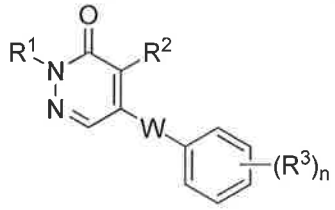
Claims

1. A method of synthesizing an imaging agent comprising the formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted;

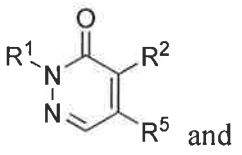
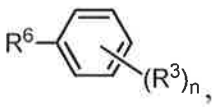
R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with an imaging moiety or heteroalkyl optionally substituted with an imaging moiety; and

n is 1, 2, 3, 4, or 5;

the method comprising steps of:

reacting precursor compounds comprising the formulae:

 and ,

wherein:

n is 1, 2, 3, 4, or 5;

R^1 is alkyl, optionally substituted;

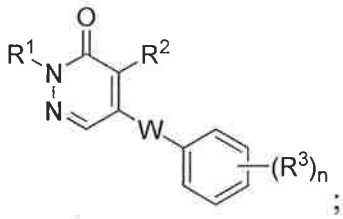
R^2 is hydrogen or halide;

R^3 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted;

R^5 is hydroxyl or halide; and

R^6 is alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted;

wherein, when R^5 is hydroxyl, at least one of R^6 and R^3 comprises a leaving group; or wherein R^5 is halide, at least one of R^6 or R^3 comprises a hydroxyl, to produce a compound comprising the formula:



;

wherein:

W is alkyl or heteroalkyl, optionally substituted;

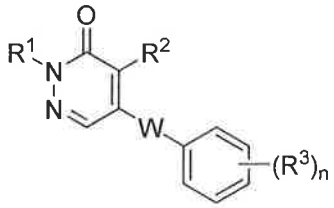
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with hydroxyl or heteroalkyl optionally substituted with hydroxyl; wherein at least one R^3 comprises hydroxyl; and

n is 1, 2, 3, 4, or 5;

reacting a compound comprising the formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

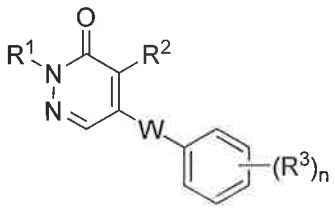
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with hydroxyl or heteroalkyl optionally substituted with hydroxyl; wherein at least one R^3 comprises hydroxyl; and

n is 1, 2, 3, 4, or 5;

with a sulfonate-containing species to produce a sulfonate-containing compound comprising the formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

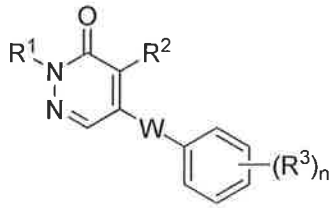
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with a sulfonate-containing group or heteroalkyl optionally substituted with a sulfonate-containing group; wherein at least one R^3 comprises a sulfonate-containing group; and

n is 1, 2, 3, 4, or 5;

replacing the sulfonate-containing group of the sulfonate-containing compound with an imaging moiety in the presence of a bicarbonate salt to yield an imaging agent comprising the formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

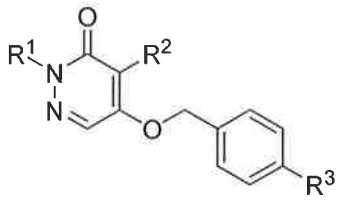
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with an imaging moiety or heteroalkyl optionally substituted with an imaging moiety; and

n is 1, 2, 3, 4, or 5; provided that at least one imaging moiety is present in the imaging agent.

2. A method of synthesizing a product comprising an ^{18}F-species, comprising reacting a compound comprising the formula:



wherein:

R^1 is alkyl;

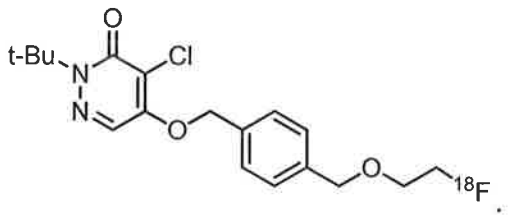
R^2 is hydrogen or halogen; and

R^3 is alkyl substituted with a sulfonate-containing group, alkoxy substituted with a sulfonate-containing group, or alkoxyalkyl substituted with a sulfonate-containing group; with an ^{18}F-containing species in the presence of a bicarbonate salt to form the product comprising the ^{18}F-species.

3. The method of claim 2, wherein the sulfonate-containing group is mesylate, tosylate, triflate, or 1,2-cyclic sulfate.

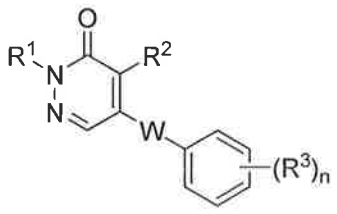
4. The method of claim 2, wherein R^1 is a methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl.

5. The method of claim 2, wherein the product comprises the formula:



6. A method of synthesizing an imaging agent precursor comprising:

reacting a compound comprising formula (III):



(III)

wherein:

W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with a leaving group or heteroalkyl optionally substituted with a leaving group; and

n is 1, 2, 3, 4, or 5;

provided at least one R^3 is substituted with a leaving group;

with a nucleophile, wherein the nucleophile replaces the leaving group to produce the imaging agent precursor.

7. A method of claim 6, wherein reacting the compound with the nucleophile occurs in the presence of a base.

8. A method of claim 7, wherein the base is a metal or metal salt.

9. A method of claim 6, wherein reacting the compound with the nucleophile occurs in the presence of a catalyst.

10. A method of claim 9, wherein the catalyst is a tetraalkylammonium iodide.

11. A method of claim 6, wherein:

W is $-O(CH_2)-$;

R^1 is *t*-butyl;

R^2 is chloride; and

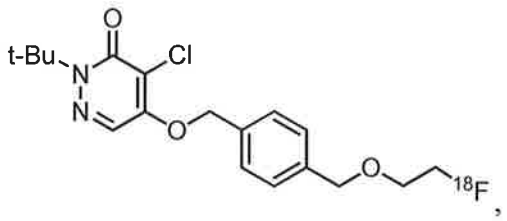
R^3 is alkyl substituted with a leaving group.

12. A method of synthesizing an imaging agent, comprising:

contacting an imaging agent precursor with a fluoride species and a bicarbonate salt under conditions that result in the fluoride species replacing the leaving group to produce an imaging agent comprising the fluoride species,

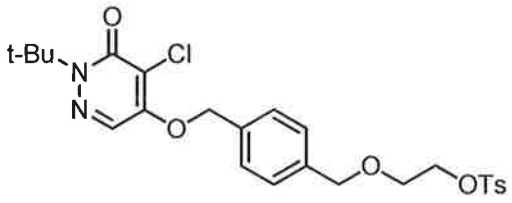
wherein the molar ratio of bicarbonate salt to imaging agent precursor is less than about 1.5:1.

13. A method of manufacturing an imaging agent comprising the formula:



wherein the method comprises,

(a) contacting a tosylate precursor comprising the structure:



with a fluoride species associated with an ammonium salt in the presence of a bicarbonate salt;

(b) heating the mixture of (a);

(c) cooling the heated mixture;

(d) adding H_2O to the cooled mixture;

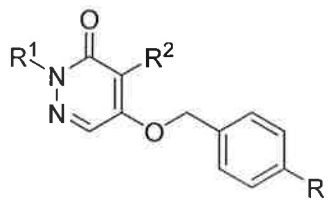
(e) purifying the mixture from the hydrated mixture of (d) using HPLC with an H_2O/MeCN eluent; and

(f) diluting the eluent with a solution of ascorbic acid or a salt thereof.

14. A method of synthesizing a fluorinated compound comprising ^{18}F, comprising:

reacting, in the presence of a bicarbonate salt, (i) a precursor of the fluorinated compound comprising an alkoxyalkyl group substituted with a halide or a sulfonate-containing group, with (ii) a salt comprising a fluoride species and weakly coordinating cation, wherein the fluoride species is enriched in ^{18}F.

15. A method of synthesizing a product comprising an ^{18}F-species, comprising reacting a compound comprising the formula:

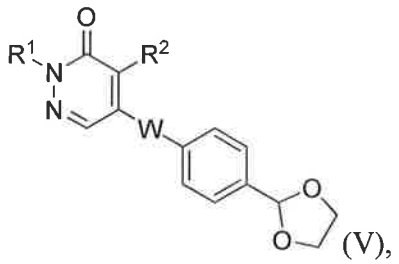


wherein R is –(lower alkyl)-sulfonate, R^1 is an C_1-C_{10} alkyl, and R^2 is H or a halogen;

with an ^{18}F-containing species in the presence of a tetraalkylammonium bicarbonate salt to form the product comprising the ^{18}F-species.

16. A method comprising:

reacting a compound comprising formula (V):



(V),

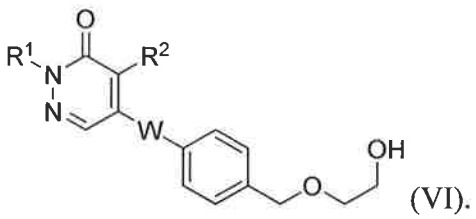
wherein:

W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted; and

R^2 is hydrogen or halide,

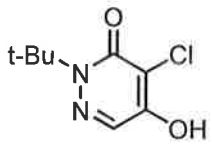
with a nucleophile or a radical species to produce a compound comprising formula (VI):



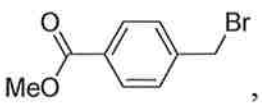
(VI).

17. A method comprising:

reacting precursor compounds comprising formulae:

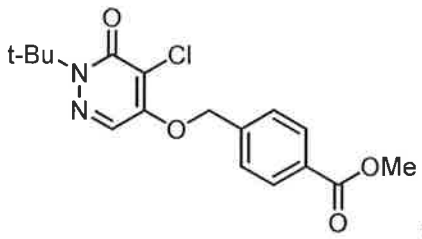


and



,

via an etherification reaction to form a first compound comprising the formula:

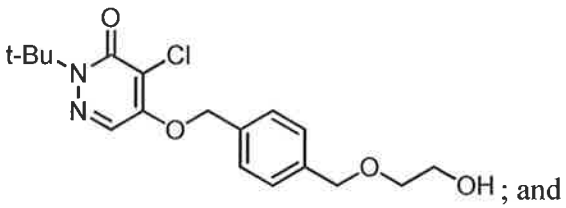


;

exposing the first compound to a reducing agent to form a second compound comprising a benzylic alcohol;

treating the second compound with phosphorus tribromide to form a third compound comprising a benzylic bromide;

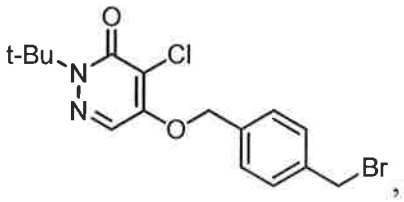
reacting the third compound with ethylene glycol to produce a fourth compound comprising the formula:



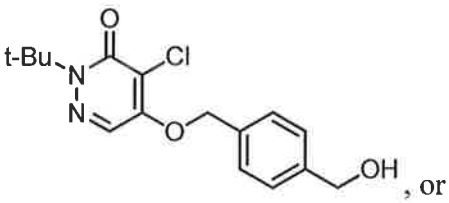
; and

reacting the fourth compound with a sulfonate-containing species to form a product comprising a sulfonate-containing precursor of an imaging agent.

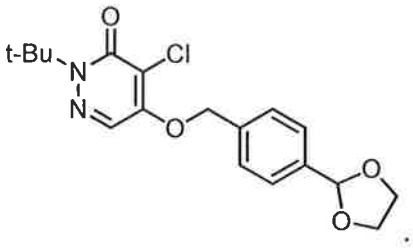
18. A compound comprising formula:



,



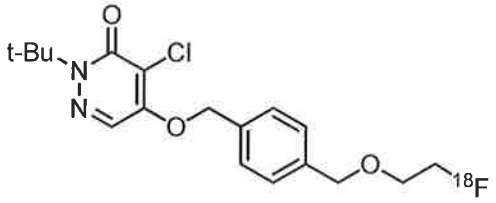
, or



19. A method of imaging a subject, comprising:

subjecting a subject to stress;

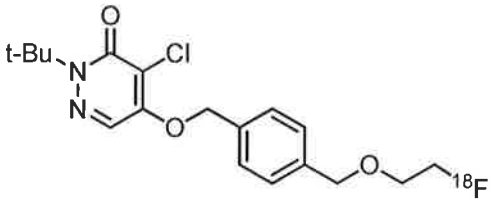
administering to the subject a dose of an imaging agent comprising the formula:



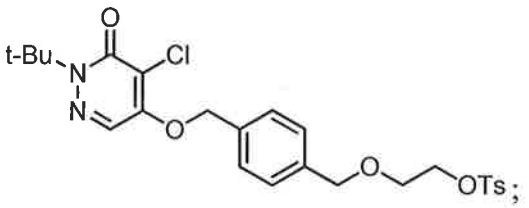
in an amount less than about 20 mCi; and

acquiring at least one first image of a portion of the subject.

20. A cassette for the preparation of an imaging agent comprising the formula:



comprising: (i) a vessel containing an imaging agent precursor comprising the formula:

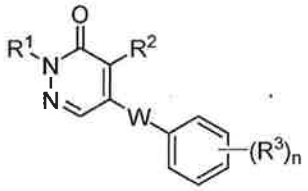


and (ii) a conduit for adding a source of ^{18}F.

Claims

What is claimed:

1. A method of synthesizing an imaging agent comprising formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

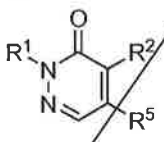
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

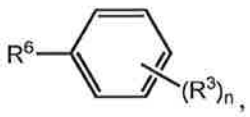
each R^3 can be the same or different and is alkyl optionally substituted with an imaging moiety or heteroalkyl optionally substituted with an imaging moiety; and

n is 1, 2, 3, 4, or 5; the method comprising steps of:

etherification of precursor compounds comprising formulae:



and



wherein:

n is 1, 2, 3, 4, or 5;

R^1 is alkyl, optionally substituted;

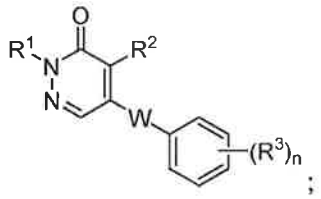
R^2 is hydrogen or halide;

R^3 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted,

R^5 is hydroxyl or halide; and

R^6 is alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted,

wherein, when R^5 is hydroxyl, at least one of R^6 and R^3 comprises a leaving group; or wherein R^5 is halide, at least one of R^6 or R^3 comprises a hydroxyl, to produce a compound comprising formula:



;

wherein:

W is alkyl or heteroalkyl, optionally substituted;

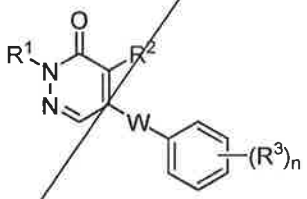
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with hydroxyl or heteroalkyl optionally substituted with hydroxyl; wherein at least one R^3 comprises hydroxyl; and

n is 1, 2, 3, 4, or 5;

reacting a compound comprising formula:



wherein:

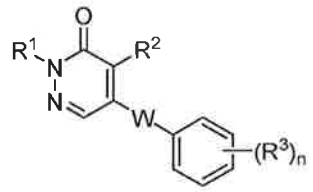
W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with hydroxyl or heteroalkyl optionally substituted with hydroxyl; wherein at least one R^3 comprises hydroxyl; and

n is 1, 2, 3, 4, or 5; with a sulfonate-containing species to produce a sulfonate-containing compound comprising formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

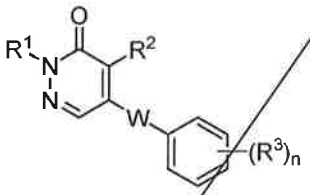
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with a sulfonate-containing group or heteroalkyl optionally substituted with a sulfonate-containing group; wherein at least one R^3 comprises a sulfonate-containing group; and

n is 1, 2, 3, 4, or 5;

replacing the sulfonate-containing group of the sulfonate-containing compound with an imaging moiety to yield a compound comprising formula:



wherein:

W is alkyl or heteroalkyl, optionally substituted;

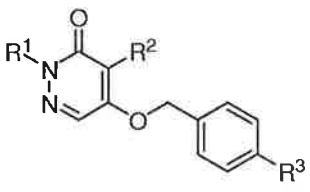
R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with an imaging moiety or heteroalkyl optionally substituted with an imaging moiety; and

n is 1, 2, 3, 4, or 5; provided that at least one fluorine species is present in the compound.

2. A method for ^{18}F-labeling a compound comprising formula:



wherein:

R^1 is alkyl;

R^2 is hydrogen or halogen; and

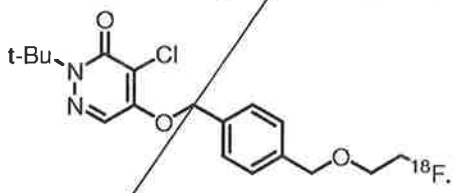
R^3 is alkyl substituted with a sulfonate-containing group, alkoxy substituted with a sulfonate-containing group, or alkoxyalkyl substituted with a sulfonate-containing group, comprising:

reacting the compound with an ^{18}F species in the presence of an ammonium salt or a bicarbonate salt to form a product comprising the ^{18}F species.

3. The method of claim 2, wherein the sulfonate-containing group is mesylate, tosylate, triflate, or 1,2-cyclic sulfate.

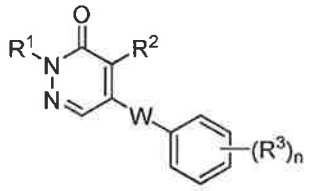
4. The method of claim 2, wherein R^1 is a methyl, ethyl, propyl, *n*-butyl, *s*-butyl, or *t*-butyl.

5. The method of claim 2, wherein the product comprising formula:



6. A method for synthesizing a precursor to an imaging agent comprising:

reacting a compound comprising formula (III):



(III)

wherein:

W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

each R^3 can be the same or different and is alkyl optionally substituted with a leaving group or heteroalkyl optionally substituted with a leaving group; and

n is 1, 2, 3, 4, or 5;

provided at least one R^3 is substituted with a leaving group;

with a nucleophile, wherein the nucleophile replaces the at least one leaving group to produce the precursor.

7. A method of claim 6, wherein reacting the compound with the nucleophile occurs in the presence of a base.

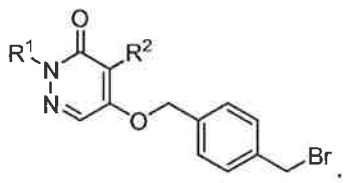
8. A method of claim 7, wherein the base is a metal or metal salt.

9. A method of claim 6 or 7, wherein reacting the compound with the nucleophile occurs in the presence of a catalyst.

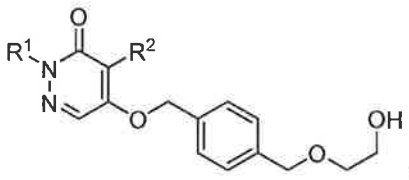
10. A method of claim 9, wherein the catalyst is a tetraalkylammonium iodide.

11. A method of claim 6, wherein:
W is $-O(CH_2)-$;
R^1 is *t*-butyl;
R^2 is chloride; and
R^3 is alkyl substituted with a leaving group.

12. A method of claim 6, wherein the compound comprising formula (III) comprises the structure:



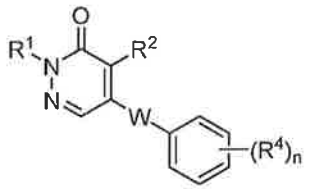
13. A method of claim 6, wherein the precursor comprises the structure:



14. A method of claim 12 or 13, wherein R^1 is *t*-butyl; and R^2 is Cl.

15. A method of claim 6, further comprising:

reacting a compound comprising formula (IV):



(IV)

wherein:

R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

W is alkyl or heteroalkyl, optionally substituted;

each R^4 can be the same or different and is alkyl optionally substituted with hydroxyl or heteroalkyl optionally substituted with hydroxyl; and

n is 1, 2, 3, 4, or 5;

provided at least one R^4 is substituted with hydroxyl;

with a reactant comprising a leaving group to produce a compound comprising formula (III), wherein the at least one hydroxyl is replaced with the leaving group.

16. A method of claim 15, wherein reacting the compound comprising formula (IV) is performed in the presence of a halogenation reagent.

17. A method of claim 16, wherein the halogenation reagent is a brominating reagent.

18. A method of claim 17, wherein the brominating reagent is phosphorus tribromide, pyridinium dibromide, or a combination of carbon tetrabromide and triphenylphospine.

19. A method of claim 15, wherein:

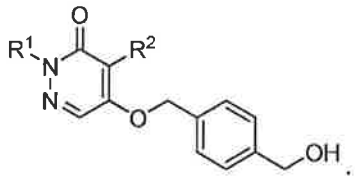
W is $-O(CH_2)-$;

R^1 is *t*-butyl;

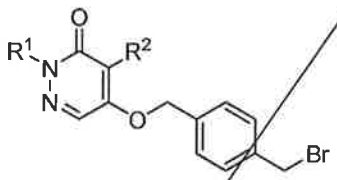
R^2 is chloride; and

R^4 is alkyl substituted with hydroxyl.

20. A method of claim 15, wherein the compound comprising formula (IV) comprises the structure:

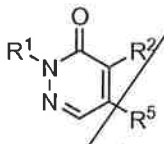
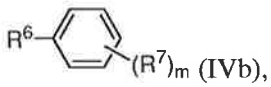


21. A method of claim 15, wherein the product comprises the structure:



22. A method of claim 20 or 21, wherein R^1 is *t*-butyl and R^2 is Cl.

23. A method of claim 15, wherein the compound comprising formula (IV) is formed by etherification of precursor compounds comprising formulae (IVa) and (IVb):

 (IVa) and  (IVb),

wherein:

m is 1, 2, 3, 4, or 5 or greater;

R^1 is alkyl, optionally substituted;

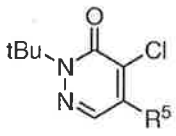
R^2 is hydrogen or halide;

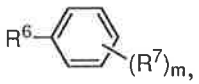
R^5 is hydroxyl or halide; and

R^6 and R^7 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted,

wherein, when R^5 is hydroxyl, at least one of R^6 and R^7 comprises a leaving group or a group that can be replaced by a leaving group or when R^5 is halide, at least one of R^6 and R^7 comprise a hydroxyl.

24. A method of claim 15, wherein the compound comprising formula (IV) is formed by etherification of the compounds comprising formulae:



and


wherein:

m is 1 or greater;

R^1 is alkyl, optionally substituted;

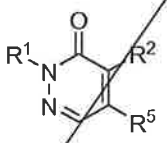
R^2 is hydrogen or halide;

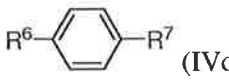
R^5 is hydroxyl or halide; and

R^6 and R^7 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, any of which may be substituted,

wherein, when R^5 is hydroxyl, at least one of R^6 and R^7 comprises a leaving group or a group that can be replaced by a leaving group, or when R^5 is halide, at least one of R^6 and R^7 comprises a hydroxyl.

25. A method of claim 15, wherein the compound comprising formula (IV) is formed by etherification of precursor compounds comprising formulae (IVa) and (IVd):



(IVa) and


(IVd),

wherein:

R^1 is alkyl, optionally substituted;

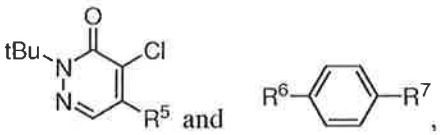
R^2 is hydrogen or halide;

R^5 is hydroxyl or halide; and

R^6 and R^7 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, each optionally substituted,

wherein, when R^5 is hydroxyl, at least one of R^6 and R^7 comprises a leaving group, or when R^5 is halide, at least one of R^6 and R^7 comprises a hydroxyl.

26. A method of claim 15, wherein the compound comprising formula (IV) is formed by etherification of compounds comprising formulae:



wherein:

R^1 is alkyl, optionally substituted;

R^2 is hydrogen or halide;

R^5 is hydroxyl or halide; and

R^6 and R^7 can be the same or different and are alkyl, heteroalkyl, or a carbonyl-containing group, any of which may be substituted,

wherein, when R^5 is hydroxyl, at least one of R^6 and R^7 comprises a leaving group, or when R^5 is halide, at least one of R^6 and R^7 comprises a hydroxyl.

27. A method of claim 26, wherein etherification comprises reacting the precursor compounds in the presence of a base.

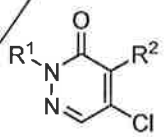
28. A method of claim 27, wherein the base comprises a carbonate ion.

29. A method of any one of claims 25-28, wherein:

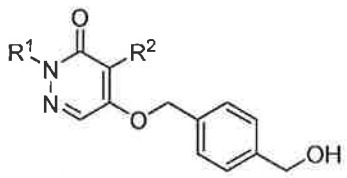
R^5 is halide; and

R^6 and R^7 are each substituted alkyl.

30. A method of claim 15, wherein the compound comprising formula (IV) is synthesized by etherification of precursor compounds comprising formulae:

 (IVe) and  (IVf)

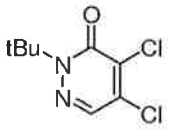
to form a product comprising formula:

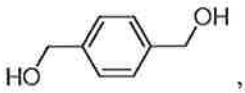


wherein R^1 is alkyl, optionally substituted; and

R^2 is hydrogen or halide.

31. A method of claim 15, wherein the compound comprising formula (IV) is synthesized by etherification of compounds comprising formulae:



and 

,

to form a product comprising formula:



.

32. A method of claim 24 or 25, wherein:

R^5 is hydroxyl;

R^6 is a carbonyl-containing group; and

R^7 is a substituted alkyl.

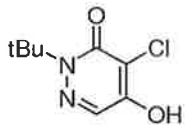
33. A method of claim 24 or 25, wherein:

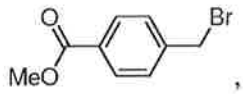
R^5 is hydroxyl;

R^6 is an ester; and

R^7 is alkyl substituted with a leaving group.

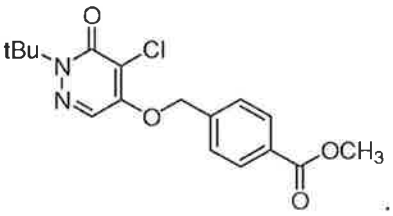
34. A method of claim 15, wherein the compound comprising formula (IV) is synthesized by etherification of the compounds comprising formulae:



and 

,

to form a product comprising the formula:



.

35. A method of claim 34, further comprising the act of exposing the product to a reducing agent to convert the ester group to an alcohol.

36. A method for synthesizing an imaging agent, comprising:

contacting an imaging agent precursor with a fluoride species and an ammonium salt under conditions that result in the fluoride species replacing the leaving group to produce an imaging agent comprising the fluoride species wherein the molar ratio of ammonium salt to imaging agent precursor is less than about 1.5:1.

37. A method of claim 36, wherein the molar ratio of ammonium salt to imaging agent precursor is about 1:1 or less, or about 0.75:1 or less, or about 0.5:1 or less, or about 0.25:1 or less, or about 0.05:1 or less.

38. A method of claim 36, wherein the molar ratio of ammonium salt to imaging agent precursor is from about 0.5:1 to about 1:1.

39. A method of claim 36, wherein the ammonium salt is an ammonium bicarbonate salt, ammonium hydroxide salt, ammonium acetate salt, ammonium lactate salt, ammonium trifluoroacetate salt, ammonium methanesulfonate salt, ammonium p-toluenesulfonate salt, ammonium nitrate salt, ammonium iodide salt, or ammonium bisulfate salt.

40. A method of claim 36, wherein the ammonium salt is a tetraalkylammonium salt.

41. A method for synthesizing an imaging agent, comprising:

contacting an imaging agent precursor with a fluoride species and a bicarbonate salt under conditions that result in the fluoride species replacing the leaving group to produce an imaging agent comprising the fluoride species,

wherein the molar ratio of bicarbonate salt to imaging agent precursor is less than about 1:5:1.

42. A method of claim 41, wherein the molar ratio of bicarbonate salt to imaging agent precursor is about 1:1 or less, or about 0.75:1 or less, or about 0.5:1 or less, or about 0.25:1 or less, or about 0.05:1 or less.

43. A method of claim 41, wherein the molar ratio of bicarbonate salt to imaging agent precursor is from about 0.5:1 to about 1:1.

44. A method of claim 41, wherein the bicarbonate salt is a metal bicarbonate.

45. A method of claim 41, wherein the bicarbonate salt is sodium bicarbonate, calcium bicarbonate, potassium bicarbonate, or magnesium bicarbonate.

46. A method of claim 41, wherein the bicarbonate salt is an ammonium bicarbonate.

47. A method of claim 41, wherein the bicarbonate salt is an tetraalkylammonium bicarbonate.

48. A method of claim 36 or 41, wherein the ammonium salt or the bicarbonate salt comprising the formula:

$$R_4NHCO_3,$$

wherein R is alkyl.

49. A method of claim 36 or 41, wherein the ammonium salt or the bicarbonate salt is Et_4NHCO_3.

50. A method of claim 41, wherein the imaging agent precursor is further exposed to a cryptand.

51. A method of claim 41, wherein the contacting is performed in the absence of a carbonate salt.

52. A method of claim 41, wherein the contacting is performed in the absence of a cryptand.

53. A method for synthesizing an imaging agent, comprising:

contacting an imaging agent precursor with a fluoride species under conditions that result in the fluoride species replacing the leaving group to produce an imaging agent comprising the fluoride species,

wherein the contacting is performed at a pH below 7, or at a pH below 6, or at a pH below 5.

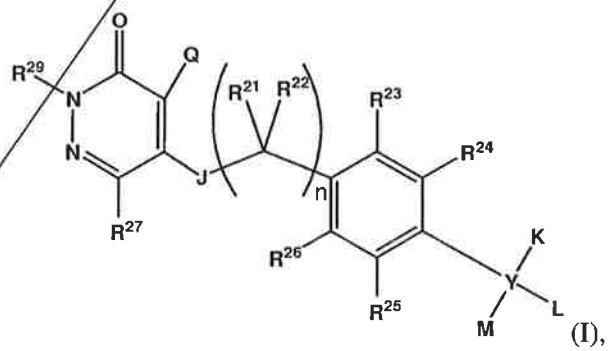
54. A method of claim 53, wherein the contacting is performed at a pH between 5 and 6.

55. A method of claim 53, wherein the leaving group is a sulfonate-containing group.

56. A method of claim 53, wherein the leaving group is a mesylate, tosylate, triflate, or 1,2,-cyclic sulfate group.

57. A method of claim 53, wherein the fluoride species is an ^{18}F ion.

58. A method of claim 53, wherein the imaging agent precursor comprising formula (I):



(I),

wherein:

J is selected from the group consisting of $N(R^{28})$, S, O, C(=O), C(=O)O, $NHCH_2CH_2O$, a bond, and $C(=O)N(R^{27})$;

when present, K is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with a leaving group, alkyloxy optionally substituted with a leaving group, aryl optionally substituted with a leaving group, C_1-C_6 alkyl optionally

substituted with a leaving group, heteroaryl optionally substituted with a leaving group, and a leaving group;

when present, L is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with a leaving group, alkyloxy optionally substituted with a leaving group, aryl optionally substituted with a leaving group, C_1-C_6 alkyl optionally substituted with a leaving group, heteroaryl optionally substituted with a leaving group, and a leaving group;

M is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with a leaving group, alkyloxy optionally substituted with a leaving group, aryl optionally substituted with a leaving group, C_1-C_6 alkyl optionally substituted with a leaving group, heteroaryl optionally substituted with a leaving group, and a leaving group; or

L and M, together with the atom to which they are attached, may form a three-, four-, five-, or six-membered carbocyclic ring;

Q is halo or haloalkyl;

n is 0, 1, 2, or 3;

R^{21}, R^{22}, R^{27}, and R^{28} are independently selected from hydrogen, C_1-C_6 alkyl optionally substituted with a leaving group, and a leaving group;

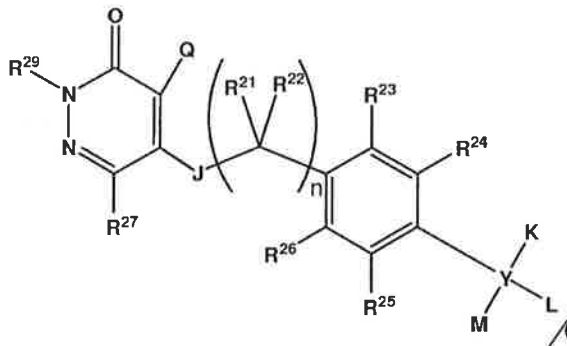
R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from hydrogen, halogen, hydroxyl, alkyloxy, C_1-C_6 alkyl optionally substituted with a leaving group, and a leaving group;

R^{29} is C_1-C_6 alkyl optionally substituted with a leaving group;

Y is selected from the group consisting of a bond, carbon, and oxygen; provided that when Y is a bond, K and L are absent, and M is selected from the group consisting of aryl optionally substituted with a leaving group and heteroaryl optionally substituted with a leaving group; and provided that when Y is oxygen, K and L are absent, and M is selected from hydrogen, alkoxyalkyl optionally substituted with a leaving group, aryl optionally substituted with a leaving group, C_1-C_6 alkyl optionally substituted with a leaving group, and heteroaryl optionally substituted with a leaving group;

provided that at least one leaving group is present in formula (I).

59. A method of claim 58, wherein the imaging agent comprising formula (II):



(II),

wherein:

J is selected from the group consisting of $N(R^{28})$, S, O, C(=O), C(=O)O, $NHCH_2CH_2O$, a bond, and $C(=O)N(R^{27})$;

when present, K is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with an imaging moiety, alkyloxy optionally substituted with an imaging moiety, aryl optionally substituted with an imaging moiety, C_1-C_6 alkyl optionally substituted with an imaging moiety, heteroaryl optionally substituted with an imaging moiety, and an imaging moiety;

when present, L is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with an imaging moiety, alkyloxy optionally substituted with an imaging moiety, aryl optionally substituted with an imaging moiety, C_1-C_6 alkyl optionally substituted with an imaging moiety, heteroaryl optionally substituted with an imaging moiety, and an imaging moiety;

M is selected from the group consisting of hydrogen, alkoxyalkyl optionally substituted with an imaging moiety, alkyloxy optionally substituted with an imaging moiety, aryl optionally substituted with an imaging moiety, C_1-C_6 alkyl optionally substituted with an imaging moiety, heteroaryl optionally substituted with an imaging moiety, and an imaging moiety; or

L and M, together with the atom to which they are attached, may form a three-, four-, five-, or six-membered carbocyclic ring;

Q is halo or haloalkyl;

n is 0, 1, 2, or 3;

R^{21}, R^{22}, R^{27}, and R^{28} are independently selected from hydrogen, C_1-C_6 alkyl optionally substituted with an imaging moiety, and an imaging moiety;

R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from hydrogen, halogen, hydroxyl, alkyloxy, C_1-C_6 alkyl optionally substituted with an imaging moiety, and an

imaging moiety;

R^{29} is C_1-C_6 alkyl optionally substituted with an imaging moiety; and

Y is selected from the group consisting of a bond, carbon, and oxygen; provided that when Y is a bond, K and L are absent, and M is selected from the group consisting of aryl optionally substituted with an imaging moiety and heteroaryl optionally substituted with an imaging moiety; and provided that when Y is oxygen, K and L are absent, and M is selected from hydrogen, alkoxyalkyl optionally substituted with an imaging moiety, aryl optionally substituted with an imaging moiety, C_1-C_6 alkyl optionally substituted with an imaging moiety, and heteroaryl optionally substituted with an imaging moiety;

provided that at least one imaging moiety is present in formula (II).

60. A method of claim 58, wherein J is O.

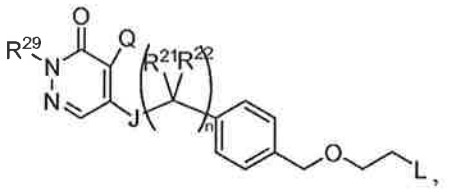
61. A method of claim 58, wherein R^{29} is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, or *t*-butyl, each optionally substituted with a leaving group.

62. A method of claim 58, wherein Q is chloro.

63. A method of claim 58, wherein each of R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, and R^{27} are hydrogen.

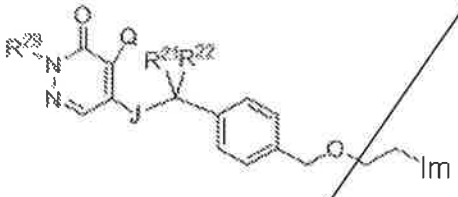
64. A method of claim 58, wherein Y is carbon, K and L are hydrogen, and M is selected from the group consisting of alkoxyalkyl optionally substituted with a leaving group, alkyloxy optionally substituted with a leaving group, aryl optionally substituted with a leaving group, C_1-C_6 alkyl optionally substituted with a leaving group, heteroaryl optionally substituted with a leaving group, and a leaving group.

65. A method of claim 58, wherein the imaging agent precursor comprises the formula:



wherein L is a leaving group.

66. A method of claim 59, wherein the imaging agent comprises the formula:



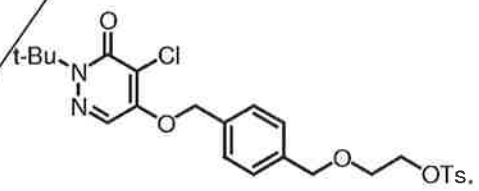
(X),

wherein Im is an imaging moiety.

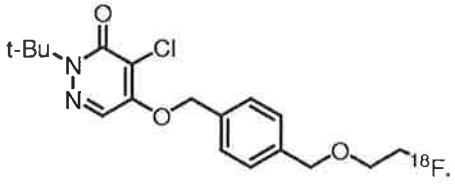
67. A method of claim 65, wherein J is O, and R^{21} and R^{22} is each H.

68. A method of claim 66, wherein J is O, and R^{21} and R^{22} is each H.

69. A method of claim 66, wherein the imaging agent precursor comprises the formula:



70. A method of claim 66, wherein the imaging agent comprises the formula:



71. A method of claim 66, further comprising:

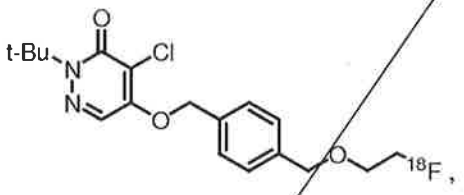
purifying the imaging agent using at least one purification technique.

72. A method of claim 66, further comprising:

combining the imaging agent with a stabilizing agent.

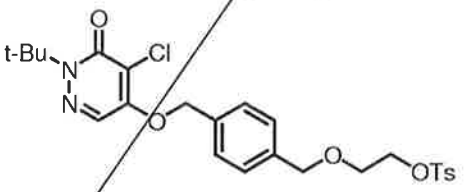
73. A method of claim 72, wherein the stabilizing agent is ascorbic acid or a salt thereof.

74. A method for manufacturing an imaging agent comprises the formula:



the method comprising,

(a) contacting a tosylate precursor comprising the structure:



with an anhydrous fluoride species associated with an ammonium salt;

(b) heating the mixture of (a);

(c) cooling the heated mixture;

(d) adding H_2O to the cooled mixture;

(e) purifying the mixture from the hydrated mixture of (d) using HPLC with an H_2O/MeCN eluent; and

(f) diluting the eluent with a solution of ascorbic acid or a salt thereof.

75. The method of claim 74, wherein step (b) comprises heating the mixture to a temperature between 50 °C and 250 °C.

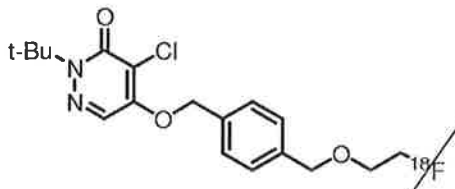
76. The method of claim 74 or 75, wherein heating step (b) comprises heating the mixture for less than 5 minutes, less than 10 minutes, less than 20, minutes, or less than 30 minutes.

77. The method any one of claims 74-76, further comprising:

(g) contacting the diluted eluent of (f) with a C18 resin;

(h) washing the contacted C18 resin with a solution of ascorbic acid or a salt thereof;

(i) eluting



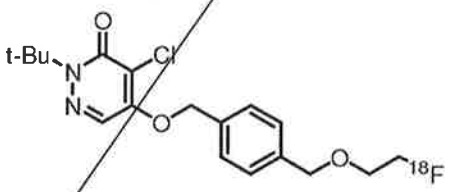
from the C18 resin with absolute ethanol; and

(j) diluting the eluent of (i) with a solution of ascorbic acid or a salt thereof.

78. The method of claim 77, further comprising:

(k) aseptically filtering the diluted eluent of (j), and

(l) optionally, determining the presence of



in a sample of the aseptic filtrate of (k).

79. An imaging agent made by a method of claim 74.

80. A method for synthesizing a fluorinated compound, comprising:

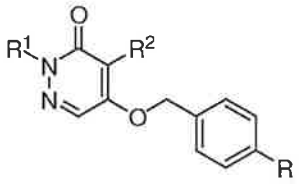
reacting, in the presence of a carbonate or bicarbonate, (i) a precursor of the fluorinated compound comprising an alkoxyalkyl group substituted with a halide or a sulfonate-containing group, with (ii) a salt comprising a fluoride species and weakly coordinating cation.

81. The method of claim 80, wherein the alkoxyalkyl group is substituted with a sulfonate-containing group.

82. The method of claim 80, wherein the weakly coordinating cation is a tetraalkylammonium cation.

83. The method of claim 80, wherein the fluoride is enriched with ^{18}F isotope.

84. A method for ^{18}F-labeling a compound comprising the formula:



wherein R is –(lower alkyl)-sulfonate, R^1 is an C_1-C_{10} alkyl, and R^2 is H or a halogen, comprising reacting the compound with ^{18}F in the presence of a tetraalkylammonium bicarbonate or tetraalkylammonium carbonate.

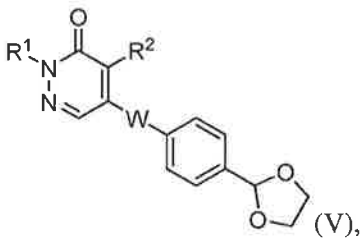
85. The method of claim 84, wherein R is $-(CH_2)O(CH_2)_n$-sulfonate-containing group, wherein n is an integer from 1 to 5.

86. The method of claim 84, wherein the sulfonate-containing group is mesylate, tosylate, triflate, or 1,2-cyclic sulfate.

87. The method of any of claims 84-86, wherein R^2 is a halogen.

88. The method of any of claims 84-87, wherein R^1 is methyl, ethyl, propyl or butyl.

89. A method for synthesizing a precursor to an imaging agent, comprising:
reacting a compound comprising formula (V):



(V),

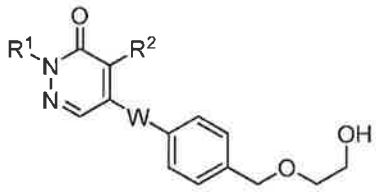
wherein:

W is alkyl or heteroalkyl, optionally substituted;

R^1 is alkyl, optionally substituted; and

R^2 is hydrogen or halide,

with a nucleophile or a radical species to produce a compound comprising formula (VI):



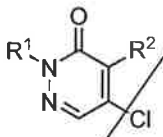
(VI).

90. A method of claim 89, wherein the nucleophile is a hydride ion.

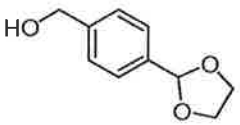
91. A method of claim 90, wherein the hydride is generated from diisobutylaluminum hydride.

92. A method of claim 89, wherein the radical species is H•.

93. A method of claim 89, wherein the compound comprising formula (V) wherein W is $-O(CH_2)-$ is synthesized by etherification of precursor compounds comprising formulae (Va) and (Vb):

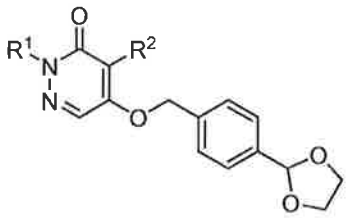


(Va) and



(Vb)

to form a product comprising formula:



wherein R^1 is alkyl, optionally substituted; and

R^2 is hydrogen or halide,.

94. A method of claim 93 or 94, wherein R^1 is *t*-butyl and R^2 is Cl.

95. A method of claim 93 or 94, wherein etherification comprises reacting the precursor compounds in the presence of a base.

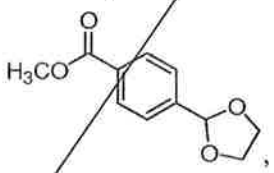
96. A method of claim 95, wherein the base comprises a carbonate ion.

97. A method of claim 95, wherein the base comprises a hydroxide ion.

98. A method of claim 97, wherein the base is sodium hydroxide or tetramethyl ammonium hydroxide.

99. A method of claim 93 or 94, wherein the etherification reaction comprises exposure to sodium hydroxide and benzyl triethylammonium chloride.

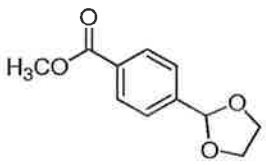
100. A method of claim 93, wherein the compound comprising formula (Vb) is produced by exposing the compound comprising formula:



to a reducing agent.

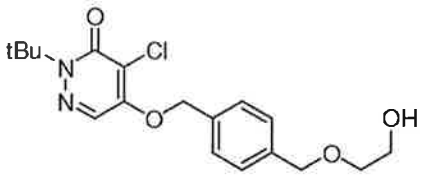
101. A method of claim 100, wherein the reducing agent is lithium aluminum hydride or lithium borohydride.

102. A method of claim 100, wherein the compound comprises formula:



is produced by reacting methyl 4-formyl benzoate with ethylene glycol in the presence of an acid.

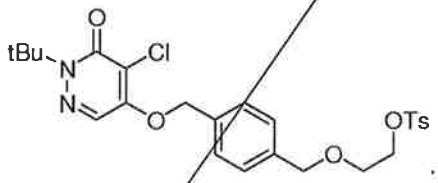
103. A method for forming a sulfonate-containing precursor of an imaging agent, comprising reacting a compound comprising formula:



with a sulfonate-containing species to form a product comprising a sulfonate-containing precursor of an imaging agent.

104. A method of claim 103, wherein the sulfonate-containing group is mesylate, tosylate, or triflate.

105. A method of claim 103, wherein the sulfonate-containing precursor of an imaging agent comprises formula:

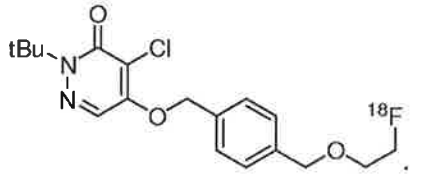


106. A method of claims 103, 104, or 105, further comprising reacting the sulfonate-containing precursor with an imaging moiety to form an imaging agent.

107. A method of claim 106, wherein the imaging moiety is a radioisotope.

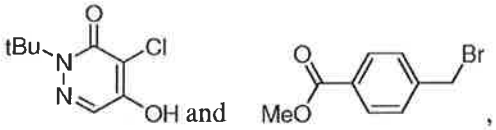
108. A method of claim 107, wherein the imaging moiety is ^{11}C, ^{13}N, ^{18}F, ^{123}I, ^{125}I, ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, or ^{68}Ga.

109. A method of claim 106, wherein the imaging agent comprises formula:

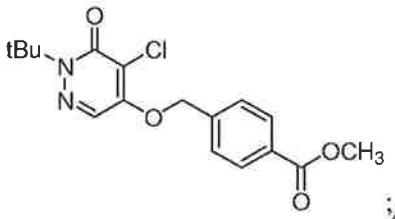


110. A method for synthesizing an imaging agent, comprising:

reacting precursor compounds comprising formulae:



via an etherification reaction to form a first compound comprising the formula:

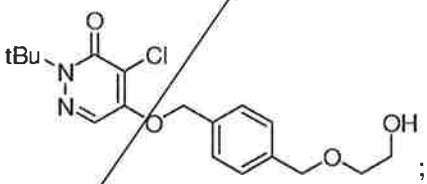


;

exposing the first compound to a reducing agent to form a second compound comprising a benzylic alcohol;

treating the second compound with phosphorus tribromide to form a third compound comprising a benzylic bromide;

reacting the third compound with ethylene glycol to produce a fourth compound comprising the formula:

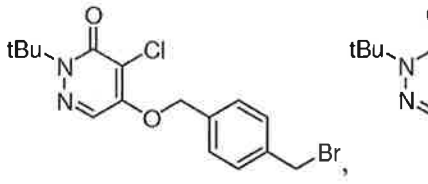


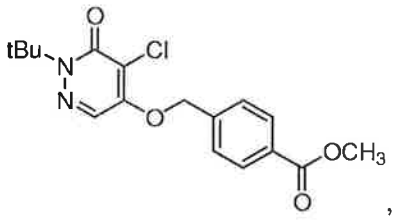
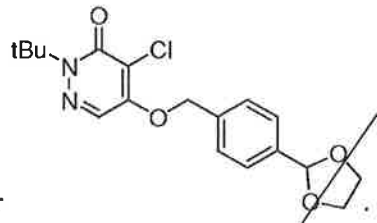
; and

reacting the fourth compound with a sulfonate-containing species to form a product comprising a sulfonate-containing precursor of an imaging agent.

111. The method of claim 110, further comprising reacting the sulfonate-containing precursor of an imaging agent with an imaging moiety to form the imaging agent.

112. A compound comprising formula:

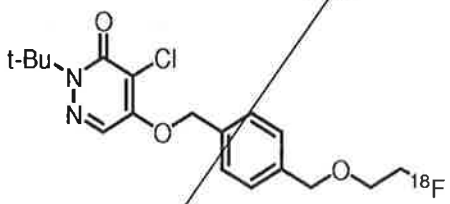


, or .

113. A method of imaging a subject, comprising:

administering to a subject a first dose of imaging agent comprising the formula:



in an amount between about 1 mCi and about 4 mCi;

acquiring at least one first image of a portion of the subject;

subjecting the subject to stress;

administering to the subject undergoing stress a second dose of the imaging agent in an amount greater than the first dose of the imaging agent by at least about 1.5 times the first dose of the imaging agent; and

acquiring at least one second image of the portion of the subject.

114. The method of claim 113, wherein the second dose of the imaging agent is administered within less than about 48 hours, about 24 hours, about 18 hours, about 12 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 30 minutes, or about 15 minutes after acquiring the at least one first image.

115. The method of claim 113, wherein the second dose of the imaging agent is at least about 2.0 times greater than the first dose of the imaging agent.

116. The method of claim 113, wherein the first image is obtained during an image acquisition period between about 1 and about 20 minutes.

117. The method of claim 113, wherein the second image is obtained during an image acquisition period between about 1 and about 20 minutes.

118. The method of claim 113, wherein the portion of the subject is at least a portion of the cardiovascular system.

119. The method of claim 118, wherein the portion of the cardiovascular system is at least a portion of the heart.

120. The method of claim 113, wherein the acquiring employs positron emission tomography.

121. The method of claim 113, further comprising determining the presence or absence of a cardiovascular disease or condition in the subject.

122. The method of claim 121, wherein the cardiovascular disease is coronary artery disease or myocardial ischemia.

123. The method of claim 113, wherein the imaging agent is administered as a formulation comprising water, less than about 5% ethanol, and less than about 50 mg/mL sodium ascorbate.

124. The method of claim 123, wherein the formulation comprising the imaging agent is administered via an intravenous bolus injection.

125. The method of claim 113, wherein the stress is induced by exercising the subject.

126. The method of claim 125, wherein the second dose of the imaging agent is administered during the exercise.

127. The method of claim 125, wherein the wait time between acquiring at least one first image of a portion of the subject and administering to the subject a second dose of the imaging agent is about 60 minutes.

128. The method of claim 113, wherein the second dose of the imaging agent is administered in an amount that is at least about 2.5, or at least about 3.0 times greater than the first dose of the imaging agent.

129. The method of claim 128, wherein the second dose of the imaging agent is administered in an amount between about 2.5 and about 5.0, or about 2.5 and about 4.0, or about 3.0 and about 4.0, or about 3.0 and about 5.0 times greater than the first dose of the imaging agent.

130. The method of claim 125, wherein the second dose of the imaging agent is between about 8.6 mCi and about 9.0 mCi, or between about 9.0 and about 9.5 mCi, or between about 8.6 mCi and about 9.5 mCi.

131. The method of claim 113, wherein the stress is pharmacological stress.

132. The method of claim 131, wherein the pharmacological stress is induced by administering a pharmacological stress agent to the subject.

133. The method of claim 132, wherein the pharmacological stress agent is a vasodilator.

134. The method of claim 133, wherein the vasodilator is adenosine, regadenoson, and apadenoson.

135. The method of claim 131, wherein the second dose of the imaging agent is administered after the subject has been administered the pharmacological stress agent.

136. The method of claim 131, wherein the second dose of the imaging agent is administered when the subject is at peak vasodilation from the pharmacological stress agent.

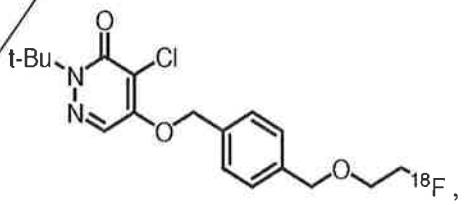
137. The method of claim 113, wherein the first dose of the imaging agent is between about 2.0 mCi to about 3.5 mCi.

138. The method of claim 137, wherein the first dose of the imaging agent is between about 2.4 mCi to about 2.9 mCi, or between about 2.5 mCi to about 3.0 mCi, or between about 2.5 mCi and about 3.5 mCi.

139. The method of claim 138, wherein the second dose of the imaging agent is between about 5.7 mCi and about 6.2 mCi, or between about 6.0 mCi and about 6.5 mCi, and about 5.7 mCi and about 6.5 mCi.

140. The method of claim 113, wherein the total of the first and second dose of the imaging agent does not exceed about 14 mCi.

141. A syringe comprising a composition comprising the imaging agent comprising the formula:



wherein the syringe adsorbs less than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13% 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0.5% of the imaging agent.

142. The syringe of claim 141, wherein the syringe comprises a plunger that adsorbs less than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13% 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0.5% of the imaging agent.

143. The syringe of claim 141, wherein the syringe comprises a plunger that is not rubber-tipped.

144. The syringe of claim 141, wherein the syringe further comprises sodium ascorbate, ethanol, and water.

145. The syringe of claim 142, wherein the imaging agent is in a solution comprising less than 4% ethanol and less than 50 mg/mL sodium ascorbate in water.

146. The syringe of claim 141, wherein the imaging agent in the syringe is between about 1.5 and about 14 mCi.

147. The syringe of claim 141, wherein the syringe comprises no rubber, and no silicon lubricants.

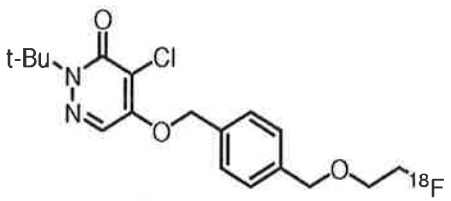
148. The syringe of claim 141, wherein the syringe is a non-reactive syringe.

149. The syringe of claim 142, wherein the syringe adsorbs between about 1% and about 20%, or between about 5% and about 15%, or between about 1% and about 15%, or between 2% and about 10%, or between about 5% and about 20%.

150. A method of imaging a subject, comprising:

subjecting a subject to stress;

administering to the subject a first dose of an imaging agent comprising the formula:



in an amount between about 1 mCi and about 4 mCi;

acquiring at least one first image of a portion of the subject;

administering to the subject a second dose of the imaging agent in an amount greater than the first dose of the imaging agent; and

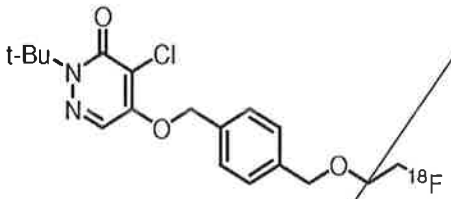
acquiring at least one second image of the portion of the subject.

151. The method of claim 150, wherein the amount of the second dose is more than about 1.5 times the amount of the first dose.

152. A method of imaging a subject, comprising:

subjecting a subject to stress;

administering to the subject a dose of an imaging agent comprising the formula:



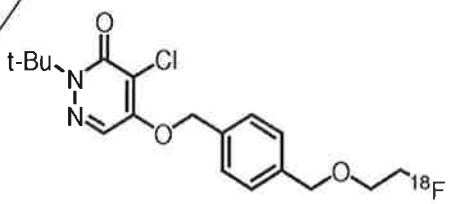
in an amount less about 20 mCi; and

acquiring at least one first image of a portion of the subject.

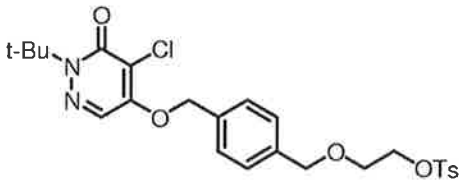
153. The method of claim 152, wherein the amount of the dose is less than about 14 mCi.

154. The method of claim 152, wherein the amount of the dose is between about 1 mCi and about 4 mCi.

155. A cassette for the preparation of an imaging agent comprising the formula:



comprising: (i) a vessel containing an imaging agent precursor comprising the formula:,



and (ii) a conduit for adding a source of ^{18}F.

156. An automated reaction system, comprising:

the cassette of claim 155.

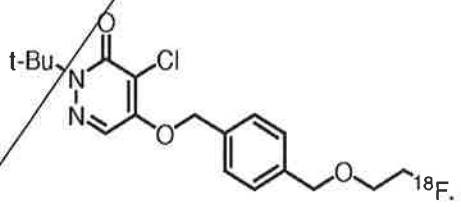
157. An apparatus for synthesizing an imaging agent comprising a linear arrangement of a plurality of stopcock manifolds connected to one or more of the components selected from the group consisting of a $[^{18}O]H_2O$ recovery system, gas inlet, reservoir with solution of imaging agent precursor, vial, anion exchange cartridge, C-18 cartridge, syringe, solvent reservoir, reaction vessel, HPLC system, collection vessel, reservoir for solution of ascorbic acid or salt thereof, and exhaust outlet.

158. The apparatus of claim 157, further comprising tubing.

159. The apparatus of claim 158, further comprising an imaging agent synthesis module, wherein the apparatus is fluidically connected to the apparatus.

160. The apparatus of claim 159, wherein the apparatus is capable of carrying out the method of claim 74.

161. The apparatus of claim 157, wherein the apparatus is capable of preparing an imaging agent comprising the formula:



162. The apparatus of claim 157, with the components arranged as shown in Figure 8.

163. The apparatus of claim 157, comprising components arranged in the order: (1) gas inlet; (2) $[^{18}O]H_2O$ recovery system; (3) anion exchange cartridge; (4) MeCN reservoir; (5) syringe; (6) reservoir with solution of imaging agent precursor; (7) reaction vessel; (8) HPLC system; (9) reservoir with solution of ascorbic acid or a salt thereof; (10) collection vessel; (11) ethanol reservoir; (12) vial with final product; (13) Sep-pack cartridge; (14) reservoir with solution of ascorbic acid or a salt thereof; (15) reaction vessel; and (16) exhaust outlet.