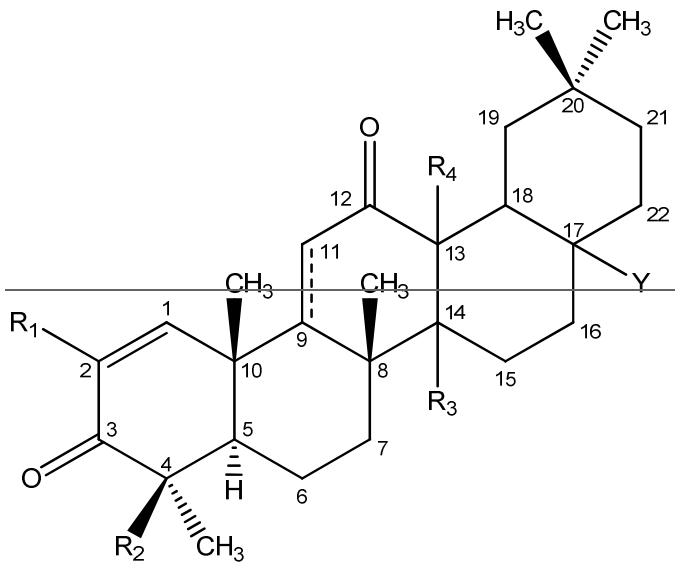
59. The method of claim 57, wherein the patient has been identified as having or at risk of having restenosis.

60. The method of claim 57, wherein the patient has been identified as having or at risk of having pulmonary hypertension.

61. The method of claim 57, wherein the patient has been identified as having or at risk of having pulmonary arterial hypertension.

62. The method of claim 57, wherein the patient has been identified as having or at risk of having thrombosis.

63. A method of treating or preventing pulmonary arterial hypertension in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound of the formula:



(I),

wherein:

R_1 is –CN, halo, $–CF_3$, or $–C(O)R_a$, wherein R_a is –OH, $alkoxy_{(C1-4)}$, $–NH_2$, $alkylamino_{(C1-4)}$, or $–NH–S(O)_2–alkyl_{(C1-4)}$;

R_2 is hydrogen or methyl;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_e; and

Y is:

–H, –OH, –SH, –CN, –F, $–CF_3$, $–NH_2$ or =NCO;

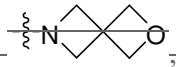
$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $alkylthio_{(C\leq8)}$, $acylthio_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or substituted versions of any of these groups;

$alkanediyl_{(C\leq8)}$–R_b, $alkenediyl_{(C\leq8)}$–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

$heteroaryl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $heteroarylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, –OC(O)NH–$alkyl_{(C\leq8)}$, –OC(O)CH_2NHC(O)O–*t* butyl, –OCH_2–$alkylthio_{(C\leq8)}$, or a substituted version of any of these groups;

$–(CH_2)_mC(O)R_e$, wherein m is 0–6 and R_e is:

hydrogen, hydroxy, halo, amino, –NHOH, , or thio; or

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, –NH–$alkoxy_{(C\leq8)}$, –NH–$heterocycloalkyl_{(C\leq8)}$, –NHC(NOH)–$alkyl_{(C\leq8)}$, –NH–$amido_{(C\leq8)}$, or a substituted version of any of these groups;

R_e and R_3, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or $alkyl_{(C\leq4)}$; or

R_e and R_4, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or $alkyl_{(C\leq4)}$; or

–NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

64. The method of claim 63, wherein the pressure in the pulmonary artery of the patient has been measured or will be measured.

65. The method of claim 64, wherein the pressure in the pulmonary artery of the patient has been measured prior to administering the compound and will be measured after administering the compound.

66. The method according to any one of claims 63-65, wherein the patient does not have a history of left-sided myocardial disease.

67. The method according to any one of claims 63-65, wherein the patient has a history of left-sided myocardial disease.

68. The method according to any one of claims 63-65, wherein the patient does not have a history of left-sided heart failure.

69. The method according to any one of claims 63-65, wherein the patient has a history of left-sided heart failure.

70. The method according to any one of claims 63-69, wherein the patient does not have an elevated B-type natriuretic peptide (BNP) level.

71. ~~The method according to any one of claims 63-69, wherein the patient has an elevated BNP level.~~

72. ~~The method of claim 71, wherein the elevated BNP level is greater than 200 pg/mL.~~

73. ~~The method according to any one of claims 63-72, wherein the patient does not have an elevated albumin/creatinine ratio (ACR).~~

74. ~~The method according to any one of claims 63-72, wherein the patient has an elevated ACR.~~

75. ~~The method according of claim 74, wherein the elevated ACR is greater than 300 mg/g.~~

76. ~~The method according to any one of claims 63-75, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 45 mL/min/1.73 m^2.~~

77. ~~The method according to any one of claims 63-76, wherein the patient's eGFR is greater than or equal to 60 mL/min/1.73 m^2.~~

78. ~~The method according to any one of claims 63-75, wherein the patient's eGFR is less than 60 mL/min/1.73 m^2.~~

79. ~~The method according to any one of claims 63-78, wherein the patient less than 75 years old.~~

80. ~~The method of claim 79, wherein the patient is less than 70 years old.~~

81. ~~The method of claim 80, wherein the patient is less than 65 years old.~~

82. ~~The method of claim 81, wherein the patient is less than 60 years old.~~

83. ~~The method of claim 82, wherein the patient is less than 55 years old.~~

84. ~~The method according to any one of claims 63-83, wherein the patient has been identified as having chronic obstructive pulmonary disease (COPD).~~

~~85. The method according to any one of claims 63-83, wherein the patient has been identified as not having COPD.~~

~~86. The method according to any one of claims 63-83, wherein the patient is a smoker.~~

~~87. The method according to any one of claims 63-83, wherein the patient is not a smoker.~~

~~88. The method according to any one of claims 63-87, wherein the patient suffers from renal disease.~~

~~89. The method according to any one of claims 63-87, wherein the patient does not suffer from renal disease.~~

~~90. The method according to any one of claims 63-87, wherein the patient has elevated levels of at least one biomarker associated with renal disease.~~

~~91. The method according to any one of claims 63-89, wherein the patient does not have elevated levels of a biomarker associated with renal disease.~~

~~92. The method of either one of claims 90 and 91, wherein the biomarker is serum creatinine.~~

~~93. The method of either one of claims 90 and 91, wherein the biomarker is cystatin C.~~

~~94. The method of either one of claims 90 and 91, wherein the biomarker is uric acid.~~

~~95. The method according to any one of claims 63-87, wherein the patient does not have elevated levels of any biomarker associated with renal disease.~~

~~96. The method according to any one of claims 63-95, wherein the patient has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.~~

~~97. The method according to any one of claims 63-95, wherein the patient does not have CKD.~~

~~98. The method according to any one of claims 63-95, wherein the patient does not exhibit any symptoms of CKD.~~

~~99. The method according to any one of claims 63-95, wherein the patient has been identified as having CKD.~~

~~100. The method according to any one of claims 63-95, wherein the patient has been identified as not having CKD.~~

~~101. The method according to any one of claims 63-95, wherein the patient does not have stage 4 CKD.~~

~~102. The method of claim 101, wherein the patient does not have stage 3 or stage 4 CKD.~~

~~103. The method of claim 102, wherein the patient does not have stage 2, stage 3 or stage 4 CKD.~~

~~104. The method according to any one of claims 63-103, wherein the level of a marker of CKD in the patient has been measured or will be measured.~~

~~105. The method of claim 104, wherein the marker is the level of serum creatinine.~~

~~106. The method of claim 105, wherein the level of serum creatinine in the blood of the patient has been measured or will be measured.~~

~~107. The method of claim 106, wherein the administering reduces the level of serum creatinine in the patient.~~

~~108. The method according to any one of claims 63-107, wherein the patient has been identified as having cancer.~~

~~109. The method according to any one of claims 63-107, wherein the patient has been identified as not having cancer.~~

~~110. The method according to any one of claims 63-107, wherein the patient has been identified as having type 2 diabetes.~~

~~111. The method according to any one of claims 63-107, wherein the patient has been identified as not having type 2 diabetes.~~

~~112. The method according to any one of claims 63-107, wherein the patient has been identified as having cardiovascular disease.~~

~~113. The method of claim 112, wherein the patient has been identified as having or at risk of having atherosclerosis, restenosis, pulmonary hypertension, or thrombosis.~~

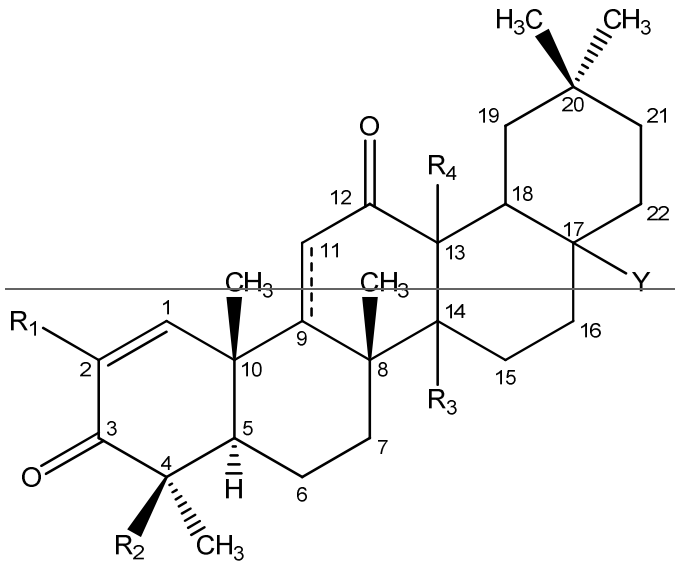
~~114. The method of claim 113, wherein the patient has been identified as having or at risk of having atherosclerosis.~~

~~115. The method of claim 113, wherein the patient has been identified as having or at risk of having restenosis.~~

~~116. The method of claim 113, wherein the patient has been identified as having or at risk of having pulmonary hypertension.~~

~~117. The method of claim 113, wherein the patient has been identified as having or at risk of having thrombosis.~~

~~118. A method of reducing the pressure in a patient's pulmonary artery, comprising administering to the patient a compound of the formula:~~



~~(I),~~

wherein:

R_1 is $-CN$, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is $-OH$, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$;

R_2 is hydrogen or methyl;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_e; and

Y is:

$-H$, $-OH$, $-SH$, $-CN$, $-F$, $-CF_3$, $-NH_2$ or $=NCO$;

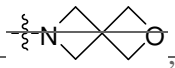
$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $alkylthio_{(C\leq8)}$, $acylthio_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq8)}-R_b$, $-alkenediyl_{(C\leq8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

$heteroaryl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $heteroarylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, $-OC(O)NH-alkyl_{(C\leq8)}$, $-OC(O)CH_2NHC(O)O-t$ butyl, $-OCH_2-alkylthio_{(C\leq8)}$, or a substituted version of any of these groups;

$-(CH_2)_mC(O)R_e$, wherein m is 0–6 and R_e is:

hydrogen, hydroxy, halo, amino, $-NHOH$, , or thio; or

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$,

alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–alkoxy$_{(C\leq 8)}$, –NH–heterocycloalkyl$_{(C\leq 8)}$, –NHC(NOH)–alkyl$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_e and R_3, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

R_e and R_4, taken together, are –O– or –NR_d–, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

–NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof,

in an amount sufficient to reduce pressure in the patient's pulmonary artery, wherein the patient has been identified as having pulmonary arterial hypertension.

119. The method of claim 118, wherein the pressure in the pulmonary artery of the patient has been measured or will be measured.

120. The method of claim 119, wherein the pressure in the pulmonary artery of the patient has been measured prior to administering the compound and will be measured after administering the compound.

121. The method according to any one of claims 118-120, wherein the patient does not have a history of left-sided myocardial disease.

122. The method according to any one of claims 118-120, wherein the patient has a history of left-sided myocardial disease.

~~123. The method according to any one of claims 118-120, wherein the patient does not have a history of left-sided heart failure.~~

~~124. The method according to any one of claims 118-120, wherein the patient has a history of left-sided heart failure.~~

~~125. The method according to any one of claims 118-124, wherein the patient does not have an elevated B-type natriuretic peptide (BNP) level.~~

~~126. The method according to any one of claims 118-124, wherein the patient has an elevated BNP level.~~

~~127. The method of claim 126, wherein the elevated BNP level is greater than 200 pg/mL.~~

~~128. The method according to any one of claims 118-127, wherein the patient does not have an elevated albumin/creatinine ratio (ACR).~~

~~129. The method according to any one of claims 118-127, wherein the patient has an elevated ACR.~~

~~130. The method according of claim 129, wherein the elevated ACR is greater than 300 mg/g.~~

~~131. The method according to any one of claims 118-130, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 45 mL/min/1.73 m^2.~~

~~132. The method according to any one of claims 118-131, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 60 mL/min/1.73 m^2.~~

~~133. The method according to any one of claims 118-130, wherein the patient's estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m^2.~~

~~134. The method according to any one of claims 118-133, wherein the patient less than 75 years old.~~

~~135. The method of claim 134, wherein the patient is less than 70 years old.~~

~~136. The method of claim 135, wherein the patient is less than 65 years old.~~

~~137. The method of claim 136, wherein the patient is less than 60 years old.~~

~~138. The method of claim 137, wherein the patient is less than 55 years old.~~

~~139. The method according to any one of claims 118-138, wherein the patient has been identified as having chronic obstructive pulmonary disease (COPD).~~

~~140. The method according to any one of claims 118-138, wherein the patient has been identified as not having COPD.~~

~~141. The method according to any one of claims 118-138, wherein the patient is a smoker.~~

~~142. The method according to any one of claims 118-138, wherein the patient is not a smoker.~~

~~143. The method according to any one of claims 118-142, wherein the patient suffers from renal disease.~~

~~144. The method according to any one of claims 118-142, wherein the patient does not suffer from renal disease.~~

~~145. The method according to any one of claims 118-142, wherein the patient has elevated levels of at least one biomarker associated with renal disease.~~

~~146. The method according to any one of claims 118-142, wherein the patient does not have elevated levels of a biomarker associated with renal disease.~~

~~147. The method of either one of claims 145 and 146, wherein the biomarker is serum creatinine.~~

~~148. The method of either one of claims 145 and 146, wherein the biomarker is cystatin C.~~

~~149. The method of either one of claims 145 and 146, wherein the biomarker is uric acid.~~

~~150. The method according to any one of claims 118-142, wherein the patient does not have elevated levels of any biomarker associated with renal disease.~~

~~151. The method according to any one of claims 118-150, wherein the patient has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.~~

~~152. The method according to any one of claims 118-150, wherein the patient does not have CKD.~~

~~153. The method according to any one of claims 118-150, wherein the patient does not exhibit any symptoms of CKD.~~

~~154. The method according to any one of claims 118-150, wherein the patient has been identified as having CKD.~~

~~155. The method according to any one of claims 118-150, wherein the patient has been identified as not having CKD.~~

~~156. The method according to any one of claims 118-150, wherein the patient does not have stage 4 CKD.~~

~~157. The method of claim 156, wherein the patient does not have stage 3 or stage 4 CKD.~~

~~158. The method of claim 157, wherein the patient does not have stage 2, stage 3 or stage 4 CKD.~~

~~159. The method according to any one of claims 118-158, wherein the level of a marker of CKD in the patient has been measured or will be measured.~~

~~160. The method of claim 159, wherein the marker is the level of serum creatinine.~~

~~161. The method of claim 160, wherein the level of serum creatinine in the blood of the patient has been measured or will be measured.~~

~~162. The method of claim 161, wherein the administering reduces the level of serum creatinine in the patient.~~

~~163. The method according to any one of claims 118-162, wherein the patient has been identified as having cancer.~~

~~164. The method according to any one of claims 118-162, wherein the patient has been identified as not having cancer.~~

~~165. The method according to any one of claims 118-162, wherein the patient has been identified as having type 2 diabetes.~~

~~166. The method according to any one of claims 118-162, wherein the patient has been identified as not having type 2 diabetes.~~

~~167. The method according to any one of claims 118-162, wherein the patient has been identified as having cardiovascular disease.~~

~~168. The method of claim 167, wherein the patient has been identified as having or at risk of having atherosclerosis, restenosis, pulmonary hypertension, or thrombosis.~~

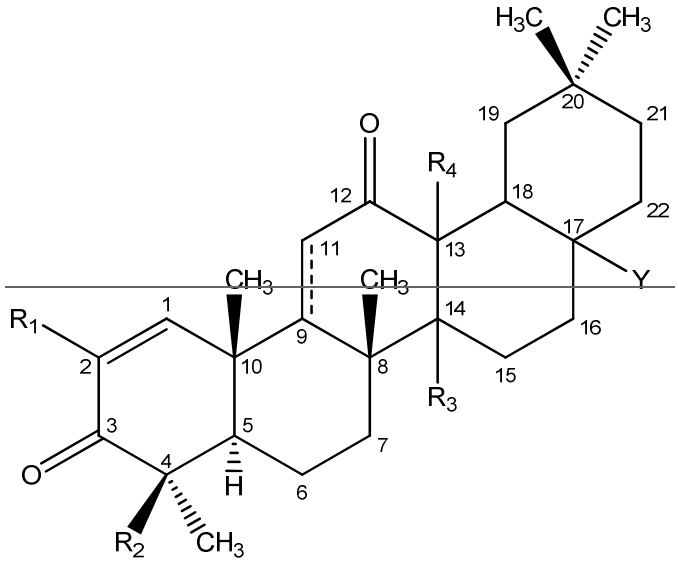
~~169. The method of claim 168, wherein the patient has been identified as having or at risk of having atherosclerosis.~~

~~170. The method of claim 168, wherein the patient has been identified as having or at risk of having restenosis.~~

~~171. The method of claim 168, wherein the patient has been identified as having or at risk of having pulmonary hypertension.~~

~~172. The method of claim 168, wherein the patient has been identified as having or at risk of having thrombosis.~~

173. A method of treating or preventing a cardiovascular disease in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound of the formula:



(I),

wherein:

R_1 is –CN, halo, $–CF_3$, or $–C(O)R_a$, wherein R_a is –OH, $alkoxy_{(C1-4)}$, $–NH_2$, $alkylamino_{(C1-4)}$, or $–NH–S(O)_2–alkyl_{(C1-4)}$;

R_2 is hydrogen or methyl;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_e; and

Y is:

–H, –OH, –SH, –CN, –F, $–CF_3$, $–NH_2$ or =NCO;

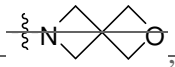
$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $alkylthio_{(C\leq8)}$, $acylthio_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or substituted versions of any of these groups;

$–alkanediyl_{(C\leq8)}–R_b$, $–alkenediyl_{(C\leq8)}–R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, $-OC(O)NH$-alkyl$_{(C\leq 8)}$, $-OC(O)CH_2NHC(O)O$-*t* butyl, $-OCH_2$-alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

$-(CH_2)_mC(O)R_e$, wherein m is 0-6 and R_e is:

hydrogen, hydroxy, halo, amino, $-NHOH$, , or thio; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, NH-alkoxy$_{(C\leq 8)}$, NH-heterocycloalkyl$_{(C\leq 8)}$, NHC(NOH)-alkyl$_{(C\leq 8)}$, NH-amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_e and R_3, taken together, are O or NR_d, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

R_e and R_4, taken together, are O or NR_d, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

$-NHC(O)R_e$, wherein R_e is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof,

wherein the patient has been identified as not having at least one of the following characteristics:

(a) a history of left-sided myocardial disease;

(b) an elevated B-type natriuretic peptide (BNP) level;

(c) an elevated albumin/creatinine ratio (ACR); and

(d) chronic kidney disease (CKD).

174. The method of claim 173, wherein the patient has been identified as having or at risk of having atherosclerosis, restenosis, pulmonary hypertension, pulmonary arterial hypertension, or thrombosis.

175. The method of claim 174, wherein the patient has been identified as having or at risk of having atherosclerosis.

176. The method of claim 174, wherein the patient has been identified as having or at risk of having restenosis.

177. The method of claim 174, wherein the patient has been identified as having or at risk of having pulmonary hypertension.

178. The method of claim 174, wherein the patient has been identified as having or at risk of having pulmonary arterial hypertension.

179. The method of claim 174, wherein the patient has been identified as having or at risk of having thrombosis.

180. The method according to any one of claims 173-179, wherein the patient has been identified as not having at least two of the characteristics.

181. The method according to any one of claims 173-179, wherein the patient has been identified as not having at least three of the characteristics.

182. The method according to any one of claims 173-179, wherein the patient has been identified as not having all four of the characteristics.

183. The method according to any one of claims 173-182, wherein the pressure in the pulmonary artery of the patient has been measured or will be measured.

184. The method of claim 183, wherein the pressure in the pulmonary artery of the patient has been measured prior to administering the compound and will be measured after administering the compound.

185. The method according to any one of claims 173-184, wherein the patient does not have a history of left-sided myocardial disease.

186. The method according to any one of claims 173-184, wherein the patient has a history of left-sided myocardial disease.

187. The method according to any one of claims 173-184, wherein the patient does not have a history of left-sided heart failure.

188. The method according to any one of claims 173-181 and 183-184, wherein the patient has a history of left-sided heart failure.

189. The method according to any one of claims 173-188, wherein the patient does not have an elevated BNP level.

190. The method according to any one of claims 173-181 and 183-188, wherein the patient has an elevated BNP level.

191. The method of claim 190, wherein the elevated BNP level is greater than 200 pg/mL.

192. The method according to any one of claims 173-191, wherein the patient does not have an elevated ACR.

193. The method according to any one of claims 173-181 and 183-191, wherein the patient has an elevated ACR.

194. The method of claim 193, wherein the elevated ACR is greater than 300 mg/g.

195. The method according to any one of claims 173-194, wherein the patient's estimated glomerular filtration rate (eGFR) is greater than or equal to 45 mL/min/1.73 m^2.

196. The method according to any one of claims 173-195, wherein the patient's eGFR is greater than or equal to 60 mL/min/1.73 m^2.

197. The method according to any one of claims 173-194, wherein the patient's eGFR is less than 60 mL/min/1.73 m^2.

198. The method according to any one of claims 173-197, wherein the patient is less than 75 years old.

199. The method of claim 198, wherein the patient is less than 70 years old.

200. The method of claim 199, wherein the patient is less than 65 years old.

201. The method of claim 200, wherein the patient is less than 60 years old.

202. The method of claim 201, wherein the patient is less than 55 years old.

203. The method according to any one of claims 173-202, wherein the patient has been identified as having chronic obstructive pulmonary disease (COPD).

204. The method according to any one of claims 173-202, wherein the patient has been identified as not having COPD.

205. The method according to any one of claims 173-202, wherein the patient is a smoker.

206. The method according to any one of claims 173-202, wherein the patient is not a smoker.

207. The method according to any one of claims 173-206, wherein the patient suffers from renal disease.

208. The method according to any one of claims 173-206, wherein the patient does not suffer from renal disease.

~~209. The method according to any one of claims 173-206, wherein the patient has elevated levels of at least one biomarker associated with renal disease.~~

~~210. The method according to any one of claims 173-206, wherein the patient does not have elevated levels of a biomarker associated with renal disease.~~

~~211. The method of either one of claims 209 and 210, wherein the biomarker is serum creatinine.~~

~~212. The method of either one of claims 209 and 210, wherein the biomarker is cystatin C.~~

~~213. The method of either one of claims 209 and 210, wherein the biomarker is uric acid.~~

~~214. The method according to any one of claims 173-206, wherein the patient does not have elevated levels of any biomarker associated with renal disease.~~

~~215. The method according to any one of claims 173-214, wherein the patient has chronic kidney disease (CKD) or exhibits one or more symptoms of CKD.~~

~~216. The method according to any one of claims 173-214, wherein the patient does not have CKD.~~

~~217. The method according to any one of claims 173-214, wherein the patient does not exhibit any symptoms of CKD.~~

~~218. The method according to any one of claims 173-~~181 and 183-~~214, wherein the patient has been identified as having CKD.~~

~~219. The method according to any one of claims 173-214, wherein the patient has been identified as not having CKD.~~

~~220. The method according to any one of claims 173-214, wherein the patient does not have stage 4 CKD.~~

~~221. The method of claim 220, wherein the patient does not have stage 3 or stage 4 CKD.~~

~~222. The method of claim 221, wherein the patient does not have stage 2, stage 3 or stage 4 CKD.~~

~~223. The method according to any one of claims 173-222, wherein the level of a marker of CKD in the patient has been measured or will be measured.~~

~~224. The method of claim 223, wherein the marker is the level of serum creatinine.~~

~~225. The method of claim 224, wherein the level of serum creatinine in the blood of the patient has been measured or will be measured.~~

~~226. The method of claim 225, wherein the administering reduces the level of serum creatinine in the patient.~~

~~227. The method according to any one of claims 173-226, wherein the patient has been identified as having cancer.~~

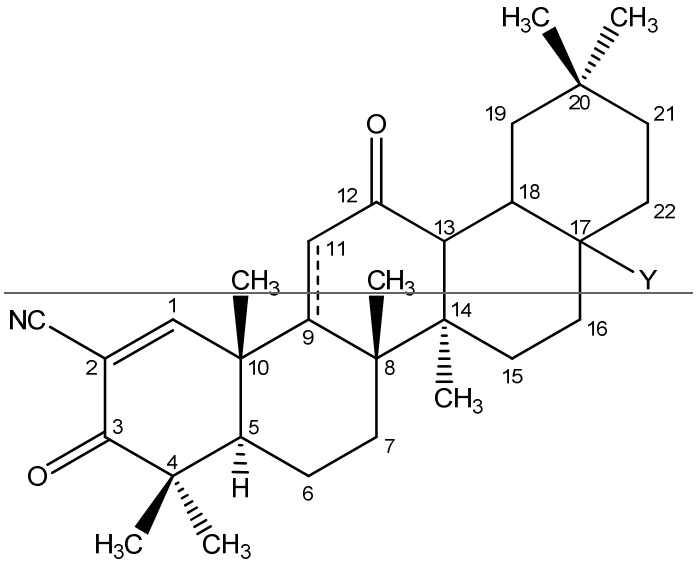
~~228. The method according to any one of claims 173-226, wherein the patient has been identified as not having cancer.~~

~~229. The method according to any one of claims 173-226, wherein the patient has been identified as having type 2 diabetes.~~

~~230. The method according to any one of claims 173-226, wherein the patient has been identified as not having type 2 diabetes.~~

~~231~~20. The ~~method~~ use according to any one of claims 1-19~~230~~, wherein the patient is a human patient.

232. The method according to any one of claims 1-231, wherein the compound is further defined as:



(II),

wherein:

Y is:

–H, –OH, –SH, –CN, –F, $-CF_3$, $-NH_2$ or =NCO;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

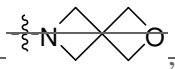
$-alkanediyl_{(C\leq 8)}-R_b$, $-alkenediyl_{(C\leq 8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

$heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-OC(O)NH-alkyl_{(C\leq 8)}$,

~~–OC(O)CH_2NHC(O)O–*t*-butyl, –OCH_2–alkylthio$_{(C\leq8)}$, or a substituted version of any of these groups;~~

~~–$(CH_2)_m$C(O)R_e, wherein m is 0–6 and R_e is:~~

~~hydrogen, hydroxy, halo, amino, –NHOH,~~  ~~, or thio; or~~

~~alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, alkynyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, aralkyl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, alkenyloxy$_{(C\leq8)}$, aryloxy$_{(C\leq8)}$, aralkoxy$_{(C\leq8)}$, heteroaryloxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, arylamino$_{(C\leq8)}$, alkylsulfonylamino$_{(C\leq8)}$, amido$_{(C\leq8)}$, –NH–alkoxy$_{(C\leq8)}$, –NH–heterocycloalkyl$_{(C\leq8)}$, –NHC(NOH)–alkyl$_{(C\leq8)}$, –NH–amido$_{(C\leq8)}$, or a substituted version of any of these groups;**

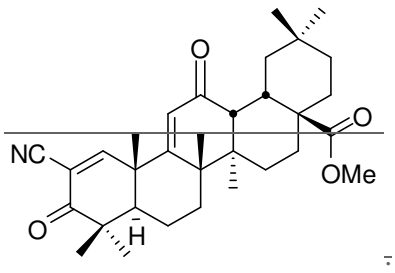
~~–NHC(O)R_e, wherein R_e is:~~

~~hydrogen, hydroxy, amino; or~~

~~alkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, alkynyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, aralkyl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, aryloxy$_{(C\leq8)}$, aralkoxy$_{(C\leq8)}$, heteroaryloxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, arylamino$_{(C\leq8)}$, or a substituted version of any of these groups;~~

~~or a pharmaceutically acceptable salt or tautomer thereof.~~

~~233. The method of claim 232, wherein the compound is further defined as:~~



~~234~~21. The ~~method~~ use according to any one of claim~~s~~ ~~233~~1-20, wherein at least a portion of the compound is present as a crystalline form having an X-ray diffraction pattern (CuKα) comprising significant diffraction peaks at about 8.8, 12.9, 13.4, 14.2 and 17.4 °2θ.

~~2352~~2. The ~~method~~ use of claim ~~2342~~1, wherein the X-ray diffraction pattern (CuKα) is substantially as shown in FIG. 1A or FIG. 1B.

~~2362~~3. The ~~method~~ use according to any one of claims ~~233~~1-20, wherein at least a portion of the compound is present as an amorphous form having an X-ray diffraction pattern (CuKα) with a halo peak at approximately 13.5 °2θ, substantially as shown in FIG. 1C, and a transition glass temperature (T_g).

~~2372~~4. The ~~method~~ use of claim ~~2362~~3, wherein the T_g value is in the range of about 120 °C to about 135 °C.

~~2382~~5. The ~~method~~ use of claim ~~2372~~4, wherein the T_g value is in the range of about 125 °C to about 130 °C.

~~2392~~6. The ~~method~~ use according to any one of claims 1-~~2382~~5, wherein the pharmaceutically effective amount is a daily dose from about 0.1 mg to about 300 mg of the compound.

~~240. The method of claim 239, wherein the daily dose is from about 0.5 mg to about 200 mg of the compound.~~

~~241. The method of claim 240, wherein the daily dose is from about 1 mg to about 150 mg of the compound.~~

~~242. The method of claim 241, wherein the daily dose is from about 1 mg to about 75 mg of the compound.~~

~~243. The method of claim 242, wherein the daily dose is from about 1 mg to about 20 mg of the compound.~~

~~2442~~7. The ~~method~~ use of claim ~~2392~~6, wherein the daily dose is from about 2.5 mg to about 30 mg of the compound.

~~2452~~8. The ~~method~~ use of claim ~~2442~~7, wherein the daily dose is about 2.5 mg of the compound.

~~2462~~9. The ~~method~~ use of claim ~~2442~~7, wherein the daily dose is about 5 mg of the compound.

~~247~~30. The ~~method~~ use of claim ~~244~~27, wherein the daily dose is about 10 mg of the compound.

~~248~~31. The ~~method~~ use of claim ~~244~~27, wherein the daily dose is about 20 mg of the compound.

~~249~~32. The ~~method~~ use of claim ~~244~~27, wherein the daily dose is about 30 mg of the compound.

~~250. The method according to any of claims 1-238, wherein the pharmaceutically effective amount is a daily dose is 0.01 – 100 mg of compound per kg of body weight.~~

~~251. The method of claim 250, wherein the daily dose is 0.05 – 30 mg of compound per kg of body weight.~~

~~252. The method of claim 251, wherein the daily dose is 0.1 – 10 mg of compound per kg of body weight.~~

~~253. The method of claim 252, wherein the daily dose is 0.1 – 5 mg of compound per kg of body weight.~~

~~254. The method of claim 253, wherein the daily dose is 0.1 – 2.5 mg of compound per kg of body weight.~~

~~255. The method according to any of claims 1-238, wherein the pharmaceutically effective amount is administered in a single dose per day.~~

~~256. The method according to any of claims 1-238, wherein the pharmaceutically effective amount is administered in two or more doses per day.~~

~~257~~33. The ~~method~~ use according to any one of claims 1-~~238~~32, wherein the ~~compound is administered~~medicament is formulated for administration orally, intraarterially or intravenously.

~~258. The method according to any one of claims 1-238, wherein the compound is formulated as a hard or soft capsule or a tablet.~~

~~259~~34. The ~~method~~ use according to any one of claims 1-~~238~~33, wherein the ~~compound~~ medicament is formulated as a solid dispersion comprising (i) the compound and (ii) an excipient.

~~260~~35. The ~~method~~ use of claim ~~259~~34, wherein the excipient is a methacrylic acid – ethyl acrylate copolymer.

~~261~~36. The ~~method~~ use of claim ~~260~~35, wherein the copolymer comprises methacrylic acid and ethyl acrylate at a 1:1 ratio.

~~262. The method according to any of claims 1-261, further comprising a second therapy.~~

~~263. The method of claim 262, wherein the second therapy comprises administering to said patient a pharmaceutically effective amount of a second drug.~~

~~264. The method of claim 263, wherein the second drug is a Rho kinase inhibitor, a tyrosine kinase inhibitor, an epoprostenol derivative, a serotonin receptor antagonist, an endothelin receptor antagonist, a phosphodiesterase (PDE) inhibitor, a calcium channel blocker, a soluble guanylate cyclase stimulator, or nitric oxide.~~

~~265. The method of claim 264, wherein the Rho kinase inhibitor is HA-1077, HA-1152P, or Y-27632.~~

~~266. The method of claim 264, wherein the tyrosine kinase inhibitor is Gleevec.~~

~~267. The method of claim 264, wherein the epoprostenol derivative is treprostinil, beraprost, or iloprost.~~

~~268. The method of claim 264, wherein the serotonin receptor antagonist is sarpogrelate.~~

~~269. The method of claim 264, wherein the endothelin receptor antagonist is bosentan, sitaxsentan, ambrisentan, TBC3711, or macitentan.~~

~~270. The method of claim 264, wherein the PDE inhibitor is amrinone, sildenafil, tadalafil, vardenafil, enoximone, udenafil, or milrinone.~~

~~271. The method of claim 264, wherein the calcium channel blocker is amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil.~~

~~272. The method of claim 264, wherein the soluble guanylate cyclase stimulator is riociguat.~~