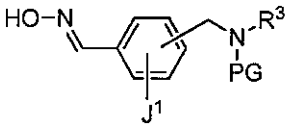
CLAIMS

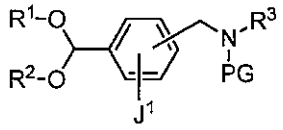
We claim:

1. A process for preparing a compound of formula **4**:



4

from a compound of formula **3**:



3

under suitable oxime formation conditions;

wherein

R^1 is $C_{1\text{-}6}$alkyl;

R^2 is $C_{1\text{-}6}$alkyl;

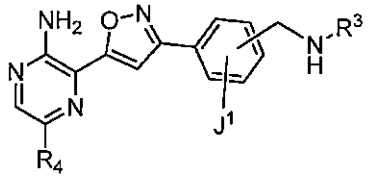
or R^1 and R^2, together with the oxygen atoms to which they are attached, form an optionally substituted 5 or 6 membered saturated heterocyclic ring having two oxygen atoms;

R^3 is hydrogen, $C_{1\text{-}6}$alkyl, or a 3-6 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the heterocyclyl is optionally substituted with 1 occurrence of halo or $C_{1\text{-}3}$alkyl;

J^1 is H, halo, $C_{1\text{-}4}$alkyl, or $C_{1\text{-}4}$alkoxy;

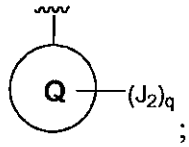
PG is a carbamate protecting group.

2. The process of claim 1, wherein the process is used to make a compound of formula I:



I

wherein

R^4 is  ;

J^1 is halo, C_{1-4}alkyl, or C_{1-4}alkoxy;

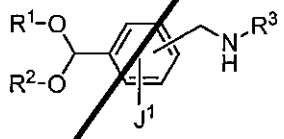
Q is phenyl, pyridyl, or an N-alkylated pyridone;

J^2 is halo; CN; phenyl; oxazolyl; or a C_{1-6}aliphatic group wherein up to 2 methylene units are optionally replaced with O, NR", C(O), S, S(O), or $S(O)_2$; said C_{1-6}aliphatic group is optionally substituted with 1-3 fluoro or CN;

q is 0, 1, or 2; and

R^3 is hydrogen, C_{1-6}alkyl, or a 3-6 membered saturated or partially unsaturated heterocyclyl having 1-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; wherein the heterocyclyl is optionally substituted with 1 occurrence of halo or C_{1-3}alkyl.

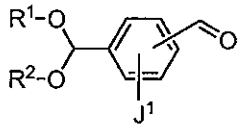
3. The process of claim 1 or claim 2, further comprising the step of protecting a compound of formula **2**:



2

under suitable protection conditions to form the compound of formula **3**.

4. The process of claim 3, further comprising the step of reacting a compound of formula 1:

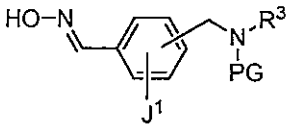


1

with a suitable ligand under suitable reductive amination conditions to form a compound of formula 2.

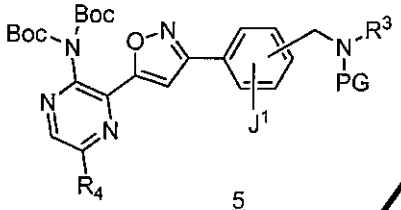
5. The process of claim 4, wherein the suitable ligand is an amine.

6. The process of claim 4, further comprising the step of reacting a compound of formula **4**:

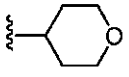
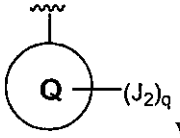
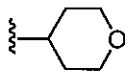


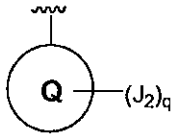
4

under suitable isoxazole formation conditions to form a compound of formula **5**:



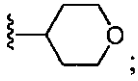
5

7. The process of claim 6, further comprising the step of reacting a compound of formula **5** under suitable coupling conditions followed by suitable deprotection conditions to form a compound of formula I.
8. The process of claim 1, comprising one or more of the following limitations:
   a) R^1 is ethyl and R^2 ethyl;
   b) R^3 is CH_3 or  ; and
   c) J^1 is H.
9. The process of claim 2, wherein R^4 is  wherein Q is phenyl, q is 1, and J^2 is a C_{1-6}aliphatic group wherein up to 1 methylene unit is optionally replaced with $S(O)_2$.
10. The process of claim 9, J^2 is $-S(O)_2-(C_{1-5}alkyl)$.
11. The process of claim 2, wherein
    R^1 is ethyl; R^2 is ethyl;
    R^3 is CH_3 or  ;
    PG is Boc or Cbz;
    J^1 is H;

R^4 is  wherein Q is phenyl; J^2 is $-S(O)_2-CH(CH_3)_2$; and q is 1.

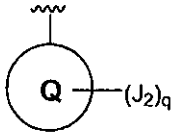
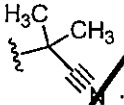
12. The process of claim 2, wherein

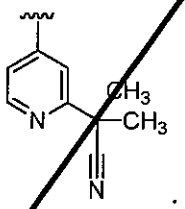
R^1 is ethyl; R^2 is ethyl;

R^3 is ;

PG is Boc;

J^1 is H;

R^4 is  wherein Q is pyridyl; J^2 is ; and q is 1.

13. The process of claim 12, wherein R^4 is .

14. The process of any one of claims 1-13, wherein the suitable oxime formation conditions consist of either a single step sequence or a two step sequence.

15. The process of claim 14, wherein the two step sequence consists of first deprotecting the ketal group in the compound of formula 3 into an aldehyde under suitable deprotection conditions, and then forming the oxime of formula 4 under suitable oxime formation conditions.

16. The process of claim 15, wherein

a) suitable deprotection conditions comprise adding an acid, acetone, and water; and

b) suitable oxime formation conditions comprise mixing together hydroxylamine, an acid, an organic solvent, and optionally either water or a dehydrating agent.

17. The process of claim 16, wherein the acid is pTSA or HCl, the organic solvent a chlorinated solvents selected from dichloromethane (DCM), dichloroethane (DCE),

CH_2Cl_2, and chloroform; an ether selected from THF, 2-MeTHF and dioxane; or an aromatic hydrocarbons selected from toluene and xylenes.

18. The process of claim 16, wherein the acid is pTSA or HCl, the dehydrating agent is molecular sieves or dimethoxyacetone, and the organic solvent is an alcoholic solvent selected from methanol or ethanol.

19. The process of claim 14, wherein the single step sequence comprises adding $NH_2OH.HCl$ and a mixture of THF and water.

20. The process of claim 19, wherein 1 equivalent of the compound of formula **3** is combined with a 1.1 equivalents of $NH_2OH.HCl$ in a 10:1 v/v mixture of THF/water.

21. The process of any one of claims 1-13, wherein PG is selected from Boc or Cbz.

22. The process of claim 21, wherein the protection conditions are selected from the group consisting of
    a) R-OCOCl, a suitable tertiary amine base, and a suitable solvent; wherein R is $C_{1\text{-}6}$alkyl optionally substituted with phenyl;
    b) $R(CO_2)OR'$, a suitable solvent, and optionally a catalytic amount of base, wherein R is and R' are each independently $C_{1\text{-}6}$alkyl optionally substituted with phenyl;
    c) $[RO(C=O)]_2O$, a suitable base, and a suitable solvent.

23. The process of claim 22, wherein the suitable base is Et_3N, diisopropylamine, and pyridine; and the suitable solvent is selected from a chlorinated solvent, an ether, or an aromatic hydrocarbon.

24. The process of claim 23, wherein the suitable base is Et_3N, the suitable solvent is a chlorinated solvent selected from DCM.

25. The process of claim 23, wherein the protection conditions comprise adding 1.20 equivalents of $(Boc)_2O$ and 1.02 equivalents of Et_3N in DCM.

26. The process of any one of claims 7-13, wherein the suitable coupling conditions comprise adding a suitable palladium catalyst with a suitable base in a suitable solvent.

27. The process of claim 26, wherein the suitable palladium catalyst is selected from $Pd[P(tBu)_3]_2$, $Pd(dtbpf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PCy_3)_2Cl_2$, $Pd(dppf)Cl_2$, and $Pd(dppe)Cl_2$; one or more of the following: toluene, MeCN, water, EtOH, IPA, 2-Me-THF, or IPAc; and the suitable base is selected from K_2CO_3, Na_2CO_3, or K_3PO_4.

28. The process of claim 26, wherein the suitable palladium catalyst is $Pd[P(tBu)_3]_2$, the suitable solvent is a mixture of acetonitrile and water; and the suitable base is sodium carbonate.

29. The process of claim 26, wherein the suitable coupling conditions comprise adding 0.1 equivalents of $Pd[P(tBu)_3]_2$; 1 equivalent of boronic acid or ester; and 2 equivalents of sodium carbonate in a 2:1 ratio v/v of acetonitrile/water at 60-70°C.

30. The process of any one of claims 7-13, wherein the suitable deprotection conditions comprise combining the compound of formula 5 with a suitable Boc deprotecting agent in a suitable solvent.

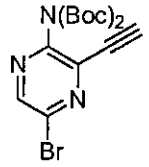
31. The process of claim 30, wherein the suitable Boc deprotecting agent is selected from TMS-Cl, HCl, TBAF, H_3PO_4, or TFA and the suitable solvent is selected from acetone, toluene, methanol, ethanol, 1-propanol, isopropanol, CH_2Cl_2, EtOAc, isopropyl acetate, tetrahydrofuran, 2-methyltetraydrofuran, dioxane, or diethylether.

32. The process of claim 30, wherein the suitable Boc deprotecting agent is selected from HCl, TBAF, H_3PO_4, or TFA and the suitable solvent is selected from methanol, ethanol, CH_2Cl_2, EtOAc, THF, dioxane, toluene, or diethylether.

33. The process of claim 30, wherein the suitable Boc deprotecting agent is HCl or TFA and the suitable solvent is acetone, toluene, isopropanol, or isopropyl acetate.

34. The process of claim 6, wherein the suitable isoxazole-formation conditions consists of two steps, the first step comprising reacting the compound of formula 4 under suitable chlorooxime formation conditions to form a chlorooxime intermediate; the second step comprising reacting the chlorooxime intermediate with an acetylene under suitable cycloaddition conditions to form a compound of formula 5.

35. The process of claim 34, wherein the acetylene is a compound of formula 4-iii.



4-iii.

36. The process of claim 34, wherein the suitable chlorooxime formation conditions are selected from

d) N-chlorosuccinimide and suitable solvent or

e) potassium peroxymonosulfate, HCl, and dioxane.

37. The process of claim 36, wherein the suitable solvent is selected from a nonprotic solvent, an aromatic hydrocarbon, or an alkyl acetate.

38. The process of claim 37, wherein the suitable chlorooxime formation conditions are 1.05 equivalents of N-chlorosuccinimide in isopropylacetate at 40-50°C.

39. The process of any one of claims 34-38, wherein suitable cycloaddition conditions consist of a suitable base and a suitable solvent.

40. The process of claim 39, wherein the suitable base is selected from pyridine, DIEA, TEA, t-BuONa, and K_2CO_3 and the suitable solvent is selected from acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, MTBE, EtOAc, i-PrOAc, DCM, toluene, DMF, and methanol.

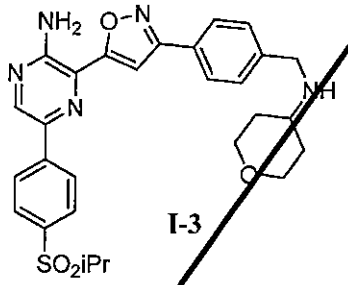
41. The process of claim 40, wherein the suitable base is selected from Et_3N and the suitable solvent is selected from DCM.

42. The process of claim 34, wherein the second step comprises reacting 1 equivalent of acetylene with 1.2 equivalents of the chlorooxime intermediate and 1.3 equivalents of Et_3N in DCM at room temperature.

43. The process of claim 6, wherein the suitable isoxazole-formation conditions comprise combining the compound of formula 4 with an oxidant in a suitable solvent.

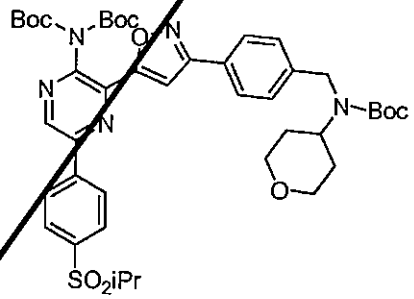
44. The process of claim 43, wherein said oxidant is [bis(trifluoroacetoxy)iodo] benzene and said solvent is a 1:1:1 mixture of methanol, water, and dioxane.

45. A process for preparing a compound of formula I-3:



I-3

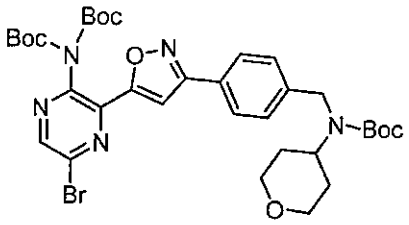
comprising the step of deprotecting a compound of formula A-6:



A-6

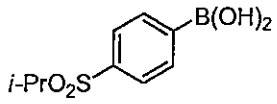
under suitable Boc deprotection conditions optionally followed by treatment under basic aqueous conditions to form a compound of formula I-3.

46. The process of claim 45, further comprising the step of reacting a compound of formula A-5:



A-5

with a compound of formula A-5-i:

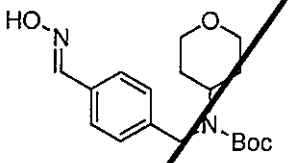


A-5-i

under suitable coupling conditions to form the compound of formula A-6.

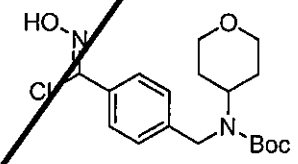
47. The process of claim 46, further comprising the steps of:

a) reacting a compound of formula A-4:



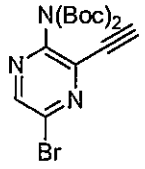
A-4

under suitable chlorooxime formation conditions to form the compound of formula A-4-i:



A-4-i

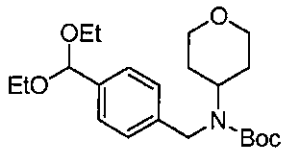
b) reacting the compound of formula A-4-i with a compound of formula A-4-ii:



A-4-ii

under suitable cycloaddition conditions to form the compound of formula A-5.

48. The process of claim 47, further comprising the step of reacting a compound of formula A-3:

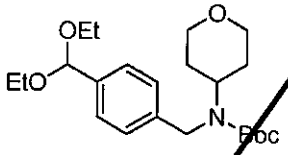


A-3

under suitable oxime formation conditions to form the compound of formula A-4.

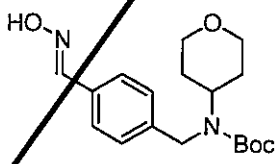
49. The process of claim 48, wherein the suitable oxime formation conditions consist of either a single step sequence or a two step sequence.

50. The process of claim 49, wherein the two step sequence consists of first deprotecting the ketal group in the compound of formula A-3:



A-3

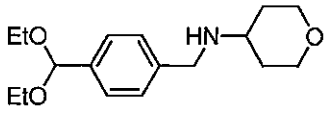
into an aldehyde under suitable deprotection conditions, and then forming the oxime of formula A-4:



A-4

under suitable oxime formation conditions.

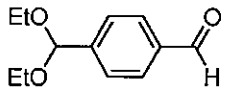
51. The process of claim 50, further comprising the step of reacting a compound of formula A-2:



A-2

under suitable Boc protection conditions to form the compound of formula A-3.

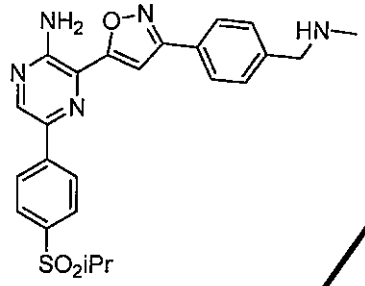
52. The process of claim 51, further comprising the step of reacting a compound of formula A-1:



A-1

with tetrahydro-2*H*-pyran-4-amine under suitable reductive amination conditions to form the compound of formula A-2.

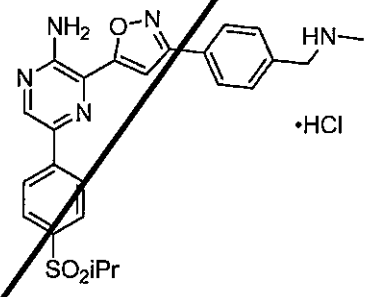
53. A process for preparing Compound I-2• HCl :



Compound I-2

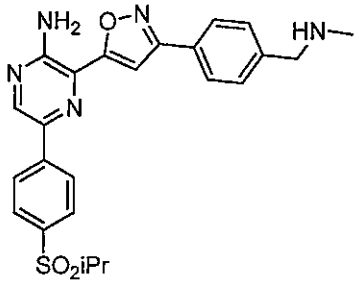
comprising stirring a suspension of Compound I-2• 2HCl in *i*-PrOH and water.

54. A process for preparing Compound I-2• HCl :

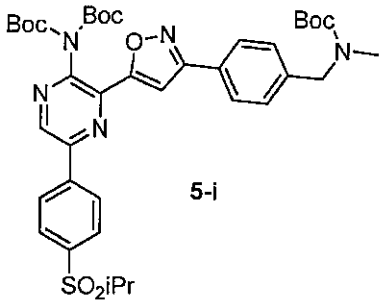


comprising combining about 1 equivalent of an aqueous solution of of HCl with the free base of Compound I-2 in acetone.

55. A process for preparing a compound of formula I-2:



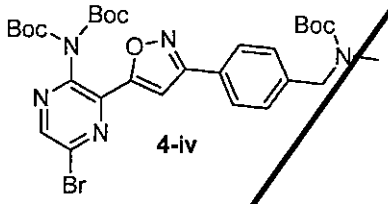
comprising the step of deprotecting a compound of formula 5-i:



5-i

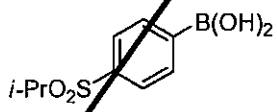
under suitable Boc deprotection conditions optionally followed by treatment under basic aqueous conditions to form a compound of formula I-2.

56. The process of claim 55, further comprising the step of reacting a compound of formula 4-iv:



4-iv

with



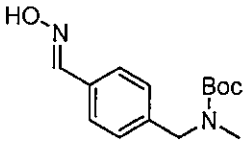
under suitable coupling conditions to form the compound of formula 5-i.

57. The process of claim 46 or 56, wherein the suitable coupling conditions comprise combining a suitable palladium catalyst with a suitable base in a suitable solvent.

58. The process of claim 57 wherein the suitable palladium catalyst is selected from $Pd[P(tBu)_3]_2$, $Pd(dtbpf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PCy_3)_2Cl_2$, $Pd(dppf)Cl_2$, and $Pd(dppe)Cl_2$; the suitable solvent is selected from one or more of the following: toluene, MeCN, water, EtOH, IPA, 2-Me-THF, or IPAc; and the suitable base is selected from K_2CO_3, Na_2CO_3, or K_3PO_4.

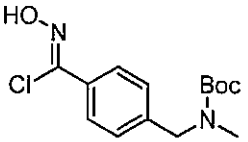
59. The process of claim 53 or 56, comprising the steps of

a) reacting a compound of formula 4-i



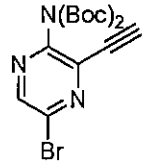
4-i

under suitable chlorooxime formation conditions to form the compound of formula 4-ii:



4-ii

b) reacting the compound of formula 4-ii with a compound of formula 4-iii:



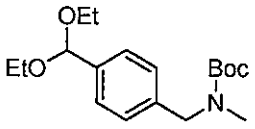
4-iii

under suitable cycloaddition conditions to form the compound of formula 4-iv.

60. The process of claim 47 or 59, wherein the suitable cycloaddition conditions comprises a suitable base selected from pyridine, DIEA, TEA, t-BuONa, or K_2CO_3 and a suitable solvent selected from acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, MTBE, EtOAc, i-PrOAc, DCM, toluene, DMF, and methanol.

61. The process of claim 47 or 59, wherein the suitable chlorooxime formation conditions comprise adding HCl in dioxae to a solution of the oxime in the presence of NCS in a suitable solvent selected from a nonprotic solvents (DCM, DCE, THF, and dioxane), aromatic hydrocarbons (e.g. toluene, xylenes), and alkyl acetates (e.g., isopropyl acetate, ethyl acetate).

62. The process of claim 59, further comprising the step of reacting a compound of formula **3b**:



3b

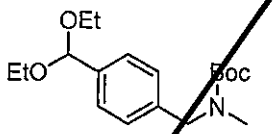
under suitable oxime formation conditions to form the compound of formula 4-i.

63. The process of claim 62, wherein the suitable oxime formation conditions consist of either a single step sequence or a two step sequence.

64. The process of claim 49 or 63, wherein the single step sequence comprises adding $NH_2OH.HCl$ and a mixture of THF and water.

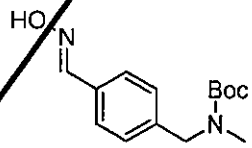
65. The process of claim 64, wherein 1 equivalent of the compound of formula 3b is combined with a 1.1 equivalents of $NH_2OH.HCl$ in a 10:1 v/v mixture of THF/water.

66. The process of claim 63, wherein the two step sequence consists of first deprotecting the ketal group in the compound of formula 3b:



3b

into an aldehyde under suitable deprotection conditions, and then forming the oxime of formula 5a:



5a

under suitable oxime formation conditions.

67. The process of claim 50 or 66, wherein

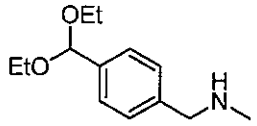
a) suitable deprotection conditions comprise adding an acid, acetone, and water; and

b) suitable oxime formation conditions comprise mixing together hydroxylamine, an optional acid, an organic solvent, and water.

68. The process of claim 67, wherein the acid is pTSA or HCl, the organic solvent a chlorinated solvents selected from dichloromethane (DCM), dichloroethane (DCE), CH_2Cl_2, and chloroform; an ether selected from THF, 2-MeTHF and dioxane; or an aromatic hydrocarbons selected from toluene and xylenes. [other aprotic solvents]

69. The process of claim 68, wherein suitable oxime formation conditions comprise adding hydroxylamine hydrochloride to a solution of the compound of 3b in THF and water.

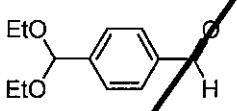
70. The process of any one of claims 62-69 further comprising the step of reacting a compound of formula 2b:



2b

under suitable Boc protection conditions to form the compound of formula 3b.

71. The process of claim 70, further comprising the step of reacting a compound of formula 1b:



1b

with methylamine under suitable reductive amination conditions to form the compound of formula **2b**.

72. The process of claim 52 or 71 wherein the suitable reductive amination conditions comprise adding a reducing agent selected from $NaBH_4$ $NaBH_4$, $NaBH_3CN$, or $NaBH(OAc)_3$ in the presence of a solvent selected from dichloromethane (DCM), dichloroethane (DCE), an alcoholic solvent selected from methanol, ethanol, 1-propanol, isopropanol, or a nonprotic solvent selected from dioxane, tetrahydrofuran, or 2-methyltetrahydrofuran and optionally a base selected from Et_3N or diisopropylethylamine.

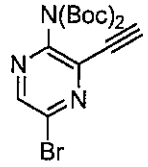
73. The process of claim 72, wherein the suitable reductive amination conditions comprise adding 1.2 equivalents of $NaBH_4$ caplets in the presence Et_3N in MeOH.

74. The process of any one of claim 45-73, wherein the suitable Boc deprotection conditions comprises adding a suitable Boc deprotecting agent selected from TMS-Cl, HCl, TBAF, H_3PO_4, or TFA and the suitable solvent is selected from acetone, toluene,

methanol, ethanol, 1-propanol, isopropanol, CH_2Cl_2, EtOAc, isopropyl acetate, tetrahydrofuran, 2-methyltetraydrofuran, dioxane, or diethylether.

75. The process of claim 74, wherein the suitable Boc deprotecting agent is HCl or TFA and the suitable solvent is acetone or CH_2Cl_2.

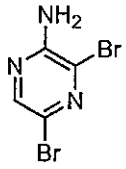
76. A process for preparing a compound of formula A-4-ii:



A-4-ii

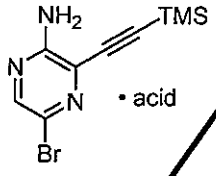
comprising one or more of the following steps:

f) reacting a compound of formula C-1:



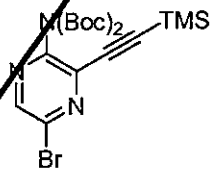
C-1

under suitable metal-mediated couplings conditions with TMS-acetylene to form a compound of formula C-2:



C-2 ;

g) reacting a compound of formula C-2 under suitable Boc protection conditions to form a compound of formula C-3:



C-3

h) reacting a compound of formula C-3 suitable TMS deprotection conditions to form a compound of formula A-4-ii.

77. The process of claim 70 or claim 76, wherein the Boc protection conditions are to add $(Boc)_2O$, a suitable base, and a suitable solvent.

78. The process of claim 77, wherein the suitable base is Et_3N, diisopropylamine, and pyridine; and the suitable solvent is selected from a chlorinated solvent, an ether, or an aromatic hydrocarbon.

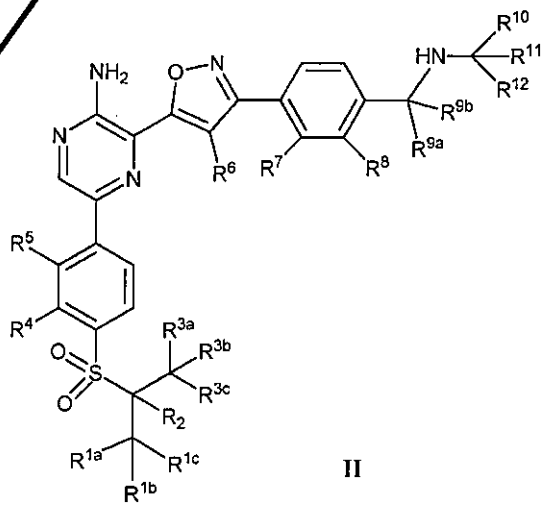
79. The process of claim 78, wherein the suitable base is Et_3N, the suitable solvent is DCM, tetrahydrofuran or 2-methyltetrahydrofuran.

80. The process of claim 79, wherein the Boc protection conditions comprise adding 1.05 equivalents of $(Boc)_2O$ in 2-methyltetrahydrofuran or DCM.

81. The process of claim 76, wherein the suitable metal-mediated coupling conditions are Sonogashira coupling conditions; the Boc protection conditions comprise adding $(Boc)_2O$ in 2-methyltetrahydrofuran or DCM; and the suitable TMS deprotection conditions comprise adding a suitable base, suitable organic solvent, and water.

82. The process of claim 81, wherein the Sonogashira coupling conditions comprise combining 1 equivalent of TMS-acetylene, 0.010 equivalents of $Pd(PPH_3)_2Cl_2$, 0.015 equivalents of CuI and 1.20 equivalents of NMM with Compound C-1 in isopropanol; the Boc protection conditions comprise adding 1.05 equivalents of $(Boc)_2O$ in 2-methyltetrahydrofuran or DCM; and the TMS deprotection conditions comprise adding K_2CO_3, EtOAc, EtOH, and water.

83. A compound of formula II:



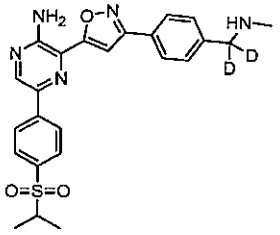
II

or a pharmaceutically acceptable salt thereof,

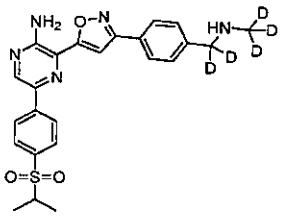
wherein each R^{1a}, R^{1b}, R^{1c}, R^2, R^{3a}, R^{3b}, R^{3c}, R^4, R^5, R^6, R^7, R^8, R^{9a}, R^{9b}, R^{10a}, R^{10b}, and R^{10c} is independently hydrogen or deuterium, and

at least one of R^{1a}, R^{1b}, R^{1c}, R^2, R^{3a}, R^{3b}, R^{3c}, R^4, R^5, R^6, R^7, R^8, R^{9a}, R^{9b}, R^{10a}, R^{10b}, and R^{10c} is deuterium.

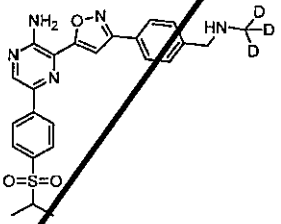
84. The compounmd of claim 81, selected from the group consisting of:



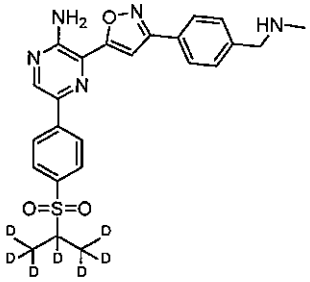
II-1



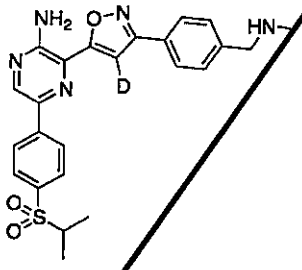
II-2



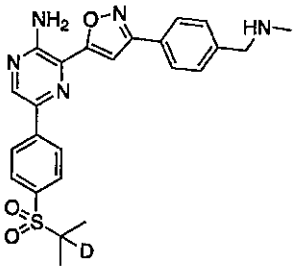
II-3



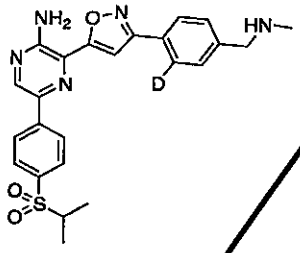
II-4



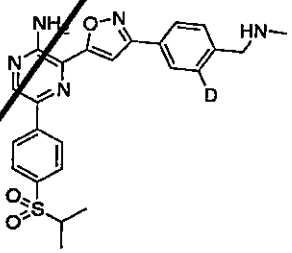
II-5



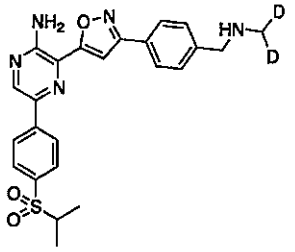
II-6



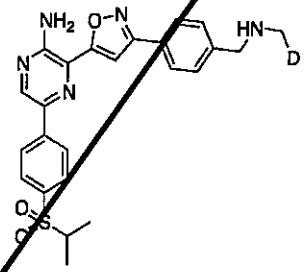
II-7



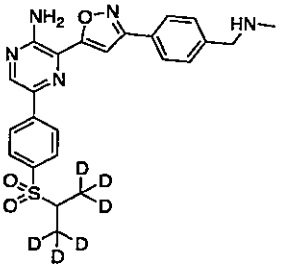
II-8



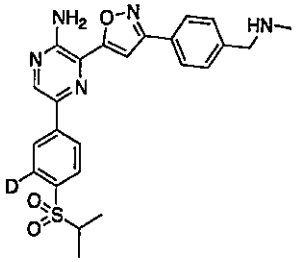
II-9



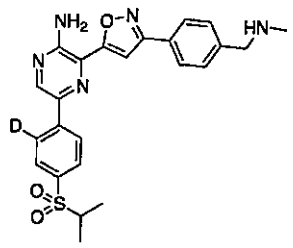
II-10



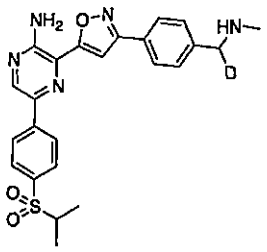
II-11



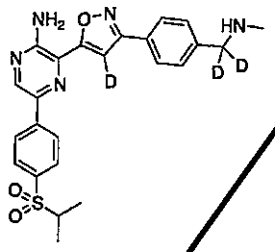
II-12



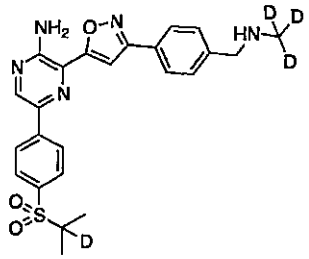
II-13



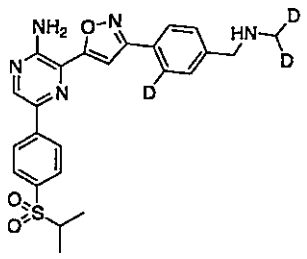
II-14



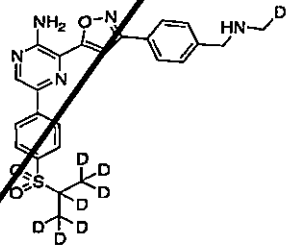
II-15



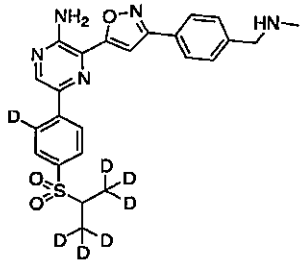
II-16



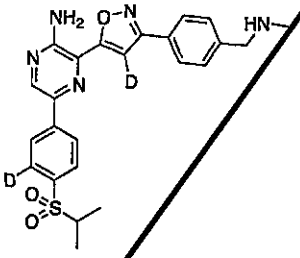
II-17



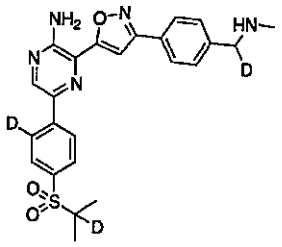
II-18



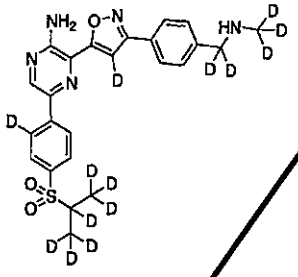
II-19



II-20



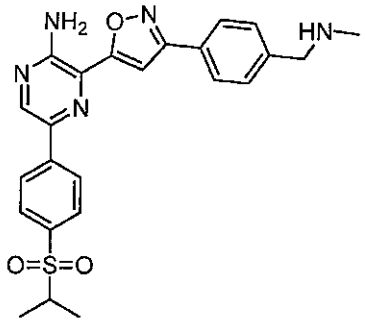
II-21



and II-22.

85. The compound of claim 81, selected from the group consisting of compound II-1, II-2, II-3, or II-4.

86. A solid form of a compound of formula I-2:



I-2

wherein the form is selected from the group consisting of Compound I-2 free base, Compound I-2• HCl, Compound I-2 • HCl • H_2O, Compound I-2 • HCl • $2H_2O$, and Compound I-2 •2-hydrochloric acid.

87. The solid form of claim 86, wherein the form is Compound I-2 free base.
88. The solid form of claim 86, wherein the form is crystalline compound I-2 free base.
89. The solid form of claim 88, having a monoclinic crystal system, having a $P2_1/n$ space group, and having the following unit cell dimensions in Å when measured at 120K:

    a = 8.9677 (1) Å

    b = 10.1871 (1) Å

    c = 24.5914 (3) Å.
90. The solid form of claim 88, characterized by a weight loss of from about 1.9 % in a temperature range of from about 25 °C to about 215 °C.
91. The solid form of claim 88, characterized by one or more peaks expressed in 2-theta ± 0.2 at about 14.2, 25.6, 18.1, 22.0, and 11.1 degrees in a X-ray powder diffraction pattern obtained using Cu K alpha radiation.
92. The solid form of claim 88, characterized as having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1a.
93. The solid form of claim 86, wherein the form is Compound I-2 • HCl.
94. The solid form of claim 86, wherein the form is crystalline Compound I-2 • HCl.
95. The solid form of of claim 94, wherein the compound:HCl are in a ratio of 1:1.
96. The solid form of claim 94, having a monoclinic crystal system, having a $P2_1/n$ space group, and having the following unit cell dimensions in Å when measured at 120K:

    a = 5.3332 (2) Å

    b = 35.4901 (14) Å

    c = 13.5057 (5) Å.

97. The solid form of claim 94, characterized by a weight loss of from about 1.1 % in a temperature range of from about 25 °C to about 100 °C, and about 0.8% from 110 °C to about 240 °C.
98. The solid form of claim 94, characterized by one or more peaks expressed in 2-theta ± 0.2 at about 13.5, 28.8, 15.0, 18.8, and 15.4 degrees in a X-ray powder diffraction pattern obtained using Cu K alpha radiation.
99. The solid form of claim 94, characterized by one or more peaks at about 171.7, 153.4, 132.9, 31.8, and 15.7 ppm in solid state ^{13}CNMR.
100. The solid form of claim 94, characterized as having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1b.
101. The solid form of claim 86, wherein the form is Compound I-2•2-hydrochloric acid.
102. The solid form of claim 86, wherein the form is Crystalline Compound I-2• 2HCl.
103. The solid form of claim 102, wherein the compound:HCl are in a ratio of 1:2.
104. The solid form of claim 102, characterized by one or more peaks at about 15.1, 18.5, 11.5, 13.1, and 5.7 in an X-ray powder diffraction pattern.
105. The solid form of claim 102, characterized as having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1c.
106. The solid form of claim 102, having a monoclinic crystal system, having a $P2_1/n$ space group, and having the following unit cell dimensions in Å when measured at 120K:

a = 5.3332 (2) Å
b = 35.4901 (14) Å
c = 13.5057 (5) Å.

107. The solid form of claim 102, characterized by a weight loss of from about 7% in a temperature range of from about 25 °C to about 188 °C.
108. The solid form of claim 102, characterized by one or more peaks at about 15.1, 18.5, 11.5, 13.1, and 5.7 degrees in a X-ray powder diffraction pattern obtained using Cu K alpha radiation.
109. The solid form of claim 102, characterized as having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1c.
110. The solid form of claim 102, characterized by one or more peaks at about 166.5, 137.6, 136.1, 34.2, and 16.4 ppm in solid state ^{13}CNMR.
111. The solid form of claim 86, wherein the form is Compound I-2• 2HCl • H_2O.

112. The solid form of claim 86, wherein the form is Crystalline compound I-2• 2HCl • H_2O.

113. The solid form of claim 112, wherein the compound:HCl:H_2O are in a ratio of 1:2:1.

114. The solid form of claim 112 characterized by a weight loss of from about 2.9% in a temperature range of from about 25 °C to about 100 °C and a weight loss of about 0.6% from about 100 °C to about 222 °C.

115. The solid form of claim 112 characterized by one or more peaks at about 6.6, 19.5, 24.7, 8.1, and 11.2 degrees in a X-ray powder diffraction pattern obtained using Cu K alpha radiation.

116. The solid form of claim 112, characterized as having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1d.

117. The solid form of claim 86, wherein the form is Compound I-2 • HCl• $2H_2O$.

118. The solid form of claim 86, wherein the form is Crystalline compound I-2 • HCl• $2H_2O$.

119. The solid form of claim 118 wherein the compound:HCl:H_2O are in a ratio of 1:1:2.

120. The solid form of claim 118 characterized by a weight loss of from about 6% in a temperature range of from about 25 °C to about 100 °C

121. The solid form of claim 118 characterized by one or more peaks at about 26.6, 7.6, 6.3, 23.3, and 24.6 degrees in a X-ray powder diffraction pattern obtained using Cu K alpha radiation.

122. A pharmaceutical composition comprising a solid form of claim 86 and a pharmaceutically acceptable carrier.

123. Use of a solid form of claim 86 for the manufacture of a medicament for treating cancer.

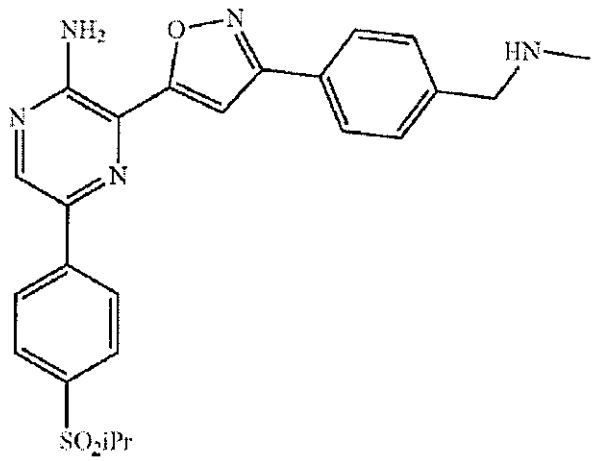
124. Use of a solid form of claim 86 for treating cancer.

125. The use according to claim 123 or claim 124, wherein the cancer is pancreatic cancer or non small cell lung cancer.

We claim:

1. A process for preparing a compound of formula I-2:

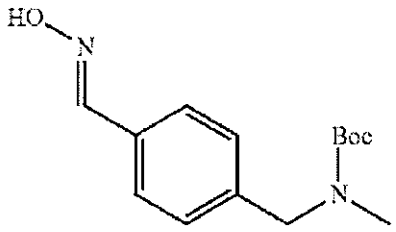
I-2



comprising the steps of

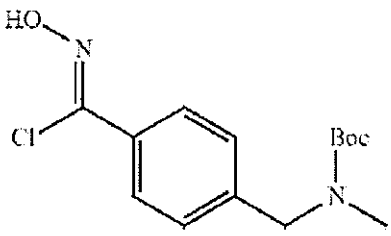
a) reacting a compound of formula 4-i

4-i



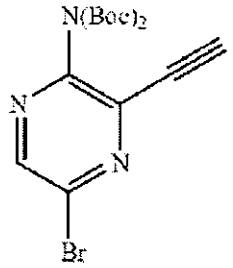
under suitable chlorooxime formation conditions to form the compound of formula 4-ii:

4-ii



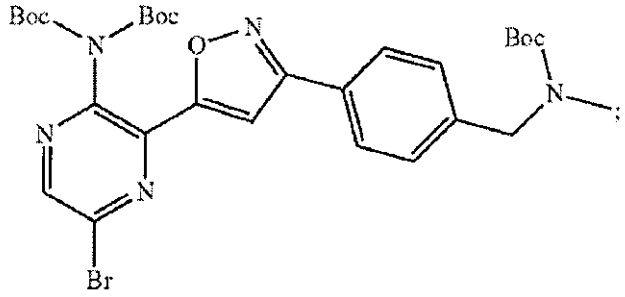
b) reacting the compound of formula 4-ii with a compound of formula 4-iii:

4-iii

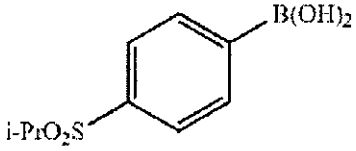


under suitable cycloaddition conditions to form the compound of formula 4-iv

4-iv

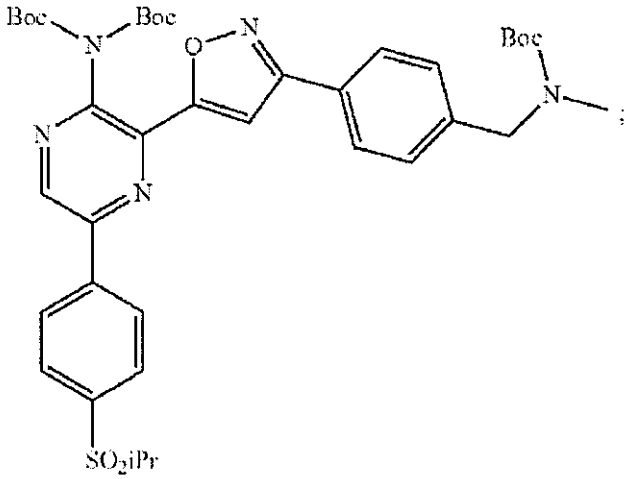


c) reacting the compound of formula 4-iv with



under suitable coupling conditions to form a compound of formula 5-i:

5-i

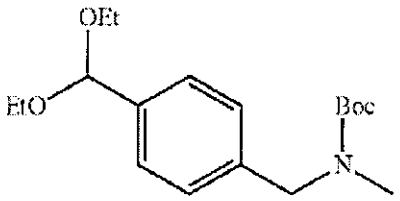


and

d) deprotecting the compound of formula 5-i under suitable Boc deprotection conditions optionally followed by treatment under basic aqueous conditions to form the compound of formula I-2.

2. The process of claim 1, further comprising the step of reacting a compound of formula 3b:

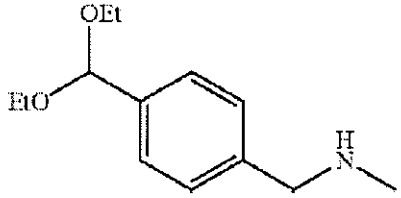
3b



under suitable oxime formation conditions to form the compound of formula 4-i.

3. The process of claim 2 further comprising the step of reacting a compound of formula 2b:

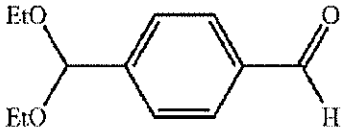
2b



under suitable Boc protection conditions to form the compound of formula 3b.

4. The process of claim 3, further comprising the step of reacting a compound of formula 1b:

1b

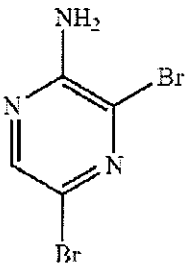


with methylamine under suitable reductive amination conditions to form the compound of formula 2b.

5. The process of claim 1, further comprising the step

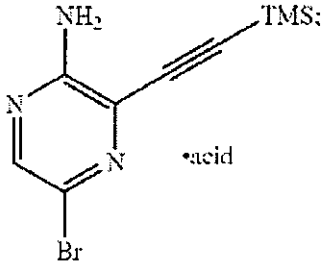
1) reacting a compound of formula C-1:

C-1



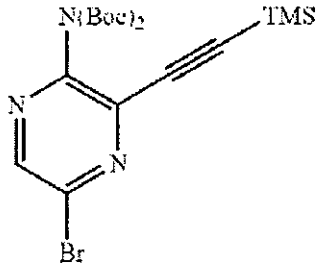
under suitable metal-mediated coupling conditions with trimethylsilyl (TMS)-acetylene to form a compound of formula C-2:

C-2



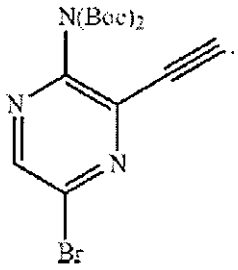
2) reacting a compound of formula C-2 under suitable Boc protection conditions to form a compound of formula C-3:

C-3



3) reacting a compound of formula C-3 under suitable TMS deprotection conditions to form a compound of formula 4-iii:

4-iii



6. The process of claim 1, wherein the suitable coupling conditions comprise combining a suitable palladium catalyst with a suitable base in a suitable solvent.

7. The process of claim 6 wherein the suitable palladium catalyst is selected from bis(tri-tert-butylphosphine)palladium(0) ($Pd[P(tBu)_3]_2$), 1,1'-bis(di-tert-butylphosphino) ferrocene]dichloropalladium (II)[,] ($Pd(dtbpf)Cl_2$), bis(triphenylphosphine) dichloropalladium (II) ($Pd(PPh_3)_2Cl_2$), bis(tricyclohexylphosphine) dichloropalladium (II) ($Pd(PCy_3)_2Cl_2$), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) ($Pd(dppf)Cl_2$), or 1,2-bis(diphenylphosphino)ethane dichloropalladium (II) ($Pd(dppe)Cl_2$); the suitable solvent is selected from one or more of the following: toluene, acetonitrile (MeCN), water (H_2O), ethanol (EtOH), isopropyl alochol (IPA), 2-methyl tetrahydrofuran (2-Me-THF), or isopropylacetate (IPAc); and the suitable base is selected from potassium carbonate (K_2CO_3), sodium carbonate (Na_2CO_3), or potassium phosphate (K_3PO_4).

8. The process of claim 1, wherein the suitable cycloaddition conditions comprise a suitable base selected from pyridine, diisopropylethylamine, triethylamine, sodium tert-butoxide (t-BuONa), or potassium carbonate (K_2CO_3); and a suitable solvent selected from acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, methyl tertiary butyl ether (MTBE), ethyl acetate (EtOAc), isopropyl acetate (IPAc), dichloromethane (DCM), toluene, dimethylformamide (DMF), or methanol.

9. The process of claim 1, wherein the suitable chlorooxime formation conditions comprise adding HCl in dioxane to a solution of the oxime in the presence of N-chlorosuccinimide (NCS) in a suitable solvent selected from DCM, dichloroethane (DCE), tetrahydrofuran (THF), dioxane, an aromatic hydrocarbon, or an alkyl acetate.

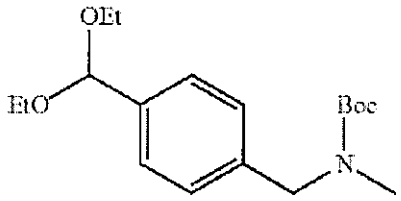
10. The process of claim 2, wherein the suitable oxime formation conditions consist of either a single step or a two step sequence.

11. The process of claim 10, wherein the single step sequence comprises adding $NH_2OH.HCl$ to a mixture of THF and water.

12. The process of claim 11, wherein 1 equivalent of the compound of formula 3b is combined with a 1.1 equivalents of $NH_2OH.HCl$ in a 10:1 v/v mixture of THF/water.

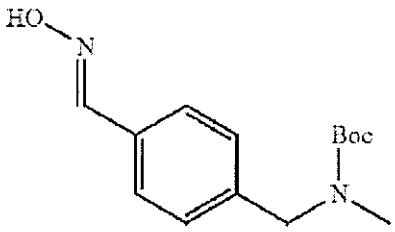
13. The process of claim 10, wherein the two step sequence consists of first converting the ketal group in the compound of formula 3b:

3b



into an aldehyde under suitable deprotection conditions, and then forming the oxime of formula 4i:

4i



under suitable oxime formation conditions.

14. The process of claim 13, wherein

a) suitable deprotection conditions comprise adding an acid, acetone, and water; and
b) suitable oxime formation conditions comprise mixing together hydroxylamine, an optional acid, an organic solvent, and water.

15. The process of claim 14, wherein the acid is p-toluenesulfonic acid (pTSA) or hydrochloric acid (HCl), the organic solvent is selected from one or more of the following: a chlorinated solvent selected from dichloromethane (DCM), dichloroethane (DCE), dichloromethane (DCM), and chloroform; an ether selected from tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF) and dioxane; or an aromatic hydrocarbon selected from toluene and xylenes.

16. The process of claim 15, wherein suitable oxime formation conditions comprise adding hydroxylamine hydrochloride to a solution of the compound of 3b in tetrahydrofuran (THF) and water.

17. The process of claim 4 wherein the suitable reductive amination conditions comprise adding a reducing agent selected from $NaBH_4$, $NaBH_3CN$, or $NaBH(OAc)_3$ in the presence of a solvent selected from dichloromethane (DCM), dichloroethane (DCE), an alcoholic solvent selected from methanol, ethanol, 1-propanol, isopropanol, or a nonprotic solvent selected from dioxane, tetrahydrofuran, or 2-methyltetrahydrofuran and optionally a base selected from triethylamine or diisopropylethylamine.

18. The process of any one of claims 1, 2, and 3-4, wherein the suitable Boc deprotection conditions comprises adding a suitable Boc deprotecting agent selected from trimethylsilyl chloride (TMS-Cl), CHl, tetrabutylammonium fluoride (TBAF), H_3PO_4, or trifluoroacetic acid (TFA) and the suitable solvent is selected from acetone, toluene, methanol, ethanol, 1-propanol, isopropanol, dichloromethane (DCM), EtOAc, isopropyl acetate, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, or diethyl ether.

19. The process of claim 18, wherein the suitable Boc deprotecting agent is HCl or trifluoroacetic acid (TFA) and the suitable solvent is acetone or dichloromethane (DCM).

20. The process of claim 3, wherein the Boc protection conditions comprise adding di-tert-butyl dicarbonate [$(Boc)_2O$], a suitable base, and a suitable solvent.

21. The process of claim 20, wherein the suitable base is selected from triethylamine, diisopropylamine, or pyridine; and the suitable solvent is selected from a chlorinated solvent, an ether, or an aromatic hydrocarbon.

22. The process of claim 21, wherein the suitable base is triethylamine, the suitable solvent is DCM, tetrahydrofuran or 2-methyltetrahydrofuran.

23. The process of claim 22, wherein the Boc protection conditions comprise adding 1.05 equivalents of $(Boc)_2O$ per equivalent of compound 2b in 2-methyltetrahydrofuran or DCM.

24. The process of claim 5, wherein the suitable metal-mediated coupling conditions are Sonogashira coupling conditions; the Boc protection conditions comprise adding $(Boc)_2O$ in 2-methyltetrahydrofuran or DCM; and the suitable TMS deprotection conditions comprise adding a suitable base, suitable organic solvent, and water.